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Molecular Actions of PPAR α in Lipid Metabolism and Inflammation

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29 **Abstract**

30 Peroxisome proliferator-activated receptor alpha (PPAR α) is a nuclear receptor of
31 clinical interest as a drug target in various metabolic disorders. PPAR α also exhibits
32 marked anti-inflammatory capacities. The first generation PPAR α agonists, the
33 fibrates, have however been hampered by drug-drug interaction issues, statin drop-in
34 and ill-designed cardiovascular intervention trials. Notwithstanding, understanding the
35 molecular mechanisms by which PPAR α works will enable control of its activities as
36 a drug target for metabolic diseases with an underlying inflammatory component.
37 Given its role in reshaping the immune system, the full potential of this nuclear
38 receptor subtype as a versatile drug target with high plasticity becomes increasingly
39 clear, and a novel generation of agonists may pave the way for novel fields of
40 applications.

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50 **Outline**

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94 **I. Introduction to PPAR family members**

95 The peroxisome proliferator-activated receptors (PPARs) are ligand-inducible
96 transcription factors that belong to the nuclear receptor (NR) superfamily. Three
97 PPAR subtypes have been identified: PPAR α (NR1C1), PPAR β/δ (NR1C2) and
98 PPAR γ (NR1C3) (1-5).

99 The first member of the PPAR family, PPAR α , was identified in 1990 and named by
100 its ability to become activated by chemicals known to induce peroxisome proliferation
101 in rodents (6). Peroxisomes are subcellular organelles found in most plant and animal
102 cells and harbor a complex set of enzymes acting on various metabolic functions
103 including β -oxidation of fatty acids (FA), bile acid and cholesterol metabolism (7).

104 Peroxisome proliferators cover a various set of synthetic and structurally diverse
105 industrial and pharmaceutical chemicals, including herbicides, industrial solvents and
106 hypolipidemic drugs, that cause significant increases in the size and number of
107 peroxisomes in liver, liver hypertrophy, liver hyperplasia and hepatocarcinogenesis in
108 rodents (8). Following the initial discovery of mouse PPAR α , the two other PPAR
109 subtypes, PPAR β/δ and PPAR γ were identified by homology screens (2,9).
110 Contradicting their name, the latter two subtypes do not cause peroxisome
111 proliferation in mice (8). The PPAR subtypes are encoded by distinct genes located on
112 different chromosomes (reviewed in (10)) and share a high degree of structural and
113 sequence homology, but each subtype displays a divergent pattern of tissue-specific
114 expression and ligand-binding specificity (9,11).

115 PPARs were originally described as orphan nuclear receptors, but shortly thereafter a
116 plethora of potential endogenous ligands were described (12), acknowledging PPARs
117 to be activated by a wide range of endogenous ligands including fatty acids and fatty
118 acid metabolites, such as hydroxylated eicosanoids, prostaglandins and leukotrienes,

119 and by many synthetic compounds including fibrates and antidiabetic
120 thiazolidinedione drugs (10,13).

121 Most of the physiological functions of PPARs can be explained by their activity as
122 transcription factors that modulate the expression of specific target genes (14-17).

123 PPARs can bind to sequence-specific target elements in the promoter region of target
124 genes following heterodimerization with the retinoid receptor to drive several aspects
125 of normal cellular physiology as well as pathology (15,18). This includes lipid
126 metabolism, glucose homeostasis, cell differentiation, proliferation, obesity, cancer
127 and inflammation (19,20). In addition to positively regulating gene expression,
128 activated PPARs can inhibit gene expression by negatively interfering with the
129 activity of pro-inflammatory transcription factors including signal transducer and
130 activator of transcription (STATs), activator protein-1 (AP-1), and nuclear factor- κ B
131 (NF- κ B) (21-23). Such transrepression mechanisms are likely to participate in the
132 anti-inflammatory actions of PPARs (24).

133 In this review, we will focus mainly on the molecular biology of the PPAR α subtype
134 and its role in inflammation control and inflammation-related disorders. Hereby, the
135 focus is on liver, adipose, cardiovascular and immune system as prime tissues/organ
136 systems of interest.

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144 **II. PPAR α expression profile, gene and protein structure**

145 PPAR α controls the expression of numerous genes involved in a plethora of lipid
146 metabolic pathways, including microsomal, peroxisomal and mitochondrial fatty acid
147 oxidation (FAO), fatty acid binding and activation, fatty acid elongation and
148 desaturation, synthesis and breakdown of triglycerides (TGs) and lipid droplets,
149 lipoprotein metabolism, gluconeogenesis, bile acid metabolism, and various other
150 metabolic pathways and genes (25). Consistent herewith, PPAR α is widely expressed
151 in tissues with high fatty acid oxidation rates, such as heart, liver and skeletal muscle,
152 and functions as a major regulator of fatty acid homeostasis (26-28). PPAR α
153 expression is also significant in brown adipose, adrenal and kidney tissue, as well as
154 in several inflammatory/immune cell types such as monocytes/macrophages
155 (26,27,29).

156 It is generally agreed that active PPAR α is predominantly localized in the nucleus
157 (30). However, PPAR α was reported to be localized in the cytoplasm of rat
158 chondrocyte primary cultures (31). Similarly, in differentiated human macrophages,
159 PPAR α was also much more localized in the cytoplasm (32). Hence, as with other
160 nuclear receptors, PPAR α displays a dynamic shuttling between the cytosol and the
161 nucleus. This shuttling is influenced by Ca²⁺ signaling and ligand binding, the latter
162 enhancing nuclear import of PPAR α (33). In this way, internal and/or external cell
163 signals can be translated into changes in subcellular localization and turnover/stability
164 of PPAR α and, as a consequence, affect its regulation of cellular functions (33). The
165 observation of a nucleo-cytoplasmic shuttling is not only restricted to PPAR α , but
166 also applies to PPAR γ . MEK-dependent export of PPAR γ from the nucleus reduces its
167 transcriptional activity and therefore represents a mechanism by which nuclear
168 activities of PPAR γ and possibly also other NR are downregulated (34). Further

169 investigations are required to fully elucidate the underlying molecular mechanism of
170 nucleo-cytoplasmic shuttling as well as the subcellular functions of this receptor.
171 Moreover, a better understanding of where and how PPARs are activated, turned over
172 and regulated is of the utmost importance.

173 The human and mouse PPAR α genes, located on chromosome 22 and chromosome 15
174 respectively, encode 468 amino acid (AA) polypeptides with 91% homology (35). As
175 in the mouse, the human PPAR α gene encoded mRNA is derived from 8 exons with a
176 5' untranslated region encoded by exons 1, 2, and part of exon 3. The remainder of
177 exon 3 and exons 4-8 contribute to the coding region of PPAR α (35,36) (**Fig. 1A**).
178 The last 232 bp of exon 8 contribute to the 3'-untranslated region (37). In
179 correspondence with other nuclear receptors and PPARs, the encoded PPAR α protein
180 displays four distinguishable functional domains whose cooperation modulate
181 receptor activity (38). These domains are: an N-terminal region (A/B domain), a
182 central DNA-binding domain (DBD, C domain), a flexible hinge region (D domain)
183 and a C-terminal ligand-binding domain (LBD, E domain) (39,40) (**Fig. 1B**) (**Table**
184 **1**).

185 The N-terminal A/B domain, which is the least conserved domain among PPARs,
186 harbors a ligand-independent activation function-1 (AF-1) region. This region,
187 enriched with acidic amino acids, has a low level of basal transcriptional activity and
188 can function independently of ligand-binding (tested via GAL4-fusion proteins in
189 one-hybrid assays) (35,40). Although the A/B domain suffers from a poor structural
190 organization, secondary structure formation in this domain is suggested as an
191 important step towards AF-1-mediated transactivation (38,40). The importance of the
192 A/B domain is emphasized by the fact that its deletion results in a gene-dependent
193 alteration in PPAR α transcriptional activity. For example, A/B domain deletion

194 interrupts PPAR α -mediated transactivation of the acyl-CoA oxidase (ACOX)
195 promoter, however, transactivation of the cytochrome P450 4A6 (CYP4A6) promoter
196 is unaffected (40,45). In addition, AF-1 has also been proposed to be a key
197 determinant of subtype-selective target gene expression amongst the PPAR subtypes.
198 For example, addition of the PPAR α A/B domain to PPAR γ Δ AB (A/B domain
199 truncated) enhances its ability to activate PPAR α -specific target genes (38). Vice
200 versa, addition of the PPAR γ A/B domain to the non-adipogenic PPAR β/δ Δ AB was
201 sufficient to provide adipogenic potential to the resulting PPAR β/δ chimeric protein
202 (44). Post-translational modifications (PTMs) further fine-tune PPAR α functionality.
203 PPAR α AF-1 domain phosphorylation leads to changes in transcriptional activity and
204 even ligand binding of the receptor (43). For example, MAPK-mediated
205 phosphorylation of serine 12 and 21 in the human PPAR α A/B domain increases the
206 transcriptional activity in response to mitogenic stimuli, such as high concentration of
207 insulin (58). On the other hand, glycogen synthase kinase 3 (GSK3)-mediated
208 phosphorylation of serine 73 increases the ubiquitination and degradation of PPAR α
209 (42). Concerning its relation/association with other domains in the protein, PPAR α
210 AF-1 synergistically activates transcription together with AF-2, as found for other
211 nuclear receptors (40).

212 The DBD, which is highly conserved and rich in cysteine and basic amino acids,
213 consists of two zinc-finger binding motifs (45). This domain is responsible for
214 physical interaction with DNA. Like other PPAR subtypes, PPAR α binds DNA as an
215 obligate heterodimer with retinoid X receptors (RXR) (NR2B) (49). The receptor can
216 be activated not only by phosphorylation of the A/B domain or via ligand binding to
217 PPARs themselves, but also via associating with RXR, which for example binds 9-cis
218 retinoic acid. The latter activation mechanism is referred to as the permissive effect.

219 Ligand binding of either receptor thus activates the PPAR-RXR complex; however,
220 simultaneous binding of both ligands can lead to a more potent or even synergistic
221 activation (59-65). These different activation mechanisms allow fine-tuning of PPAR
222 activity.

223 The PPAR α -RXR heterodimer recognizes and binds to PPAR response elements
224 (PPREs), which are localized in gene regulatory regions and organized as a direct
225 repeat type 1 (DR-1). DR-1 consists of two copies of the hexameric nucleotide
226 recognition motif 5'-AGGTCA-3' separated by a single nucleotide (47,48). An
227 additional consensus AACT motif is positioned 5' to the DR1 (66,67). Binding to the
228 PPRE occurs in such a way that PPAR α binds to the 5' extended half-site of the
229 response element, while RXR occupies the 3' half-site (5,66,68). The PPAR α -RXR
230 heterodimers can form independently of the PPAR α ligand. These unliganded
231 heterodimers recruit the corepressor protein complex and inhibit target gene
232 transcription (69). Upon ligand binding, the corepressor complex is released from the
233 PPAR α -RXR heterodimer and the coactivator complexes will be recruited to the
234 promoter region of target genes, thereby initiating transcription (70) (**Fig. 2A**).

235 The first natural PPRE was found in the promoter region of the ACOX gene (36,71).
236 In addition, recent genome-wide profiling of PPAR α binding sites revealed about
237 46% of PPAR α -RXR binding sites within intronic regions (72). Using PPAR γ as
238 study case, chromatin accessibility in general was identified as a major determinant
239 for transcriptional activity, as PPAR-RXR heterodimers were found to primarily bind
240 in open chromatin regions (73-75).

241 While PPAR α binds DNA only as a heterodimer and not as a monomer, deletion of its
242 N-terminal A/B domain generates a truncated protein that binds DNA non-specifically
243 as a monomer in *in vitro* assays (45). Although the physiological significance of such

244 binding is not completely understood, it may serve as evidence of an interdomain
245 communication. The DBD of PPAR γ was shown to form an interface with its own
246 LBD as well as with the LBD of its heterodimeric partner, hereby influencing ligand
247 binding (76). More crystallization efforts are needed to challenge or validate this
248 interface concept in the case of PPAR α . The DBD of PPAR α (and PPAR γ) is also
249 subject to phosphorylation, which serves to further modulate the transcriptional
250 activity of the receptor (46).

251 Like PPARs, many other nuclear receptor members also need RXRs as their
252 obligatory heterodimerization partner, raising therefore the possibility of a
253 competition between particular NRs for their common binding partner (77). This
254 competition may have important biological outcomes. For instance, liver X receptor α
255 (LXR α) activation by either overexpression of LXR α or ligand activation suppresses
256 PPAR α signaling through reduction of active PPAR α -RXR heterodimers in the liver
257 and thus diminished PPRE occupancy. RXR α supplementation restored the LXR-
258 mediated inhibition of PPAR α activity (78). Conversely, excess PPAR α in the
259 presence of its ligands suppresses the sterol regulatory element-binding protein-1c
260 (SREBP-1c) promoter that contains two LXR response elements (79), indicating that
261 the mechanism of competition for RXR α between PPAR α and LXR may be reciprocal
262 (78). This relationship between PPAR α , LXR and RXR could be crucial for a mutual
263 regulation of both LXR and PPAR α activities, and thus for the nutritional regulation
264 of their downstream target genes. However, the physiological validation of these
265 mechanisms still remains to be demonstrated. Another example of competition for
266 RXR α between RXR-partnering NRs was described for the thyroid hormone receptor
267 (TR) with LXR (80).

268 Of note, Silent information regulator 1 (SIRT1) was also shown to bind PPAR α ,
269 through a region homologous to the PPAR α binding domain in RXR α . Interestingly,
270 the balance between SIRT1 and RXR appears to determine whether PPAR α is a
271 positive or negative regulator of genes involved in fatty acid metabolism (81).
272 Additionally, the PPAR α -SIRT1 complex would directly bind a single hexameric
273 motif embedded in estrogen-related receptor (ERR) elements (ERREs), thus
274 competitively downregulating ERR target genes, at least in the heart. These findings
275 suggest a PPAR α -dependent transcriptional repression mechanism in the control of
276 ERR-driven mitochondrial respiration and cardiac contraction (82,83). In addition,
277 exposure to a high-fat diet (HFD) also induces the formation of a PPAR α -SIRT1
278 complex, impairing an association of PPAR α with the pro-inflammatory transcription
279 factor p65. Collectively, this shift is expected to lead to the repression of PPAR α -
280 target genes involved in fatty acid oxidation and enhancement of pro-inflammatory
281 pathways in the heart (84). Albeit intriguing, more experimental evidence is necessary
282 to prove that PPAR α can bind DNA as an RXR-independent monomer and whether
283 this mechanism is also operative in other tissues such as the liver.

284 Immediately adjacent to the DBD is the highly flexible hinge domain (D), connecting
285 the DBD and the LBD (35). This region binds corepressor proteins, such as the
286 nuclear receptor corepressor (NCoR), to the receptor in its inactive, unliganded state
287 (51) and serves as a target for PTMs including phosphorylation on serines 179 and
288 230 catalyzed by PKC and the SUMOylation at lysine 185 that promote NCoR
289 recruitment (52,53). In addition, mutation of a potential phosphorylation site within
290 the PPAR α hinge was shown to prevent dimerization capacities (46). Another study
291 on truncated PPAR α lacking part of the hinge region and LBD suggested that the
292 hinge region might contain a nuclear localization signal (NLS) (50). Consistently, a

293 series of truncation mutants revealed that PPAR nuclear transport is mediated by at
294 least two nuclear localization signals, i.e. one in the DBD-hinge region and one in the
295 AF-1 domain (33). It was suggested that the hinge region also interferes with PPAR α
296 binding to DNA and hence takes up an important suppressor role (85). More
297 specifically, the ribosomal protein L11 (rpL11) was shown to interact with the D-
298 domain of PPAR α and to inhibit PPRE-driven reporter activity (85). Furthermore,
299 heat shock protein 90 (Hsp90) was reported to associate with both the hinge and LBD
300 of PPAR α . Using several approaches to disrupt Hsp90 complexes within the cell,
301 Hsp90 was confirmed as a repressor of PPAR α (and PPAR β/δ) activity (54).

302 Next, the PPAR α -LBD harbors a ligand-dependent transactivation function (AF-2)
303 and has a structure consisting of an α -helical sandwich and a four-stranded β -sheet,
304 forming a Y-shaped cavity of 1400 Å called the ligand-binding pocket (LBP) (55).
305 The volume of the PPAR α -LBP is quite comparable to other PPAR subtypes, but is
306 substantially larger as compared to most other NRs. Among the PPARs, The PPAR α
307 LBP is more lipophilic which potentially explains the greater affinity of PPAR α to
308 bind the more saturated fatty acids (55). Following ligand-binding, the AF-2 domain
309 undergoes conformational changes, which allows for the interaction with various
310 coactivators carrying LXXLL motifs (L–leucine, X–any amino acid) (55), such as
311 cAMP-response element-binding protein (CBP)/p300 and steroid receptor
312 coactivator-1 (SRC-1/NCoA-1) (55). In addition, the LBD is crucial for dimerization
313 with RXR; this was confirmed in studies involving deletion of PPAR α helix 10-12 as
314 well as a L433R mutation in PPAR α , which caused impaired heterodimerization with
315 RXR (51,57). PPAR α furthermore possesses two nuclear export signals (NES) in the
316 DBD and LBD regions, which are recognized by the export receptors calreticulin and
317 chromosomal maintenance 1 (CRM1), respectively. A recent study confirmed the

318 presence of a functional NES in the LBD, i.e. at AA 300-308 in human PPAR α
319 (86,87).

320 As mentioned earlier, human and murine PPAR α show 85% identity at the nucleotide
321 level and 91% identity at the amino acid level, however evidence exists for a genetic
322 heterogeneity in the functional coding sequence of human PPAR α that translates into
323 functional differences in receptor activity. For example PPAR α L162V, a variant of
324 the human PPAR α gene resulting in the introduction of an amino acid substitution
325 within the PPAR α DBD, is found at an allelic frequency of \sim 0.025–0.073 in
326 ethnically diverse populations (88-90), while being more frequent (0.745) in North
327 Indians (91). Functional studies on the L162V gene variant demonstrate enhanced
328 ligand-induced activity when compared to the wild-type (88,91). Importantly, in
329 various studies the L162V polymorphism is correlated with dyslipidaemia, coronary
330 ischemic events (37,88-90,92-94) and adiposity (95,96). However, other studies have
331 not replicated these correlations (97,98). These inconsistencies could be due to
332 differing environments, genetic background and disease status between the studied
333 populations. In this context, the effect of the L162V polymorphism could be
334 modulated via gene-drug and gene-nutrient interactions (94,99,100). For example, the
335 association of the L162V genotype with a particular lipoprotein profile may be
336 modified by dietary fats (94,101).

337 V227A, a natural variant in which the PPAR α hinge region is affected, was identified
338 in a Japanese population with a frequency of 5.0% (102-104) and in a Chinese
339 population with a frequency of approx. 4% (105). This variant attenuates the PPAR α -
340 mediated transcription of CYP4A6 and the mitochondrial 3-hydroxy-3-
341 methylglutaryl-CoA (mHMG-CoA) synthase genes in the presence of fibrates. This
342 transcriptional repression was ascribed, at least partially, to increased corepressor

343 binding to PPAR α and defective release of NCoR from chromatin (106). Interestingly,
344 the V227A variant was associated with perturbations in plasma lipid levels and
345 modulated the association between dietary polyunsaturated fatty acid intake and high-
346 density lipoprotein (HDL) cholesterol concentrations (105). Of note, the PPAR α
347 V227A polymorphism may be involved in the pathogenesis of non-alcoholic fatty
348 liver disease (NAFLD) and may play a protective role in obesity (107). Although
349 epidemiological and interventional studies demonstrate a link between PPAR α
350 polymorphisms and metabolic parameters, more studies are required to understand
351 whether and how the response to fibrate drugs and other PPAR α -regulated pathways
352 are affected by the polymorphisms.

353 In addition to polymorphic variants, a truncated splice variant of PPAR α , generated
354 by alternative splicing resulting in the skipping of exon 6, has been detected in human
355 PPAR α (**Fig. 1A**) (50,108). This variant lacks the hinge region and the entire LBD
356 and is unable to bind to PPREs. As a consequence, it exerts a dominant negative
357 transcriptional repressive activity on full-length PPAR α through titration of the
358 coactivator CBP by competing for coactivators. It was speculated that differences in
359 the expression level of truncated hPPAR α might be implicated in the heterogeneity in
360 response to fibrates among different patients (50). Of interest, genome-wide
361 correlation analysis with subsequent pathway enrichment analysis indicated a
362 selective role for truncated PPAR α as an anti-proliferative and anti-inflammatory
363 factor (109). Further experimental manipulation of human and mouse hepatocytes by
364 specific knock-down and overexpression analysis substantiated this hypothesis (109).
365 *In vivo* evidence for a dominant negative transcriptional repressive activity is lacking
366 so far. Therefore, whether this variant has any specific physiological significance with

367 regard to metabolic processes, inflammation as well as its relevance for
368 hepatocarcinogenesis still needs to be revealed and requires further investigation.

369

370 **III. Modulating factors of PPAR α activity**

371 **PPAR α gene and protein expression**

372 The expression of the PPAR α gene is regulated by various physiological conditions
373 such as stress, glucocorticoids (GCs), growth hormones, insulin and leptin. As an
374 important physiological response, PPAR α expression is induced during fasting
375 resulting in an enhanced expression of PPAR α target genes in liver to operate fatty
376 acid oxidation and to form substrates that can be metabolized by other tissues. Vice
377 versa, PPAR α also controls, directly or indirectly, lipogenic pathways (which will be
378 further discussed in detail in section V). Liver lipogenesis particularly allows FA
379 synthesis in a fed state when dietary carbohydrates are abundant (110,111).
380 Adipocyte-derived factors may further influence the expression level and subsequent
381 PPAR α activity. Consistent with this, administering leptin, considered pro-
382 inflammatory, correlated with an increased PPAR α hepatic expression in ob/ob mice
383 (112). The mechanisms underlying the induction of PPAR α transcription by leptin
384 may be connected to changes in fatty acid flux mediated by leptin signaling (112).
385 Leptin-stimulated PPAR α gene expression was also observed in muscle cells, through
386 the activation of and changes in the subcellular localization of AMPK- α 2 (113).
387 Additionally, leptin was found to enhance PPAR α gene transcription in pancreatic β -
388 cells (114) but not in adipose tissue (115). The basis for this discrepancy is not
389 known, but findings generated using isolated model systems will definitely require
390 further confirmation *in vivo*.

391 On the other hand, the anti-inflammatory adipokine adiponectin also increased
392 PPAR α -responsive promoter activity in H4IIEC3 cells, an effect that required co-
393 expression of PPAR γ coactivator-1 α (PGC-1 α), suggesting that adiponectin-induced
394 PPAR α activity may be mediated through up-regulation of PGC-1 α expression (116).

395 In contrast, growth hormone (GH) has been shown to rather decrease PPAR α mRNA
396 in cultured rat hepatocytes (117,118). A similar effect was shown in
397 hypophysectomized rats (119). In addition, GH also decreases PPAR α transcriptional
398 activity (120) as well as the expression level of PPAR α (121). Similarly, treatment of
399 primary hepatocytes for 3 days with another anabolic signal, insulin, also led to
400 reduced PPAR α levels (122), whereas short-term exposure to this hormone increased
401 PPAR α transactivation via phosphorylation of the ligand-independent AF-1 domain
402 (123).

403 Next to tissue-specific differences in PPAR α levels, the expression of PPAR α in a
404 given tissue further oscillates under the control of the circadian rhythm. For example,
405 PPAR α expression peaks during daytime in mice, which correlates with the timing of
406 fasting in these nocturnal rodents (124). These diurnal patterns thus correspond well
407 with known functions of PPAR α in physiology but also pathophysiology (125).
408 PPAR α is under the transcriptional control of the GC-activated glucocorticoid
409 receptor (GR) in rat hepatocytes (126). As such, PPAR α expression follows a diurnal
410 rhythm, which parallels that of circulating corticosterone and the levels of PPAR α are
411 also up-regulated during times of stress (127). Moreover, the circadian expression of
412 PPAR α was reported to be directly regulated by the core-clock transcription factors
413 brain and muscle Arnt-like protein (BMAL) and circadian locomotor output cycles
414 kaput (CLOCK) both *in vivo* and *in vitro* (128). In another study, the proline- and
415 acidic amino acid-rich basic leucine zipper (PARbZip) proteins were also shown to
416 modulate the rhythmic expression and activity of PPAR α . The mechanism was
417 proposed to be indirect and involved a cyclic generation of PPAR α ligands which
418 initiate a feed-forward loop, in which PPAR α enhances transcription from its own
419 gene (129). In addition, enhanced PPAR α transcript levels were observed in both B

420 and T cells upon GCs treatment (130), indicative of a function of PPAR α in the
421 immune system (see further below under section 6).

422 Additionally, PPAR α expression is also reported to be related to aging. In this line of
423 reasoning, examination of mRNA expression in mouse spleens revealed an age-
424 associated decline in the levels of mRNA encoding PPAR α and its concomitant target
425 genes ACOX and catalase, which was accompanied by a constitutive pro-
426 inflammatory cytokine production (131). Similarly, a recent study has shown that
427 aging inhibits PPAR α activation as assessed by diminished mRNA levels of its target
428 genes ACOX and carnitine palmitoyl transferase 1 (CPT1) in aged rat livers (132).

429 Metabolite levels also affect PPAR α expression; intriguingly, glucose and metabolites
430 (glucose-1-phosphate and glucose-6-phosphate) were shown to bind PPAR α with high
431 affinity resulting in a significantly altered PPAR α secondary structure (133). In this
432 report, in vitro addition of glucose alone reduced the interaction of PPAR α with its
433 coactivator SRC-1. Conversely, in the presence of the activating ligands arachidonic
434 acid and clofibric acid, glucose rather increased PPAR α interaction with SRC-1, DNA
435 binding and activation of the β -oxidation pathway (133). In addition, high glucose
436 levels regulate PPAR α expression in human macrophages. Incubation of murine J774
437 macrophages with high glucose concentrations increased the expression of PPAR α at
438 the mRNA and protein levels and enhanced its binding to the PPRE of the lipoprotein
439 lipase (LPL) promoter (134). In contrast, glucose decreases PPAR α expression in
440 pancreatic β -cells leading to a reduced FAO and increased phospholipids and TG
441 synthesis, a mechanism believed to underlie β -cell glucolipototoxicity (135).

442 NF- κ B-driven cytokines such as TNF α , IL-1 β and IL-6 also affect the expression of
443 PPAR α . In TNF α -treated male Sprague Dawley-rats, PPAR α mRNA and
444 corresponding PPAR α protein levels were significantly reduced, likely contributing to

445 the decrease of peroxisomal β -oxidation (136). IL-1 β and IL-6 both repress the
446 induction of PPAR α expression exerted by the combined action of clofibric acid and
447 the GC dexamethasone in fetal rat hepatocytes (137).

448 The presence or absence of the activity of other transcription factors also impacts
449 PPAR α levels and activity. In hepatocytes, Krüppel-like factor 6 (KLF6) deficiency
450 reduces PPAR α protein expression and downstream targets resulting in attenuation of
451 lipid and glucose abnormalities associated with a HFD. KLF6 mediated induction of
452 PPAR α protein expression through miRNA 10b repression (138). PPAR α is also
453 regulated at the transcriptional level by other nuclear receptors such as hepatocyte
454 nuclear factor 4 (HNF4), chicken ovalbumin upstream promoter-transcription factor II
455 (COUP-TFII), and others. While HNF4 positively regulates hPPAR α expression via a
456 DR1 element present in the hPPAR α promoter, COUP-TFII also bound this site but
457 antagonized this effect (139). The regulation of PPAR α by HNF4, consistent with the
458 tissue-expression pattern of PPAR α , was also demonstrated *in vivo* using HNF4-
459 deficient mice that display significantly lower PPAR α mRNA levels compared with
460 the wild-type mice (140). Exemplary of another metabolite, bile acids stimulate
461 hPPAR α expression in a species-specific manner through a mechanism involving the
462 binding of Farnesoid X receptor (FXR) on its promoter (141). Moreover, PPAR α
463 expression in the mouse small intestine was shown to be under the control of LXR
464 and the pregnane X receptor (PXR) (142).

465 Cross-talk with other nuclear receptor signaling pathways may also modulate PPAR
466 activity, as illustrated by the direct control of the PPAR β promoter by the vitamin D
467 receptor (143). In this respect, and as mentioned earlier, nuclear receptors that
468 function as heterodimers with RXR can potentially compete with PPAR α signaling in
469 tissues in which the amount of RXR is limiting (77).

470 Furthermore, PPAR α turnover is controlled by ligand specificity and availability (**Fig.**
471 **3**). In this context, Blanquart *et al.* demonstrated that synthetic PPAR α ligands such as
472 Wy14,643, GW7647 or fibrates prolonged half-life and increased stability of the
473 receptor, preventing thereby its ubiquitination and its subsequent degradation via the
474 proteasome (41). Besides, PPAR α agonists, such as fenofibrate, markedly up-
475 regulated hPPAR α mRNA levels in primary cultures of human hepatocytes as well as
476 hPPAR α promoter activity suggesting that PPAR α positively autoregulates its own
477 expression (139).

478 Of note, hPPAR α mRNA levels in the liver vary among individuals (50,109),
479 suggesting that PPAR α is strongly regulated at the gene level in human liver by
480 genetic and/or environmental factors (50).

481 Last but not least, the function of PPAR α as a transcription factor is controlled by its
482 PMTs and cofactor recruitment (**Fig. 3**), which will be further discussed in detail in
483 the next sections.

484 Together, regulation of the PPAR α expression levels efficiently modulates PPAR α
485 activator responses and thus may affect downstream pathways involved in metabolism
486 and inflammatory processes.

487

488 **PPAR α cofactors**

489 As with other nuclear receptors, PPAR α transactivation activity is regulated by the
490 presence of coregulators, which may function as corepressors or coactivators
491 depending on the context. In the absence of a specific ligand, PPAR α binds co-
492 repressors, such as NCoR and silencing mediator for retinoid and thyroid hormone
493 receptors (SMRT) (26). The receptor interacting protein 140 (RIP140) is a PPAR α
494 corepressor, which is known to repress the activity of NRs by competing with

495 coactivators and by recruiting downstream effectors such as histone deacetylases
496 (HDACs) (144). Interestingly, mice devoid of the corepressor protein RIP140 show
497 resistance to HFD-induced obesity and hepatic steatosis in association with
498 upregulation of genes involved in energy dissipation. Such phenotype may be
499 suggestive of a role for this corepressor in PPAR α signaling (145). Whether or not
500 PPAR α is directly involved remains to be shown. On the other hand, known
501 coactivators that have been found in a large complex with PPAR α /RXR heterodimers
502 include PGC-1 α , PGC-1 β , CBP/p300, SRC-1, PPAR-interacting protein (PRIP),
503 PPAR-binding protein (PBP/TRAP220/DRIP205/Med1) as well as coactivator-
504 associated proteins PIMT (NCoA6IP) and coactivator-associated arginine
505 methyltransferase-1 (CARM-1). Some of the coactivators, including the SRC-1
506 family and CBP/p300, contain intrinsic histone acetyltransferase (HAT) activities
507 required to facilitate chromatin remodeling (Reviewed in (146)). The PPAR α -
508 interacting cofactor (PRIC) complex isolated from rat liver nuclear extracts reveals
509 the presence of many of these coregulators, likely forming one mega complex (147).
510 Most cofactors are not receptor-exclusive, yet, emerging gene knockout mouse
511 models show that some of the coactivators are essential for PPAR α signaling. For
512 example, conditional deletion of PBP/MED1 gene in liver results in the abolition of
513 PPAR α ligand-induced pleiotropic effects, indicating that PBP/MED1 is essential for
514 the function of PPAR α (148).

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518 **PPAR α post-translational modifications**

519 As for other nuclear receptors, PPAR α activity is finely tuned by various PTMs
520 including phosphorylation, ubiquitination and SUMOylation (41,53,149).

521 PPAR α is a phosphoprotein of which the transcriptional activity is affected by cross-
522 talk with several kinases, including MAPK (ERK1/2), c-Jun N-terminal kinases
523 (JNK)/p38), AMPK, protein kinase A and C (PKA, PKC) and GSK3 (**Table 2**). The
524 effects of phosphorylation on PPAR α activity depend on a number of features such as
525 the nature of the modified residue, as well as the stimulus and the kinase involved.

526 PPAR α phosphorylations may also have different functional outcomes depending on
527 the context, with effects on receptor stability, susceptibility to proteosomal
528 degradation, enhanced recruitment of cofactors and transactivation. PPAR α was first
529 shown to be phosphorylated in primary rat adipocytes in culture in response to insulin,
530 resulting in the stimulation of basal as well as ligand-dependent transcriptional
531 activity (149). Along the same line of interest, insulin treatment of human HepG2
532 hepatoma cells increases PPAR α phosphorylation enhancing thereby its
533 transcriptional activity. This insulin-mediated phosphorylation of PPAR α via the
534 ERK1/2 MAPK pathway involves amino acids Ser12 and Ser21 in the AF-1 domain
535 resulting in transcriptional activation probably by relieving inhibition by corepressors
536 (42,58). In line with this, in rat neonatal cardiac myocytes, stress-activated p38
537 MAPK phosphorylates Ser 6, 12 and 21 residues located within the N-terminal A/B
538 domain of the PPAR α protein leading to an increase in ligand-dependent
539 transactivation of targets and enhanced cooperativity with the transcriptional
540 coactivator PGC-1. It was speculated that PPAR α phosphorylation and the subsequent
541 specific recruitment of PGC-1 favor cardiac mitochondrial fatty acid β -oxidation
542 during periods of stress (150). In contrast, during cardiac hypertrophic growth, the
543 ERK-mediated phosphorylation of PPAR α was shown to have an opposite effect to

544 that of p38 kinase resulting in a reduced capacity for myocardial lipid and energy
545 homeostasis (151) demonstrating therefore the importance of cellular context. In FAO
546 hepatic-derived cells PPAR α phosphorylation level is increased by ciprofibrate,
547 subsequently enhancing its transcriptional activity as demonstrated by a rise in ACOX
548 gene expression (152).

549 Given that substrates for MAPK phosphatase 1 (MKP-1, also known as DUSP1)
550 include many members of the MAPK family including ERK1/2 and p38 MAPK,
551 overexpression of MKP-1 in turn affected the constitutive PPAR α activity, thus acting
552 in a feedback control mechanism (153). Taken together, these studies hint at pivotal
553 activating roles of MAPK on PPAR α activity, thereby placing this receptor under the
554 control of growth factors and various cellular stressors, as already mentioned above.

555 *In vivo* phosphorylation studies show that the level of phosphorylated PPAR α is
556 increased by treatment with its agonist Wy-14,643 as well as the PKC activator
557 phorbol myristoyl acetate (PMA) (46). Particular modifications can increase a subset
558 of PPAR-mediated functions, e.g. phosphorylation at serine 179 and 230 in the
559 PPAR α hinge region by PKC leads to enhanced transactivation potential, but impairs
560 its transrepression activity (52). Consistently, PKC inhibition impairs ligand-activated
561 PPAR α transcriptional activity and decreases PPAR α ligand-induction of its target
562 genes including PPAR α itself and CPT1, but enhances PPAR α transrepression
563 properties. Thus, the PKC signaling pathway acts as a molecular switch dissociating
564 the transactivation and transrepression functions of PPAR α (52). In support, it was
565 proposed that the capacity of simvastatin to mitigate PKC action indirectly stimulates
566 PPAR α transrepression activities towards NF- κ B and as such explains statin-mediated
567 acute anti-inflammatory effects (154). As indicated earlier, PKC phosphorylation is
568 believed to be important for PPAR α and RXR interaction as mutation of the PKC

569 phosphorylation sites T129 and S179 in the hinge region of PPAR α reduces
570 heterodimerization (46).

571 The fasting-responsive kinase PKA enhances PPAR α activity converging in the
572 stimulation of PPAR α target genes. It was speculated that under stress, fasting or
573 exercise, PPAR α phosphorylation in response to PKA leads to an enhancement of β -
574 oxidation, production of glucose and ketone bodies, which serve as fuel for muscles
575 and brain (155). Thus, physiological cAMP modulators such as fasting, stress or
576 exercise potentially modulate PPAR α activity. Of note, PKA-mediated PPAR α
577 phosphorylation occurs mainly in the DBD, while the enhancement of activity
578 generally involves the AF-2 domain (155), suggesting an effect of phosphorylation on
579 interdomain communication. As another starvation-linked kinase, AMPK activity may
580 influence the expression of PPAR α and PPAR α target genes in certain tissues. In the
581 murine muscle cell line C2C12, for example, leptin stimulates PPAR α gene
582 expression and subsequent FAO through the activation of α 2-subunit containing
583 AMPK (113). Moreover, AMPK activation increases mRNA expression of PPAR α
584 and its target genes such as ACOX and CPT1 as well as PGC-1; this effect was
585 correlated with an increased FAO in skeletal muscle (156). In addition, AMPK and
586 p38 MAPK were involved in the activation of PPAR α by adiponectin in muscle cells
587 (157). However, whether and which residues within PPAR α may be phosphorylated,
588 remains an unresolved issue. Next to adiponectin, AMPK was also described as a
589 modulator of PPAR α expression in response to glucose levels (158,159) suggesting
590 that cellular energy levels might affect the PPAR α -regulated signaling network in a
591 ligand-independent manner. Recently, a novel mechanism was uncovered by which
592 AMPK controls PPAR α -driven gene expression in murine liver subjected to a
593 prolonged fasting. Activated AMPK was recruited to promoters of glucose and lipid

594 metabolism genes that are co-controlled by PPAR α and GR α (160). For the latter
595 example in liver, it also remains to be discovered which residue(s) of involved
596 transcription factors, PPAR α , GR or both, may be phosphorylated by AMPK.
597 PPAR α phosphorylation, besides affecting target gene regulation, also affects the
598 stability and turnover of PPAR α through ubiquitination (41,161). Ubiquitination
599 involves the conjugation of a small protein, ubiquitin, to the target protein via a
600 sequential action of particular enzymes which primarily leads to degradation of the
601 receptor by the 26S proteasome. PPAR α is targeted by the E3 enzyme murine double
602 minute 2 (MDM2), which leads, depending on the cellular PPAR α levels, to
603 stabilization of receptor levels or degradation via the ubiquitin-proteasome pathway
604 (162). The effect of degradation on the transcriptional activity is still under debate;
605 Blanquart *et al.* showed an inverse correlation between PPAR α degradation and
606 activity, which is in contrast to results obtained by the group of Vanden Heuvel
607 (41,42). Recently, a muscle ring finger-1 (MuRF1)-mediated monoubiquitination of
608 cardiomyocyte PPAR α was discovered that enhances nuclear export of the receptor
609 and consequently inhibits PPAR α -induced FAO in cardiac tissue (87).
610 GSK3 is a key enzyme of glycogen metabolism and able to inactivate glycogen
611 synthase. Its activation phosphorylates PPAR α predominantly at serine 73 in the A/B
612 domain. This modification negatively affects PPAR α stability and promotes ubiquitin
613 proteasome-mediated degradation (42). PPAR α ubiquitination may thus constitute a
614 regulatory pathway that may contribute to the duration and the magnitude of the
615 response to PPAR α activators (41,161). Function-wise, when blocking GSK3 by
616 biliverdin reductase A (BVRA) in the liver, a protective effect against steatosis is
617 inferred, due to a preservation of hepatic PPAR α activity (163).

618 Next to phosphorylation and ubiquitination, PPARs can be modified by
619 SUMOylation. SUMOylation is a reversible modification that entails the covalent
620 attachment of small ubiquitin-related modifier (SUMO) proteins via specific enzymes
621 (164). Murine PPAR α was shown to be SUMOylated on lysine 358 (56). This
622 particular SUMOylation triggers the interaction with GA-binding protein α bound to
623 the 7 α -hydroxylase cytochrome P450 7b1(*cyp7b1*) promoter resulting in specific
624 down-regulation of this gene. Hence, SUMO modification can be regarded as a
625 positive regulator of mPPAR α transrepressive activity (56). Likewise, human PPAR α
626 undergoes SUMOylation by SUMO-1 on lysine 185 in the hinge region, leading to
627 down-regulation of its transactivation capacity through the selective recruitment of
628 NCoR (53) (**Table 3**). Both SUMOylation sites are targeted by the E3 enzyme protein
629 inhibitor of activated STAT (PIAS) γ (78,164).

630 Finally, another means of regulating PPAR α activity indirectly includes the
631 phosphorylation of RXR and of various associated cofactors such as PGC-1 α , SMRT
632 and NCoR (reviewed in (26)).

633 PTMs play a key role in modulating PPAR α activity in (patho)physiological contexts.
634 The modifying enzymes themselves are modulated by the cellular metabolic status
635 and environment, hereby positioning PPAR α into a very complex regulatory network.
636 The level of complexity is even intensified knowing that PPAR α forms part of a
637 physical assembly for variable corepressor or coactivator complexes, which are also
638 on their turn subjected to PTMs (26). Full understanding of these complex patterns of
639 regulation requires more high-throughput technologies to characterize the PPAR α
640 interactome, its dynamic interactions with modifying enzymes as well as the
641 mechanisms by which these interactions modulate PPAR α activity. These might point

642 to drugs that can modulate the PPAR α PTMs status with regard to metabolic disorders
643 and inflammation.

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666 **IV. PPAR α natural and synthetic ligands**

667 **PPAR α natural ligands**

668 Adoption of orphan NRs through the identification of their endogenous ligands is key
669 towards understanding their biology (13). The promiscuity of PPAR α for its ligands
670 can be attributed to the large size of the LBP. PPAR α is activated by a wide range of
671 endogenous or naturally occurring biological molecules encompassing a variety of
672 FAs and FA derivatives, including acyl-CoAs, oxidized FAs, eicosanoids,
673 endocannabinoids, phytanic acids (165-167) and long chain dietary FAs (166,168)
674 (listed in Table 4). As such, FAs and their metabolites that interact with PPAR α can
675 be derived from the diet or obtained via *de novo* synthesis. Many of those FAs exhibit
676 an affinity for PPAR α within a nanomolar range (166). This supports the fact that
677 PPAR α serves as an intracellular lipid sensor. It was proposed that PPAR α senses
678 certain endogenous lipid metabolism intermediates as ligands to regulate the
679 expression of target genes involved in their metabolism (169). *In vivo* evidence for
680 this came from studies using ACOX1 knockout mice. The disruption of this first and
681 rate-limiting enzyme of the peroxisomal FAO pathway caused accumulation of long
682 chain fatty acyl-CoA coinciding with an increased peroxisome proliferation,
683 hepatocarcinoma and profound activation of PPAR α in rodents (169,170). These
684 findings suggested that substrates of the ACOX1 enzyme may possibly be PPAR α
685 agonists. Numerous arachidonic acid metabolites serve as ligands for PPAR α ; in this
686 context, 8(*S*)-HETE, an intracellular hydroxy FA derived from the oxygenation of
687 arachidonic acid, mainly by lipoxygenases and monooxygenases, was shown to be a
688 strong activator of PPAR α (171). In addition, 20-hydroxyeicosatetraenoic acid (20-
689 HETE), a main product of cytochrome P450 (CYP4A and CYP4F) activity that
690 catalyzes the conversion of arachidonic acid, can bind to and activate PPAR α in

691 HepG2 cells leading to enhanced expression of the PPAR α target gene, apolipoprotein
692 A-I (APOA1) (172). Leukotriene B4 (LTB₄) is another putative PPAR α ligand, which
693 connects the receptor to inflammation and immune responses. Its ability to act as a
694 PPAR α agonist has been reported in several studies (165,173,174), and the binding
695 affinity is found to be within the nanomolar range (174). Stimulation of 5-
696 lipoygenase activity leads to activation of PPAR α via production of intracellular
697 LTB₄ (165,175). In endothelial cells, oxidized phospholipids were found to activate
698 PPAR α in a phospholipase A₂-dependent manner suggesting that phospholipids may
699 be precursor of endogenously generated PPAR α ligands (176).

700 Mice with liver-specific inactivation of fatty acid synthase (FAS), a key lipogenic
701 enzyme, developed hypoglycemia, fatty liver and defects in expression of PPAR α
702 target genes when subject to a fat-depleted diet. These effects were reversed by a
703 synthetic PPAR α agonist, identifying thereby the *de novo* synthesized end products of
704 FAS as endogenous activators of PPAR α in adult liver (177). This phenomenon is not
705 limited to the liver. Indeed, selective inactivation of FAS in the hypothalamus is
706 found to affect PPAR α -dependent gene expression and feeding behavior, which are
707 corrected after hypothalamic infusion of a PPAR α activator (178). These observations
708 suggest that FAS, which is known to be regulated by nutrition, is involved in the
709 generation of endogenous PPAR α ligands. The same research group demonstrated
710 that FAS generates 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine (16:0/18:1-
711 GPC), which seems to be a putative PPAR α ligand (179).

712 Other natural compounds such as polyphenols have been identified as ligands of
713 PPAR α (180,181). PPAR α activation with resveratrol, a natural polyphenol, and some
714 of its derivatives and analogs, results in a brain protection against stroke (182,183).
715 Resveratrol was identified as an AMPK activator, linking this sensor of the nutritional

716 status again to PPAR α functionality (184) (see chapter 3). Since PPAR α acts as an
717 intracellular sensor of FAs levels, of which an alteration is associated with the
718 development of several diseases such as diabetes, obesity, atherosclerosis and
719 inflammation, finding a way of regulating the receptor activity through modulating
720 (levels of) endogenous ligands may have the potential to generate new therapies.

721

722 **PPAR α synthetic ligands**

723 Synthetic PPAR α ligands include fibrates such as clofibrate, fenofibrate, and
724 bezafibrate (listed in **Table 4**). Fibrates are used in the pharmacological treatment of
725 hypertriglyceridaemia (48,185) despite the low potencies of these first generation
726 agonists on PPAR α . Fibrates act by decreasing TG-rich lipoproteins in serum through
727 an increase in genes involved in FAO and a decrease in apolipoprotein C-III (APOC3)
728 gene expression (186,187). See further chapter 6 for a current status of PPAR α -
729 targeted therapies in a clinical setting.

730 Other synthetic compounds that are not approved for clinical use, but are often used
731 for research purposes to activate PPAR α include GW7647, GW9578 and Wy-14,643
732 (also known as pirinixic acid) (29). In addition, other chemicals with environmental
733 impact, particularly plasticizers (example DEHP-used in the manufacturing of
734 plastics) and herbicides have been shown to function as PPAR α ligands (28). As their
735 potential impact in human health is unclear, further research is necessary to address
736 this with respect to lifetime health.

737

738 **Selective PPAR α modulators (SPPARMs)**

739 The development of a selective PPAR α agonist may provide a good approach to
740 maximize the therapeutic potential of these drug targets. Accordingly, a new

741 generation of highly potent and selective PPAR α -modulators (SPPARM α) is being
742 developed to enable greater pharmacological effects and to dissociate the benefits of
743 the PPAR α agonists from their side effects (188). A number of SPPARM α have to
744 date been identified by *in vitro* and preclinical studies and some have entered early
745 clinical trial studies with promising results (see further **section 6**). Among these
746 modulators, elafibranor (GFT505), a dual PPAR α/δ agonist, shows protective effects
747 on liver steatosis, inflammation and fibrosis (189). Pemafibrate (K-877), a recently
748 developed highly specific PPAR α agonist with SPPARM properties (190) shows
749 more potent PPAR α -activating efficacy *in vitro*, better effects on TGs and high-
750 density lipoprotein-cholesterol (HDL-C) levels in patients with atherogenic
751 dyslipidaemia and a reduced risk of side effect as compared to fenofibrate. Recently,
752 pemafibrate was shown to exert beneficial effects on lipid metabolism, reverse
753 cholesterol transport (RCT) and inflammation, resulting in anti-atherogenic
754 properties. Therefore, pemafibrate thus seems an ideal next-generation PPAR α -
755 triggering candidate to target atherogenic dyslipidaemia and cardiovascular disease
756 risk (190).

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764 **V. PPAR α target genes and their function**

765 Numerous studies with PPAR α -deficient mice during the past years have
766 demonstrated the critical roles played by this receptor in energy metabolism, hepatic
767 functions, inflammation, cardiac pathophysiology, cell cycle alterations and rodent
768 hepatocarcinogenesis (27). We will next discuss functionalities of PPAR α target
769 genes and proteins per tissue type. **Table 5** summarizes the many genes that have
770 been identified as PPAR α target genes in different organs since the end of the 1990s.
771 We have indicated whether the regulation was found to be direct or indirect.

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773 **PPAR α target genes in liver**

774 The PPAR α subtype exerts its main functions in the liver, where the receptor is
775 involved in various aspects of lipid metabolism. These functions range from FA
776 transport, binding, uptake, synthesis, degradation through mitochondrial or
777 peroxisomal oxidation, storage, lipoprotein metabolism and ketogenesis under fasting
778 conditions (111). Hence, although the phenotype of PPAR α -deficient mice is normal,
779 fasting results in increased plasma free FA (207) levels, accumulation of lipids in the
780 liver, hypoketonaemia, hypoglycaemia and hypothermia (110,208-210). The wide
781 range of genes that are expressed after PPAR α activation indicates that this receptor
782 has a central regulatory role in lipid metabolism (211). Recently, in a hepatocyte-
783 specific PPAR α knockout mouse model impairment in liver and whole-body FA
784 homeostasis was observed, resulting in hepatic lipid accumulation and
785 hypercholesterolemia during aging (212). Still today, novel mechanisms are
786 discovered. The molecular pathway that leads to the upregulation of PPAR α during
787 fasting was recently investigated by Maus and coworkers. They found that FFAs bind
788 to PLC γ -coupled cell surface receptors, such as the fatty acid transporter CD36, in the

789 liver and heart. This binding activates a specific pathway that leads to Ca^{2+} influx
790 across the plasma membrane, called store-operated Ca^{2+} entry (SOCE). Subsequently,
791 increased intracellular Ca^{2+} levels induce in a cAMP-dependent manner PGC-1 α and
792 PPAR α expression, ultimately leading to a transcriptional reprogramming of the cell
793 to FA utilization (213).

794 Altogether these data demonstrate that PPAR α is a master regulator of FA catabolism
795 by governing the regulation of key enzymes involved in peroxisomal, mitochondrial
796 and microsomal FAO.

797 Additionally, PPAR α also plays an important role in ketogenesis by regulating
798 expression of HMG-CoA synthase 2 (Hmgcs2), a rate-limiting enzyme of
799 ketogenesis, which catalyzes condensation of acetyl-CoA and acetoacetyl-CoA to
800 generate HMG-CoA (214). Accordingly, the expression of mHMG-CoA synthase
801 gene, harboring a functional PPRE (214) in its promoter, is impaired in PPAR α null
802 mouse liver (215). Of note, HMG-CoA synthase specifically stimulates its own
803 transcription rate by acting as a coactivator of PPAR α . A recent report identified
804 liver-specific PPAR α as a critical factor for ketogenesis. It was shown that PPAR α
805 protects from fish oil-induced oxidative stress leading to acute liver failure through its
806 regulatory actions on ketone body levels, hence suggesting a potential therapeutic
807 advantage of ketone bodies such as β -hydroxybutyrate in preventing lipid
808 peroxidation-induced liver damage (216). Of particular importance in regulating
809 ketogenesis, in addition to FAO, is the metabolic fibroblast growth factor 21 (FGF21).
810 Its hepatic expression is PPAR α -dependent and is induced by fasting, a ketogenic diet
811 and fenofibrate (217). Moreover, upon fasting, FGF21 production required c-AMP-
812 responsive element-binding protein H (CREBH), the liver-enriched transcription
813 factor. Interestingly, it was reported that CREBH and PPAR α act as interactive trans-

814 activators that regulate each other's expression and act in synergy to activate the
815 expression of their target gene FGF21 to regulate lipolysis, FAO and ketogenesis
816 upon fasting or under an atherogenic HFD (218). Of note, CREBH acetylation is
817 required for the fasting-induced CREBH-PPAR α interaction *in vivo* (219). These
818 findings on synergistic cross-talk between PPAR α and CREBH might provide a
819 regulatory mechanism for nuclear receptors or transcription factors to extend their
820 biological actions and thereby coordinate adaptive physiological responses.

821 As far as lipogenesis is concerned, besides examples listed in **Table 5**, Oosterveer *et*
822 *al.* showed that induction of some lipogenic genes upon fibrate treatment is regulated
823 transcriptionally by SREBP-1c. Consistently, in SREBP-1^{-/-} mice, chronic PPAR α
824 activation with fenofibrate failed to induce lipogenic genes such as stearoyl-CoA
825 desaturase (Scd1) and FA desaturase 2 (Fads2) suggesting an indirect regulatory
826 mechanism (220). In line, in primary hepatocytes, the PPAR α agonists Wy-14,643
827 and GW7647 increased SREBP-1c activity by triggering PPAR α activity on a DR-1
828 element in the human SREBP-1c promoter (221). Moreover, in PPAR α -deficient
829 mice, a disturbance in the normal regulation of SREBP-1-sensitive lipogenic genes
830 such as acetyl-CoA carboxylase (ACC) and FAS was observed (222). The effect of
831 PPAR α agonists on SREBP targets has been ascribed to increased activation of
832 SREBP-1c via enhanced proteolytic cleavage (223). PPAR α agonists increase the
833 protein levels of the mature form of SREBP-1c, by increasing the rate of proteolytic
834 cleavage of its membrane-bound precursor form, without changing its mRNA levels.

835 Of note, PPAR α can also indirectly modulate SREBP-1c transcription via cross-
836 regulation with LXR α signaling pathway. In this line, Hebbachi *et al.* reported that the
837 intact PPAR α is required to mediate the LXR α -dependent response of Scd-1 and FAS
838 gene expression to insulin and that an exogenous non-steroidal synthetic ligand of

839 LXR α , TO-901317, was effective in rescuing PPAR α deficiency, suggesting
840 participation of PPAR α in generating endogenous LXR α ligands (224).

841 In addition, malonyl-CoA decarboxylase (MCD) is transcriptionally upregulated
842 following PPAR α activation. MCD degrades the lipogenic intermediate malonyl-
843 CoA, which is both a precursor of FA biosynthesis and an inhibitor of the
844 mitochondrial fatty acid transporter CPT-1 (225). PPAR α hence might inhibit the
845 lipogenic pathway indirectly by inducing MCD, in line with its role in promoting
846 energy expenditure (226,227).

847 Evidence exists for a functional role of PPAR α in bile acid homeostasis; however the
848 mechanism is not understood. While various studies have reported on the expression
849 modulation of Cyp7A1, a microsomal cytochrome P450 isoenzyme that regulates *de*
850 *novo* hepatic biosynthesis of bile acids by PPAR α , contradictory observations were
851 made (listed in **Table 5**). In transfected cells, both murine and human cholesterol 7 α -
852 hydroxylase (Cyp7a1) gene promoters were stimulated by FA or Wy-14,643
853 treatments, however, the murine promoter harboring an additional PPRE displayed a
854 greater activity (228). In addition, the expression level of Cyp7a1 diminished in
855 PPAR α -deficient mice, thus revealing the involvement of PPAR α (229). In contrast,
856 bezafibrate treatment decreases liver bile acids and Cyp7a1 expression in wild-type
857 mice and PPAR α -deficient mice (230). Moreover, a Cyp7a1 decrease was observed in
858 wild-type mice upon ciprofibrate treatment but not in PPAR α -deficient mice (231).

859 Besides, other genes involved in bile acid synthesis are regulated by PPAR α including
860 cholesterol 27 α -hydroxylase (Cyp27a1) whose activity was downregulated by
861 ciprofibrate treatment in a PPAR α -dependent manner (231) and sterol-12 α -
862 hydroxylase (rat Cyp8B1), which was reported to be directly upregulated by PPAR α
863 through a functional PPRE (229).

864 PPAR α -deficient mice display severe hypoglycemia after fasting (110), illuminating
865 the central role of PPAR α in glucose metabolism. Plasma glucose is maintained
866 during fasting by combination processes including *de novo* glucose synthesis
867 (gluconeogenesis), glycogen breakdown (glycogenolysis), and control of peripheral
868 glucose utilization. Fasting-induced hypoglycemia could be caused by inhibition of
869 either of these pathways. Interestingly, genes involved in gluconeogenesis have been
870 identified as PPAR α targets including phosphoenolpyruvate carboxykinase (Pck1),
871 pyruvate carboxylase (Pcx), and lactate dehydrogenase A (Ldha) (232). Although it
872 was originally proposed that Pck1 may be specifically regulated by PPAR α in human
873 but not mouse hepatocytes (233), PPAR α was shown to activate Pck1 promoter
874 activity in murine hepatoma Hepalclc7 cells (234), whereas in the livers of rats
875 treated with clofibrate a reduced expression level of Pck1 was observed (235). In
876 addition, PPAR α promotes the metabolic conversion of glycerol into glucose through
877 the induction of several hepatic enzymes such as glycerol-3-phosphate dehydrogenase
878 (GPDH) and glycerol kinase, and of glycerol transporters aquaporins 3 and 9; all of
879 these genes are identified as targets of PPAR α (233). Moreover, PPAR α contributes to
880 gluconeogenesis by inducing the expression of pyruvate dehydrogenase kinase
881 isoform 4 (Pdk4) (236) Pdk4 phosphorylates and thereby inactivates the pyruvate
882 dehydrogenase complex, resulting in a conservation of pyruvate as gluconeogenic
883 substrate (237). Besides, PPAR α targets glycogen synthesis in liver by regulating its
884 direct target, glycogen synthase 2 (Gys-2), which is a rate-limiting enzyme in the
885 storage of glycogen in liver and adipose tissue. In consistence, Wy-14,643 was shown
886 to stimulate Gys-2 expression in wild-type but not in PPAR α -/- hepatocytes (238).
887 TRB3, another PPAR α -target gene, is induced in liver during fasting and in diabetic
888 mice in a PGC-1-dependent manner. Upregulation of TRB3 expression through direct

889 transcriptional control by PPAR α inhibits insulin signaling by binding to and
890 preventing activation of Akt/PKB. The latter kinase is a positive regulator of the
891 cellular response to insulin (239,240). How this can be reconciled with the profile of
892 PPAR α agonists in other models or clinical, in man, is as yet unclear.
893 PPAR α has also a profound impact on amino acid metabolism; specifically, it
894 downregulates genes involved in major pathways of amino acid metabolism including
895 transamination, deamination, urea cycle, oxidation of α keto acids and synthesis of
896 amino acid-derived-products. In support of a role of PPAR α in amino acids gene
897 expression, plasma urea levels are elevated in PPAR α -deficient mice. The molecular
898 mechanisms underlying downregulation of amino acid metabolism by PPAR α remain
899 elusive; however, some studies proposed that PPAR α may modulate the activity of
900 other transcription factors that are directly involved in amino acid homeostasis,
901 including HNF4 α and C/EBP α (241).

902

903 **PPAR α target genes in heart**

904 During the transition from fetal to adult cardiomyocytes, both PPAR α and PGC-1 α
905 expression are increased, corresponding with the primary use of FAO as an energy
906 source (242). In the context of a pathological cardiac hypertrophy, the expression of
907 PPAR α itself is also downregulated (151,243). Conversely, PPAR α activity is
908 increased in the diabetic heart, which is characterized by increased lipid oxidation.
909 Correspondingly, overexpression of PPAR α leads to a cardiomyopathy mimicking a
910 diabetic heart (244-246). To dissect the *in vivo* role of PPAR α in myocardial
911 metabolism, transgenic mice with cardiac-specific expression of PPAR α were
912 generated (245,247). Interestingly, Myosin Heavy Chain (MHC)-PPAR α mice, which
913 developed hepatic insulin resistance, also displayed enhanced IL-6 levels in the

914 circulation (245). Consistent with the metabolic phenotype of myocardial lipid
915 accumulation in MHC-PPAR α mice, the expression of genes involved in cellular FA
916 transport was activated by PPAR α . Conversely, cardiac glucose transport and
917 glycolytic genes were repressed in MHC-PPAR α mice (247), likely occurring via a
918 transcriptional mechanism, since fenofibrate also downregulated GLUT4-promoter-
919 driven luciferase reporter gene expression upon cotransfection with PPAR α
920 expression plasmid into rat neonatal ventricular cardiomyocytes (247). As mentioned
921 also above, Oka *et al.* have recently demonstrated that SIRT1, which plays an
922 important role in metabolic adaptation to starvation conditions, suppresses FAO in
923 failing hearts possibly by inhibiting the heterodimerization of PPAR α and RXR α ,
924 suggesting thereby that preventing PPAR α -SIRT1 or restoring PPAR α -RXR
925 heterodimerization may improve the progression of heart failure through modulation
926 of metabolic remodeling (81). Together, these findings highlight the complexity of a
927 balanced cardiac energy metabolism and the necessity of distinguishing the etiology
928 of heart failure to be able to predict the outcome of PPAR α agonists.

929

930 **PPAR α target genes in lipid metabolism**

931 PPAR α agonists have a pronounced effect on lipoprotein metabolism, which is
932 involved in lipid and cholesterol transport. In this regard, PPAR α ligands reduce very
933 low-density lipoprotein (VLDL) production and enhance the catabolism of TG-rich
934 particles, which indirectly decreases small dense LDL (sdLDL) particles and enhance
935 the formation of HDL particles and hepatic elimination of excess cholesterol (27).
936 More specifically, PPAR α activators decrease plasma TG-rich particles levels by
937 increasing the activity of LPL (48,248), which is the key enzyme in the hydrolysis of
938 TGs. PPAR α controls LPL gene expression directly through a functional PPRE

939 located in its promoter region (249), and indirectly by reducing the levels of APOC3,
940 a natural inhibitor of LPL activity (250), likely via a mechanism involving the
941 transcription factors Rev-erba, HNF4 α or (Forkhead box protein O1) FOXO1 (251-
942 253). Rev-erba, itself induced by fibrates via a PPRE in the Rev-erba gene promoter,
943 negatively interferes with the HNF4-mediated activation of APOC3 gene promoter
944 (253). FOXO1 stimulates APOC3 expression via specific binding to its target site
945 (CCAAACA) in the APOC3 promoter. The association of FOXO1 with the APOC3
946 promoter was significantly reduced in response to PPAR α activation, in line with the
947 inhibition of APOC3 promoter activity in PPAR α -expressing HepG2 cells (252).
948 Besides APOC3, LPL activity is tightly modulated by other factors such as
949 apolipoprotein A-V (APOA5), angiopoietin-like protein 3 (ANGPTL3) and
950 angiopoietin-like protein 4 (ANGPTL4). In line, PPAR α increases expression levels
951 of APOA5, which is critical for sustaining normal plasma TG levels, through
952 functional PPREs located in its promoter (254,255). Moreover, PPAR α upregulates
953 the expression levels of ANGPTL4 (256), which acts as an inhibitor of LPL activity
954 by converting active LPL dimers to inactive monomers (257), which may play a role
955 in tissue-specific directing of FA. PPAR α activators affect also the metabolism of
956 HDL by regulation the expression of its major apolipoproteins, AI (APOA1) and AII
957 (APOA2). In humans, it increases the expression of these two genes by binding to
958 PPREs in their promoters, contributing to increased plasma HDL levels (258,259). In
959 rodents, however, gene expression of APOA1 is not promoted by PPAR α because of
960 disabling mutations within the PPRE. In fact, the murine APOA1 gene is even
961 negatively regulated by PPAR α agonists through an indirect mechanism involving the
962 PPAR α -dependent induction of the NR Rev-erba, a negative regulator of transcription
963 (260).

964 **PPAR α target gene expression in immune cells**

965 The functional expression of PPAR α by several immune cell types suggests that this
966 receptor may play an important role in regulation of immune responses. The exact
967 role of PPAR α in, for instance, innate host defense mechanisms is however largely
968 unknown. PPAR α was shown essential for anti-mycobacterial responses in murine
969 bone marrow-derived macrophage cells, involving gene activation of transcription
970 factor EB (TFEB) and induction of lipid catabolism (261). PPAR α deficiency resulted
971 in an increased bacterial load and exaggerated inflammatory responses during
972 mycobacterial infection (261). In human macrophages, PPAR α activation upregulates
973 the expression ABCA1, a member of the ATP-binding cassette-transporter family, by
974 an indirect mechanism involving the induction of LXR α expression. The increase in
975 ABCA1 expression promotes APOA1-mediated cholesterol efflux (262). Adiponectin
976 receptor 2 (AdipoR2), an LXR target gene, is positively regulated by PPAR α both in
977 primary and THP-1 differentiated macrophages (263). Given that AdipoR2 is
978 expressed in human atherosclerotic lesions and macrophages, modulating the
979 expression of this gene by PPAR α and LXR α may provide beneficial effects in the
980 treatment of cardiovascular disease. This finding highlights a mechanism of crosstalk
981 between adiponectin and PPAR α -LXR α signaling pathways (263). In murine
982 macrophages, PPAR α activation was also shown to upregulate the expression of the
983 classic PPAR α target gene CPT1 (154). Further in mice, PPAR α activation in hepatic
984 K \ddot{u} pfper cells or monocyte-recruited macrophages results in anti-inflammatory effects
985 via the down-regulation of IL-15 and IL-18 (264).

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989 **PPAR α targets linked to the rodent-only hepatocarcinoma side effect**

990 Sustained induction of the peroxisomal FAO system accounts for the massive
991 proliferation of peroxisomes, which may contribute to hepatocarcinoma, a property
992 intrinsic to mouse and rat PPAR α but not observed in humans (25,27). By using
993 hepatocyte-specific PPAR α -deficient mice, PPAR α agonist treatment was shown to
994 induce hepatomegaly via hepatocyte PPAR α activation. Interestingly, the proliferative
995 response was mediated exclusively by PPAR α activation in hepatocytes (264).

996 Several mechanisms have been proposed to elucidate the species difference in
997 response to peroxisome proliferators. For example, in humans, lower expression
998 levels of PPAR α or the presence of splice variants was suggested to contribute to the
999 resistance of humans to peroxisome proliferation upon treatment with fibrate drugs
1000 (50,108). However, most of the proposed mechanisms have been met with reasonable
1001 criticism (reviewed in (265)). The work of Cheung *et al.* with “humanized” PPAR α
1002 mice suggests that there are inherent species differences in the receptor that may be
1003 more critical. In this regard, PPAR α -humanized mice that express human PPAR α in a
1004 mouse PPAR α null background exhibit, unlike wild-type mice, a diminished
1005 hepatocellular proliferation while the induction of mitochondrial and peroxisomal
1006 FAO enzymes was comparable to wild-type (266). Moreover, it was proposed that the
1007 mechanism by which peroxisome proliferators lead to mitogenic and
1008 hepatocarcinogenic effects in mouse liver is due to murine PPAR α -dependent
1009 downregulation of let7c microRNA, which in turn releases the repression of c-myc, an
1010 important oncogene that is related to liver cancer development. Interestingly, this
1011 effect does not occur in the humanized PPAR α mice (267), thus the induced
1012 expression of c-myc protein through species-specific regulation of a microRNA,
1013 contributes to PPAR α ligand-induced liver hyperplasia in mice (267). Still, some

1014 questions arise regarding the fact that the PPAR α -humanized mouse does not
1015 precisely model humans because there could be species differences in coactivators,
1016 corepressor and target gene response elements.

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1037 **VI. PPAR α agonists in a clinical setting**

1038 PPAR α is widely expressed and serves to activate FAO pathways in the liver in
1039 response to fasting. This re-tunes energy metabolism to permit efficient use of
1040 mobilized lipids in the fasted state. The resulting changes may lower secretion of
1041 TGs from the liver and promote TG clearance from plasma, and thereby also reduce
1042 atherogenic lipoprotein particles. It was this activity that prompted therapeutic
1043 development to reduce cardiovascular risk in patients with raised plasma lipids. In
1044 clinical trials, a marked reduction in circulating TGs with a rise in HDL-C was
1045 consistently documented, with reductions in LDL cholesterol (LDL-C) depending on
1046 the pre-treatment TG levels (reviewed in (27)).

1047 By virtue of their TG-lowering capacity, the official indication for fibrates is
1048 hypertriglyceridaemia. For hypertriglyceridaemia, fibrates are the first choice when a
1049 change of diet is not sufficient. For dyslipidaemia and hypercholesterolemia, statins
1050 remain the first choice because of a higher potency in lowering LDL-C (329).

1051 Fibrates are generally well-tolerated drugs and have a good safety profile irrespective
1052 of concomitant therapy (330). However, changes in biochemical markers, some of
1053 which related to pathological states, may occur. Among these are elevations in
1054 homocysteine, creatinine levels, alanine aminotransferase and aspartate
1055 aminotransferase. Of note, lowering of homocysteine with folic acid did not affect
1056 cardiovascular diseases (CVD) (331,332). Along the same line, even after prolonged
1057 treatment, the increase of creatinine is rapidly reversible upon treatment stop
1058 indicating absence of irreversible tissue damage (333). Muscle-related adverse effects,
1059 such as an increase in creatine kinase and myalgia may occur but rhabdomyolysis has
1060 only been observed upon combining gemfibrozil and cerivastatin, an effect due to

1061 classical P450-mediated drug interaction. Rhabdomyolysis was found to be rare with
1062 (single) fibrate therapies (334).

1063

1064 **PPAR α agonists and effects on lipid and lipoprotein metabolism in humans**

1065 The prominent role of PPAR α in governing lipoprotein and lipid metabolism in
1066 humans was demonstrated by the fact that fibrates, widely prescribed drugs to treat
1067 dyslipidaemia, act by binding to PPAR α and induce PPAR α -dependent gene
1068 transcription (6,335).

1069 A plethora of clinical studies have shown that fibrate treatment lowers serum TG
1070 concentration by about 30% (-35% P<0.01 (336); -30% P<0.045 (337); -40-20%
1071 P<0.001 (338); -37% (339); -38% (329)), reduces VLDL TG by about 40% (-41%
1072 P<0.01 (336); -44-20% P<0.001 (338)) and reduces (in combination with statins) the
1073 atherogenic sd-LDL by about 20% (-23% (329)). Additionally, HDL increases
1074 slightly (+19% P<0.02 (336); +82-106% P<0.005 (338); +14% (329)) and serum
1075 concentration of APOA1 and APOA2 increase by about 20% (+19% P<0.02
1076 (258,336)). In obese patients with type 2 diabetes, fenofibrate decreased serum TG
1077 concentrations, while glycated haemoglobin increased (340). In contrast, the
1078 Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to
1079 Control Cardiovascular Risk in Diabetes (ACCORD) studies show glucose-neutral
1080 effects of fenofibrate, supporting the notion that the first generations of fibrates are
1081 not antidiabetic drugs (330,333). In line, insulin sensitivity was not affected by
1082 fenofibrate administration (337,340). Nevertheless, yet controversial, a more recent
1083 study reported that fenofibrate may increase insulin sensitivity by inhibiting adipose
1084 tissue expression of retinol-binding-protein-4 (RBP-4), an adipocytokine (341). For
1085 LPL, in patients on gemfibrozil (6 weeks), there was no significant change in LPL in

1086 adipose tissue (342), possibly due to pharmacokinetic effects. Nevertheless, plasma
1087 TG levels decreased by 46% and several patients demonstrated increases in muscle
1088 LPL activity, though these were inconsistent and not statistically significant (342).
1089 Previous studies, using other PPAR α agonists did report a significant increase of
1090 skeletal muscle LPL activity (+39% P<0.05 (336); +50% P<0.005 (339)) and even
1091 adipose tissue LPL activity (343). It was originally proposed that gemfibrozil
1092 predominantly decreases TG levels by decreasing hepatic VLDL secretion
1093 (337,342,344). However increased lipolysis may rather be caused by a primary liver
1094 effect (e.g. APOC3 decreased and APOA5 increased). Additionally, although
1095 fenofibrate reduces plasma TG levels, it does not seem to lower concentrations or
1096 turnover rates of non-esterified FAs in adipose tissue (337), correlating with a lack of
1097 effect on insulin sensitivity.

1098

1099 **PPAR α agonists and effects on liver in humans**

1100 Dyslipidaemia and insulin resistance are known risk factors for NAFLD. As PPAR α
1101 activation reduced hepatic steatosis in mice, applicability of fibrates was suggested as
1102 a potential treatment for NAFLD in humans (111). In a relatively small (16 patients)
1103 and phenotypically heterogeneous cohort study, patients completed 48 weeks of
1104 therapy with fenofibrate without adverse events (345). Significant decreases in TG,
1105 glucose, alkaline phosphatase and gamma-glutamyl transpeptidase, and an increase of
1106 APOA1 levels were found, yet, effects on fibrosis as addressed by liver histology
1107 were minimal (345). Similar studies with fenofibrate for 3 months confirmed results
1108 of a lowered TG yet unchanged hepatic fat content (346). Short-term treatment (2-8
1109 weeks) with bezafibrate combined with diet and exercise of steatosis-suffering donors
1110 for liver transplantation was found to decrease macrovesicular steatosis (347),

1111 although in this particular study the impact of bezafibrate alone was not addressed.
1112 Treatment of non-alcoholic steatohepatitis (348) patients with gemfibrozil (for 4
1113 weeks) lowers ALT, AST and γ GT plasma levels (349), but not in a pilot study with
1114 clofibrate (for 12 months) (350). The relatively weak potency of these fibrates
1115 combined with lower expression level of PPAR α in human as compared to mouse
1116 liver was presented as an explanation (351). However, in all studies, plasma TG levels
1117 effectively decreased. Novel PPAR α agonists with greater potency and efficacy, such
1118 as pemafibrate, or with dual (elafibranor) or triple (lanifibranor) agonism, may prove
1119 to be more useful in the treatment of NASH/NAFLD (352). As mentioned also in
1120 section 5.5, it is important to emphasize that humans are resistant to the induction of
1121 neoplasms by fibrate drugs in contrast to rodents (25,353). This implies that following
1122 ligand activation, the PPAR α -mediated pathways controlling lipid metabolism work
1123 independent from those controlling cell proliferation pathways (266).

1124

1125 **PPAR α agonists and effects on the cardiovascular system in humans**

1126 As in rodents, PPAR α is downregulated in the failing human heart (354). PPAR α
1127 protein levels were compared between homogenates from left ventricular biopsies
1128 from five control donor hearts vs biopsies from five patients with compensated end-
1129 stage heart failure at the time of transplantation (354). Whether augmenting PPAR α
1130 activity would improve the progression of heart failure is an interesting, but to date
1131 unanswered question. Sub-group analysis of the Helsinki Heart Study (HHS) trial
1132 suggested potential benefit in preventing heart failure with gemfibrozil compared to
1133 placebo (13.3% vs. 10.6%, HR 0.76; P=0.04) (355). Potential mechanisms may relate
1134 to direct cardiac and/or on PPAR α 's lipid lowering effects. PPAR α agonists may also
1135 improve cardiac performance by decreased transcription of pro-inflammatory

1136 cytokines as shown in vitro (356) and/or as in rodent studies, by reduced activation of
1137 aldosterone-mediated myocardial apoptosis (357) and/or by decreased endothelin-1-
1138 mediated cardiac fibrosis (358). Further research is needed to assess whether or not
1139 fibrates, and especially the novel SPPARMs (see further **section 6.5**) can prevent or
1140 ameliorate chronic heart failure in man.

1141 Gemfibrozil was shown to decrease the incidence of coronary heart disease in both
1142 HHS and Veterans Affairs HDL Intervention Trial (VA-HIT). Treatment was
1143 concomitant with a marked increase in HDL-C and reductions in serum levels of total,
1144 low-density lipoprotein and non-HDL-C and TGs (199,355), yet there is no definite
1145 proof that these events are the mode of action leading to a decrease incidence of
1146 coronary heart disease.

1147 Investigating a role for fibrates in the prevention of cardiovascular disease, a pooled
1148 meta-analysis of long-term randomized placebo-controlled clinical trials pointed out
1149 that fibrates significantly reduce the odds of nonfatal myocardial infarction, but not of
1150 cardiovascular mortality, fatal myocardial infarction or stroke, compared to placebo
1151 (359). Fibrates can reduce the risk of major cardiovascular events predominantly by
1152 prevention of coronary events, and might have a role in individuals at high risk of
1153 cardiovascular events and in those with combined dyslipidaemia (360,361). Further,
1154 in a small-scale pilot study, bezafibrate was found to induce plaque regression in
1155 thoracic and abdominal aortas with marked TG reduction and HDL-C increase (362).

1156

1157 **Human clinical trials and clinical trial endpoints**

1158 Primary endpoint results from the HHS and VA-HIT studies as well as the post-hoc
1159 and analysis of the ACCORD and FIELD trials suggest that fibrates may benefit
1160 patients with high TG (≥ 200 mg/dl) and low HDL-C (330,333). This hypothesis is

1161 now formally being tested in a phase 3 study with pemafibrate, called Pemafibrate to
1162 Reduce Cardiovascular Outcomes by Reducing Triglycerides IN patients With
1163 diabetes (PROMINENT).

1164 Clinical trials have found that fibrate treatment of atherogenic dyslipidaemia reduces
1165 vascular atherosclerosis and CV risk (363). In the Bezafibrate Coronary
1166 Atherosclerosis Intervention Trial (BECAIT), bezafibrate treatment decreased
1167 angiographic evidence of coronary atherosclerosis (364,365). Moreover, in the HHS,
1168 gemfibrozil decreased cardiovascular events, especially among patients with diabetes
1169 (355). Data from the VA-HIT (366), and subgroup analyses from the Bezafibrate
1170 Infarction Prevention Trial (BIPT) (367) have demonstrated that fibrate therapy
1171 significantly reduces the risk of cardiovascular events in particular in patients with
1172 diabetes with raised TGs and low HDL-C. However, large, well-powered
1173 interventional studies resulted in disappointing outcomes. The FIELD trial saw no
1174 benefit of fenofibrate, with the intervention group showing only non-significant
1175 differences compared to the controls (330). One potential explanation for this failure
1176 was the relatively high drop-in usage of statins in the placebo group and the lower
1177 overall rates of cardiovascular events. The ACCORD study looked at addition of
1178 fenofibrate to simvastatin, but enrolled patients with little dyslipidaemia (368-371).

1179 The currently running phase 3 trial PROMINENT will test the efficacy of pemafibrate
1180 in diabetic patients with high baseline TG levels (372). Meanwhile, fibrates are
1181 mainly prescribed for the management of raised TGs in patients at risk of pancreatitis.

1182 One clinical feature noted through many of the fenofibrate studies was reduction in
1183 markers of systemic inflammation, including C-reactive protein (CRP) and IL-6.
1184 These reductions occurred even in populations lacking a significant change in lipid
1185 parameters, suggesting that the effect was direct, and not mediated through changes in

1186 lipid-mediated vascular damage (373). This phenomenon may be the physiological
1187 consequence of immune cell PPAR activation and cross-talk/inhibition of NF- κ B
1188 signaling. The combination of anti-inflammatory efficacy along with promotion of
1189 hepatic FAO suggested that PPAR α activation may prevent the progression of liver
1190 steatosis to NASH and ultimately cirrhosis. The dual PPAR α/δ agonist elafibranor
1191 was tested for efficacy in patients with liver steatosis. A reduction in histological end-
1192 points of acute NASH was seen, although the trial did not achieve its originally set
1193 target of NASH resolution (206). Therapeutic efficacy of elafibranor is currently
1194 assessed in the phase 3 trial RESOLVE-IT, enrolling patients with active NASH and
1195 fibrosis stage F1-3 (374).

1196

1197 **Selective PPAR α modulators (SPPARMs) in humans**

1198 Overall it is surprising that there are so few therapeutic applications for fibrates,
1199 considering the important role that PPAR α has in regulating hepatic energy
1200 metabolism in response to the fasted state. Furthermore, although we have good
1201 evidence for cross-talk between PPAR α and inflammatory signaling pathways,
1202 including NF- κ B, the fibrates have not found a role in the management of chronic
1203 inflammatory diseases.

1204 In an attempt to maximize the therapeutic potential of PPAR α as a drug target,
1205 SPPARM α are being developed to gain greater pharmacological effect (375,376). A
1206 restricted activation potential can be explained at the molecular level by a general
1207 decrease in affinity for cofactors due to partial activation, binding to different target
1208 gene promoters and, but not limited by, the induction of a differential receptor
1209 conformation, which leads to a changed PTM status and the recruitment of a specific

1210 subset of PPAR cofactors, also according to their expression level in different organs
1211 (26,375,377).

1212 Pemafibrate is an example of a high affinity PPAR α agonist with SPPARM properties
1213 which is currently in phase 3 clinical development (203). Pemafibrate was designed to
1214 possess higher PPAR α activity and selectivity over existing PPAR α agonists.
1215 Pemafibrate monotherapy induced atheroprotective effects in several murine models
1216 of atherosclerosis. As a multi-level strategy compound, pemafibrate acts on
1217 inflammation, lipid metabolism and RCT (190,378). Promising results were achieved
1218 with pemafibrate for the treatment of a severe complication of type 2 diabetes, i.e.
1219 diabetic nephropathy, by targeting the pathways leading to renal oxidative stress
1220 (379). The first-line treatment for hypercholesterolaemia, a common feature of
1221 atherosclerotic cardiovascular disease (ASCVD), is statins, which lower the levels of
1222 LDL-C. However, remaining residual risks, such as elevated TG levels and decreased
1223 HDL-C, underscore the necessity for complementary therapies. Pemafibrate was
1224 found superior to fenofibrate with regard to serum TG-lowering effect and hepatic and
1225 renal safety, when used over 24 weeks in adults with dyslipidaemia (203).
1226 Consequently, in recent randomized, double-blind, placebo-controlled clinical trials in
1227 patients with dyslipidaemia, statins were combined with the SPPARM α pemafibrate,
1228 which showed a favorable benefit-to-risk ratio during phase 2 clinical trials for the
1229 treatment of combined dyslipidaemia (380,381). The compound was used as an add-
1230 on therapy in combination with statin treatment to treat the residual CV risk. Next to
1231 decreasing TG levels, this drug combination targets also several other atherogenic
1232 lipoproteins, hereby improving apolipoprotein ratios and lowering LDL-C levels
1233 (380,381). In patients with type 2 diabetes with hypertriglyceridaemia, pemafibrate
1234 was also shown to ameliorate lipid abnormalities, and well tolerated (382).

1235 Next to SPPARMs, combining selective RXR agonists with statins can be an
1236 alternative option for the treatment of atherosclerosis. Suboptimal doses of both
1237 treatments not only minimized dose-related adverse effects, but also resulted in
1238 synergistic beneficial effects on endothelial function, compared to each drug alone.
1239 The anti-inflammatory effects were mediated in part by increased RXR α -PPAR α and
1240 RXR α -PPAR γ interactions (383).

1241 Finally, dual or pan-PPAR modulators with partial or selective activation profiles may
1242 be good alternatives, depending on the clinical application.

1243 Metabolic disorders such as diabetes, atherosclerosis, hyperlipidaemia and obesity,
1244 rarely occur in isolation, but usually arise in the same individuals. This complex
1245 phenotype is called the metabolic syndrome or syndrome X (4,375,384). Treatment of
1246 this aggregation of metabolic abnormalities, usually accompanied by an inflammatory
1247 context, would benefit from a more holistic approach, such as the application of a
1248 pan-PPAR agonist, to target the multiple facets of this complex disease phenotype.

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1259 **VII. Inflammation-priming and inflammation-resolving**
1260 **molecular actions of PPAR α**

1261 Evidence suggests that PPAR α can counter inflammation via multiple, distinct
1262 mechanisms (23,385,386). Both *in vitro* and *in vivo* studies identified PPAR α
1263 influences on both acute and chronic inflammatory processes (154,165,387,388).

1264 The first indication of a beneficial role for PPAR α in suppressing inflammation came
1265 from studies on LTB₄ action in PPAR α -deficient mice. Compared to WT mice, the
1266 duration of LTB₄-induced ear-swelling responses was prolonged. This anti-
1267 inflammatory effect correlated with LTB₄ activation of PPAR α , thereby identifying a
1268 feedback loop through PPAR α to limit LTB₄ action. These findings implied that
1269 some of the anti-inflammatory actions of PPAR α occur through up regulation of
1270 enzymes involved in ω and β -oxidation pathways and thereby accelerated degradation
1271 of signaling lipids including LTB₄ (165). Subsequently, Poynter *et al.* showed that
1272 PPAR α -deficient murine splenocytes had NF- κ B activity, and thereby produced more
1273 IL-6 and IL-12 in response to lipopolysaccharide (LPS), supporting PPAR α -
1274 dependent anti-inflammatory effects in non-metabolic tissues (131). Most recent
1275 research has focused on the anti-inflammatory actions of PPAR α . Hence, the majority
1276 of the subchapters below discuss the many and diverse molecular mechanisms
1277 accounting for the anti-inflammatory effect of PPAR α in various models (**Fig. 4 and**
1278 **Fig. 5**). However, under certain conditions PPAR α induces target genes that are more
1279 consistent with a pro-inflammatory profile (see further below), suggestive of
1280 inflammation-priming (**Fig. 6**) or -sensitization, the phenomenon of sequential signals
1281 leading to cellular adaptation and affecting subsequent responses, specifically in a
1282 context of inflammation. The augmented second response may well be gene-specific
1283 and transient, as has been described for the response of synoviocytes to a repeated

1284 treatment with pro-inflammatory cytokines (389). These consecutive signals may
1285 encompass pro-inflammatory mediators, as in the study above, but may also combine
1286 signals of a different nature. For example, the anti-inflammatory glucocorticoid
1287 hormones transcriptionally upregulate several components of the innate immune
1288 system and thus prime pro-inflammatory responses (390-392), a circuit thought to
1289 contribute to more effective resolution of inflammation. We hypothesize similar
1290 mechanisms may also apply to PPAR α agonist action. Hence, an overall anti-
1291 inflammatory network may also comprise a component which is “pro-inflammatory”
1292 dependent on the specific inflammatory and cellular context. More work is needed to
1293 substantiate these speculations. Data that may support this concept, however limited,
1294 are discussed in the last subsection.

1295

1296 **Effector cells mediating the anti-inflammatory activity of PPAR α**

1297 The extent to which PPAR α plays a decisive role in various immune cells in humans
1298 as compared to rodents remains a point of contention. Literature and public resources
1299 such as the human immune genome project indicate that PPAR α expression is lower
1300 in human immune cells than in hepatocytes. This originally supported the concept that
1301 cell types like hepatocytes with high PPAR α are likely contributing to the immune
1302 regulatory effects by providing secondary signals to the immune cells, but data is
1303 accumulating on functional PPAR α effects in different immune cells. In addition, it is
1304 not inconceivable that during an inflammatory response, a change in the PPAR α
1305 expression profile of immune cells may turn a dormant factor into an active
1306 contributor to assist in blocking the inflammatory response. In support of that
1307 assumption, the well-known adrenal stress hormones GCs enhance PPAR α transcript
1308 levels in T and B lymphocytes (130), at least in the mouse.

1309 PPAR α is not only expressed in undifferentiated human monocytes but also in
1310 differentiated human monocyte-derived macrophages and is transcriptionally active
1311 upon ligand binding. In TNF and IFN- γ activated macrophages PPAR α can induce
1312 apoptosis (32). All three PPAR subtypes play important roles in human macrophages.
1313 For example, the anti-inflammatory properties of PPAR γ have been connected to its
1314 ability as a driver of M2 polarization in human atherosclerosis (393) .

1315 Brocker *et al.* recently compared hepatocyte- to macrophage-specific PPAR α null
1316 mice and found that the downregulation of the inflammatory cytokines IL-15 and IL-
1317 18 depended on macrophage PPAR α , identifying K \ddot{u} pfper cell PPAR α as an important
1318 mediator of the anti-inflammatory effects of PPAR α agonists (264). Functional human
1319 PPAR α was demonstrated following a global gene expression profiling experiment on
1320 human primary macrophages treated with specific PPAR α agonists (263). The role of
1321 PPARs, fatty acid signaling, and fatty acid oxidation within primary human immune
1322 cell types in a variety of inflammatory conditions requires further experimental study.

1323 Linking inflammation to metabolism, murine macrophage LXR is critical for PPAR α
1324 to promote cholesterol efflux and reverse cholesterol transport (RCT) *in vivo*,
1325 contributing to anti-atherogenic effects and hence indirectly resolving inflammatory
1326 responses within the blood vessels. In support, PPAR α activation was demonstrated to
1327 inhibit the development of atherosclerosis by promoting macrophage RCT in
1328 humanized hypercholesterolemic mice expressing the human APOA1 gene (394).

1329 Connecting metabolic and immune responses to cancer, in murine and human
1330 melanoma models, an increase in free FA species during tumor progression was
1331 shown to activate PPAR α signaling in CD8⁺ tumor-infiltrating lymphocytes.
1332 Consequently, CD8⁺ tumor-infiltrating lymphocytes switched toward FA catabolism
1333 to preserve their effector functions. Promoting FA catabolism with fenofibrate

1334 markedly improved the capacity of CD8⁺ tumor-infiltrating lymphocytes to delay
1335 tumor growth, via a synergistic mechanism involving a Programmed cell Death
1336 protein-1 (PD-1) blockade to efficiently boost the efficacy of melanoma
1337 immunotherapy (395). Together, these data highlight the interplay between the
1338 metabolic programs of T lymphocytes and tumor cells, with potential impact on
1339 melanoma immunotherapy (396). Ligand activation of PPAR α also antagonizes NF-
1340 κ B in murine T and B lymphocytes, and conversely, T cell activation results in
1341 reduced PPAR α expression. Of note, treatment of T lymphocytes with specific
1342 PPAR α activators can upregulate the expression of endogenous PPAR α -controlled
1343 genes in combination with histone deacetylase inhibitors. The presence of functional
1344 PPAR α within T and B lymphocytes again emphasizes a role for this nuclear receptor
1345 in cells of the immune system (130). In addition to targeting NF- κ B, PPAR α also
1346 counters proinflammatory signaling in T lymphocytes at the level of IL-2 and c-Jun
1347 activation (397). In evidence, genetic ablation of the PPAR α gene resulted in the loss
1348 of antagonism of NF- κ B, increased production of Th1 and decreased production of
1349 Th2 cytokines by T cells (397). In another study, the PPAR α agonist Wy-14,643 was
1350 shown to increase IL-4 secretion and to inhibit IFN- γ expression in murine mitogen-
1351 activated splenocytes, and to reduce the proliferation of human T cell lines (398).
1352 Similarly, stimulation of isolated CD4-positive human T cells with PPAR α agonists at
1353 clinically relevant concentrations decreased IFN- γ , TNF α and IL-2 production.
1354 However, in this study no effect on viability was noted (399).

1355 Epidermal Langerhans cells (LCs) play a pivotal role in initiating and maintaining
1356 primary immune responses in the skin. PPAR α is expressed in immature LC but
1357 downregulated in mature LC. Pharmacological PPAR α activation inhibits LC
1358 maturation, migratory capacity, cytokine expression, and the ability to drive T-cell

1359 proliferation. Moreover, PPAR α in LC also inhibits NF- κ B activity. Taken together,
1360 PPAR α activation by endogenous ligands may provide a molecular signal that allows
1361 LC to remain in an immature state (400). The activation of PPARs by drugs, and
1362 products of intermediary energy metabolism within the diverse cells of the immune
1363 system may reveal new opportunities to target inflammatory process or to advance
1364 adjunctive therapies to enhance anti-cancer treatment.

1365

1366 **Interactions between PPAR α and other transcription factors**

1367 The best-known mechanism by which PPAR α (as well as the other PPAR subtypes)
1368 inhibits many inflammatory genes is transrepression. In this tethering mechanism,
1369 PPAR α acts directly to negatively regulate the expression of pro-inflammatory genes
1370 by antagonizing the activities of other regulators of inflammation such as members of
1371 the NF- κ B, AP-1 and STAT families, as also already alluded to in the section above
1372 (27) (Fig. 4A).

1373 In this regard, it was found that fibrate-activated PPAR α inhibits IL-1-stimulated
1374 secretion of IL-6 and 6-keto-prostaglandin by decreasing IL-6 and COX-2 gene
1375 transcription in smooth-muscle cells (SMCs). Inhibition of COX-2 induction occurred
1376 transcriptionally as a result of PPAR α interference with NF- κ B signaling (23). This
1377 effect of PPAR α in the vascular wall may influence the progress of atherosclerosis.
1378 Accordingly, Delerive *et al.* have demonstrated that aortas from PPAR α -null mice
1379 display an exacerbated inflammatory response to LPS, as assessed by enhanced IL-6
1380 secretion, and that fibrate treatment represses IL-6 mRNA levels in LPS-stimulated
1381 aortas of PPAR α wild-type, but not of PPAR α -null mice, confirming that the observed
1382 anti-inflammatory properties of fibrates are PPAR α -dependent. This vascular anti-
1383 inflammatory response is a result of PPAR α interference with NF- κ B and AP-1

1384 transactivation capacity involving direct protein-protein interaction with p65 and c-
1385 Jun. Of note, a bidirectional antagonism between the PPAR α and NF- κ B signaling
1386 pathway exists (387).

1387 In human vascular endothelial cells, PPAR α inhibits the thrombin-mediated activation
1388 of endothelin-1, a vasoactive peptide. This inhibition occurs at the transcriptional
1389 level and occurs via interference with the AP-1 signaling pathway by preventing the
1390 binding of AP-1 proteins to their target sequence (401). Consistently, PPAR α
1391 activators prevent TNF α -induced vascular cell adhesion molecule 1 (VCAM-1)
1392 expression in human endothelial cells, partly through inhibition of the NF- κ B
1393 pathway. This PPAR α action, with a consequent decrease in monocyte adherence to
1394 endothelial cells, may have important implications on early stage of atherosclerosis
1395 (402). PPAR α agonists decrease cytokine-induced tissue factor in monocytes most
1396 likely by interfering negatively with AP-1 and/or NF- κ B activity (403,404). Because
1397 these pathways are involved in the activation of inflammatory response genes
1398 implicated in atherogenesis, PPAR α activation may be beneficial in combatting the
1399 pathogenesis of atherosclerosis. In addition, oxidized eicosapentaenoic acid (EPA)
1400 attenuates monocyte chemotactic protein 1 (MCP-1) and IL-8 expression in
1401 endothelial cells, by inhibiting NF- κ B in a PPAR α -dependent manner (405).

1402 The transcription factor, specificity protein 1 (Sp1), is also involved in the anti-
1403 inflammatory mechanism of PPAR α . PPAR α activation inhibits vascular endothelial
1404 growth factor receptor-2 (VEGFR-2) in endothelial cells, which occur at the
1405 transcriptional level via decreasing Sp1 site-dependent binding to the promoter
1406 sequence through an increased interaction with the Sp1 transcription factor (406).

1407 Thus, PPAR α activators may control inflammatory responses in part by targeting

1408 endothelial VEGFR2 signaling, which is critical for angiogenic responses during
1409 chronic inflammation.

1410 Further work has demonstrated that the mechanism of PPAR interference with NF- κ B
1411 action additionally involves a PPAR α -mediated induction of the inhibitory protein
1412 I κ B α expression. Interestingly, fibrates increase I κ B α expression in primary smooth
1413 muscle cells and hepatocytes, thus preventing nuclear p50/p65 NF- κ B translocation
1414 and thereby arresting p65-mediated gene activation, to oppose development of the
1415 inflammatory response. PPAR α -mediated I κ B α upregulation did not require a
1416 functional PPRE in the I κ B α promoter, but rather involved functional Sp1 and NF- κ B
1417 sites, in a cross-talk mechanism (407). Cytosolic retention of p50/p65 NF- κ B extends
1418 the list of candidate anti-inflammatory PPAR α mechanisms from those mainly
1419 characterized by direct binding and inactivation of transcription factors, such as p65/
1420 NF- κ B and c-Jun (23,387). In further, detailed molecular studies fibrates were found
1421 to decrease basal and IL-6-stimulated expression of the human fibrinogen gene in
1422 human primary hepatocytes and hepatoma HepG2 cells by interfering with the pro-
1423 inflammatory transcription factor CAATT/enhancer-binding protein β (C/EBP- β) via
1424 sequestration of the coactivator glucocorticoid receptor-interacting protein
1425 1/transcriptional intermediary factor 2 (GRIP1/TIF2) (408) (**Fig. 4A**). This anti-
1426 inflammatory action of PPAR α is not restricted to fibrinogen but also applies to other
1427 acute phase genes containing a C/EBP response element in their promoters (408).

1428 In addition, fibrate-activated PPAR α negatively regulates IL-1-stimulated CRP gene
1429 expression in isolated primary human hepatocytes by two mechanisms, the inhibition
1430 of p50-NF- κ B translocation and the down-regulation of basal p50-NF- κ B and C/EBP-
1431 β expression in a PPAR α -dependent fashion (409). Such observations reveal a direct
1432 contribution of PPAR α in controlling the inflammatory gene response in the liver.

1433 Furthermore, chronic PPAR α agonist treatment inhibited the expression of IL-6
1434 induced acute phase response (APR) gene expression *in vivo*. This suppression occurs
1435 transcriptionally due to the down-regulation of the IL-6 receptor components gp80
1436 and gp130 in the liver, thereby reducing the phosphorylation and activation of the
1437 downstream transcription factors STAT3 and c-Jun that transduce the IL-6 signal; and
1438 to the reduction of the basal expression of the transcription factors CCAAT enhancer-
1439 binding protein- α , - β , - δ (410). Related to STAT signaling, Van der Meer *et al.*
1440 proposed that activated PPAR α may downregulate gene expression in HepG2 cells by
1441 causing the loss of STAT1 and STAT3 binding to DNA. Therefore, interfering with
1442 STAT-dependent transcriptional activity, which has been previously well documented
1443 for other PPAR subtypes, may also contribute to the anti-inflammatory action of
1444 PPAR α activation (72) (**Fig. 4A**). Inhibitory effects of PPAR α agonists on IL-1- and
1445 IL-6-induced expression of APR proteins including CRP, serum amyloid A (SAA),
1446 fibrinogen and haptoglobin, were also observed in mice displaying liver-restricted
1447 expression of PPAR α (411).

1448 PPAR α reduced the stimulation of the APR mediated by LPS and prevented the LPS-
1449 induced increase of proinflammatory mediators IL-1, IL-6 and TNF in plasma via a
1450 liver-specific transcriptional mechanism. This resulted in decreased expression of the
1451 adhesion molecules, intercellular adhesion molecule 1 (ICAM-1) and VCAM-1 in the
1452 murine aorta, suggesting that PPAR α can control the systemic and vascular
1453 inflammatory response via a liver-specific action (411). Importantly, this implies that
1454 the spectrum of PPAR α -controlled genes may be vastly larger in a more physiological
1455 context than in isolated cells (412). Further evidence of this comes from analysis in
1456 human liver slices where there was suppression of inflammatory genes, but not in

1457 primary hepatocytes. The most highly repressed genes included chemokines, IFN- γ -
1458 induced genes and other immune-related genes (412).

1459 Fibrate activation of PPAR α inhibits hepatic inflammatory responses, which
1460 unimpeded lead to liver injury and progression to fibrosis, by a mechanism relying on
1461 transrepressive activity, rather than binding to cognate PPRES and activation of lipid
1462 metabolism genes (388). These findings indicate that PPAR α agonists with
1463 dissociated activity, selectively modulating PPAR α transrepression, might have the
1464 potential to prevent the progression of NASH to liver fibrosis through a direct
1465 counteraction of inflammatory responses independent of effects on intrahepatic lipid
1466 accumulation. In the same line, a recent report has shown that PPAR α gene and
1467 protein expression are decreased in NASH (413). The PPAR α levels were restored by
1468 pharmacological inhibition or genetic suppression of miRNA-21, a micro-RNA
1469 upregulated in the liver of patients with NASH, decreasing thereby liver injury,
1470 inflammation and fibrosis (413). These findings suggest that inhibition of the miRNA-
1471 21 pathway might be an interesting new therapeutic strategy to combine with some of
1472 the current PPAR α pharmacological agonists in NASH (413).

1473 A PPRE-dependent mechanism of PPAR α -NF- κ B interference in the regulation of
1474 complement C3 transcription has been observed in a human hepatoma cell line,
1475 identifying transactivation as another mechanism for the anti-inflammatory effects of
1476 PPAR α (**Fig. 2B**). Ligand-dependent activation of PPAR α abolishes TNF α -mediated
1477 upregulation of complement C3 through a physical interaction of PPRE-bound
1478 PPAR α with p65 within the C3 promoter (414).

1479 Finally, the transcription factor Sp1 is also involved in the anti-inflammatory
1480 mechanism of PPAR α . PPAR α activation inhibits vascular endothelial growth factor
1481 receptor-2 (VEGFR-2) in endothelial cells, which occur at the transcriptional level via

1482 decreasing Sp1 site-dependent binding to the promoter sequence through an increased
1483 interaction with the Sp1 transcription factor (406).

1484

1485 **Cooperation between PPAR α and other anti-inflammatory nuclear receptors**

1486 Simultaneous activation of PPAR α and GR α , a well-characterized NF- κ B repressor,
1487 enhances transrepression of NF- κ B-driven gene expression and additively represses
1488 proinflammatory cytokine production, including MCP-1 and IL-6 in various cell lines
1489 (385) (**Fig. 4B**). This finding offers a rationale for the control of inflammation by
1490 GR α and PPAR α by inflammatory gene repression and suggests new approaches for
1491 the treatment of inflammatory diseases where combinations of PPAR α and GR α
1492 activation could offer a more effective anti-inflammatory intervention.

1493 This phenomenon is not restricted to PPAR α since a similar proof of concept was
1494 recently also shown for PPAR γ agonists in skin and lung. Indeed, house-dust mite
1495 induced skin sensitization, which aggravates asthmatic responses in mice via a mixed
1496 Th2/Th17 response, was prevented by treatment combining glucocorticoids with
1497 rosiglitazone (415). Similarly, the role of PPAR α in estrogen-mediated anti-
1498 inflammatory activity in lungs was shown by the demonstration of a weakened
1499 response to estrogen in PPAR α -deficient mice (416).

1500

1501 **Regulation of MAPK and PKC kinase activities**

1502 Given that inflammatory responses are driven in part by the activation of MAPKs,
1503 PPAR α ligands were also shown to modulate the degree of macrophage inflammation
1504 not only by reducing NF- κ B activation, but also by reducing MAPK phosphorylation,
1505 hence effectively decreasing the expression of the proinflammatory mediator COX-2
1506 and inducible nitric oxide synthase (163,417).

1507 PPAR α was further shown to polarize T-cell differentiation processes, also via a
1508 modulation of MAPK activities. In CD4(+) T lymphocytes, unliganded PPAR α
1509 suppressed p38 MAPK phosphorylation. Ligand activation reversed this inhibition,
1510 augmenting the expression of the transcription factor of T cells (T-bet), a lineage-
1511 determinant of Th1 inflammatory responses (418) which drives IFN- γ expression.
1512 PPAR α thus reduced the level of activation-induced IFN- γ produced by CD4⁺ T cells.
1513 Mechanistically, the control of PPAR α over T-bet expression occurs via a DNA-
1514 binding independent mechanism, mediated through the ability of PPAR α to repress
1515 the phosphorylation of p38-MAP kinase following T cell activation. These data
1516 suggested a novel and important function for PPAR α within T cells. Both in
1517 transformed T and B lymphocytes, PPAR α ligands effectively repress NF- κ B activity
1518 (130). Additionally, the anti-inflammatory effects of PPAR α in macrophages involve
1519 an inhibition of the PKC signaling pathway (52,154). Little is known about the exact
1520 molecular mechanisms underlying the PPAR α -mediated modulation of (potentially
1521 other) kinase activities and to what extent this may contribute to an overall anti-
1522 inflammatory action.

1523

1524 **Anti-inflammatory activity of PPAR α in a PPRE-dependent manner**

1525 In addition to down-regulating the expression of pro-inflammatory genes, PPAR α also
1526 suppresses the inflammatory response by direct up-regulation of genes with anti-
1527 inflammatory properties, suggesting a possible cooperation between PPAR α -
1528 dependent transactivation and transrepression to govern anti-inflammatory pathways.
1529 Besides the upregulation of I κ B α , discussed above, as a mechanism contributing to its
1530 anti-inflammatory actions (409,419), activated PPAR α strongly up-regulated the
1531 hepatic expression of IL-1 receptor antagonist (IL-1ra), an inhibitor of cytokine

1532 signaling, during LPS-induced inflammation, while numerous inflammatory genes
1533 including STAT3, SAA and IL-18 were found to be down-regulated (420).
1534 Transactivation and chromatin immunoprecipitation studies identified IL-1ra as a
1535 direct positive target gene of PPAR α with a functional PPRE present in the promoter.
1536 Moreover, up-regulation of IL-1ra by PPAR α was conserved in human HepG2
1537 hepatoma cells and the human monocyte/macrophage THP-1 cell line (420).
1538 In the same context, Heme Oxygenase-1 (HO-1), a PPAR α target gene with a
1539 functional PPRE, is also directly upregulated by PPAR α ligands and contributes to the
1540 anti-inflammatory effects in human vascular cells (421).
1541 Interestingly, the gene coding for vanin-1 (Vnn1), a protein with anti-inflammatory
1542 potential, is robustly activated in liver by PPAR α agonists, such as Wy-14,643,
1543 fenofibrate, and clofibrate (211), and functional PPRE sites have been identified in the
1544 Vnn1 promoter (422). Vanin activity prevents steatosis development in response to
1545 fasting, while its deficiency affects multiple genes involved in
1546 inflammation/immunity (423).
1547 Considering the above studies, it is clear that PPAR α may affect markers of
1548 inflammation in a direct or indirect manner. Below, we continue the discussion on
1549 recent findings regarding the role of PPARs in some specific examples of
1550 inflammatory disease models.

1551

1552 **PPAR α in the metabolic syndrome as an inflammatory disease**

1553 Inflammation is a critical component of the metabolic syndrome, which represents a
1554 cluster of risk factors that include dyslipidemia, insulin resistance, hypertension,
1555 inflammation and coagulation disorders. Consequently, PPAR α , being on the
1556 crossroad between inflammation and metabolism, is an important regulator of the

1557 metabolic syndrome (27,424). It is now well-accepted that pro-inflammatory
1558 cytokines and specific immune cell populations promote metabolic disease
1559 progression. Accordingly, a chronic low-grade inflammatory condition, which is
1560 characterized by increased circulating inflammatory cytokines and acute phase
1561 proteins and which often accompanies the metabolic syndrome, has been implicated
1562 as a major factor both in the establishment of the metabolic syndrome and its
1563 associated pathophysiological consequences (207). PPAR α , and other PPAR
1564 isoforms, have all demonstrated anti-inflammatory effects in these conditions (425).
1565 In hyperlipidemic patients and patients with metabolic syndrome PPAR α activation
1566 using fenofibrate decreases plasma levels of several acute phase and inflammatory
1567 proteins that are normally increased during inflammatory conditions, such as high-
1568 sensitivity CRP and IL-6 (23,373,410). In addition, fenofibrate treatment also reduces
1569 plasma concentrations of the cytokines interferon- γ (IFN- γ) and TNF α in
1570 hyperlipoproteinemia type IIb patients (426). Addition of fenofibrate to simvastatin-
1571 treated patients with atherosclerosis and early glucose metabolism disturbances
1572 further reduces lymphocyte release of IL-2, IFN- γ and TNF- α , accompanied by a
1573 reduction in plasma CRP levels, compared to statin alone (427). It was also found that
1574 fibrates have an anti-inflammatory effect in the interaction between adipocytes and
1575 macrophages in obese adipose tissue, thereby improving the dysregulated
1576 adipocytokine production and obesity-related metabolic syndrome (428).

1578 **PPAR α in age-related inflammation**

1579 Enhancing PPAR α levels and activity was shown to ameliorate age-related
1580 inflammatory processes. Increased inflammatory marker levels during aging correlate
1581 with a decreased PPAR α activity. Administration of PPAR α activators improved the
1582 splenocyte cellular redox balance and reduced the age-associated elevations in NF- κ B

1583 activity and constitutive pro-inflammatory cytokine production (131,429). The PPAR
1584 pan agonist MHY2013 alleviated age-related hepatic lipid accumulation, in part by
1585 upregulating β -oxidation signaling and suppressing inflammation in the liver (430).

1586 In a similar context, a recent study has demonstrated that LPS-induced liver
1587 inflammation and lipid accumulation were associated with a chronically overactive
1588 inflammasome/IL-1 β pathway in aged rat livers and that these effects were due to the
1589 dysregulation of PPAR α and SREBP1c. Indeed, in these aged rat livers, PPAR α was
1590 consistently inactivated and the levels of SREBP1c were chronically increased (132).
1591 Therefore, targeting PPAR α signaling might reduce the age-related sensitivity to
1592 endotoxin-induced liver inflammation.

1593 These data, positioning PPAR α at the crossroad of aerobic metabolism and
1594 inflammation, fit the observations that link non-aerobic glycolytic ATP generation to
1595 the production of pro-inflammatory cytokines (80). To illustrate, complex host
1596 responses to the TLR9 agonist CpGA were found to be mediated by plasmacytoid
1597 dendritic cell (pDC) production of IFNs, operating in an autocrine fashion. FAO was
1598 necessary for full pDC activation, pointing to PPAR α as a potential target to modulate
1599 downstream effects of type I IFNs (431).

1600

1601 **PPAR α in inflammatory bowel disease**

1602 Considering the intestine as an organ contributing to immune system, a link between
1603 PPAR α signaling and the control of colitis was found upon studying the IL-10 gene
1604 deficient mouse as a model for human inflammatory bowel disease. In this model
1605 anti-inflammatory IL-10 gene expression changes were related to PPAR α activation
1606 although the mechanisms responsible remain undefined (432). Infectious disease
1607 control in intestine also involves PPAR α activation. As such, clearance of a *Giardia*

1608 muris infection was found to coincide not only with IL-17 production, contributing to
1609 protection, but also with an early PPAR α induction (433). Along similar lines,
1610 fenofibrate represses IL-17 and IFN- γ expression and improves colitis in IL-10-
1611 deficient animals, suggesting a possible therapeutic potential in Crohn's disease (434).
1612 Of note, PPAR α protects the intestine from colitis-induced permeability (435)

1613

1614 **PPAR α in inflammatory skin disease**

1615 PPAR α activation impaired epidermal Langerhans Cell (LCs) maturation and
1616 migratory capacity and alters cytokine production through the inhibition of NF- κ B
1617 phosphorylation (400), suggesting a role for PPAR α in combatting inflammatory skin
1618 diseases (436). In this regard, PPAR α -deficient mice exhibit impaired recruitment of
1619 neutrophils and monocytes/macrophages to the wound bed and present a transient
1620 delay in healing, which coincides with the inflammatory phase (437). These data
1621 support the concept that PPAR α favors skin healing via a modulation of the
1622 inflammatory phase (437). In addition, PPAR α activation is beneficial in mouse
1623 models with a hyperproliferative epidermis (438) and in models of irritant and allergic
1624 dermatitis (439). The anti-inflammatory properties of PPAR α agonists, coupled with
1625 their anti-proliferative and pro-differentiating effects, suggest that they could be
1626 beneficial for the treatment of a variety of cutaneous diseases (439). In a model of
1627 atopic dermatitis, topical application of the PPAR α agonist WY14643 significantly
1628 decreased antigen-induced skin inflammation, providing *in vivo* evidence for the role
1629 of PPAR α in controlling skin inflammation and pointing to a potential benefit in
1630 combating systemic inflammatory responses in patients with atopic dermatitis, a
1631 disease characterized by inflammatory infiltrates and barrier dysfunction (440).
1632 Interestingly, PPAR α may be the molecular mediator of the anti-allergic and anti-

1633 inflammatory effects of palmitoylethanolamide, a natural FA derivative present in
1634 murine skin (441). Taken together, the many observations above underscore the
1635 implications of PPAR α in inflammatory skin disorders and paves the way for trials of
1636 topical PPAR α agonist application.

1637

1638 **PPAR α in other inflammatory diseases**

1639 Expanding the applicability of PPAR α agonists to other inflammatory diseases, anti-
1640 inflammatory properties of activated PPAR α were observed in primary murine
1641 astrocytes, a cell type implicated in the pathology of experimental autoimmune
1642 encephalomyelitis (EAE), an animal model of multiple sclerosis (MS). Fibrates
1643 decreased the LPS-induced secretion of pro-inflammatory cytokines TNF α , IL-1 β and
1644 IL-6 and NO production, likely via interference with the DNA binding of NF- κ B
1645 (442), suggesting a putative function of PPAR α in controlling neurodegenerative
1646 diseases. In the same line, PPAR α activation significantly inhibited radiation-induced
1647 microglial production of pro-inflammatory cytokines such as TNF α , IL-1 β , Cox-2 and
1648 iNOS by inhibiting nuclear translocation of the NF- κ B/p65 subunit and reducing
1649 phosphorylation of nuclear c-Jun/AP-1 (443). Genetic ablation of PPAR α in an
1650 experimental model of autoimmune encephalomyelitis increased clinical symptoms in
1651 male but not female SV.129 H^{2b} mice, consistent with the finding that male mice of
1652 this strain express higher levels of PPAR α than female mice (397). Recently, PPAR α
1653 was reported to contribute to the anti-inflammatory activity of melatonin in Spinal
1654 Cord Injury (SCI), again by modulating the NF- κ B pathway. It was demonstrated that
1655 melatonin was less effective in PPAR α null, compared to WT mice, as evaluated by
1656 inhibition of the degree of spinal cord inflammation and tissue injury, neutrophil

1657 infiltration, pro-inflammatory cytokine expression, NF- κ B activation and iNOS
1658 expression (444).

1659

1660 **The paradox of PPAR α as a pro-inflammatory mediator**

1661 The above studies (**Fig. 5**) are in line with the well-accepted notion that PPAR α is
1662 involved primarily in anti-inflammatory signaling. As stated in the introduction to this
1663 chapter, PPAR α has also been ascribed potential “pro-inflammatory” effects (**Fig. 6**).

1664 Lee *et al.* suggested that oxidized phospholipids induce MCP-1 and IL-8 expression
1665 through a PPAR α -dependent signaling cascade in human aortic endothelial cells
1666 (445). These data demonstrate that PPAR α can mediate the activation of endothelial
1667 cells by stimulating the production of monocyte chemotactic activity in response to
1668 oxidized phospholipids and lipoproteins (445)

1669 Additionally, PPAR α activation by Wy-14,643 enhances IL-1 β -induced pro-
1670 inflammatory cytokine release, including IL-6, IL-8 and TNF- α , in ocular cells and
1671 induces proangiogenic responses (446). In contrast, in the FIELD and ACCORD
1672 studies (330,333) fibrates showed a protection against diabetic retinopathy. In line, the
1673 antiangiogenic activity of PPAR α ligands specifically depended on the activation of
1674 PPAR α since PPAR α ligands inhibited FGF2-corneal neovascularization in wild-type
1675 but not in PPAR α deficient mice (447). Consistent with these data fenofibrate was
1676 shown to improve diabetic retinopathy in type 1 diabetes animal models and
1677 ischemia-induced retinal neovascularization. Herewith, PPAR α -dependency also
1678 formed the mechanistic basis for the therapeutic effects of fenofibrate (448). The anti-
1679 inflammatory effects of fenofibrate-activated PPAR α were ascribed to the inhibition
1680 of NF- κ B signaling in the diabetic retina (448). The basis for these differences

1681 remains unclear but might reflect a reduced complexity of *in vitro* studies versus *in*
1682 *vivo* studies.

1683 Then again, in a mouse model of endotoxemia, fenofibrate administration strongly
1684 increased circulating LPS-induced TNF levels (449). In a rat hypertensive model,
1685 bezafibrate was shown to sensitize for endotoxin effects, concomitant with low levels
1686 of HDL and increased levels of TG (450). In murine macrophage lines and in contrast
1687 to Wy-14,643, the natural PPAR α ligands LTB₄ and 8(S)-HETE showed a pro-
1688 inflammatory potential by increasing NOS activity (348). These observations are
1689 again not restricted to PPAR α , since PPAR γ activity in T-cells and dendritic cells
1690 promotes Th2 immunity (451,452). These are interesting findings suggesting that
1691 PPAR α activation may result in different responses depending on the inflammatory
1692 settings, an effect which may involve combinatorial signaling. Although the
1693 mechanisms by which such potentially “pro-inflammatory” effects occur is not
1694 understood, these data point to the need for a careful evaluation of the effects of
1695 PPAR α agonists in the relevant cell types, and in different physiological contexts.
1696 How to reconcile these seemingly contradictory findings with the wealth of data on
1697 anti-inflammatory PPAR actions is as of yet unclear. For instance, reduced PPAR α
1698 expression has also been linked to a lower overall survival and an enhanced tissue
1699 bacterial load in sepsis (453). The timing and nature of the pro-inflammatory stimulus
1700 and/or treatment may play a decisive role. It may well be that PPAR α exerts a
1701 context-dependent immune-system priming role, as has been documented recently
1702 also for glucocorticoids (391). Given that GR and PPAR α are able to physically
1703 interact and able to co-control genes involved in both inflammatory and metabolic
1704 pathways (160,385), increases the likelihood of this assumption. More research is
1705 clearly necessary to disentangle and explain these paradoxical observations. This

1706 hitherto hidden role of PPAR α not only merits further mechanistic attention but also
1707 requires a better understanding at the level of physiological relevance.

1708 **VIII. Future perspectives**

1709 On account of their pleiotropic effects, PPARs may be targets in a number of disease
1710 conditions. It is clear there is still a lot of ground to cover, foremost by studying novel
1711 generations of more potent and better tolerated single, dual or pan PPAR agonists in
1712 the clinic. More basic research involving novel PPAR α agonists is important, as many
1713 mechanistic aspects differ from the first generation of PPAR α agonists. Plus, novel
1714 fields of application may still arise, for which the first generation of drugs did not
1715 show therapeutic benefit.

1716 Fibrates might be beneficial in the prevention of coronary heart disease. The highest
1717 benefit is achieved in cardiovascular disease patients with high TG and low HDL-C
1718 (454). A clinical benefit of PPAR α activation with novel agonists remains to be
1719 demonstrated in patients with high TG/low HDL and residual cardiovascular risk.
1720 Fibrates might be useful in the treatment and prevention of atherosclerosis, especially
1721 the new fibrates with greater potency open new perspectives. However, it remains
1722 unclear whether fibrates in general are useful in the treatment or prevention of heart
1723 failure.

1724 It is now evident that the effects of PPAR α are much more widespread and cover
1725 numerous aspects of inflammation and inflammatory related diseases, however many
1726 mechanistic fundamental details of its function still remain to be unraveled. For
1727 instance, nuclear receptor regulation of circadian rhythms in inflammatory metabolic
1728 diseases deserves more clinical investigation. There is newfound appreciation for the
1729 timing of treatment interventions. For example, a recent study shows a link between
1730 the circadian clock and perioperative myocardial injury in patients undergoing aortic
1731 valve replacement, whereby antagonism of Rev-erb α , another nuclear receptor family
1732 member and PPAR α target gene (260) seems to provide a benefit for cardioprotection

1733 (455). Moreover, the circadian clock regulates the expression and activity of genes
1734 and proteins involved in the progression of several autoimmune diseases (456,457).
1735 Future therapeutics relying on PPARs in a context of inflammation will therefore
1736 most probably have to take “the clock” into consideration.

1737 The role of PPAR α needs to be further evaluated in various pathophysiological
1738 conditions. For instance, it is unclear how PPAR α may influence immune cell
1739 (metabolic) control in immune/inflammatory diseases that are glucocorticoid resistant,
1740 such as sepsis.

1741 Defining the molecular mechanisms of PPAR α function that govern inflammatory
1742 programs will improve our understanding of its roles and will allow us to further
1743 exploit their potential in the therapeutic field.

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1758 **References**

- 1759 1. Chen F, Law SW, O'Malley BW. Identification of two mPPAR related
1760 receptors and evidence for the existence of five subfamily members. *Biochem*
1761 *Biophys Res Commun* 1993; 196:671-677
- 1762 2. Dreyer C, Krey G, Keller H, Givel F, Helftenbein G, Wahli W. Control of the
1763 peroxisomal beta-oxidation pathway by a novel family of nuclear hormone
1764 receptors. *Cell* 1992; 68:879-887
- 1765 3. Lemberger T, Desvergne B, Wahli W. Peroxisome proliferator-activated
1766 receptors: a nuclear receptor signaling pathway in lipid physiology. *Annual*
1767 *review of cell and developmental biology* 1996; 12:335-363
- 1768 4. Desvergne B, Michalik L, Wahli W. Be fit or be sick: peroxisome proliferator-
1769 activated receptors are down the road. *Mol Endocrinol* 2004; 18:1321-1332
- 1770 5. Poulsen L, Siersbaek M, Mandrup S. PPARs: fatty acid sensors controlling
1771 metabolism. *Semin Cell Dev Biol* 2012; 23:631-639
- 1772 6. Issemann I, Green S. Activation of a member of the steroid hormone receptor
1773 superfamily by peroxisome proliferators. *Nature* 1990; 347:645-650
- 1774 7. Islinger M, Cardoso MJ, Schrader M. Be different--the diversity of
1775 peroxisomes in the animal kingdom. *Biochim Biophys Acta* 2010; 1803:881-
1776 897
- 1777 8. Kersten S. Integrated physiology and systems biology of PPARalpha. *Mol*
1778 *Metab* 2014; 3:354-371
- 1779 9. Kliewer SA, Forman BM, Blumberg B, Ong ES, Borgmeyer U, Mangelsdorf
1780 DJ, Umesono K, Evans RM. Differential expression and activation of a family
1781 of murine peroxisome proliferator-activated receptors. *Proceedings of the*
1782 *National Academy of Sciences of the United States of America* 1994;
1783 91:7355-7359
- 1784 10. Escher P, Wahli W. Peroxisome proliferator-activated receptors: insight into
1785 multiple cellular functions. *Mutation research* 2000; 448:121-138
- 1786 11. Braissant O, Fougere F, Scotto C, Dauca M, Wahli W. Differential expression
1787 of peroxisome proliferator-activated receptors (PPARs): tissue distribution of
1788 PPAR-alpha, -beta, and -gamma in the adult rat. *Endocrinology* 1996;
1789 137:354-366
- 1790 12. Kliewer SA, Lehmann JM, Willson TM. Orphan nuclear receptors: shifting
1791 endocrinology into reverse. *Science (New York, NY)* 1999; 284:757-760
- 1792 13. Schupp M, Lazar MA. Endogenous ligands for nuclear receptors: digging
1793 deeper. *J Biol Chem* 2010; 285:40409-40415
- 1794 14. Barbier O, Fontaine C, Fruchart JC, Staels B. Genomic and non-genomic
1795 interactions of PPARalpha with xenobiotic-metabolizing enzymes. *Trends*
1796 *Endocrinol Metab* 2004; 15:324-330
- 1797 15. Barbier O, Torra IP, Duguay Y, Blanquart C, Fruchart JC, Glineur C, Staels B.
1798 Pleiotropic actions of peroxisome proliferator-activated receptors in lipid
1799 metabolism and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2002; 22:717-
1800 726
- 1801 16. Bocher V, Pineda-Torra I, Fruchart JC, Staels B. PPARs: transcription factors
1802 controlling lipid and lipoprotein metabolism. *Annals of the New York*
1803 *Academy of Sciences* 2002; 967:7-18
- 1804 17. Etgen GJ, Mantlo N. PPAR ligands for metabolic disorders. *Current topics in*
1805 *medicinal chemistry* 2003; 3:1649-1661
- 1806 18. Lee WS, Kim J. Peroxisome Proliferator-Activated Receptors and the Heart:
1807 Lessons from the Past and Future Directions. *PPAR Res* 2015; 2015:271983

- 1808 19. Bishop-Bailey D. Peroxisome proliferator-activated receptors in the
1809 cardiovascular system. *Br J Pharmacol* 2000; 129:823-834
- 1810 20. Chinetti G, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors
1811 and inflammation: from basic science to clinical applications. *Int J Obes Relat*
1812 *Metab Disord* 2003; 27 Suppl 3:S41-45
- 1813 21. Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of
1814 monocyte inflammatory cytokines. *Nature* 1998; 391:82-86
- 1815 22. Ren B, Thelen A, Jump DB. Peroxisome proliferator-activated receptor alpha
1816 inhibits hepatic S14 gene transcription. Evidence against the peroxisome
1817 proliferator-activated receptor alpha as the mediator of polyunsaturated fatty
1818 acid regulation of s14 gene transcription. *J Biol Chem* 1996; 271:17167-17173
- 1819 23. Staels B, Koenig W, Habib A, Merval R, Lebret M, Torra IP, Delerive P,
1820 Fadel A, Chinetti G, Fruchart JC, Najib J, Maclouf J, Tedgui A. Activation of
1821 human aortic smooth-muscle cells is inhibited by PPARalpha but not by
1822 PPARgamma activators. *Nature* 1998; 393:790-793
- 1823 24. Chinetti G, Fruchart J, Staels B. Peroxisome proliferator-activated receptors
1824 (PPARs): nuclear receptors at the crossroads between lipid metabolism and
1825 inflammation. *Inflammation research : official journal of the European*
1826 *Histamine Research Society [et al]* 2000; 49:497-505
- 1827 25. Kersten S, Stienstra R. The role and regulation of the peroxisome proliferator
1828 activated receptor alpha in human liver. *Biochimie* 2017; 136:75-84
- 1829 26. Feige JN, Gelman L, Michalik L, Desvergne B, Wahli W. From molecular
1830 action to physiological outputs: peroxisome proliferator-activated receptors
1831 are nuclear receptors at the crossroads of key cellular functions. *Prog Lipid*
1832 *Res* 2006; 45:120-159
- 1833 27. Lefebvre P, Chinetti G, Fruchart JC, Staels B. Sorting out the roles of PPAR
1834 alpha in energy metabolism and vascular homeostasis. *J Clin Invest* 2006;
1835 116:571-580
- 1836 28. Pyper SR, Viswakarma N, Yu S, Reddy JK. PPARalpha: energy combustion,
1837 hypolipidemia, inflammation and cancer. *Nucl Recept Signal* 2010; 8:e002
- 1838 29. Hamblin M, Chang L, Fan Y, Zhang J, Chen YE. PPARs and the
1839 cardiovascular system. *Antioxidants & redox signaling* 2009; 11:1415-1452
- 1840 30. Feige JN, Gelman L, Tudor C, Engelborghs Y, Wahli W, Desvergne B.
1841 Fluorescence imaging reveals the nuclear behavior of peroxisome proliferator-
1842 activated receptor/retinoid X receptor heterodimers in the absence and
1843 presence of ligand. *J Biol Chem* 2005; 280:17880-17890
- 1844 31. Bordji K, Grillasca JP, Gouze JN, Magdalou J, Schohn H, Keller JM, Bianchi
1845 A, Dauca M, Netter P, Terlain B. Evidence for the presence of peroxisome
1846 proliferator-activated receptor (PPAR) alpha and gamma and retinoid Z
1847 receptor in cartilage. PPARgamma activation modulates the effects of
1848 interleukin-1beta on rat chondrocytes. *J Biol Chem* 2000; 275:12243-12250
- 1849 32. Chinetti G, Griglio S, Antonucci M, Torra IP, Delerive P, Majd Z, Fruchart
1850 JC, Chapman J, Najib J, Staels B. Activation of proliferator-activated
1851 receptors alpha and gamma induces apoptosis of human monocyte-derived
1852 macrophages. *J Biol Chem* 1998; 273:25573-25580
- 1853 33. Umemoto T, Fujiki Y. Ligand-dependent nucleo-cytoplasmic shuttling of
1854 peroxisome proliferator-activated receptors, PPARalpha and PPARgamma.
1855 *Genes to cells : devoted to molecular & cellular mechanisms* 2012; 17:576-
1856 596

- 1857 34. Burgermeister E, Chuderland D, Hanoch T, Meyer M, Liscovitch M, Seger R.
1858 Interaction with MEK causes nuclear export and downregulation of
1859 peroxisome proliferator-activated receptor gamma. *Molecular and cellular*
1860 *biology* 2007; 27:803-817
- 1861 35. Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear
1862 control of metabolism. *Endocrine reviews* 1999; 20:649-688
- 1863 36. Sher T, Yi HF, McBride OW, Gonzalez FJ. cDNA cloning, chromosomal
1864 mapping, and functional characterization of the human peroxisome
1865 proliferator activated receptor. *Biochemistry* 1993; 32:5598-5604
- 1866 37. Vohl MC, Lepage P, Gaudet D, Brewer CG, Betard C, Perron P, Houde G,
1867 Cellier C, Faith JM, Despres JP, Morgan K, Hudson TJ. Molecular scanning
1868 of the human PPAR α gene: association of the L162v mutation with
1869 hyperapobetalipoproteinemia. *Journal of lipid research* 2000; 41:945-952
- 1870 38. Bugge A, Mandrup S. Molecular Mechanisms and Genome-Wide Aspects of
1871 PPAR Subtype Specific Transactivation. *PPAR Res* 2010; 2010
- 1872 39. Cronet P, Petersen JF, Folmer R, Blomberg N, Sjoblom K, Karlsson U,
1873 Lindstedt EL, Bamberg K. Structure of the PPAR α and -gamma ligand
1874 binding domain in complex with AZ 242; ligand selectivity and agonist
1875 activation in the PPAR family. *Structure (London, England : 1993)* 2001;
1876 9:699-706
- 1877 40. Hi R, Osada S, Yumoto N, Osumi T. Characterization of the amino-terminal
1878 activation domain of peroxisome proliferator-activated receptor alpha.
1879 Importance of alpha-helical structure in the transactivating function. *J Biol*
1880 *Chem* 1999; 274:35152-35158
- 1881 41. Blanquart C, Barbier O, Fruchart JC, Staels B, Glineur C. Peroxisome
1882 proliferator-activated receptor alpha (PPAR α) turnover by the ubiquitin-
1883 proteasome system controls the ligand-induced expression level of its target
1884 genes. *J Biol Chem* 2002; 277:37254-37259
- 1885 42. Burns KA, Vanden Heuvel JP. Modulation of PPAR activity via
1886 phosphorylation. *Biochim Biophys Acta* 2007; 1771:952-960
- 1887 43. Diradourian C, Girard J, Pegorier JP. Phosphorylation of PPARs: from
1888 molecular characterization to physiological relevance. *Biochimie* 2005; 87:33-
1889 38
- 1890 44. Castillo G, Brun RP, Rosenfield JK, Hauser S, Park CW, Troy AE, Wright
1891 ME, Spiegelman BM. An adipogenic cofactor bound by the differentiation
1892 domain of PPAR γ . *The EMBO journal* 1999; 18:3676-3687
- 1893 45. Hsu MH, Palmer CN, Song W, Griffin KJ, Johnson EF. A carboxyl-terminal
1894 extension of the zinc finger domain contributes to the specificity and polarity
1895 of peroxisome proliferator-activated receptor DNA binding. *J Biol Chem*
1896 1998; 273:27988-27997
- 1897 46. Gray JP, Burns KA, Leas TL, Perdew GH, Vanden Heuvel JP. Regulation of
1898 peroxisome proliferator-activated receptor alpha by protein kinase C.
1899 *Biochemistry* 2005; 44:10313-10321
- 1900 47. Gervois P, Chopin-Delannoy S, Fadel A, Dubois G, Kosykh V, Fruchart JC,
1901 Najib J, Laudet V, Staels B. Fibrates increase human REV-ERB α
1902 expression in liver via a novel peroxisome proliferator-activated receptor
1903 response element. *Mol Endocrinol* 1999; 13:400-409
- 1904 48. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC.
1905 Mechanism of action of fibrates on lipid and lipoprotein metabolism.
1906 *Circulation* 1998; 98:2088-2093

- 1907 49. Kliewer SA, Umesono K, Noonan DJ, Heyman RA, Evans RM. Convergence
1908 of 9-cis retinoic acid and peroxisome proliferator signalling pathways through
1909 heterodimer formation of their receptors. *Nature* 1992; 358:771-774
- 1910 50. Gervois P, Torra IP, Chinetti G, Grotzinger T, Dubois G, Fruchart JC,
1911 Fruchart-Najib J, Leitersdorf E, Staels B. A truncated human peroxisome
1912 proliferator-activated receptor alpha splice variant with dominant negative
1913 activity. *Mol Endocrinol* 1999; 13:1535-1549
- 1914 51. Dowell P, Peterson VJ, Zabriskie TM, Leid M. Ligand-induced peroxisome
1915 proliferator-activated receptor alpha conformational change. *J Biol Chem*
1916 1997; 272:2013-2020
- 1917 52. Blanquart C, Mansouri R, Paumelle R, Fruchart JC, Staels B, Glineur C. The
1918 protein kinase C signaling pathway regulates a molecular switch between
1919 transactivation and transrepression activity of the peroxisome proliferator-
1920 activated receptor alpha. *Mol Endocrinol* 2004; 18:1906-1918
- 1921 53. Pourcet B, Pineda-Torra I, Derudas B, Staels B, Glineur C. SUMOylation of
1922 human peroxisome proliferator-activated receptor alpha inhibits its trans-
1923 activity through the recruitment of the nuclear corepressor NCoR. *J Biol Chem*
1924 2010; 285:5983-5992
- 1925 54. Sumanasekera WK, Tien ES, Davis JW, 2nd, Turpey R, Perdew GH, Vanden
1926 Heuvel JP. Heat shock protein-90 (Hsp90) acts as a repressor of peroxisome
1927 proliferator-activated receptor-alpha (PPARalpha) and PPARbeta activity.
1928 *Biochemistry* 2003; 42:10726-10735
- 1929 55. Xu HE, Lambert MH, Montana VG, Plunket KD, Moore LB, Collins JL,
1930 Oplinger JA, Kliewer SA, Gampe RT, Jr., McKee DD, Moore JT, Willson
1931 TM. Structural determinants of ligand binding selectivity between the
1932 peroxisome proliferator-activated receptors. *Proceedings of the National
1933 Academy of Sciences of the United States of America* 2001; 98:13919-13924
- 1934 56. Leuenberger N, Pradervand S, Wahli W. Sumoylated PPARalpha mediates
1935 sex-specific gene repression and protects the liver from estrogen-induced
1936 toxicity in mice. *J Clin Invest* 2009; 119:3138-3148
- 1937 57. Juge-Aubry CE, Gorla-Bajszczak A, Pernin A, Lemberger T, Wahli W,
1938 Burger AG, Meier CA. Peroxisome proliferator-activated receptor mediates
1939 cross-talk with thyroid hormone receptor by competition for retinoid X
1940 receptor. Possible role of a leucine zipper-like heptad repeat. *J Biol Chem*
1941 1995; 270:18117-18122
- 1942 58. Juge-Aubry CE, Hammar E, Siegrist-Kaiser C, Pernin As, Takeshita A, Chin
1943 WW, Burger AG, Meier CA. Regulation of the Transcriptional Activity of the
1944 Peroxisome Proliferator-activated Receptor α by Phosphorylation of a
1945 Ligand-independent trans-Activating Domain. *Journal of Biological
1946 Chemistry* 1999; 274:10505-10510
- 1947 59. Benson S, Padmanabhan S, Kurtz TW, Pershadsingh HA. Ligands for the
1948 peroxisome proliferator-activated receptor-gamma and the retinoid X receptor-
1949 alpha exert synergistic antiproliferative effects on human coronary artery
1950 smooth muscle cells. *Molecular cell biology research communications* :
1951 MCBRC 2000; 3:159-164
- 1952 60. Cha BS, Ciaraldi TP, Carter L, Nikoulina SE, Mudaliar S, Mukherjee R,
1953 Paterniti JR, Jr., Henry RR. Peroxisome proliferator-activated receptor
1954 (PPAR) gamma and retinoid X receptor (RXR) agonists have complementary
1955 effects on glucose and lipid metabolism in human skeletal muscle.
1956 *Diabetologia* 2001; 44:444-452

- 1957 61. Desvergne B. RXR: from partnership to leadership in metabolic regulations.
1958 Vitamins and hormones 2007; 75:1-32
- 1959 62. Schulman IG, Shao G, Heyman RA. Transactivation by retinoid X receptor-
1960 peroxisome proliferator-activated receptor gamma (PPARgamma)
1961 heterodimers: intermolecular synergy requires only the PPARgamma
1962 hormone-dependent activation function. Molecular and cellular biology 1998;
1963 18:3483-3494
- 1964 63. Shimizu M, Moriwaki H. Synergistic Effects of PPARgamma Ligands and
1965 Retinoids in Cancer Treatment. PPAR Res 2008; 2008:181047
- 1966 64. Wu Y, Guo SW. Peroxisome proliferator-activated receptor-gamma and
1967 retinoid X receptor agonists synergistically suppress proliferation of
1968 immortalized endometrial stromal cells. Fertility and sterility 2009; 91:2142-
1969 2147
- 1970 65. Yamamoto A, Kakuta H, Miyachi H, Sugimoto Y. Involvement of the
1971 Retinoid X Receptor Ligand in the Anti-Inflammatory Effect Induced by
1972 Peroxisome Proliferator-Activated Receptor gamma Agonist In Vivo. PPAR
1973 Res 2011; 2011:840194
- 1974 66. IJpenberg A, Jeannin E, Wahli W, Desvergne B. Polarity and specific
1975 sequence requirements of peroxisome proliferator-activated receptor
1976 (PPAR)/retinoid X receptor heterodimer binding to DNA. A functional
1977 analysis of the malic enzyme gene PPAR response element. J Biol Chem
1978 1997; 272:20108-20117
- 1979 67. Harmon GS, Lam MT, Glass CK. PPARs and lipid ligands in inflammation
1980 and metabolism. Chemical reviews 2011; 111:6321-6340
- 1981 68. Bensinger SJ, Tontonoz P. Integration of metabolism and inflammation by
1982 lipid-activated nuclear receptors. Nature 2008; 454:470-477
- 1983 69. DiRenzo J, Soderstrom M, Kurokawa R, Ogliastro MH, Ricote M, Ingrey S,
1984 Horlein A, Rosenfeld MG, Glass CK. Peroxisome proliferator-activated
1985 receptors and retinoic acid receptors differentially control the interactions of
1986 retinoid X receptor heterodimers with ligands, coactivators, and corepressors.
1987 Molecular and cellular biology 1997; 17:2166-2176
- 1988 70. Dowell P, Ishmael JE, Avram D, Peterson VJ, Nevriy DJ, Leid M.
1989 Identification of nuclear receptor corepressor as a peroxisome proliferator-
1990 activated receptor alpha interacting protein. J Biol Chem 1999; 274:15901-
1991 15907
- 1992 71. Tugwood JD, Issemann I, Anderson RG, Bundell KR, McPheat WL, Green S.
1993 The mouse peroxisome proliferator activated receptor recognizes a response
1994 element in the 5' flanking sequence of the rat acyl CoA oxidase gene. The
1995 EMBO journal 1992; 11:433-439
- 1996 72. van der Meer DL, Degenhardt T, Vaisanen S, de Groot PJ, Heinaniemi M, de
1997 Vries SC, Muller M, Carlberg C, Kersten S. Profiling of promoter occupancy
1998 by PPARalpha in human hepatoma cells via ChIP-chip analysis. Nucleic acids
1999 research 2010; 38:2839-2850
- 2000 73. Boergesen M, Pedersen TA, Gross B, van Heeringen SJ, Hagenbeek D,
2001 Bindesboll C, Caron S, Lalloyer F, Steffensen KR, Nebb HI, Gustafsson JA,
2002 Stunnenberg HG, Staels B, Mandrup S. Genome-wide profiling of liver X
2003 receptor, retinoid X receptor, and peroxisome proliferator-activated receptor
2004 alpha in mouse liver reveals extensive sharing of binding sites. Molecular and
2005 cellular biology 2012; 32:852-867

- 2006 74. Sarusi Portuguese A, Schwartz M, Siersbaek R, Nielsen R, Sung MH, Mandrup
2007 S, Kaplan T, Hakim O. Hierarchical role for transcription factors and
2008 chromatin structure in genome organization along adipogenesis. *The FEBS*
2009 *journal* 2017; 284:3230-3244
- 2010 75. Siersbaek R, Nielsen R, John S, Sung MH, Baek S, Loft A, Hager GL,
2011 Mandrup S. Extensive chromatin remodelling and establishment of
2012 transcription factor 'hotspots' during early adipogenesis. *The EMBO journal*
2013 2011; 30:1459-1472
- 2014 76. Chandra V, Huang P, Hamuro Y, Raghuram S, Wang Y, Burriss TP, Rastinejad
2015 F. Structure of the intact PPAR-gamma-RXR-alpha nuclear receptor complex
2016 on DNA. *Nature* 2008:350-356
- 2017 77. Roszer T, Menendez-Gutierrez MP, Cedenilla M, Ricote M. Retinoid X
2018 receptors in macrophage biology. *Trends Endocrinol Metab* 2013; 24:460-468
- 2019 78. Ide T, Shimano H, Yoshikawa T, Yahagi N, Amemiya-Kudo M, Matsuzaka T,
2020 Nakakuki M, Yatoh S, Iizuka Y, Tomita S, Ohashi K, Takahashi A, Sone H,
2021 Gotoda T, Osuga J, Ishibashi S, Yamada N. Cross-talk between peroxisome
2022 proliferator-activated receptor (PPAR) alpha and liver X receptor (LXR) in
2023 nutritional regulation of fatty acid metabolism. II. LXRs suppress lipid
2024 degradation gene promoters through inhibition of PPAR signaling. *Mol*
2025 *Endocrinol* 2003; 17:1255-1267
- 2026 79. Yoshikawa T, Ide T, Shimano H, Yahagi N, Amemiya-Kudo M, Matsuzaka T,
2027 Yatoh S, Kitamine T, Okazaki H, Tamura Y, Sekiya M, Takahashi A, Hasty
2028 AH, Sato R, Sone H, Osuga J, Ishibashi S, Yamada N. Cross-talk between
2029 peroxisome proliferator-activated receptor (PPAR) alpha and liver X receptor
2030 (LXR) in nutritional regulation of fatty acid metabolism. I. PPARs suppress
2031 sterol regulatory element binding protein-1c promoter through inhibition of
2032 LXR signaling. *Mol Endocrinol* 2003; 17:1240-1254
- 2033 80. Hashimoto K, Cohen RN, Yamada M, Markan KR, Monden T, Satoh T, Mori
2034 M, Wondisford FE. Cross-talk between thyroid hormone receptor and liver X
2035 receptor regulatory pathways is revealed in a thyroid hormone resistance
2036 mouse model. *J Biol Chem* 2006; 281:295-302
- 2037 81. Oka S, Zhai P, Yamamoto T, Ikeda Y, Byun J, Hsu CP, Sadoshima J.
2038 Peroxisome Proliferator Activated Receptor-alpha Association With Silent
2039 Information Regulator 1 Suppresses Cardiac Fatty Acid Metabolism in the
2040 Failing Heart. *Circulation Heart failure* 2015; 8:1123-1132
- 2041 82. Oka S, Alcendor R, Zhai P, Park JY, Shao D, Cho J, Yamamoto T, Tian B,
2042 Sadoshima J. PPARalpha-Sirt1 complex mediates cardiac hypertrophy and
2043 failure through suppression of the ERR transcriptional pathway. *Cell*
2044 *metabolism* 2011; 14:598-611
- 2045 83. Oka S, Zhai P, Alcendor R, Park JY, Tian B, Sadoshima J. Suppression of
2046 ERR targets by a PPARalpha/Sirt1 complex in the failing heart. *Cell cycle*
2047 *(Georgetown, Tex)* 2012; 11:856-864
- 2048 84. Villarroya J, Redondo-Angulo I, Iglesias R, Giralt M, Villarroya F, Planavila
2049 A. Sirt1 mediates the effects of a short-term high-fat diet on the heart. *The*
2050 *Journal of nutritional biochemistry* 2015; 26:1328-1337
- 2051 85. Gray JP, Davis JW, 2nd, Gopinathan L, Leas TL, Nugent CA, Vanden Heuvel
2052 JP. The ribosomal protein rpL11 associates with and inhibits the
2053 transcriptional activity of peroxisome proliferator-activated receptor-alpha.
2054 *Toxicological sciences : an official journal of the Society of Toxicology* 2006;
2055 89:535-546

- 2056 **86.** Iwamoto F, Umemoto T, Motojima K, Fujiki Y. Nuclear transport of
2057 peroxisome-proliferator activated receptor α . *Journal of biochemistry*
2058 2011; 149:311-319
- 2059 **87.** Rodriguez JE, Liao JY, He J, Schisler JC, Newgard CB, Drujan D, Glass DJ,
2060 Frederick CB, Yoder BC, Lalush DS, Patterson C, Willis MS. The ubiquitin
2061 ligase MuRF1 regulates PPAR α activity in the heart by enhancing nuclear
2062 export via monoubiquitination. *Mol Cell Endocrinol* 2015; 413:36-48
- 2063 **88.** Flavell DM, Pineda Torra I, Jamshidi Y, Evans D, Diamond JR, Elkeles RS,
2064 Bujac SR, Miller G, Talmud PJ, Staels B, Humphries SE. Variation in the
2065 PPAR α gene is associated with altered function in vitro and plasma lipid
2066 concentrations in Type II diabetic subjects. *Diabetologia* 2000; 43:673-680
- 2067 **89.** Lacquemant C, Lepretre F, Pineda Torra I, Manraj M, Charpentier G, Ruiz J,
2068 Staels B, Froguel P. Mutation screening of the PPAR α gene in type 2
2069 diabetes associated with coronary heart disease. *Diabetes & metabolism* 2000;
2070 26:393-401
- 2071 **90.** Tai ES, Demissie S, Cupples LA, Corella D, Wilson PW, Schaefer EJ,
2072 Ordovas JM. Association between the PPARA L162V polymorphism and
2073 plasma lipid levels: the Framingham Offspring Study. *Arterioscler Thromb*
2074 *Vasc Biol* 2002; 22:805-810
- 2075 **91.** Sapone A, Peters JM, Sakai S, Tomita S, Papiha SS, Dai R, Friedman FK,
2076 Gonzalez FJ. The human peroxisome proliferator-activated receptor alpha
2077 gene: identification and functional characterization of two natural allelic
2078 variants. *Pharmacogenetics* 2000; 10:321-333
- 2079 **92.** Flavell DM, Jamshidi Y, Hawe E, Pineda Torra I, Taskinen MR, Frick MH,
2080 Nieminen MS, Kesaniemi YA, Pasternack A, Staels B, Miller G, Humphries
2081 SE, Talmud PJ, Syvanne M. Peroxisome proliferator-activated receptor alpha
2082 gene variants influence progression of coronary atherosclerosis and risk of
2083 coronary artery disease. *Circulation* 2002; 105:1440-1445
- 2084 **93.** Robitaille J, Brouillette C, Houde A, Lemieux S, Perusse L, Tchernof A,
2085 Gaudet D, Vohl MC. Association between the PPAR α -L162V
2086 polymorphism and components of the metabolic syndrome. *Journal of human*
2087 *genetics* 2004; 49:482-489
- 2088 **94.** Tai ES, Corella D, Demissie S, Cupples LA, Coltell O, Schaefer EJ, Tucker
2089 KL, Ordovas JM. Polyunsaturated fatty acids interact with the PPARA-L162V
2090 polymorphism to affect plasma triglyceride and apolipoprotein C-III
2091 concentrations in the Framingham Heart Study. *The Journal of nutrition* 2005;
2092 135:397-403
- 2093 **95.** Bosse Y, Despres JP, Bouchard C, Perusse L, Vohl MC. The peroxisome
2094 proliferator-activated receptor alpha L162V mutation is associated with
2095 reduced adiposity. *Obesity research* 2003; 11:809-816
- 2096 **96.** Evans D, Aberle J, Wendt D, Wolf A, Beisiegel U, Mann WA. A
2097 polymorphism, L162V, in the peroxisome proliferator-activated receptor alpha
2098 (PPAR α) gene is associated with lower body mass index in patients with
2099 non-insulin-dependent diabetes mellitus. *Journal of molecular medicine*
2100 (Berlin, Germany) 2001; 79:198-204
- 2101 **97.** Gouni-Berthold I, Giannakidou E, Muller-Wieland D, Faust M, Kotzka J,
2102 Berthold HK, Krone W. Association between the PPAR α L162V
2103 polymorphism, plasma lipoprotein levels, and atherosclerotic disease in
2104 patients with diabetes mellitus type 2 and in nondiabetic controls. *American*
2105 *heart journal* 2004; 147:1117-1124

- 2106 98. Skogsberg J, Kannisto K, Cassel TN, Hamsten A, Eriksson P, Ehrenborg E.
2107 Evidence that peroxisome proliferator-activated receptor delta influences
2108 cholesterol metabolism in men. *Arterioscler Thromb Vasc Biol* 2003; 23:637-
2109 643
- 2110 99. Bosse Y, Pascot A, Dumont M, Brochu M, Prud'homme D, Bergeron J,
2111 Despres JP, Vohl MC. Influences of the PPAR alpha-L162V polymorphism
2112 on plasma HDL(2)-cholesterol response of abdominally obese men treated
2113 with gemfibrozil. *Genetics in medicine : official journal of the American
2114 College of Medical Genetics* 2002; 4:311-315
- 2115 100. Brisson D, Ledoux K, Bosse Y, St-Pierre J, Julien P, Perron P, Hudson TJ,
2116 Vohl MC, Gaudet D. Effect of apolipoprotein E, peroxisome proliferator-
2117 activated receptor alpha and lipoprotein lipase gene mutations on the ability of
2118 fenofibrate to improve lipid profiles and reach clinical guideline targets among
2119 hypertriglyceridemic patients. *Pharmacogenetics* 2002; 12:313-320
- 2120 101. Paradis AM, Fontaine-Bisson B, Bosse Y, Robitaille J, Lemieux S, Jacques H,
2121 Lamarche B, Tchernof A, Couture P, Vohl MC. The peroxisome proliferator-
2122 activated receptor alpha Leu162Val polymorphism influences the metabolic
2123 response to a dietary intervention altering fatty acid proportions in healthy
2124 men. *The American journal of clinical nutrition* 2005; 81:523-530
- 2125 102. Hara M, Wang X, Paz VP, Iwasaki N, Honda M, Iwamoto Y, Bell GI.
2126 Identification of three missense mutations in the peroxisome proliferator-
2127 activated receptor alpha gene in Japanese subjects with maturity-onset
2128 diabetes of the young. *Journal of human genetics* 2001; 46:285-288
- 2129 103. Naito H, Yamanoshita O, Kamijima M, Katoh T, Matsunaga T, Lee CH, Kim
2130 H, Aoyama T, Gonzalez FJ, Nakajima T. Association of V227A PPARalpha
2131 polymorphism with altered serum biochemistry and alcohol drinking in
2132 Japanese men. *Pharmacogenetics and genomics* 2006; 16:569-577
- 2133 104. Yamakawa-Kobayashi K, Ishiguro H, Arinami T, Miyazaki R, Hamaguchi H.
2134 A Val227Ala polymorphism in the peroxisome proliferator activated receptor
2135 alpha (PPARalpha) gene is associated with variations in serum lipid levels.
2136 *Journal of medical genetics* 2002; 39:189-191
- 2137 105. Chan E, Tan CS, Deurenberg-Yap M, Chia KS, Chew SK, Tai ES. The
2138 V227A polymorphism at the PPARA locus is associated with serum lipid
2139 concentrations and modulates the association between dietary polyunsaturated
2140 fatty acid intake and serum high density lipoprotein concentrations in Chinese
2141 women. *Atherosclerosis* 2006; 187:309-315
- 2142 106. Liu MH, Li J, Shen P, Husna B, Tai ES, Yong EL. A natural polymorphism in
2143 peroxisome proliferator-activated receptor-alpha hinge region attenuates
2144 transcription due to defective release of nuclear receptor corepressor from
2145 chromatin. *Mol Endocrinol* 2008; 22:1078-1092
- 2146 107. Chen S, Li Y, Li S, Yu C. A Val227Ala substitution in the peroxisome
2147 proliferator activated receptor alpha (PPAR alpha) gene associated with non-
2148 alcoholic fatty liver disease and decreased waist circumference and waist-to-
2149 hip ratio. *Journal of gastroenterology and hepatology* 2008; 23:1415-1418
- 2150 108. Palmer CN, Hsu MH, Griffin KJ, Raucy JL, Johnson EF. Peroxisome
2151 proliferator activated receptor-alpha expression in human liver. *Molecular
2152 pharmacology* 1998; 53:14-22
- 2153 109. Thomas M, Bayha C, Klein K, Muller S, Weiss TS, Schwab M, Zanger UM.
2154 The truncated splice variant of peroxisome proliferator-activated receptor

- 2155 alpha, PPARalpha-tr, autonomously regulates proliferative and pro-
 2156 inflammatory genes. BMC cancer 2015; 15:488
- 2157 **110.** Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, Wahli W.
 2158 Peroxisome proliferator-activated receptor alpha mediates the adaptive
 2159 response to fasting. J Clin Invest 1999; 103:1489-1498
- 2160 **111.** Pawlak M, Lefebvre P, Staels B. Molecular mechanism of PPARalpha action
 2161 and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic
 2162 fatty liver disease. J Hepatol 2015; 62:720-733
- 2163 **112.** Liang CP, Tall AR. Transcriptional profiling reveals global defects in energy
 2164 metabolism, lipoprotein, and bile acid synthesis and transport with reversal by
 2165 leptin treatment in ob/ob mouse liver. J Biol Chem 2001; 276:49066-49076
- 2166 **113.** Suzuki A, Okamoto S, Lee S, Saito K, Shiuchi T, Minokoshi Y. Leptin
 2167 stimulates fatty acid oxidation and peroxisome proliferator-activated receptor
 2168 alpha gene expression in mouse C2C12 myoblasts by changing the subcellular
 2169 localization of the alpha2 form of AMP-activated protein kinase. Molecular
 2170 and cellular biology 2007; 27:4317-4327
- 2171 **114.** Zhou YT, Shimabukuro M, Wang MY, Lee Y, Higa M, Milburn JL, Newgard
 2172 CB, Unger RH. Role of peroxisome proliferator-activated receptor alpha in
 2173 disease of pancreatic beta cells. Proceedings of the National Academy of
 2174 Sciences of the United States of America 1998; 95:8898-8903
- 2175 **115.** Soukas A, Cohen P, Socci ND, Friedman JM. Leptin-specific patterns of gene
 2176 expression in white adipose tissue. Genes & development 2000; 14:963-980
- 2177 **116.** You M, Considine RV, Leone TC, Kelly DP, Crabb DW. Role of adiponectin
 2178 in the protective action of dietary saturated fat against alcoholic fatty liver in
 2179 mice. Hepatology (Baltimore, Md) 2005; 42:568-577
- 2180 **117.** Carlsson L, Linden D, Jalouli M, Oscarsson J. Effects of fatty acids and
 2181 growth hormone on liver fatty acid binding protein and PPARalpha in rat
 2182 liver. Am J Physiol Endocrinol Metab 2001; 281:E772-781
- 2183 **118.** Yamada J, Sugiyama H, Watanabe T, Suga T. Suppressive effect of growth
 2184 hormone on the expression of peroxisome proliferator-activated receptor in
 2185 cultured rat hepatocytes. Research communications in molecular pathology
 2186 and pharmacology 1995; 90:173-176
- 2187 **119.** Jalouli M, Carlsson L, Ameen C, Linden D, Ljungberg A, Michalik L, Eden S,
 2188 Wahli W, Oscarsson J. Sex difference in hepatic peroxisome proliferator-
 2189 activated receptor alpha expression: influence of pituitary and gonadal
 2190 hormones. Endocrinology 2003; 144:101-109
- 2191 **120.** Zhou YC, Waxman DJ. Cross-talk between janus kinase-signal transducer and
 2192 activator of transcription (JAK-STAT) and peroxisome proliferator-activated
 2193 receptor-alpha (PPARalpha) signaling pathways. Growth hormone inhibition
 2194 of pparalpha transcriptional activity mediated by stat5b. J Biol Chem 1999;
 2195 274:2672-2681
- 2196 **121.** Ljungberg A, Linden D, Ameen C, Bergstrom G, Oscarsson J. Importance of
 2197 PPAR alpha for the effects of growth hormone on hepatic lipid and lipoprotein
 2198 metabolism. Growth hormone & IGF research : official journal of the Growth
 2199 Hormone Research Society and the International IGF Research Society 2007;
 2200 17:154-164
- 2201 **122.** Steineger HH, Sorensen HN, Tugwood JD, Skrede S, Spydevold O, Gautvik
 2202 KM. Dexamethasone and insulin demonstrate marked and opposite regulation
 2203 of the steady-state mRNA level of the peroxisomal proliferator-activated

- 2204 receptor (PPAR) in hepatic cells. Hormonal modulation of fatty-acid-induced
 2205 transcription. *European journal of biochemistry / FEBS* 1994; 225:967-974
- 2206 **123.** Juge-Aubry CE, Hammar E, Siegrist-Kaiser C, Pernin A, Takeshita A, Chin
 2207 WW, Burger AG, Meier CA. Regulation of the transcriptional activity of the
 2208 peroxisome proliferator-activated receptor alpha by phosphorylation of a
 2209 ligand-independent trans-activating domain. *J Biol Chem* 1999; 274:10505-
 2210 10510
- 2211 **124.** Yang X, Downes M, Yu RT, Bookout AL, He W, Straume M, Mangelsdorf
 2212 DJ, Evans RM. Nuclear receptor expression links the circadian clock to
 2213 metabolism. *Cell* 2006; 126:801-810
- 2214 **125.** Staels B. When the Clock stops ticking, metabolic syndrome explodes. *Nat*
 2215 *Med* 2006; 12:54-55; discussion 55
- 2216 **126.** Lemberger T, Staels B, Saladin R, Desvergne B, Auwerx J, Wahli W.
 2217 Regulation of the peroxisome proliferator-activated receptor alpha gene by
 2218 glucocorticoids. *J Biol Chem* 1994; 269:24527-24530
- 2219 **127.** Lemberger T, Saladin R, Vazquez M, Assimacopoulos F, Staels B, Desvergne
 2220 B, Wahli W, Auwerx J. Expression of the peroxisome proliferator-activated
 2221 receptor alpha gene is stimulated by stress and follows a diurnal rhythm. *J Biol*
 2222 *Chem* 1996; 271:1764-1769
- 2223 **128.** Oishi K, Shirai H, Ishida N. CLOCK is involved in the circadian
 2224 transactivation of peroxisome-proliferator-activated receptor alpha
 2225 (PPARalpha) in mice. *The Biochemical journal* 2005; 386:575-581
- 2226 **129.** Gachon F, Leuenberger N, Claudel T, Gos P, Jouffe C, Fleury Olela F, de
 2227 Mollerat du Jeu X, Wahli W, Schibler U. Proline- and acidic amino acid-rich
 2228 basic leucine zipper proteins modulate peroxisome proliferator-activated
 2229 receptor alpha (PPARalpha) activity. *Proceedings of the National Academy of*
 2230 *Sciences of the United States of America* 2011; 108:4794-4799
- 2231 **130.** Jones DC, Ding X, Daynes RA. Nuclear receptor peroxisome proliferator-
 2232 activated receptor alpha (PPARalpha) is expressed in resting murine
 2233 lymphocytes. The PPARalpha in T and B lymphocytes is both transactivation
 2234 and transrepression competent. *J Biol Chem* 2002; 277:6838-6845
- 2235 **131.** Poynter ME, Daynes RA. Peroxisome proliferator-activated receptor alpha
 2236 activation modulates cellular redox status, represses nuclear factor-kappaB
 2237 signaling, and reduces inflammatory cytokine production in aging. *J Biol*
 2238 *Chem* 1998; 273:32833-32841
- 2239 **132.** Chung KW, Lee EK, Kim DH, An HJ, Kim ND, Im DS, Lee J, Yu BP, Chung
 2240 HY. Age-related sensitivity to endotoxin-induced liver inflammation:
 2241 Implication of inflammasome/IL-1beta for steatohepatitis. *Aging cell* 2015;
 2242 14:524-533
- 2243 **133.** Hostetler HA, Huang H, Kier AB, Schroeder F. Glucose directly links to lipid
 2244 metabolism through high affinity interaction with peroxisome proliferator-
 2245 activated receptor alpha. *J Biol Chem* 2008; 283:2246-2254
- 2246 **134.** Sartippour MR, Renier G. Differential regulation of macrophage peroxisome
 2247 proliferator-activated receptor expression by glucose : role of peroxisome
 2248 proliferator-activated receptors in lipoprotein lipase gene expression.
 2249 *Arterioscler Thromb Vasc Biol* 2000; 20:104-110
- 2250 **135.** Roduit R, Morin J, Masse F, Segall L, Roche E, Newgard CB,
 2251 Assimacopoulos-Jeannet F, Prentki M. Glucose down-regulates the expression
 2252 of the peroxisome proliferator-activated receptor-alpha gene in the pancreatic
 2253 beta -cell. *J Biol Chem* 2000; 275:35799-35806

- 2254 **136.** Beier K, Volkl A, Fahimi HD. TNF-alpha downregulates the peroxisome
2255 proliferator activated receptor-alpha and the mRNAs encoding peroxisomal
2256 proteins in rat liver. *FEBS letters* 1997; 412:385-387
- 2257 **137.** Parmentier JH, Schohn H, Bronner M, Ferrari L, Batt AM, Dauca M, Kremers
2258 P. Regulation of CYP4A1 and peroxisome proliferator-activated receptor
2259 alpha expression by interleukin-1beta, interleukin-6, and dexamethasone in
2260 cultured fetal rat hepatocytes. *Biochem Pharmacol* 1997; 54:889-898
- 2261 **138.** Bechmann LP, Vetter D, Ishida J, Hannivoort RA, Lang UE, Kocabayoglu P,
2262 Fiel MI, Munoz U, Patman GL, Ge F, Yakar S, Li X, Agius L, Lee YM,
2263 Zhang W, Hui KY, Televantou D, Schwartz GJ, LeRoith D, Berk PD, Nagai
2264 R, Suzuki T, Reeves HL, Friedman SL. Post-transcriptional activation of
2265 PPAR alpha by KLF6 in hepatic steatosis. *J Hepatol* 2013; 58:1000-1006
- 2266 **139.** Pineda Torra I, Jamshidi Y, Flavell DM, Fruchart J-C, Staels B.
2267 Characterization of the Human PPAR{alpha} Promoter: Identification of a
2268 Functional Nuclear Receptor Response Element. *Mol Endocrinol* 2002;
2269 16:1013-1028
- 2270 **140.** Hayhurst GP, Lee YH, Lambert G, Ward JM, Gonzalez FJ. Hepatocyte
2271 nuclear factor 4alpha (nuclear receptor 2A1) is essential for maintenance of
2272 hepatic gene expression and lipid homeostasis. *Molecular and cellular biology*
2273 2001; 21:1393-1403
- 2274 **141.** Pineda Torra I, Claudel T, Duval C, Kosykh V, Fruchart JC, Staels B. Bile
2275 acids induce the expression of the human peroxisome proliferator-activated
2276 receptor alpha gene via activation of the farnesoid X receptor. *Mol Endocrinol*
2277 2003; 17:259-272
- 2278 **142.** Inoue J, Satoh S, Kita M, Nakahara M, Hachimura S, Miyata M, Nishimaki-
2279 Mogami T, Sato R. PPARalpha gene expression is up-regulated by LXR and
2280 PXR activators in the small intestine. *Biochem Biophys Res Commun* 2008;
2281 371:675-678
- 2282 **143.** Dunlop TW, Vaisanen S, Frank C, Molnar F, Sinkkonen L, Carlberg C. The
2283 human peroxisome proliferator-activated receptor delta gene is a primary
2284 target of 1alpha,25-dihydroxyvitamin D3 and its nuclear receptor. *J Mol Biol*
2285 2005; 349:248-260
- 2286 **144.** White JH, Fernandes I, Mader S, Yang XJ. Corepressor recruitment by
2287 agonist-bound nuclear receptors. *Vitamins and hormones* 2004; 68:123-143
- 2288 **145.** Leonardsson G, Steel JH, Christian M, Pocock V, Milligan S, Bell J, So PW,
2289 Medina-Gomez G, Vidal-Puig A, White R, Parker MG. Nuclear receptor
2290 corepressor RIP140 regulates fat accumulation. *Proceedings of the National*
2291 *Academy of Sciences of the United States of America* 2004; 101:8437-8442
- 2292 **146.** Viswakarma N, Jia Y, Bai L, Vluggens A, Borensztajn J, Xu J, Reddy JK.
2293 Coactivators in PPAR-Regulated Gene Expression. *PPAR Res* 2010; 2010
- 2294 **147.** Surapureddi S, Yu S, Bu H, Hashimoto T, Yeldandi AV, Kashireddy P,
2295 Cherkaoui-Malki M, Qi C, Zhu YJ, Rao MS, Reddy JK. Identification of a
2296 transcriptionally active peroxisome proliferator-activated receptor alpha -
2297 interacting cofactor complex in rat liver and characterization of PRIC285 as a
2298 coactivator. *Proceedings of the National Academy of Sciences of the United*
2299 *States of America* 2002; 99:11836-11841
- 2300 **148.** Matsumoto K, Yu S, Jia Y, Ahmed MR, Viswakarma N, Sarkar J, Kashireddy
2301 PV, Rao MS, Karpus W, Gonzalez FJ, Reddy JK. Critical role for
2302 transcription coactivator peroxisome proliferator-activated receptor (PPAR)-

- 2303 binding protein/TRAP220 in liver regeneration and PPARalpha ligand-
 2304 induced liver tumor development. *J Biol Chem* 2007; 282:17053-17060
- 2305 **149.** Shalev A, Siegrist-Kaiser CA, Yen PM, Wahli W, Burger AG, Chin WW,
 2306 Meier CA. The peroxisome proliferator-activated receptor alpha is a
 2307 phosphoprotein: regulation by insulin. *Endocrinology* 1996; 137:4499-4502
- 2308 **150.** Barger PM, Browning AC, Garner AN, Kelly DP. p38 mitogen-activated
 2309 protein kinase activates peroxisome proliferator-activated receptor alpha: a
 2310 potential role in the cardiac metabolic stress response. *J Biol Chem* 2001;
 2311 276:44495-44501
- 2312 **151.** Barger PM, Brandt JM, Leone TC, Weinheimer CJ, Kelly DP. Deactivation of
 2313 peroxisome proliferator-activated receptor-alpha during cardiac hypertrophic
 2314 growth. *J Clin Invest* 2000; 105:1723-1730
- 2315 **152.** Passilly P, Schohn H, Jannin B, Cherkaoui Malki M, Boscoboinik D, Dauca
 2316 M, Latruffe N. Phosphorylation of peroxisome proliferator-activated receptor
 2317 alpha in rat Fao cells and stimulation by ciprofibrate. *Biochem Pharmacol*
 2318 1999; 58:1001-1008
- 2319 **153.** Vanden Heuvel JP, Kreder D, Belda B, Hannon DB, Nugent CA, Burns KA,
 2320 Taylor MJ. Comprehensive analysis of gene expression in rat and human
 2321 hepatoma cells exposed to the peroxisome proliferator WY14,643. *Toxicology*
 2322 and applied pharmacology 2003; 188:185-198
- 2323 **154.** Paumelle R, Blanquart C, Briand O, Barbier O, Duhem C, Woerly G,
 2324 Percevault F, Fruchart JC, Dombrowicz D, Glineur C, Staels B. Acute
 2325 antiinflammatory properties of statins involve peroxisome proliferator-
 2326 activated receptor-alpha via inhibition of the protein kinase C signaling
 2327 pathway. *Circ Res* 2006; 98:361-369
- 2328 **155.** Lazennec G, Canaple L, Saugy D, Wahli W. Activation of peroxisome
 2329 proliferator-activated receptors (PPARs) by their ligands and protein kinase A
 2330 activators. *Mol Endocrinol* 2000; 14:1962-1975
- 2331 **156.** Lee WJ, Kim M, Park HS, Kim HS, Jeon MJ, Oh KS, Koh EH, Won JC, Kim
 2332 MS, Oh GT, Yoon M, Lee KU, Park JY. AMPK activation increases fatty acid
 2333 oxidation in skeletal muscle by activating PPARalpha and PGC-1. *Biochem*
 2334 *Biophys Res Commun* 2006; 340:291-295
- 2335 **157.** Yoon MJ, Lee GY, Chung JJ, Ahn YH, Hong SH, Kim JB. Adiponectin
 2336 increases fatty acid oxidation in skeletal muscle cells by sequential activation
 2337 of AMP-activated protein kinase, p38 mitogen-activated protein kinase, and
 2338 peroxisome proliferator-activated receptor alpha. *Diabetes* 2006; 55:2562-
 2339 2570
- 2340 **158.** Joly E, Roduit R, Peyot ML, Habinowski SA, Ruderman NB, Witters LA,
 2341 Prentki M. Glucose represses PPARalpha gene expression via AMP-activated
 2342 protein kinase but not via p38 mitogen-activated protein kinase in the
 2343 pancreatic beta-cell. *Journal of diabetes* 2009; 1:263-272
- 2344 **159.** Ravnskjaer K, Boergesen M, Dalgaard LT, Mandrup S. Glucose-induced
 2345 repression of PPARalpha gene expression in pancreatic beta-cells involves
 2346 PP2A activation and AMPK inactivation. *Journal of molecular endocrinology*
 2347 2006; 36:289-299
- 2348 **160.** Ratman D, Mylka V, Bougarne N, Pawlak M, Caron S, Hennuyer N, Paumelle
 2349 R, De Cauwer L, Thommis J, Rider MH, Libert C, Lievens S, Tavernier J,
 2350 Staels B, De Bosscher K. Chromatin recruitment of activated AMPK drives
 2351 fasting response genes co-controlled by GR and PPARalpha. *Nucleic acids*
 2352 *research* 2016;

- 2353 161. Blanquart C, Mansouri R, Fruchart JC, Staels B, Glineur C. Different ways to
2354 regulate the PPARalpha stability. *Biochem Biophys Res Commun* 2004;
2355 319:663-670
- 2356 162. Gopinathan L, Hannon DB, Peters JM, Vanden Heuvel JP. Regulation of
2357 peroxisome proliferator-activated receptor-alpha by MDM2. *Toxicological*
2358 *sciences : an official journal of the Society of Toxicology* 2009; 108:48-58
- 2359 163. Hinds TD, Jr., Burns KA, Hosick PA, McBeth L, Nestor-Kalinoski A,
2360 Drummond HA, AlAmodi AA, Hankins MW, Vanden Heuvel JP, Stec DE.
2361 Biliverdin Reductase A Attenuates Hepatic Steatosis by Inhibition of
2362 Glycogen Synthase Kinase (GSK) 3beta Phosphorylation of Serine 73 of
2363 Peroxisome Proliferator-activated Receptor (PPAR) alpha. *J Biol Chem* 2016;
2364 291:25179-25191
- 2365 164. Wadosky KM, Willis MS. The story so far: post-translational regulation of
2366 peroxisome proliferator-activated receptors by ubiquitination and
2367 SUMOylation. *Am J Physiol Heart Circ Physiol* 2012; 302:H515-526
- 2368 165. Devchand PR, Keller H, Peters JM, Vazquez M, Gonzalez FJ, Wahli W. The
2369 PPARalpha-leukotriene B4 pathway to inflammation control. *Nature* 1996;
2370 384:39-43
- 2371 166. Hostetler HA, Petrescu AD, Kier AB, Schroeder F. Peroxisome proliferator-
2372 activated receptor alpha interacts with high affinity and is conformationally
2373 responsive to endogenous ligands. *J Biol Chem* 2005; 280:18667-18682
- 2374 167. Schoonjans K, Staels B, Auwerx J. Role of the peroxisome proliferator-
2375 activated receptor (PPAR) in mediating the effects of fibrates and fatty acids
2376 on gene expression. *Journal of lipid research* 1996; 37:907-925
- 2377 168. Ellinghaus P, Wolfrum C, Assmann G, Spener F, Seedorf U. Phytanic acid
2378 activates the peroxisome proliferator-activated receptor alpha (PPARalpha) in
2379 sterol carrier protein 2-/- sterol carrier protein x-deficient mice. *J Biol Chem*
2380 1999; 274:2766-2772
- 2381 169. Fan CY, Pan J, Usuda N, Yeldandi AV, Rao MS, Reddy JK. Steatohepatitis,
2382 spontaneous peroxisome proliferation and liver tumors in mice lacking
2383 peroxisomal fatty acyl-CoA oxidase. Implications for peroxisome proliferator-
2384 activated receptor alpha natural ligand metabolism. *J Biol Chem* 1998;
2385 273:15639-15645
- 2386 170. Fan CY, Pan J, Chu R, Lee D, Kluckman KD, Usuda N, Singh I, Yeldandi
2387 AV, Rao MS, Maeda N, Reddy JK. Hepatocellular and hepatic peroxisomal
2388 alterations in mice with a disrupted peroxisomal fatty acyl-coenzyme A
2389 oxidase gene. *J Biol Chem* 1996; 271:24698-24710
- 2390 171. Yu K, Bayona W, Kallen CB, Harding HP, Ravera CP, McMahon G, Brown
2391 M, Lazar MA. Differential activation of peroxisome proliferator-activated
2392 receptors by eicosanoids. *J Biol Chem* 1995; 270:23975-23983
- 2393 172. Ng VY, Huang Y, Reddy LM, Falck JR, Lin ET, Kroetz DL. Cytochrome
2394 P450 eicosanoids are activators of peroxisome proliferator-activated receptor
2395 alpha. *Drug metabolism and disposition: the biological fate of chemicals* 2007;
2396 35:1126-1134
- 2397 173. Krey G, Braissant O, L'Horsset F, Kalkhoven E, Perroud M, Parker MG, Wahli
2398 W. Fatty acids, eicosanoids, and hypolipidemic agents identified as ligands of
2399 peroxisome proliferator-activated receptors by coactivator-dependent receptor
2400 ligand assay. *Mol Endocrinol* 1997; 11:779-791

- 2401 174. Lin Q, Ruuska SE, Shaw NS, Dong D, Noy N. Ligand selectivity of the
2402 peroxisome proliferator-activated receptor alpha. *Biochemistry* 1999; 38:185-
2403 190
- 2404 175. Narala VR, Adapala RK, Suresh MV, Brock TG, Peters-Golden M, Reddy
2405 RC. Leukotriene B4 is a physiologically relevant endogenous peroxisome
2406 proliferator-activated receptor-alpha agonist. *J Biol Chem* 2010; 285:22067-
2407 22074
- 2408 176. Delerive P, Furman C, Teissier E, Fruchart J, Duriez P, Staels B. Oxidized
2409 phospholipids activate PPARalpha in a phospholipase A2-dependent manner.
2410 *FEBS letters* 2000; 471:34-38
- 2411 177. Chakravarthy MV, Pan Z, Zhu Y, Tordjman K, Schneider JG, Coleman T,
2412 Turk J, Semenkovich CF. "New" hepatic fat activates PPARalpha to maintain
2413 glucose, lipid, and cholesterol homeostasis. *Cell metabolism* 2005; 1:309-322
- 2414 178. Chakravarthy MV, Zhu Y, Lopez M, Yin L, Wozniak DF, Coleman T, Hu Z,
2415 Wolfgang M, Vidal-Puig A, Lane MD, Semenkovich CF. Brain fatty acid
2416 synthase activates PPARalpha to maintain energy homeostasis. *J Clin Invest*
2417 2007; 117:2539-2552
- 2418 179. Chakravarthy MV, Lodhi IJ, Yin L, Malapaka RR, Xu HE, Turk J,
2419 Semenkovich CF. Identification of a physiologically relevant endogenous
2420 ligand for PPARalpha in liver. *Cell* 2009; 138:476-488
- 2421 180. Esposito E, Mazzon E, Paterniti I, Dal Toso R, Pressi G, Caminiti R,
2422 Cuzzocrea S. PPAR-alpha Contributes to the Anti-Inflammatory Activity of
2423 Verbascoside in a Model of Inflammatory Bowel Disease in Mice. *PPAR Res*
2424 2010; 2010:917312
- 2425 181. Radler U, Stangl H, Lechner S, Lienbacher G, Krepp R, Zeller E, Brachinger
2426 M, Eller-Berndl D, Fischer A, Anzur C, Schoerg G, Mascher D, Laschan C,
2427 Anderwald C, Lohninger A. A combination of (omega-3) polyunsaturated
2428 fatty acids, polyphenols and L-carnitine reduces the plasma lipid levels and
2429 increases the expression of genes involved in fatty acid oxidation in human
2430 peripheral blood mononuclear cells and HepG2 cells. *Annals of nutrition &
2431 metabolism* 2011; 58:133-140
- 2432 182. Inoue H, Jiang XF, Katayama T, Osada S, Umesono K, Namura S. Brain
2433 protection by resveratrol and fenofibrate against stroke requires peroxisome
2434 proliferator-activated receptor alpha in mice. *Neuroscience letters* 2003;
2435 352:203-206
- 2436 183. Tsukamoto T, Nakata R, Tamura E, Kosuge Y, Kariya A, Katsukawa M,
2437 Mishima S, Ito T, Inuma M, Akao Y, Nozawa Y, Arai Y, Namura S, Inoue H.
2438 Vaticanol C, a resveratrol tetramer, activates PPARalpha and PPARbeta/delta
2439 in vitro and in vivo. *Nutrition & metabolism* 2010; 7:46
- 2440 184. Hardie DG. AMPK: a target for drugs and natural products with effects on
2441 both diabetes and cancer. *Diabetes* 2013; 62:2164-2172
- 2442 185. Fruchart JC, Duriez P, Staels B. Peroxisome proliferator-activated receptor-
2443 alpha activators regulate genes governing lipoprotein metabolism, vascular
2444 inflammation and atherosclerosis. *Current opinion in lipidology* 1999; 10:245-
2445 257
- 2446 186. Fruchart JC, Staels B, Duriez P. The role of fibric acids in atherosclerosis.
2447 *Current atherosclerosis reports* 2001; 3:83-92
- 2448 187. Taniguchi A, Fukushima M, Sakai M, Tokuyama K, Nagata I, Fukunaga A,
2449 Kishimoto H, Doi K, Yamashita Y, Matsuura T, Kitatani N, Okumura T,
2450 Nagasaka S, Nakaishi S, Nakai Y. Effects of bezafibrate on insulin sensitivity

- 2451 and insulin secretion in non-obese Japanese type 2 diabetic patients.
 2452 Metabolism: clinical and experimental 2001; 50:477-480
- 2453 **188.** Fruchart JC. Selective peroxisome proliferator-activated receptor alpha
 2454 modulators (SPPARMalpha): the next generation of peroxisome proliferator-
 2455 activated receptor alpha-agonists. Cardiovascular diabetology 2013; 12:82
- 2456 **189.** Staels B, Rubenstrunk A, Noel B, Rigou G, Delataille P, Millatt LJ, Baron M,
 2457 Lucas A, Tailleux A, Hum DW, Ratziu V, Cariou B, Hanf R. Hepatoprotective
 2458 effects of the dual peroxisome proliferator-activated receptor alpha/delta
 2459 agonist, GFT505, in rodent models of nonalcoholic fatty liver
 2460 disease/nonalcoholic steatohepatitis. Hepatology (Baltimore, Md) 2013;
 2461 58:1941-1952
- 2462 **190.** Hennuyer N, Duplan I, Paquet C, Vanhoutte J, Woitrain E, Touche V, Colin S,
 2463 Vallez E, Lestavel S, Lefebvre P, Staels B. The novel selective PPARalpha
 2464 modulator (SPPARMalpha) pemafibrate improves dyslipidemia, enhances
 2465 reverse cholesterol transport and decreases inflammation and atherosclerosis.
 2466 Atherosclerosis 2016; 249:200-208
- 2467 **191.** Forman BM, Chen J, Evans RM. Hypolipidemic drugs, polyunsaturated fatty
 2468 acids, and eicosanoids are ligands for peroxisome proliferator-activated
 2469 receptors alpha and delta. Proceedings of the National Academy of Sciences of
 2470 the United States of America 1997; 94:4312-4317
- 2471 **192.** Giral H, Villa-Bellosta R, Catalan J, Sorribas V. Cytotoxicity of peroxisome
 2472 proliferator-activated receptor alpha and gamma agonists in renal proximal
 2473 tubular cell lines. Toxicology in vitro : an international journal published in
 2474 association with BIBRA 2007; 21:1066-1076
- 2475 **193.** Lalloyer F, Staels B. Fibrates, glitazones, and peroxisome proliferator-
 2476 activated receptors. Arterioscler Thromb Vasc Biol 2010; 30:894-899
- 2477 **194.** Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan
 2478 receptors to drug discovery. Journal of medicinal chemistry 2000; 43:527-550
- 2479 **195.** Othman A, Benghozi R, Alecu I, Wei Y, Niesor E, von Eckardstein A,
 2480 Hornemann T. Fenofibrate lowers atypical sphingolipids in plasma of
 2481 dyslipidemic patients: A novel approach for treating diabetic neuropathy?
 2482 Journal of clinical lipidology 2015; 9:568-575
- 2483 **196.** Rubenstrunk A, Hanf R, Hum DW, Fruchart JC, Staels B. Safety issues and
 2484 prospects for future generations of PPAR modulators. Biochim Biophys Acta
 2485 2007; 1771:1065-1081
- 2486 **197.** !!! INVALID CITATION !!! {Kuwabara, 2004 #796;Rubenstrunk, 2007
 2487 #795;The Bezafibrate Infarction Prevention(BIP) Study, 2000 #202;Willson,
 2488 2000 #927};
- 2489 **198.** Bloomfield Rubins H, Davenport J, Babikian V, Brass LM, Collins D, Wexler
 2490 L, Wagner S, Papademetriou V, Rutan G, Robins SJ. Reduction in stroke with
 2491 gemfibrozil in men with coronary heart disease and low HDL cholesterol: The
 2492 Veterans Affairs HDL Intervention Trial (VA-HIT). Circulation 2001;
 2493 103:2828-2833
- 2494 **199.** Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH,
 2495 Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. Gemfibrozil for the
 2496 secondary prevention of coronary heart disease in men with low levels of
 2497 high-density lipoprotein cholesterol. Veterans Affairs High-Density
 2498 Lipoprotein Cholesterol Intervention Trial Study Group. The New England
 2499 journal of medicine 1999; 341:410-418

- 2500 **200.** Brown PJ, Winegar DA, Plunket KD, Moore LB, Lewis MC, Wilson JG,
2501 Sundseth SS, Koble CS, Wu Z, Chapman JM, Lehmann JM, Kliewer SA,
2502 Willson TM. A ureido-thioisobutyric acid (GW9578) is a subtype-selective
2503 PPARalpha agonist with potent lipid-lowering activity. *Journal of medicinal*
2504 *chemistry* 1999; 42:3785-3788
- 2505 **201.** Guerre-Millo M, Gervois P, Raspe E, Madsen L, Poulain P, Derudas B,
2506 Herbert JM, Winegar DA, Willson TM, Fruchart JC, Berge RK, Staels B.
2507 Peroxisome proliferator-activated receptor alpha activators improve insulin
2508 sensitivity and reduce adiposity. *J Biol Chem* 2000; 275:16638-16642
- 2509 **202.** Brown PJ, Stuart LW, Hurley KP, Lewis MC, Winegar DA, Wilson JG,
2510 Wilkison WO, Ittoop OR, Willson TM. Identification of a subtype selective
2511 human PPARalpha agonist through parallel-array synthesis. *Bioorganic &*
2512 *medicinal chemistry letters* 2001; 11:1225-1227
- 2513 **203.** Ishibashi S, Arai H, Yokote K, Araki E, Suganami H, Yamashita S. Efficacy
2514 and safety of pemafibrate (K-877), a selective peroxisome proliferator-
2515 activated receptor alpha modulator, in patients with dyslipidemia: Results
2516 from a 24-week, randomized, double blind, active-controlled, phase 3 trial.
2517 *Journal of clinical lipidology* 2017;
- 2518 **204.** Cariou B, Hanf R, Lambert-Porcheron S, Zair Y, Sauvinet V, Noel B, Flet L,
2519 Vidal H, Staels B, Laville M. Dual peroxisome proliferator-activated receptor
2520 alpha/delta agonist GFT505 improves hepatic and peripheral insulin sensitivity
2521 in abdominally obese subjects. *Diabetes care* 2013; 36:2923-2930
- 2522 **205.** Cariou B, Zair Y, Staels B, Bruckert E. Effects of the new dual PPAR
2523 alpha/delta agonist GFT505 on lipid and glucose homeostasis in abdominally
2524 obese patients with combined dyslipidemia or impaired glucose metabolism.
2525 *Diabetes care* 2011; 34:2008-2014
- 2526 **206.** Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, Romero-
2527 Gomez M, Boursier J, Abdelmalek M, Caldwell S, Drenth J, Anstee QM, Hum
2528 D, Hanf R, Roudot A, Megnier S, Staels B, Sanyal A. Elafibranor, an Agonist
2529 of the Peroxisome Proliferator-Activated Receptor-alpha and -delta, Induces
2530 Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening.
2531 *Gastroenterology* 2016; 150:1147-1159.e1145
- 2532 **207.** de Ferranti S, Mozaffarian D. The perfect storm: obesity, adipocyte
2533 dysfunction, and metabolic consequences. *Clinical chemistry* 2008; 54:945-
2534 955
- 2535 **208.** Aoyama T, Peters JM, Iritani N, Nakajima T, Furihata K, Hashimoto T,
2536 Gonzalez FJ. Altered constitutive expression of fatty acid-metabolizing
2537 enzymes in mice lacking the peroxisome proliferator-activated receptor alpha
2538 (PPARalpha). *J Biol Chem* 1998; 273:5678-5684
- 2539 **209.** Hashimoto T, Cook WS, Qi C, Yeldandi AV, Reddy JK, Rao MS. Defect in
2540 peroxisome proliferator-activated receptor alpha-inducible fatty acid oxidation
2541 determines the severity of hepatic steatosis in response to fasting. *J Biol Chem*
2542 2000; 275:28918-28928
- 2543 **210.** Leone TC, Weinheimer CJ, Kelly DP. A critical role for the peroxisome
2544 proliferator-activated receptor alpha (PPARalpha) in the cellular fasting
2545 response: the PPARalpha-null mouse as a model of fatty acid oxidation
2546 disorders. *Proceedings of the National Academy of Sciences of the United*
2547 *States of America* 1999; 96:7473-7478
- 2548 **211.** Rakhshandehroo M, Knoch B, Muller M, Kersten S. Peroxisome proliferator-
2549 activated receptor alpha target genes. *PPAR Res* 2010; 2010

- 2550 **212.** Montagner A, Polizzi A, Fouche E, Ducheix S, Lippi Y, Lasserre F,
2551 Barquissau V, Regnier M, Lukowicz C, Benhamed F, Iroz A, Bertrand-Michel
2552 J, Al Saati T, Cano P, Mselli-Lakhal L, Mithieux G, Rajas F, Lagarrigue S,
2553 Pineau T, Loiseau N, Postic C, Langin D, Wahli W, Guillou H. Liver
2554 PPARalpha is crucial for whole-body fatty acid homeostasis and is protective
2555 against NAFLD. *Gut* 2016; 65:1202-1214
- 2556 **213.** Maus M, Cuk M, Patel B, Lian J, Ouimet M, Kaufmann U, Yang J, Horvath
2557 R, Hornig-Do HT, Chrzanowska-Lightowlers ZM, Moore KJ, Cuervo AM,
2558 Feske S. Store-Operated Ca(2+) Entry Controls Induction of Lipolysis and the
2559 Transcriptional Reprogramming to Lipid Metabolism. *Cell metabolism* 2017;
2560 25:698-712
- 2561 **214.** Rodriguez JC, Gil-Gomez G, Hegardt FG, Haro D. Peroxisome proliferator-
2562 activated receptor mediates induction of the mitochondrial 3-hydroxy-3-
2563 methylglutaryl-CoA synthase gene by fatty acids. *J Biol Chem* 1994;
2564 269:18767-18772
- 2565 **215.** Le May C, Pineau T, Bigot K, Kohl C, Girard J, Pegorier JP. Reduced hepatic
2566 fatty acid oxidation in fasting PPARalpha null mice is due to impaired
2567 mitochondrial hydroxymethylglutaryl-CoA synthase gene expression. *FEBS*
2568 *letters* 2000; 475:163-166
- 2569 **216.** Pawlak M, Bauge E, Lalloyer F, Lefebvre P, Staels B. Ketone Body Therapy
2570 Protects From Lipotoxicity and Acute Liver Failure Upon Pparalpha
2571 Deficiency. *Mol Endocrinol* 2015; 29:1134-1143
- 2572 **217.** Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E.
2573 Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key
2574 mediator of hepatic lipid metabolism in ketotic states. *Cell metabolism* 2007;
2575 5:426-437
- 2576 **218.** Kim H, Mendez R, Zheng Z, Chang L, Cai J, Zhang R, Zhang K. Liver-
2577 enriched transcription factor CREBH interacts with peroxisome proliferator-
2578 activated receptor alpha to regulate metabolic hormone FGF21. *Endocrinology*
2579 2014; 155:769-782
- 2580 **219.** Kim H, Mendez R, Chen X, Fang D, Zhang K. Lysine Acetylation of CREBH
2581 Regulates Fasting-Induced Hepatic Lipid Metabolism. *Molecular and cellular*
2582 *biology* 2015; 35:4121-4134
- 2583 **220.** Oosterveer MH, Grefhorst A, van Dijk TH, Havinga R, Staels B, Kuipers F,
2584 Groen AK, Reijngoud DJ. Fenofibrate simultaneously induces hepatic fatty
2585 acid oxidation, synthesis, and elongation in mice. *J Biol Chem* 2009;
2586 284:34036-34044
- 2587 **221.** Fernandez-Alvarez A, Alvarez MS, Gonzalez R, Cucarella C, Muntane J,
2588 Casado M. Human SREBP1c expression in liver is directly regulated by
2589 peroxisome proliferator-activated receptor alpha (PPARalpha). *J Biol Chem*
2590 2011; 286:21466-21477
- 2591 **222.** Patel DD, Knight BL, Wiggins D, Humphreys SM, Gibbons GF. Disturbances
2592 in the normal regulation of SREBP-sensitive genes in PPAR alpha-deficient
2593 mice. *Journal of lipid research* 2001; 42:328-337
- 2594 **223.** Knight BL, Hebbachi A, Hauton D, Brown AM, Wiggins D, Patel DD,
2595 Gibbons GF. A role for PPARalpha in the control of SREBP activity and lipid
2596 synthesis in the liver. *The Biochemical journal* 2005; 389:413-421
- 2597 **224.** Hebbachi AM, Knight BL, Wiggins D, Patel DD, Gibbons GF. Peroxisome
2598 proliferator-activated receptor alpha deficiency abolishes the response of

- 2599 lipogenic gene expression to re-feeding: restoration of the normal response by
2600 activation of liver X receptor alpha. *J Biol Chem* 2008; 283:4866-4876
- 2601 **225.** Lee GY, Kim NH, Zhao ZS, Cha BS, Kim YS. Peroxisomal-proliferator-
2602 activated receptor alpha activates transcription of the rat hepatic malonyl-CoA
2603 decarboxylase gene: a key regulation of malonyl-CoA level. *The Biochemical*
2604 *journal* 2004; 378:983-990
- 2605 **226.** Mancini FP, Lanni A, Sabatino L, Moreno M, Giannino A, Contaldo F,
2606 Colantuoni V, Goglia F. Fenofibrate prevents and reduces body weight gain
2607 and adiposity in diet-induced obese rats. *FEBS letters* 2001; 491:154-158
- 2608 **227.** Rachid TL, Penna-de-Carvalho A, Bringhenti I, Aguila MB, Mandarim-de-
2609 Lacerda CA, Souza-Mello V. PPAR-alpha agonist elicits metabolically active
2610 brown adipocytes and weight loss in diet-induced obese mice. *Cell*
2611 *biochemistry and function* 2015; 33:249-256
- 2612 **228.** Cheema SK, Agellon LB. The murine and human cholesterol 7alpha-
2613 hydroxylase gene promoters are differentially responsive to regulation by fatty
2614 acids mediated via peroxisome proliferator-activated receptor alpha. *J Biol*
2615 *Chem* 2000; 275:12530-12536
- 2616 **229.** Hunt MC, Yang YZ, Eggertsen G, Carneheim CM, Gafvels M, Einarsson C,
2617 Alexson SE. The peroxisome proliferator-activated receptor alpha
2618 (PPARalpha) regulates bile acid biosynthesis. *J Biol Chem* 2000; 275:28947-
2619 28953
- 2620 **230.** Hays T, Rusyn I, Burns AM, Kennett MJ, Ward JM, Gonzalez FJ, Peters JM.
2621 Role of peroxisome proliferator-activated receptor-alpha (PPARalpha) in
2622 bezafibrate-induced hepatocarcinogenesis and cholestasis. *Carcinogenesis*
2623 2005; 26:219-227
- 2624 **231.** Post SM, Duez H, Gervois PP, Staels B, Kuipers F, Princen HM. Fibrates
2625 suppress bile acid synthesis via peroxisome proliferator-activated receptor-
2626 alpha-mediated downregulation of cholesterol 7alpha-hydroxylase and sterol
2627 27-hydroxylase expression. *Arterioscler Thromb Vasc Biol* 2001; 21:1840-
2628 1845
- 2629 **232.** Rakhshandehroo M, Sanderson LM, Matilainen M, Stienstra R, Carlberg C, de
2630 Groot PJ, Muller M, Kersten S. Comprehensive analysis of PPARalpha-
2631 dependent regulation of hepatic lipid metabolism by expression profiling.
2632 *PPAR Res* 2007; 2007:26839
- 2633 **233.** Patsouris D, Mandard S, Voshol PJ, Escher P, Tan NS, Havekes LM, Koenig
2634 W, Marz W, Tafuri S, Wahli W, Muller M, Kersten S. PPARalpha governs
2635 glycerol metabolism. *J Clin Invest* 2004; 114:94-103
- 2636 **234.** Cassuto H, Aran A, Cohen H, Eisenberger CL, Reshef L. Repression and
2637 activation of transcription of phosphoenolpyruvate carboxykinase gene during
2638 liver development. *FEBS letters* 1999; 457:441-444
- 2639 **235.** Kramer JA, Blomme EA, Bunch RT, Davila JC, Jackson CJ, Jones PF, Kolaja
2640 KL, Curtiss SW. Transcription profiling distinguishes dose-dependent effects
2641 in the livers of rats treated with clofibrate. *Toxicologic pathology* 2003;
2642 31:417-431
- 2643 **236.** Wu P, Peters JM, Harris RA. Adaptive increase in pyruvate dehydrogenase
2644 kinase 4 during starvation is mediated by peroxisome proliferator-activated
2645 receptor alpha. *Biochem Biophys Res Commun* 2001; 287:391-396
- 2646 **237.** Wei D, Tao R, Zhang Y, White MF, Dong XC. Feedback regulation of hepatic
2647 gluconeogenesis through modulation of SHP/Nr0b2 gene expression by Sirt1
2648 and FoxO1. *Am J Physiol Endocrinol Metab* 2011; 300:E312-320

- 2649 **238.** Mandard S, Stienstra R, Escher P, Tan NS, Kim I, Gonzalez FJ, Wahli W,
2650 Desvergne B, Muller M, Kersten S. Glycogen synthase 2 is a novel target gene
2651 of peroxisome proliferator-activated receptors. *Cellular and molecular life*
2652 *sciences : CMLS* 2007; 64:1145-1157
- 2653 **239.** Du K, Herzig S, Kulkarni RN, Montminy M. TRB3: a tribbles homolog that
2654 inhibits Akt/PKB activation by insulin in liver. *Science (New York, NY)*
2655 2003; 300:1574-1577
- 2656 **240.** Koo SH, Satoh H, Herzig S, Lee CH, Hedrick S, Kulkarni R, Evans RM,
2657 Olefsky J, Montminy M. PGC-1 promotes insulin resistance in liver through
2658 PPAR-alpha-dependent induction of TRB-3. *Nat Med* 2004; 10:530-534
- 2659 **241.** Kersten S, Mandard S, Escher P, Gonzalez FJ, Tafuri S, Desvergne B, Wahli
2660 W. The peroxisome proliferator-activated receptor alpha regulates amino acid
2661 metabolism. *FASEB journal : official publication of the Federation of*
2662 *American Societies for Experimental Biology* 2001; 15:1971-1978
- 2663 **242.** Lehman JJ, Kelly DP. Transcriptional activation of energy metabolic switches
2664 in the developing and hypertrophied heart. *Clinical and experimental*
2665 *pharmacology & physiology* 2002; 29:339-345
- 2666 **243.** Kaimoto S, Hoshino A, Ariyoshi M, Okawa Y, Tateishi S, Ono K, Uchihashi
2667 M, Fukai K, Iwai-Kanai E, Matoba S. Activation of PPAR-alpha in the early
2668 stage of heart failure maintained myocardial function and energetics in
2669 pressure-overload heart failure. *Am J Physiol Heart Circ Physiol* 2017;
2670 312:H305-h313
- 2671 **244.** Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, Han X,
2672 Gross RW, Kozak R, Lopaschuk GD, Kelly DP. The cardiac phenotype
2673 induced by PPARalpha overexpression mimics that caused by diabetes
2674 mellitus. *J Clin Invest* 2002; 109:121-130
- 2675 **245.** Park SY, Cho YR, Finck BN, Kim HJ, Higashimori T, Hong EG, Lee MK,
2676 Danton C, Deshmukh S, Cline GW, Wu JJ, Bennett AM, Rothermel B,
2677 Kalinowski A, Russell KS, Kim YB, Kelly DP, Kim JK. Cardiac-specific
2678 overexpression of peroxisome proliferator-activated receptor-alpha causes
2679 insulin resistance in heart and liver. *Diabetes* 2005; 54:2514-2524
- 2680 **246.** Palomer X, Salvado L, Barroso E, Vazquez-Carrera M. An overview of the
2681 crosstalk between inflammatory processes and metabolic dysregulation during
2682 diabetic cardiomyopathy. *International journal of cardiology* 2013; 168:3160-
2683 3172
- 2684 **247.** Burkart EM, Sambandam N, Han X, Gross RW, Courtois M, Gierasch CM,
2685 Shoghi K, Welch MJ, Kelly DP. Nuclear receptors PPARbeta/delta and
2686 PPARalpha direct distinct metabolic regulatory programs in the mouse heart. *J*
2687 *Clin Invest* 2007; 117:3930-3939
- 2688 **248.** Heller F, Harvengt C. Effects of clofibrate, bezafibrate, fenofibrate and
2689 probucol on plasma lipolytic enzymes in normolipaemic subjects. *European*
2690 *journal of clinical pharmacology* 1983; 25:57-63
- 2691 **249.** Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, Heyman RA, Briggs M,
2692 Deeb S, Staels B, Auwerx J. PPARalpha and PPARgamma activators direct a
2693 distinct tissue-specific transcriptional response via a PPRE in the lipoprotein
2694 lipase gene. *The EMBO journal* 1996; 15:5336-5348
- 2695 **250.** Staels B, Vu-Dac N, Kosykh VA, Saladin R, Fruchart JC, Dallongeville J,
2696 Auwerx J. Fibrates downregulate apolipoprotein C-III expression independent
2697 of induction of peroxisomal acyl coenzyme A oxidase. A potential mechanism
2698 for the hypolipidemic action of fibrates. *J Clin Invest* 1995; 95:705-712

- 2699 **251.** Hertz R, Bishara-Shieban J, Bar-Tana J. Mode of action of peroxisome
2700 proliferators as hypolipidemic drugs. Suppression of apolipoprotein C-III. *J*
2701 *Biol Chem* 1995; 270:13470-13475
- 2702 **252.** Qu S, Su D, Altomonte J, Kamagate A, He J, Perdomo G, Tse T, Jiang Y,
2703 Dong HH. PPAR $\{\alpha\}$ mediates the hypolipidemic action of fibrates by
2704 antagonizing FoxO1. *Am J Physiol Endocrinol Metab* 2007; 292:E421-434
- 2705 **253.** Raspe E, Duez H, Mansen A, Fontaine C, Fievet C, Fruchart JC, Vennstrom
2706 B, Staels B. Identification of Rev-erb α as a physiological repressor of
2707 apoC-III gene transcription. *Journal of lipid research* 2002; 43:2172-2179
- 2708 **254.** Schultze AE, Alborn WE, Newton RK, Konrad RJ. Administration of a
2709 PPAR α agonist increases serum apolipoprotein A-V levels and the
2710 apolipoprotein A-V/apolipoprotein C-III ratio. *Journal of lipid research* 2005;
2711 46:1591-1595
- 2712 **255.** Vu-Dac N, Gervois P, Jakel H, Nowak M, Bauge E, Dehondt H, Staels B,
2713 Pennacchio LA, Rubin EM, Fruchart-Najib J, Fruchart JC. Apolipoprotein A5,
2714 a crucial determinant of plasma triglyceride levels, is highly responsive to
2715 peroxisome proliferator-activated receptor α activators. *J Biol Chem* 2003;
2716 278:17982-17985
- 2717 **256.** Mandard S, Zandbergen F, Tan NS, Escher P, Patsouris D, Koenig W,
2718 Kleemann R, Bakker A, Veenman F, Wahli W, Muller M, Kersten S. The
2719 direct peroxisome proliferator-activated receptor target fasting-induced
2720 adipose factor (FIAF/PGAR/ANGPTL4) is present in blood plasma as a
2721 truncated protein that is increased by fenofibrate treatment. *J Biol Chem* 2004;
2722 279:34411-34420
- 2723 **257.** Sukonina V, Lookene A, Olivecrona T, Olivecrona G. Angiopoietin-like
2724 protein 4 converts lipoprotein lipase to inactive monomers and modulates
2725 lipase activity in adipose tissue. *Proceedings of the National Academy of*
2726 *Sciences of the United States of America* 2006; 103:17450-17455
- 2727 **258.** Vu-Dac N, Schoonjans K, Kosykh V, Dallongeville J, Fruchart JC, Staels B,
2728 Auwerx J. Fibrates increase human apolipoprotein A-II expression through
2729 activation of the peroxisome proliferator-activated receptor. *J Clin Invest*
2730 1995; 96:741-750
- 2731 **259.** Vu-Dac N, Schoonjans K, Laine B, Fruchart JC, Auwerx J, Staels B. Negative
2732 regulation of the human apolipoprotein A-I promoter by fibrates can be
2733 attenuated by the interaction of the peroxisome proliferator-activated receptor
2734 with its response element. *J Biol Chem* 1994; 269:31012-31018
- 2735 **260.** Vu-Dac N, Chopin-Delannoy S, Gervois P, Bonnelye E, Martin G, Fruchart
2736 JC, Laudet V, Staels B. The nuclear receptors peroxisome proliferator-
2737 activated receptor α and Rev-erb α mediate the species-specific
2738 regulation of apolipoprotein A-I expression by fibrates. *J Biol Chem* 1998;
2739 273:25713-25720
- 2740 **261.** Kim YS, Lee HM, Kim JK, Yang CS, Kim TS, Jung M, Jin HS, Kim S, Jang
2741 J, Oh GT, Kim JM, Jo EK. PPAR- α Activation Mediates Innate Host
2742 Defense through Induction of TFEB and Lipid Catabolism. *J Immunol* 2017;
2743 198:3283-3295
- 2744 **262.** Chinetti G, Lestavel S, Bocher V, Remaley AT, Neve B, Torra IP, Teissier E,
2745 Minnich A, Jaye M, Duverger N, Brewer HB, Fruchart JC, Clavey V, Staels
2746 B. PPAR- α and PPAR- γ activators induce cholesterol removal from
2747 human macrophage foam cells through stimulation of the ABCA1 pathway.
2748 *Nat Med* 2001; 7:53-58

- 2749 **263.** Chinetti G, Zawadski C, Fruchart JC, Staels B. Expression of adiponectin
2750 receptors in human macrophages and regulation by agonists of the nuclear
2751 receptors PPARalpha, PPARgamma, and LXR. *Biochem Biophys Res*
2752 *Commun* 2004; 314:151-158
- 2753 **264.** Brocker CN, Yue J, Kim D, Qu A, Bonzo JA, Gonzalez FJ. Hepatocyte-
2754 specific PPARA expression exclusively promotes agonist-induced cell
2755 proliferation without influence from nonparenchymal cells. *American journal*
2756 *of physiology Gastrointestinal and liver physiology* 2017; 312:G283-g299
- 2757 **265.** Peters JM, Cheung C, Gonzalez FJ. Peroxisome proliferator-activated
2758 receptor-alpha and liver cancer: where do we stand? *Journal of molecular*
2759 *medicine (Berlin, Germany)* 2005; 83:774-785
- 2760 **266.** Cheung C, Akiyama TE, Ward JM, Nicol CJ, Feigenbaum L, Vinson C,
2761 Gonzalez FJ. Diminished hepatocellular proliferation in mice humanized for
2762 the nuclear receptor peroxisome proliferator-activated receptor alpha. *Cancer*
2763 *Res* 2004; 64:3849-3854
- 2764 **267.** Shah YM, Morimura K, Yang Q, Tanabe T, Takagi M, Gonzalez FJ.
2765 Peroxisome proliferator-activated receptor alpha regulates a microRNA-
2766 mediated signaling cascade responsible for hepatocellular proliferation.
2767 *Molecular and cellular biology* 2007; 27:4238-4247
- 2768 **268.** Frohnert BI, Hui TY, Bernlohr DA. Identification of a functional peroxisome
2769 proliferator-responsive element in the murine fatty acid transport protein gene.
2770 *J Biol Chem* 1999; 274:3970-3977
- 2771 **269.** Martin G, Schoonjans K, Lefebvre AM, Staels B, Auwerx J. Coordinate
2772 regulation of the expression of the fatty acid transport protein and acyl-CoA
2773 synthetase genes by PPARalpha and PPARgamma activators. *J Biol Chem*
2774 1997; 272:28210-28217
- 2775 **270.** Motojima K, Passilly P, Peters JM, Gonzalez FJ, Latruffe N. Expression of
2776 putative fatty acid transporter genes are regulated by peroxisome proliferator-
2777 activated receptor alpha and gamma activators in a tissue- and inducer-specific
2778 manner. *J Biol Chem* 1998; 273:16710-16714
- 2779 **271.** Sato O, Kuriki C, Fukui Y, Motojima K. Dual promoter structure of mouse
2780 and human fatty acid translocase/CD36 genes and unique transcriptional
2781 activation by peroxisome proliferator-activated receptor alpha and gamma
2782 ligands. *J Biol Chem* 2002; 277:15703-15711
- 2783 **272.** Ramakrishnan SK, Khuder SS, Al-Share QY, Russo L, Abdallah SL, Patel PR,
2784 Heinrich G, Muturi HT, Mopidevi BR, Oyarce AM, Shah YM, Sanchez ER,
2785 Najjar SM. PPARalpha (Peroxisome Proliferator-activated Receptor alpha)
2786 Activation Reduces Hepatic CEACAM1 Protein Expression to Regulate Fatty
2787 Acid Oxidation during Fasting-refeeding Transition. *J Biol Chem* 2016;
2788 291:8121-8129
- 2789 **273.** Schoonjans K, Watanabe M, Suzuki H, Mahfoudi A, Krey G, Wahli W,
2790 Grimaldi P, Staels B, Yamamoto T, Auwerx J. Induction of the acyl-coenzyme
2791 A synthetase gene by fibrates and fatty acids is mediated by a peroxisome
2792 proliferator response element in the C promoter. *J Biol Chem* 1995;
2793 270:19269-19276
- 2794 **274.** Beigneux AP, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. The acute
2795 phase response is associated with retinoid X receptor repression in rodent
2796 liver. *J Biol Chem* 2000; 275:16390-16399
- 2797 **275.** Poirier H, Niot I, Monnot MC, Braissant O, Meunier-Durmort C, Costet P,
2798 Pineau T, Wahli W, Willson TM, Besnard P. Differential involvement of

- 2799 peroxisome-proliferator-activated receptors alpha and delta in fibrate and
 2800 fatty-acid-mediated inductions of the gene encoding liver fatty-acid-binding
 2801 protein in the liver and the small intestine. *The Biochemical journal* 2001;
 2802 355:481-488
- 2803 **276.** Lee SS, Pineau T, Drago J, Lee EJ, Owens JW, Kroetz DL, Fernandez-
 2804 Salguero PM, Westphal H, Gonzalez FJ. Targeted disruption of the alpha
 2805 isoform of the peroxisome proliferator-activated receptor gene in mice results
 2806 in abolishment of the pleiotropic effects of peroxisome proliferators.
 2807 *Molecular and cellular biology* 1995; 15:3012-3022
- 2808 **277.** Hughes ML, Liu B, Halls ML, Wagstaff KM, Patil R, Velkov T, Jans DA,
 2809 Bunnett NW, Scanlon MJ, Porter CJ. Fatty Acid-binding Proteins 1 and 2
 2810 Differentially Modulate the Activation of Peroxisome Proliferator-activated
 2811 Receptor alpha in a Ligand-selective Manner. *J Biol Chem* 2015; 290:13895-
 2812 13906
- 2813 **278.** Sandberg MB, Bloksgaard M, Duran-Sandoval D, Duval C, Staels B,
 2814 Mandrup S. The gene encoding acyl-CoA-binding protein is subject to
 2815 metabolic regulation by both sterol regulatory element-binding protein and
 2816 peroxisome proliferator-activated receptor alpha in hepatocytes. *J Biol Chem*
 2817 2005; 280:5258-5266
- 2818 **279.** Helledie T, Grontved L, Jensen SS, Kiilerich P, Rietveld L, Albrektsen T,
 2819 Boysen MS, Nohr J, Larsen LK, Fleckner J, Stunnenberg HG, Kristiansen K,
 2820 Mandrup S. The gene encoding the Acyl-CoA-binding protein is activated by
 2821 peroxisome proliferator-activated receptor gamma through an intronic
 2822 response element functionally conserved between humans and rodents. *J Biol*
 2823 *Chem* 2002; 277:26821-26830
- 2824 **280.** Louet JF, Chatelain F, Decaux JF, Park EA, Kohl C, Pineau T, Girard J,
 2825 Pegorier JP. Long-chain fatty acids regulate liver carnitine
 2826 palmitoyltransferase I gene (L-CPT I) expression through a peroxisome-
 2827 proliferator-activated receptor alpha (PPARalpha)-independent pathway. *The*
 2828 *Biochemical journal* 2001; 354:189-197
- 2829 **281.** Barrero MJ, Camarero N, Marrero PF, Haro D. Control of human carnitine
 2830 palmitoyltransferase II gene transcription by peroxisome proliferator-activated
 2831 receptor through a partially conserved peroxisome proliferator-responsive
 2832 element. *The Biochemical journal* 2003; 369:721-729
- 2833 **282.** Fischer M, You M, Matsumoto M, Crabb DW. Peroxisome proliferator-
 2834 activated receptor alpha (PPARalpha) agonist treatment reverses PPARalpha
 2835 dysfunction and abnormalities in hepatic lipid metabolism in ethanol-fed mice.
 2836 *J Biol Chem* 2003; 278:27997-28004
- 2837 **283.** Gulick T, Cresci S, Caira T, Moore DD, Kelly DP. The peroxisome
 2838 proliferator-activated receptor regulates mitochondrial fatty acid oxidative
 2839 enzyme gene expression. *Proceedings of the National Academy of Sciences of*
 2840 *the United States of America* 1994; 91:11012-11016
- 2841 **284.** Zhao Q, Yang R, Wang J, Hu DD, Li F. PPARalpha activation protects against
 2842 cholestatic liver injury. *Scientific reports* 2017; 7:9967
- 2843 **285.** Hashimoto T, Fujita T, Usuda N, Cook W, Qi C, Peters JM, Gonzalez FJ,
 2844 Yeldandi AV, Rao MS, Reddy JK. Peroxisomal and mitochondrial fatty acid
 2845 beta-oxidation in mice nullizygous for both peroxisome proliferator-activated
 2846 receptor alpha and peroxisomal fatty acyl-CoA oxidase. Genotype correlation
 2847 with fatty liver phenotype. *J Biol Chem* 1999; 274:19228-19236

- 2848 **286.** Djouadi F, Aubey F, Schlemmer D, Ruitter JP, Wanders RJ, Strauss AW,
2849 Bastin J. Bezafibrate increases very-long-chain acyl-CoA dehydrogenase
2850 protein and mRNA expression in deficient fibroblasts and is a potential
2851 therapy for fatty acid oxidation disorders. *Human molecular genetics* 2005;
2852 14:2695-2703
- 2853 **287.** Yang Y, Feng Y, Zhang X, Nakajima T, Tanaka N, Sugiyama E, Kamijo Y,
2854 Aoyama T. Activation of PPARalpha by Fatty Acid Accumulation Enhances
2855 Fatty Acid Degradation and Sulfatide Synthesis. *The Tohoku journal of*
2856 *experimental medicine* 2016; 240:113-122
- 2857 **288.** Mandard S, Muller M, Kersten S. Peroxisome proliferator-activated receptor
2858 alpha target genes. *Cellular and molecular life sciences : CMLS* 2004; 61:393-
2859 416
- 2860 **289.** Yamazaki K, Kuromitsu J, Tanaka I. Microarray analysis of gene expression
2861 changes in mouse liver induced by peroxisome proliferator- activated receptor
2862 alpha agonists. *Biochem Biophys Res Commun* 2002; 290:1114-1122
- 2863 **290.** Mukherjee R, Strasser J, Jow L, Hoener P, Paterniti JR, Jr., Heyman RA. RXR
2864 agonists activate PPARalpha-inducible genes, lower triglycerides, and raise
2865 HDL levels in vivo. *Arterioscler Thromb Vasc Biol* 1998; 18:272-276
- 2866 **291.** Zhang B, Marcus SL, Sajjadi FG, Alvares K, Reddy JK, Subramani S,
2867 Rachubinski RA, Capone JP. Identification of a peroxisome proliferator-
2868 responsive element upstream of the gene encoding rat peroxisomal enoyl-CoA
2869 hydratase/3-hydroxyacyl-CoA dehydrogenase. *Proceedings of the National*
2870 *Academy of Sciences of the United States of America* 1992; 89:7541-7545
- 2871 **292.** Nicolas-Frances V, Dasari VK, Abruzzi E, Osumi T, Latruffe N. The
2872 peroxisome proliferator response element (PPRE) present at positions -681/-
2873 669 in the rat liver 3-ketoacyl-CoA thiolase B gene functionally interacts
2874 differently with PPARalpha and HNF-4. *Biochem Biophys Res Commun*
2875 2000; 269:347-351
- 2876 **293.** Lawrence JW, Li Y, Chen S, DeLuca JG, Berger JP, Umbenhauer DR, Moller
2877 DE, Zhou G. Differential gene regulation in human versus rodent hepatocytes
2878 by peroxisome proliferator-activated receptor (PPAR) alpha. PPAR alpha fails
2879 to induce peroxisome proliferation-associated genes in human cells
2880 independently of the level of receptor expression. *J Biol Chem* 2001;
2881 276:31521-31527
- 2882 **294.** Rakhshandehroo M, Hooiveld G, Muller M, Kersten S. Comparative analysis
2883 of gene regulation by the transcription factor PPARalpha between mouse and
2884 human. *PLoS One* 2009; 4:e6796
- 2885 **295.** Shimizu M, Takeshita A, Tsukamoto T, Gonzalez FJ, Osumi T. Tissue-
2886 selective, bidirectional regulation of PEX11 alpha and perilipin genes through
2887 a common peroxisome proliferator response element. *Molecular and cellular*
2888 *biology* 2004; 24:1313-1323
- 2889 **296.** Li X, Baumgart E, Dong GX, Morrell JC, Jimenez-Sanchez G, Valle D, Smith
2890 KD, Gould SJ. PEX11alpha is required for peroxisome proliferation in
2891 response to 4-phenylbutyrate but is dispensable for peroxisome proliferator-
2892 activated receptor alpha-mediated peroxisome proliferation. *Molecular and*
2893 *cellular biology* 2002; 22:8226-8240
- 2894 **297.** Johnson EF, Hsu MH, Savas U, Griffin KJ. Regulation of P450 4A expression
2895 by peroxisome proliferator activated receptors. *Toxicology* 2002; 181-
2896 182:203-206

- 2897 **298.** Kawashima H, Naganuma T, Kusunose E, Kono T, Yasumoto R, Sugimura K,
2898 Kishimoto T. Human fatty acid omega-hydroxylase, CYP4A11: determination
2899 of complete genomic sequence and characterization of purified recombinant
2900 protein. *Archives of biochemistry and biophysics* 2000; 378:333-339
- 2901 **299.** Savas U, Machemer DE, Hsu MH, Gaynor P, Lasker JM, Tukey RH, Johnson
2902 EF. Opposing roles of peroxisome proliferator-activated receptor alpha and
2903 growth hormone in the regulation of CYP4A11 expression in a transgenic
2904 mouse model. *J Biol Chem* 2009; 284:16541-16552
- 2905 **300.** Lundasen T, Hunt MC, Nilsson LM, Sanyal S, Angelin B, Alexson SE,
2906 Rudling M. PPARalpha is a key regulator of hepatic FGF21. *Biochem*
2907 *Biophys Res Commun* 2007; 360:437-440
- 2908 **301.** Inagaki T, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, Li Y,
2909 Goetz R, Mohammadi M, Esser V, Elmquist JK, Gerard RD, Burgess SC,
2910 Hammer RE, Mangelsdorf DJ, Kliewer SA. Endocrine regulation of the
2911 fasting response by PPARalpha-mediated induction of fibroblast growth factor
2912 21. *Cell metabolism* 2007; 5:415-425
- 2913 **302.** Miller CW, Ntambi JM. Peroxisome proliferators induce mouse liver stearyl-
2914 CoA desaturase 1 gene expression. *Proceedings of the National Academy of*
2915 *Sciences of the United States of America* 1996; 93:9443-9448
- 2916 **303.** Guillou H, Martin P, Jan S, D'Andrea S, Roulet A, Catheline D, Rioux V,
2917 Pineau T, Legrand P. Comparative effect of fenofibrate on hepatic desaturases
2918 in wild-type and peroxisome proliferator-activated receptor alpha-deficient
2919 mice. *Lipids* 2002; 37:981-989
- 2920 **304.** Tabor DE, Kim JB, Spiegelman BM, Edwards PA. Identification of conserved
2921 cis-elements and transcription factors required for sterol-regulated
2922 transcription of stearyl-CoA desaturase 1 and 2. *J Biol Chem* 1999;
2923 274:20603-20610
- 2924 **305.** Tang C, Cho HP, Nakamura MT, Clarke SD. Regulation of human delta-6
2925 desaturase gene transcription: identification of a functional direct repeat-1
2926 element. *Journal of lipid research* 2003; 44:686-695
- 2927 **306.** Matsuzaka T, Shimano H, Yahagi N, Amemiya-Kudo M, Yoshikawa T, Hasty
2928 AH, Tamura Y, Osuga J, Okazaki H, Iizuka Y, Takahashi A, Sone H, Gotoda
2929 T, Ishibashi S, Yamada N. Dual regulation of mouse Delta(5)- and Delta(6)-
2930 desaturase gene expression by SREBP-1 and PPARalpha. *Journal of lipid*
2931 *research* 2002; 43:107-114
- 2932 **307.** Castelein H, Gulick T, Declercq PE, Mannaerts GP, Moore DD, Baes MI. The
2933 peroxisome proliferator activated receptor regulates malic enzyme gene
2934 expression. *J Biol Chem* 1994; 269:26754-26758
- 2935 **308.** Sanderson LM, Degenhardt T, Koppen A, Kalkhoven E, Desvergne B, Muller
2936 M, Kersten S. Peroxisome proliferator-activated receptor beta/delta
2937 (PPARbeta/delta) but not PPARalpha serves as a plasma free fatty acid sensor
2938 in liver. *Molecular and cellular biology* 2009; 29:6257-6267
- 2939 **309.** Tobin KA, Steineger HH, Alberti S, Spydevold O, Auwerx J, Gustafsson JA,
2940 Nebb HI. Cross-talk between fatty acid and cholesterol metabolism mediated
2941 by liver X receptor-alpha. *Mol Endocrinol* 2000; 14:741-752
- 2942 **310.** Kok T, Wolters H, Bloks VW, Havinga R, Jansen PL, Staels B, Kuipers F.
2943 Induction of hepatic ABC transporter expression is part of the PPARalpha-
2944 mediated fasting response in the mouse. *Gastroenterology* 2003; 124:160-171
- 2945 **311.** Patel DD, Knight BL, Soutar AK, Gibbons GF, Wade DP. The effect of
2946 peroxisome-proliferator-activated receptor-alpha on the activity of the

- 2947 cholesterol 7 alpha-hydroxylase gene. *The Biochemical journal* 2000; 351 Pt
 2948 3:747-753
- 2949 **312.** Marrapodi M, Chiang JY. Peroxisome proliferator-activated receptor alpha
 2950 (PPARalpha) and agonist inhibit cholesterol 7alpha-hydroxylase gene
 2951 (CYP7A1) transcription. *Journal of lipid research* 2000; 41:514-520
- 2952 **313.** Tontonoz P, Hu E, Devine J, Beale EG, Spiegelman BM. PPAR gamma 2
 2953 regulates adipose expression of the phosphoenolpyruvate carboxykinase gene.
 2954 *Molecular and cellular biology* 1995; 15:351-357
- 2955 **314.** Sugden MC, Bulmer K, Gibbons GF, Knight BL, Holness MJ. Peroxisome-
 2956 proliferator-activated receptor-alpha (PPARalpha) deficiency leads to
 2957 dysregulation of hepatic lipid and carbohydrate metabolism by fatty acids and
 2958 insulin. *The Biochemical journal* 2002; 364:361-368
- 2959 **315.** Motojima K, Seto K. Fibrates and statins rapidly and synergistically induce
 2960 pyruvate dehydrogenase kinase 4 mRNA in the liver and muscles of mice.
 2961 *Biological & pharmaceutical bulletin* 2003; 26:954-958
- 2962 **316.** Kersten S, Mandard S, Tan NS, Escher P, Metzger D, Chambon P, Gonzalez
 2963 FJ, Desvergne B, Wahli W. Characterization of the fasting-induced adipose
 2964 factor FIAF, a novel peroxisome proliferator-activated receptor target gene. *J*
 2965 *Biol Chem* 2000; 275:28488-28493
- 2966 **317.** Berthou L, Duverger N, Emmanuel F, Langouet S, Auwerx J, Guillouzo A,
 2967 Fruchart JC, Rubin E, Deneffe P, Staels B, Branellec D. Opposite regulation of
 2968 human versus mouse apolipoprotein A-I by fibrates in human apolipoprotein
 2969 A-I transgenic mice. *J Clin Invest* 1996; 97:2408-2416
- 2970 **318.** Desager JP, Horsmans Y, Vandenplas C, Harvengt C. Pharmacodynamic
 2971 activity of lipoprotein lipase and hepatic lipase, and pharmacokinetic
 2972 parameters measured in normolipidaemic subjects receiving ciprofibrate (100
 2973 or 200 mg/day) or micronised fenofibrate (200 mg/day) therapy for 23 days.
 2974 *Atherosclerosis* 1996; 124 Suppl:S65-73
- 2975 **319.** Peters JM, Hennuyer N, Staels B, Fruchart JC, Fievet C, Gonzalez FJ, Auwerx
 2976 J. Alterations in lipoprotein metabolism in peroxisome proliferator-activated
 2977 receptor alpha-deficient mice. *J Biol Chem* 1997; 272:27307-27312
- 2978 **320.** Staels B, van Tol A, Andreu T, Auwerx J. Fibrates influence the expression of
 2979 genes involved in lipoprotein metabolism in a tissue-selective manner in the
 2980 rat. *Arteriosclerosis and thrombosis : a journal of vascular biology* 1992;
 2981 12:286-294
- 2982 **321.** Haubenwallner S, Essenburg AD, Barnett BC, Pape ME, DeMattos RB,
 2983 Krause BR, Minton LL, Auerbach BJ, Newton RS, Leff T, et al.
 2984 Hypolipidemic activity of select fibrates correlates to changes in hepatic
 2985 apolipoprotein C-III expression: a potential physiologic basis for their mode of
 2986 action. *Journal of lipid research* 1995; 36:2541-2551
- 2987 **322.** Brandt JM, Djouadi F, Kelly DP. Fatty acids activate transcription of the
 2988 muscle carnitine palmitoyltransferase I gene in cardiac myocytes via the
 2989 peroxisome proliferator-activated receptor alpha. *J Biol Chem* 1998;
 2990 273:23786-23792
- 2991 **323.** Young ME, Patil S, Ying J, Depre C, Ahuja HS, Shipley GL, Stepkowski SM,
 2992 Davies PJ, Taegtmeyer H. Uncoupling protein 3 transcription is regulated by
 2993 peroxisome proliferator-activated receptor (alpha) in the adult rodent heart.
 2994 *FASEB journal : official publication of the Federation of American Societies*
 2995 *for Experimental Biology* 2001; 15:833-845

- 2996 **324.** Watanabe K, Fujii H, Takahashi T, Kodama M, Aizawa Y, Ohta Y, Ono T,
2997 Hasegawa G, Naito M, Nakajima T, Kamijo Y, Gonzalez FJ, Aoyama T.
2998 Constitutive regulation of cardiac fatty acid metabolism through peroxisome
2999 proliferator-activated receptor alpha associated with age-dependent cardiac
3000 toxicity. *J Biol Chem* 2000; 275:22293-22299
- 3001 **325.** Mascaro C, Acosta E, Ortiz JA, Marrero PF, Hegardt FG, Haro D. Control of
3002 human muscle-type carnitine palmitoyltransferase I gene transcription by
3003 peroxisome proliferator-activated receptor. *J Biol Chem* 1998; 273:8560-8563
- 3004 **326.** Holness MJ, Bulmer K, Gibbons GF, Sugden MC. Up-regulation of pyruvate
3005 dehydrogenase kinase isoform 4 (PDK4) protein expression in oxidative
3006 skeletal muscle does not require the obligatory participation of peroxisome-
3007 proliferator-activated receptor alpha (PPARalpha). *The Biochemical journal*
3008 2002; 366:839-846
- 3009 **327.** Peters JM, Aoyama T, Burns AM, Gonzalez FJ. Bezafibrate is a dual ligand
3010 for PPARalpha and PPARbeta: studies using null mice. *Biochim Biophys Acta*
3011 2003; 1632:80-89
- 3012 **328.** Colin S, Bourguignon E, Boullay AB, Tousaint JJ, Huet S, Caira F, Staels B,
3013 Lestavel S, Lobaccaro JM, Delerive P. Intestine-specific regulation of
3014 PPARalpha gene transcription by liver X receptors. *Endocrinology* 2008;
3015 149:5128-5135
- 3016 **329.** Tokuno A, Hirano T, Hayashi T, Mori Y, Yamamoto T, Nagashima M,
3017 Shiraishi Y, Ito Y, Adachi M. The effects of statin and fibrate on lowering
3018 small dense LDL- cholesterol in hyperlipidemic patients with type 2 diabetes.
3019 *Journal of atherosclerosis and thrombosis* 2007; 14:128-132
- 3020 **330.** Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai
3021 A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman
3022 P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term
3023 fenofibrate therapy on cardiovascular events in 9795 people with type 2
3024 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*
3025 (London, England) 2005; 366:1849-1861
- 3026 **331.** Marti-Carvajal AJ, Sola I, Lathyris D, Dayer M. Homocysteine-lowering
3027 interventions for preventing cardiovascular events. *The Cochrane database of*
3028 *systematic reviews* 2017; 8:Cd006612
- 3029 **332.** Wrone EM, Hornberger JM, Zehnder JL, McCann LM, Coplon NS, Fortmann
3030 SP. Randomized trial of folic acid for prevention of cardiovascular events in
3031 end-stage renal disease. *Journal of the American Society of Nephrology :*
3032 *JASN* 2004; 15:420-426
- 3033 **333.** Bonds DE, Craven TE, Buse J, Crouse JR, Cuddihy R, Elam M, Ginsberg HN,
3034 Kirchner K, Marcovina S, Mychaleckyj JC, O'Connor PJ, Sperl-Hillen JA.
3035 Fenofibrate-associated changes in renal function and relationship to clinical
3036 outcomes among individuals with type 2 diabetes: the Action to Control
3037 Cardiovascular Risk in Diabetes (ACCORD) experience. *Diabetologia* 2012;
3038 55:1641-1650
- 3039 **334.** Cziraky MJ, Willey VJ, McKenney JM, Kamat SA, Fisher MD, Guyton JR,
3040 Jacobson TA, Davidson MH. Risk of hospitalized rhabdomyolysis associated
3041 with lipid-lowering drugs in a real-world clinical setting. *Journal of clinical*
3042 *lipidology* 2013; 7:102-108
- 3043 **335.** Gottlicher M, Widmark E, Li Q, Gustafsson JA. Fatty acids activate a chimera
3044 of the clofibric acid-activated receptor and the glucocorticoid receptor.

- 3045 Proceedings of the National Academy of Sciences of the United States of
3046 America 1992; 89:4653-4657
- 3047 **336.** Vessby B, Lithell H, Ledermann H. Elevated lipoprotein lipase activity in
3048 skeletal muscle tissue during treatment of hypertriglyceridaemic patients with
3049 bezafibrate. *Atherosclerosis* 1982; 44:113-118
- 3050 **337.** Vega GL, Cater NB, Hadizadeh DR, 3rd, Meguro S, Grundy SM. Free fatty
3051 acid metabolism during fenofibrate treatment of the metabolic syndrome.
3052 *Clinical pharmacology and therapeutics* 2003; 74:236-244
- 3053 **338.** Goldberg AP, Applebaum-Bowden DM, Bierman EL, Hazzard WR, Haas LB,
3054 Sherrard DJ, Brunzell JD, Huttunen JK, Ehnholm C, Nikkila EA. Increase in
3055 lipoprotein lipase during clofibrate treatment of hypertriglyceridemia in
3056 patients on hemodialysis. *The New England journal of medicine* 1979;
3057 301:1073-1076
- 3058 **339.** Lithell H, Boberg J, Hellsing K, Lundqvist G, Vessby B. Increase of the
3059 lipoprotein-lipase activity in human skeletal muscle during clofibrate
3060 administration. *European journal of clinical investigation* 1978; 8:67-74
- 3061 **340.** Anderlova K, Dolezalova R, Housova J, Bosanska L, Haluzikova D, Kremen
3062 J, Skrha J, Haluzik M. Influence of PPAR-alpha agonist fenofibrate on insulin
3063 sensitivity and selected adipose tissue-derived hormones in obese women with
3064 type 2 diabetes. *Physiological research* 2007; 56:579-586
- 3065 **341.** Wu H, Wei L, Bao Y, Lu J, Huang P, Liu Y, Jia W, Xiang K. Fenofibrate
3066 reduces serum retinol-binding protein-4 by suppressing its expression in
3067 adipose tissue. *Am J Physiol Endocrinol Metab* 2009; 296:E628-634
- 3068 **342.** Simsolo RB, Ong JM, Kern PA. Effect of gemfibrozil on adipose tissue and
3069 muscle lipoprotein lipase. *Metabolism: clinical and experimental* 1993;
3070 42:1486-1491
- 3071 **343.** Taylor KG, Holdsworth G, Galton DJ. Clofibrate increases lipoprotein-lipase
3072 activity in adipose tissue of hypertriglyceridaemic patients. *Lancet (London,*
3073 *England)* 1977; 2:1106-1107
- 3074 **344.** Dumont M, Mauriege P, Bergeron J, Despres JP, Prud'homme D. Effect of a
3075 six month gemfibrozil treatment and dietary recommendations on the
3076 metabolic risk profile of visceral obese men. *Int J Obes Relat Metab Disord*
3077 2001; 25:1136-1143
- 3078 **345.** Fernandez-Miranda C, Perez-Carreras M, Colina F, Lopez-Alonso G, Vargas
3079 C, Solis-Herruzo JA. A pilot trial of fenofibrate for the treatment of non-
3080 alcoholic fatty liver disease. *Digestive and liver disease : official journal of the*
3081 *Italian Society of Gastroenterology and the Italian Association for the Study of*
3082 *the Liver* 2008; 40:200-205
- 3083 **346.** Bajaj M, Suraamornkul S, Hardies LJ, Glass L, Musi N, DeFronzo RA.
3084 Effects of peroxisome proliferator-activated receptor (PPAR)-alpha and
3085 PPAR-gamma agonists on glucose and lipid metabolism in patients with type
3086 2 diabetes mellitus. *Diabetologia* 2007; 50:1723-1731
- 3087 **347.** Nakamuta M, Morizono S, Soejima Y, Yoshizumi T, Aishima S, Takasugi S,
3088 Yoshimitsu K, Enjoji M, Kotoh K, Taketomi A, Uchiyama H, Shimada M,
3089 Nawata H, Maehara Y. Short-term intensive treatment for donors with hepatic
3090 steatosis in living-donor liver transplantation. *Transplantation* 2005; 80:608-
3091 612
- 3092 **348.** Colville-Nash PR, Qureshi SS, Willis D, Willoughby DA. Inhibition of
3093 inducible nitric oxide synthase by peroxisome proliferator-activated receptor

- agonists: correlation with induction of heme oxygenase 1. *J Immunol* 1998; 161:978-984
- 3096 **349.** Basaranoglu M, Acbay O, Sonsuz A. A controlled trial of gemfibrozil in the
3097 treatment of patients with nonalcoholic steatohepatitis. *J Hepatol* 1999; 31:384
- 3098 **350.** Laurin J, Lindor KD, Crippin JS, Gossard A, Gores GJ, Ludwig J, Rakela J,
3099 McGill DB. Ursodeoxycholic acid or clofibrate in the treatment of non-
3100 alcohol-induced steatohepatitis: a pilot study. *Hepatology (Baltimore, Md)*
3101 1996; 23:1464-1467
- 3102 **351.** Holden PR, Tugwood JD. Peroxisome proliferator-activated receptor alpha:
3103 role in rodent liver cancer and species differences. *Journal of molecular*
3104 *endocrinology* 1999; 22:1-8
- 3105 **352.** Sumida Y, Yoneda M. Current and future pharmacological therapies for
3106 NAFLD/NASH. *Journal of gastroenterology* 2017;
- 3107 **353.** Ashby J, Brady A, Elcombe CR, Elliott BM, Ishmael J, Odum J, Tugwood JD,
3108 Kettle S, Purchase IF. Mechanistically-based human hazard assessment of
3109 peroxisome proliferator-induced hepatocarcinogenesis. *Human &*
3110 *experimental toxicology* 1994; 13 Suppl 2:S1-117
- 3111 **354.** Karbowska J, Kochan Z, Smolenski RT. Peroxisome proliferator-activated
3112 receptor alpha is downregulated in the failing human heart. *Cellular &*
3113 *molecular biology letters* 2003; 8:49-53
- 3114 **355.** Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK,
3115 Kaitaniemi P, Koskinen P, Manninen V, et al. Helsinki Heart Study: primary-
3116 prevention trial with gemfibrozil in middle-aged men with dyslipidemia.
3117 Safety of treatment, changes in risk factors, and incidence of coronary heart
3118 disease. *The New England journal of medicine* 1987; 317:1237-1245
- 3119 **356.** Delerive P, De Bosscher K, Besnard S, Vanden Berghe W, Peters JM,
3120 Gonzalez FJ, Fruchart JC, Tedgui A, Haegeman G, Staels B. Peroxisome
3121 proliferator-activated receptor alpha negatively regulates the vascular
3122 inflammatory gene response by negative cross-talk with transcription factors
3123 NF-kappaB and AP-1. *J Biol Chem* 1999; 274:32048-32054
- 3124 **357.** De Silva DS, Wilson RM, Hutchinson C, Ip PC, Garcia AG, Lancel S, Ito M,
3125 Pimentel DR, Sam F. Fenofibrate inhibits aldosterone-induced apoptosis in
3126 adult rat ventricular myocytes via stress-activated kinase-dependent
3127 mechanisms. *Am J Physiol Heart Circ Physiol* 2009; 296:H1983-1993
- 3128 **358.** Ogata T, Miyauchi T, Sakai S, Irukayama-Tomobe Y, Goto K, Yamaguchi I.
3129 Stimulation of peroxisome-proliferator-activated receptor alpha (PPAR alpha)
3130 attenuates cardiac fibrosis and endothelin-1 production in pressure-overloaded
3131 rat hearts. *Clinical science (London, England : 1979)* 2002; 103 Suppl
3132 48:284s-288s
- 3133 **359.** Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR. The role of fibrates in
3134 the prevention of cardiovascular disease--a pooled meta-analysis of long-term
3135 randomized placebo-controlled clinical trials. *American heart journal* 2007;
3136 154:943-953
- 3137 **360.** Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, Grobbee DE, Cass A,
3138 Chalmers J, Perkovic V. Effects of fibrates on cardiovascular outcomes: a
3139 systematic review and meta-analysis. *Lancet (London, England)* 2010;
3140 375:1875-1884
- 3141 **361.** Staels B. Fibrates in CVD: a step towards personalised medicine. *Lancet*
3142 (London, England) 2010; 375:1847-1848

- 3143 362. Ayaori M, Momiyama Y, Fayad ZA, Yonemura A, Ohmori R, Kihara T,
3144 Tanaka N, Nakaya K, Ogura M, Sawada S, Taniguchi H, Kusuhara M, Nagata
3145 M, Nakamura H, Ohsuzu F. Effect of bezafibrate therapy on atherosclerotic
3146 aortic plaques detected by MRI in dyslipidemic patients with
3147 hypertriglyceridemia. *Atherosclerosis* 2008; 196:425-433
- 3148 363. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for
3149 cardiovascular risk reduction in persons with atherogenic dyslipidemia: a
3150 meta-analysis. *Atherosclerosis* 2011; 217:492-498
- 3151 364. Brown JD, Plutzky J. Peroxisome proliferator-activated receptors as
3152 transcriptional nodal points and therapeutic targets. *Circulation* 2007;
3153 115:518-533
- 3154 365. Ericsson CG, Hamsten A, Nilsson J, Grip L, Svane B, de Faire U.
3155 Angiographic assessment of effects of bezafibrate on progression of coronary
3156 artery disease in young male postinfarction patients. *Lancet (London,
3157 England)* 1996; 347:849-853
- 3158 366. Robins SJ, Rubins HB, Faas FH, Schaefer EJ, Elam MB, Anderson JW,
3159 Collins D. Insulin resistance and cardiovascular events with low HDL
3160 cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes
3161 care* 2003; 26:1513-1517
- 3162 367. The Bezafibrate Infarction Prevention(BIP) Study. Secondary prevention by
3163 raising HDL cholesterol and reducing triglycerides in patients with coronary
3164 artery disease. *Circulation* 2000; 102:21-27
- 3165 368. Cushman WC, Evans GW, Byington RP, Goff DC, Jr., Grimm RH, Jr., Cutler
3166 JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L,
3167 Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi
3168 F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *The
3169 New England journal of medicine* 2010; 362:1575-1585
- 3170 369. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB,
3171 Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Jr., Probstfield JL,
3172 Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in
3173 type 2 diabetes. *The New England journal of medicine* 2008; 358:2545-2559
- 3174 370. Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff DC, Jr.,
3175 Probstfield JL, Cushman WC, Ginsberg HN, Bigger JT, Grimm RH, Jr.,
3176 Byington RP, Rosenberg YD, Friedewald WT. Long-term effects of intensive
3177 glucose lowering on cardiovascular outcomes. *The New England journal of
3178 medicine* 2011; 364:818-828
- 3179 371. Ginsberg HN, Elam MB, Lovato LC, Crouse JR, 3rd, Leiter LA, Linz P,
3180 Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-
3181 Beigi F, Bigger JT, Goff DC, Jr., Cushman WC, Simons-Morton DG,
3182 Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus.
3183 *The New England journal of medicine* 2010; 362:1563-1574
- 3184 372. ClinicalTrials.gov US National Institutes of Health. PemaFibrate to Reduce
3185 Cardiovascular Outcomes by Reducing Triglycerides IN patiENTs With
3186 diabeTes (PROMINENT). Identifier: NCT03071692
3187 <https://clinicaltrials.gov/ct2/show/NCT03071692>.
- 3188 373. Belfort R, Berria R, Cornell J, Cusi K. Fenofibrate reduces systemic
3189 inflammation markers independent of its effects on lipid and glucose
3190 metabolism in patients with the metabolic syndrome. *J Clin Endocrinol Metab*
3191 2010; 95:829-836

- 3192 **374.** ClinicalTrials.gov US National Institutes of Health. Phase 3 Study to Evaluate
3193 the Efficacy and Safety of Elafibranor Versus Placebo in Patients With
3194 Nonalcoholic Steatohepatitis (NASH) (RESOLVE-IT). Identifier:
3195 NCT02704403 <https://clinicaltrials.gov/ct2/show/NCT02704403>
- 3196 **375.** Gross B, Pawlak M, Lefebvre P, Staels B. PPARs in obesity-induced T2DM,
3197 dyslipidaemia and NAFLD. *Nature reviews Endocrinology* 2017; 13:36-49
- 3198 **376.** Sahebkar A, Chew GT, Watts GF. New peroxisome proliferator-activated
3199 receptor agonists: potential treatments for atherogenic dyslipidemia and non-
3200 alcoholic fatty liver disease. *Expert opinion on pharmacotherapy* 2014;
3201 15:493-503
- 3202 **377.** Dubois V, Eeckhoutte J, Lefebvre P, Staels B. Distinct but complementary
3203 contributions of PPAR isotypes to energy homeostasis. *J Clin Invest* 2017;
3204 127:1202-1214
- 3205 **378.** Takei K, Nakagawa Y, Wang Y, Han SI, Satoh A, Sekiya M, Matsuzaka T,
3206 Shimano H. Effects of K-877, a novel selective PPARalpha modulator, on
3207 small intestine contribute to the amelioration of hyperlipidemia in low-density
3208 lipoprotein receptor knockout mice. *J Pharmacol Sci* 2017; 133:214-222
- 3209 **379.** Maki T, Maeda Y, Sonoda N, Makimura H, Kimura S, Maeno S, Takayanagi
3210 R, Inoguchi T. Renoprotective effect of a novel selective PPARalpha
3211 modulator K-877 in db/db mice: A role of diacylglycerol-protein kinase C-
3212 NAD(P)H oxidase pathway. *Metabolism: clinical and experimental* 2017;
3213 71:33-45
- 3214 **380.** Arai H, Yamashita S, Yokote K, Araki E, Suganami H, Ishibashi S. Efficacy
3215 and safety of K-877, a novel selective peroxisome proliferator-activated
3216 receptor alpha modulator (SPPARMalpha), in combination with statin
3217 treatment: Two randomised, double-blind, placebo-controlled clinical trials in
3218 patients with dyslipidaemia. *Atherosclerosis* 2017; 261:144-152
- 3219 **381.** Camejo G. Phase 2 clinical trials with K-877 (pemafibrate): A promising
3220 selective PPAR-alpha modulator for treatment of combined dyslipidemia.
3221 *Atherosclerosis* 2017; 261:163-164
- 3222 **382.** Araki E, Yamashita S, Arai H, Yokote K, Satoh J, Inoguchi T, Nakamura J,
3223 Maegawa H, Yoshioka N, Tanizawa Y, Watada H, Suganami H, Ishibashi S.
3224 Effects of Pemafibrate, a Novel Selective PPARalpha Modulator, on Lipid and
3225 Glucose Metabolism in Patients With Type 2 Diabetes and
3226 Hypertriglyceridemia: A Randomized, Double-Blind, Placebo-Controlled,
3227 Phase 3 Trial. *Diabetes care* 2018;
- 3228 **383.** Escudero P, Martinez de Maranon A, Collado A, Gonzalez-Navarro H,
3229 Hermenegildo C, Peiro C, Piqueras L, Sanz MJ. Combined sub-optimal doses
3230 of rosuvastatin and bexarotene impair angiotensin II-induced arterial
3231 mononuclear cell adhesion through inhibition of Nox5 signaling pathways and
3232 increased RXR/PPARalpha and RXR/PPARgamma interactions. *Antioxidants*
3233 *& redox signaling* 2015; 22:901-920
- 3234 **384.** Kersten S, Desvergne B, Wahli W. Roles of PPARs in health and disease.
3235 *Nature* 2000; 405:421-424
- 3236 **385.** Bougarne N, Paumelle R, Caron S, Hennuyer N, Mansouri R, Gervois P,
3237 Staels B, Haegeman G, De Bosscher K. PPAR{alpha} blocks glucocorticoid
3238 receptor {alpha}-mediated transactivation but cooperates with the activated
3239 glucocorticoid receptor {alpha} for transrepression on NF- κ B.
3240 *Proceedings of the National Academy of Sciences of the United States of*
3241 *America* 2009;

- 3242 **386.** Cuzzocrea S, Bruscoli S, Mazzon E, Crisafulli C, Donato V, Di Paola R,
3243 Velardi E, Esposito E, Nocentini G, Riccardi C. Peroxisome Proliferator-
3244 Activated Receptor-alpha Contributes to the Anti-Inflammatory Activity of
3245 Glucocorticoids. *Mol Pharmacol* 2008; 73:323-337
- 3246 **387.** Delerive P, De Bosscher K, Besnard S, Vanden Berghe W, Peters JM,
3247 Gonzalez FJ, Fruchart J-C, Tedgui A, Haegeman G, Staels B. Peroxisome
3248 Proliferator-activated Receptor alpha Negatively Regulates the Vascular
3249 Inflammatory Gene Response by Negative Cross-talk with Transcription
3250 Factors NF-kappa B and AP-1. *J Biol Chem* 1999; 274:32048-32054
- 3251 **388.** Pawlak M, Bauge E, Bourguet W, De Bosscher K, Lalloyer F, Tailleux A,
3252 Lebherz C, Lefebvre P, Staels B. The transrepressive activity of peroxisome
3253 proliferator-activated receptor alpha is necessary and sufficient to prevent liver
3254 fibrosis in mice. *Hepatology (Baltimore, Md)* 2014; 60:1593-1606
- 3255 **389.** Crowley T, O'Neil JD, Adams H, Thomas AM, Filer A, Buckley CD, Clark
3256 AR. Priming in response to pro-inflammatory cytokines is a feature of adult
3257 synovial but not dermal fibroblasts. *Arthritis research & therapy* 2017; 19:35
- 3258 **390.** Busillo JM, Azzam KM, Cidlowski JA. Glucocorticoids sensitize the innate
3259 immune system through regulation of the NLRP3 inflammasome. *J Biol Chem*
3260 2011; 286:38703-38713
- 3261 **391.** Cruz-Topete D, Cidlowski JA. One hormone, two actions: anti- and pro-
3262 inflammatory effects of glucocorticoids. *Neuroimmunomodulation* 2015;
3263 22:20-32
- 3264 **392.** Lannan EA, Galliher-Beckley AJ, Scoltock AB, Cidlowski JA.
3265 Proinflammatory actions of glucocorticoids: glucocorticoids and TNFalpha
3266 coregulate gene expression in vitro and in vivo. *Endocrinology* 2012;
3267 153:3701-3712
- 3268 **393.** Bouhrel MA, Derudas B, Rigamonti E, Dievart R, Brozek J, Haulon S,
3269 Zawadzki C, Jude B, Torpier G, Marx N, Staels B, Chinetti-Gbaguidi G.
3270 PPARgamma activation primes human monocytes into alternative M2
3271 macrophages with anti-inflammatory properties. *Cell metabolism* 2007; 6:137-
3272 143
- 3273 **394.** Nakaya K, Tohyama J, Naik SU, Tanigawa H, MacPhee C, Billheimer JT,
3274 Rader DJ. Peroxisome proliferator-activated receptor-alpha activation
3275 promotes macrophage reverse cholesterol transport through a liver X receptor-
3276 dependent pathway. *Arterioscler Thromb Vasc Biol* 2011; 31:1276-1282
- 3277 **395.** Zhang Y, Kurupati R, Liu L, Zhou XY, Zhang G, Hudaihed A, Filisio F,
3278 Giles-Davis W, Xu X, Karakousis GC, Schuchter LM, Xu W, Amaravadi R,
3279 Xiao M, Sadek N, Krepler C, Herlyn M, Freeman GJ, Rabinowitz JD, Ertl
3280 HCJ. Enhancing CD8(+) T Cell Fatty Acid Catabolism within a Metabolically
3281 Challenging Tumor Microenvironment Increases the Efficacy of Melanoma
3282 Immunotherapy. *Cancer cell* 2017; 32:377-391.e379
- 3283 **396.** Ho PC, Kaech SM. Reenergizing T cell anti-tumor immunity by harnessing
3284 immunometabolic checkpoints and machineries. *Current opinion in*
3285 *immunology* 2017; 46:38-44
- 3286 **397.** Dunn SE, Ousman SS, Sobel RA, Zuniga L, Baranzini SE, Youssef S, Crowell
3287 A, Loh J, Oksenberg J, Steinman L. Peroxisome proliferator-activated receptor
3288 (PPAR)alpha expression in T cells mediates gender differences in
3289 development of T cell-mediated autoimmunity. *J Exp Med* 2007; 204:321-330

- 3290 **398.** Cunard R, Ricote M, DiCampli D, Archer DC, Kahn DA, Glass CK, Kelly CJ.
3291 Regulation of cytokine expression by ligands of peroxisome proliferator
3292 activated receptors. *J Immunol* 2002; 168:2795-2802
- 3293 **399.** Marx N, Kehrle B, Kohlhammer K, Grub M, Koenig W, Hombach V, Libby
3294 P, Plutzky J. PPAR activators as antiinflammatory mediators in human T
3295 lymphocytes: implications for atherosclerosis and transplantation-associated
3296 arteriosclerosis. *Circ Res* 2002; 90:703-710
- 3297 **400.** Dubrac S, Stoitzner P, Pirkebner D, Elentner A, Schoonjans K, Auwerx J,
3298 Saeland S, Hengster P, Fritsch P, Romani N, Schmuth M. Peroxisome
3299 proliferator-activated receptor-alpha activation inhibits Langerhans cell
3300 function. *J Immunol* 2007; 178:4362-4372
- 3301 **401.** Delerive P, Martin-Nizard F, Chinetti G, Trottein F, Fruchart JC, Najib J,
3302 Duriez P, Staels B. Peroxisome proliferator-activated receptor activators
3303 inhibit thrombin-induced endothelin-1 production in human vascular
3304 endothelial cells by inhibiting the activator protein-1 signaling pathway. *Circ*
3305 *Res* 1999; 85:394-402
- 3306 **402.** Marx N, Sukhova GK, Collins T, Libby P, Plutzky J. PPARalpha activators
3307 inhibit cytokine-induced vascular cell adhesion molecule-1 expression in
3308 human endothelial cells. *Circulation* 1999; 99:3125-3131
- 3309 **403.** Marx N, Mackman N, Schonbeck U, Yilmaz N, Hombach V, Libby P, Plutzky
3310 J. PPARalpha activators inhibit tissue factor expression and activity in human
3311 monocytes. *Circulation* 2001; 103:213-219
- 3312 **404.** Neve BP, Corseaux D, Chinetti G, Zawadzki C, Fruchart JC, Duriez P, Staels
3313 B, Jude B. PPARalpha agonists inhibit tissue factor expression in human
3314 monocytes and macrophages. *Circulation* 2001; 103:207-212
- 3315 **405.** Mishra A, Chaudhary A, Sethi S. Oxidized omega-3 fatty acids inhibit NF-
3316 kappaB activation via a PPARalpha-dependent pathway. *Arterioscler Thromb*
3317 *Vasc Biol* 2004; 24:1621-1627
- 3318 **406.** Meissner M, Stein M, Urbich C, Reisinger K, Suske G, Staels B, Kaufmann R,
3319 Gille J. PPARalpha activators inhibit vascular endothelial growth factor
3320 receptor-2 expression by repressing Sp1-dependent DNA binding and
3321 transactivation. *Circ Res* 2004; 94:324-332
- 3322 **407.** Delerive P, Gervois P, Fruchart JC, Staels B. Induction of IkappaBalpha
3323 expression as a mechanism contributing to the anti-inflammatory activities of
3324 peroxisome proliferator-activated receptor-alpha activators. *J Biol Chem* 2000;
3325 275:36703-36707
- 3326 **408.** Gervois P, Vu-Dac N, Kleemann R, Kockx M, Dubois G, Laine B, Kosykh V,
3327 Fruchart JC, Kooistra T, Staels B. Negative regulation of human fibrinogen
3328 gene expression by peroxisome proliferator-activated receptor alpha agonists
3329 via inhibition of CCAAT box/enhancer-binding protein beta. *J Biol Chem*
3330 2001; 276:33471-33477
- 3331 **409.** Kleemann R, Gervois PP, Verschuren L, Staels B, Princen HM, Kooistra T.
3332 Fibrates down-regulate IL-1-stimulated C-reactive protein gene expression in
3333 hepatocytes by reducing nuclear p50-NFkappa B-C/EBP-beta complex
3334 formation. *Blood* 2003; 101:545-551
- 3335 **410.** Gervois P, Kleemann R, Pilon A, Percevault F, Koenig W, Staels B, Kooistra
3336 T. Global suppression of IL-6-induced acute phase response gene expression
3337 after chronic in vivo treatment with the peroxisome proliferator-activated
3338 receptor-alpha activator fenofibrate. *J Biol Chem* 2004; 279:16154-16160

- 3339 411. Mansouri RM, Bauge E, Staels B, Gervois P. Systemic and distal
3340 repercussions of liver-specific peroxisome proliferator-activated receptor-
3341 alpha control of the acute-phase response. *Endocrinology* 2008; 149:3215-
3342 3223
- 3343 412. Janssen AW, Betzel B, Stoopen G, Berends FJ, Janssen IM, Peijnenburg AA,
3344 Kersten S. The impact of PPARalpha activation on whole genome gene
3345 expression in human precision cut liver slices. *BMC genomics* 2015; 16:760
- 3346 413. Loyer X, Paradis V, Henique C, Vion AC, Colnot N, Guerin CL, Devue C, On
3347 S, Scetbun J, Romain M, Paul JL, Rothenberg ME, Marcellin P, Durand F,
3348 Bedossa P, Prip-Buus C, Bauge E, Staels B, Boulanger CM, Tedgui A, Rautou
3349 PE. Liver microRNA-21 is overexpressed in non-alcoholic steatohepatitis and
3350 contributes to the disease in experimental models by inhibiting PPARalpha
3351 expression. *Gut* 2016; 65:1882-1894
- 3352 414. Mogilenko DA, Kudriavtsev IV, Shavva VS, Dizhe EB, Vilenskaya EG,
3353 Efremov AM, Perevozchikov AP, Orlov SV. Peroxisome proliferator-
3354 activated receptor alpha positively regulates complement C3 expression but
3355 inhibits tumor necrosis factor alpha-mediated activation of C3 gene in
3356 mammalian hepatic-derived cells. *J Biol Chem* 2013; 288:1726-1738
- 3357 415. Deckers J, Bougarne N, Mylka V, Desmet S, Luybaert A, Devos M, Tanghe
3358 G, Van Moorleghem J, Vanheerswynghels M, De Cauwer L, Thommis J,
3359 Vuylsteke M, Tavernier J, Lambrecht B, Hammad H, De Bosscher K. Co-
3360 activation of GR and PPARgamma in murine skin prevents worsening of
3361 atopic march. *J Invest Dermatol* 2017;
- 3362 416. Crisafulli C, Bruscoli S, Esposito E, Mazzon E, Di Paola R, Genovese T,
3363 Bramanti P, Migliorati G, Cuzzocrea S. PPAR-alpha contributes to the anti-
3364 inflammatory activity of 17beta-estradiol. *The Journal of pharmacology and*
3365 *experimental therapeutics* 2009; 331:796-807
- 3366 417. Crisafulli C, Cuzzocrea S. The role of endogenous and exogenous ligands for
3367 the peroxisome proliferator-activated receptor alpha (PPAR-alpha) in the
3368 regulation of inflammation in macrophages. *Shock* 2009; 32:62-73
- 3369 418. Jones DC, Ding X, Zhang TY, Daynes RA. Peroxisome proliferator-activated
3370 receptor alpha negatively regulates T-bet transcription through suppression of
3371 p38 mitogen-activated protein kinase activation. *J Immunol* 2003; 171:196-
3372 203
- 3373 419. Delerive P, De Bosscher K, Vanden Berghe W, Fruchart J-C, Haegeman G,
3374 Staels B. DNA Binding-Independent Induction of I{kappa}B{alpha} Gene
3375 Transcription by PPAR{alpha}. *Mol Endocrinol* 2002; 16:1029-1039
- 3376 420. Stienstra R, Mandard S, Tan NS, Wahli W, Trautwein C, Richardson TA,
3377 Lichtenauer-Kaligis E, Kersten S, Muller M. The Interleukin-1 receptor
3378 antagonist is a direct target gene of PPARalpha in liver. *J Hepatol* 2007;
3379 46:869-877
- 3380 421. Kronke G, Kadl A, Ikonomu E, Bluml S, Furnkranz A, Sarembock IJ,
3381 Bochkov VN, Exner M, Binder BR, Leitinger N. Expression of heme
3382 oxygenase-1 in human vascular cells is regulated by peroxisome proliferator-
3383 activated receptors. *Arterioscler Thromb Vasc Biol* 2007; 27:1276-1282
- 3384 422. Rommelaere S, Millet V, Gensollen T, Bourges C, Eeckhoutte J, Hennuyer N,
3385 Bauge E, Chasson L, Cacciatore I, Staels B, Pitari G, Galland F, Naquet P.
3386 PPARalpha regulates the production of serum Vanin-1 by liver. *FEBS letters*
3387 2013; 587:3742-3748

- 3388 **423.** van Diepen JA, Jansen PA, Ballak DB, Hijmans A, Hooiveld GJ, Rommelaere
3389 S, Galland F, Naquet P, Rutjes FP, Mensink RP, Schrauwen P, Tack CJ, Netea
3390 MG, Kersten S, Schalkwijk J, Stienstra R. PPAR-alpha dependent regulation
3391 of vanin-1 mediates hepatic lipid metabolism. *J Hepatol* 2014; 61:366-372
3392 **424.** Staels B. PPAR agonists and the metabolic syndrome. *Therapie* 2007; 62:319-
3393 326
3394 **425.** Wahli W, Michalik L. PPARs at the crossroads of lipid signaling and
3395 inflammation. *Trends Endocrinol Metab* 2012; 23:351-363
3396 **426.** Madej A, Okopien B, Kowalski J, Zielinski M, Wysocki J, Szygula B, Kalina
3397 Z, Herman ZS. Effects of fenofibrate on plasma cytokine concentrations in
3398 patients with atherosclerosis and hyperlipoproteinemia IIb. *International*
3399 *journal of clinical pharmacology and therapeutics* 1998; 36:345-349
3400 **427.** Krysiak R, Gdula-Dymek A, Okopien B. The effect of fenofibrate on
3401 lymphocyte release of proinflammatory cytokines and systemic inflammation
3402 in simvastatin-treated patients with atherosclerosis and early glucose
3403 metabolism disturbances. *Basic & clinical pharmacology & toxicology* 2013;
3404 112:198-202
3405 **428.** Toyoda T, Kamei Y, Kato H, Sugita S, Takeya M, Suganami T, Ogawa Y.
3406 Effect of peroxisome proliferator-activated receptor-alpha ligands in the
3407 interaction between adipocytes and macrophages in obese adipose tissue.
3408 *Obesity (Silver Spring)* 2008; 16:1199-1207
3409 **429.** Poynter ME, Daynes RA. Age-associated alterations in splenic iNOS
3410 regulation: influence of constitutively expressed IFN-gamma and correction
3411 following supplementation with PPARalpha activators or vitamin E. *Cellular*
3412 *immunology* 1999; 195:127-136
3413 **430.** An HJ, Lee B, Kim SM, Kim DH, Chung KW, Ha SG, Park KC, Park YJ,
3414 Kim SJ, Yun HY, Chun P, Yu BP, Moon HR, Chung HY. A PPAR Pan
3415 Agonist, MHY2013 Alleviates Age-Related Hepatic Lipid Accumulation by
3416 Promoting Fatty Acid Oxidation and Suppressing Inflammation. *Biological &*
3417 *pharmaceutical bulletin* 2018; 41:29-35
3418 **431.** Wu D, Sanin DE, Everts B, Chen Q, Qiu J, Buck MD, Patterson A, Smith
3419 AM, Chang CH, Liu Z, Artyomov MN, Pearce EL, Cella M, Pearce EJ. Type
3420 1 Interferons Induce Changes in Core Metabolism that Are Critical for
3421 Immune Function. *Immunity* 2016; 44:1325-1336
3422 **432.** Knoch B, Barnett MP, Cooney J, McNabb WC, Barraclough D, Laing W, Zhu
3423 S, Park ZA, Maclean P, Knowles SO, Roy NC. Molecular Characterization of
3424 the Onset and Progression of Colitis in Inoculated Interleukin-10 Gene-
3425 Deficient Mice: A Role for PPARalpha. *PPAR Res* 2010; 2010:621069
3426 **433.** Dreesen L, De Bosscher K, Grit G, Staels B, Lubberts E, Bauge E, Geldhof P.
3427 *Giardia muris* infection in mice is associated with a protective interleukin 17A
3428 response and induction of peroxisome proliferator-activated receptor alpha.
3429 *Infection and immunity* 2014; 82:3333-3340
3430 **434.** Lee JW, Bajwa PJ, Carson MJ, Jeske DR, Cong Y, Elson CO, Lytle C, Straus
3431 DS. Fenofibrate represses interleukin-17 and interferon-gamma expression and
3432 improves colitis in interleukin-10-deficient mice. *Gastroenterology* 2007;
3433 133:108-123
3434 **435.** Mazzon E, Cuzzocrea S. Absence of functional peroxisome proliferator-
3435 activated receptor-alpha enhanced ileum permeability during experimental
3436 colitis. *Shock* 2007; 28:192-201

- 3437 436. Michalik L, Wahli W. Peroxisome proliferator-activated receptors (PPARs) in
3438 skin health, repair and disease. *Biochim Biophys Acta* 2007; 1771:991-998
- 3439 437. Michalik L, Desvergne B, Tan NS, Basu-Modak S, Escher P, Rieusset J,
3440 Peters JM, Kaya G, Gonzalez FJ, Zakany J, Metzger D, Chambon P, Duboule
3441 D, Wahli W. Impaired skin wound healing in peroxisome proliferator-
3442 activated receptor (PPAR)alpha and PPARbeta mutant mice. *The Journal of*
3443 *cell biology* 2001; 154:799-814
- 3444 438. Komuves LG, Hanley K, Lefebvre AM, Man MQ, Ng DC, Bikle DD,
3445 Williams ML, Elias PM, Auwerx J, Feingold KR. Stimulation of PPARalpha
3446 promotes epidermal keratinocyte differentiation in vivo. *J Invest Dermatol*
3447 2000; 115:353-360
- 3448 439. Sheu MY, Fowler AJ, Kao J, Schmuth M, Schoonjans K, Auwerx J, Fluhr JW,
3449 Man MQ, Elias PM, Feingold KR. Topical peroxisome proliferator activated
3450 receptor-alpha activators reduce inflammation in irritant and allergic contact
3451 dermatitis models. *J Invest Dermatol* 2002; 118:94-101
- 3452 440. Staumont-Salle D, Abboud G, Brenuchon C, Kanda A, Roumier T, Lavogiez
3453 C, Fleury S, Remy P, Papin JP, Bertrand-Michel J, Terce F, Staels B,
3454 Delaporte E, Capron M, Dombrowicz D. Peroxisome proliferator-activated
3455 receptor alpha regulates skin inflammation and humoral response in atopic
3456 dermatitis. *J Allergy Clin Immunol* 2008; 121:962-968.e966
- 3457 441. Lo Verme J, Fu J, Astarita G, La Rana G, Russo R, Calignano A, Piomelli D.
3458 The nuclear receptor peroxisome proliferator-activated receptor-alpha
3459 mediates the anti-inflammatory actions of palmitoylethanolamide. *Molecular*
3460 *pharmacology* 2005; 67:15-19
- 3461 442. Xu J, Chavis JA, Racke MK, Drew PD. Peroxisome proliferator-activated
3462 receptor-alpha and retinoid X receptor agonists inhibit inflammatory responses
3463 of astrocytes. *Journal of neuroimmunology* 2006; 176:95-105
- 3464 443. Ramanan S, Kooshki M, Zhao W, Hsu FC, Robbins ME. PPARalpha ligands
3465 inhibit radiation-induced microglial inflammatory responses by negatively
3466 regulating NF-kappaB and AP-1 pathways. *Free radical biology & medicine*
3467 2008; 45:1695-1704
- 3468 444. Paterniti I, Campolo M, Cordaro M, Impellizzeri D, Siracusa R, Crupi R,
3469 Esposito E, Cuzzocrea S. PPAR-alpha Modulates the Anti-Inflammatory
3470 Effect of Melatonin in the Secondary Events of Spinal Cord Injury. *Molecular*
3471 *neurobiology* 2017; 54:5973-5987
- 3472 445. Lee H, Shi W, Tontonoz P, Wang S, Subbanagounder G, Hedrick CC, Hama
3473 S, Borromeo C, Evans RM, Berliner JA, Nagy L. Role for peroxisome
3474 proliferator-activated receptor alpha in oxidized phospholipid-induced
3475 synthesis of monocyte chemotactic protein-1 and interleukin-8 by endothelial
3476 cells. *Circ Res* 2000; 87:516-521
- 3477 446. Zhang JZ, Ward KW. WY-14 643, a selective PPAR{alpha} agonist, induces
3478 proinflammatory and proangiogenic responses in human ocular cells.
3479 *International journal of toxicology* 2010; 29:496-504
- 3480 447. Panigrahy D, Kaipainen A, Huang S, Butterfield CE, Barnes CM, Fannon M,
3481 Laforme AM, Chaponis DM, Folkman J, Kieran MW. PPARalpha agonist
3482 fenofibrate suppresses tumor growth through direct and indirect angiogenesis
3483 inhibition. *Proceedings of the National Academy of Sciences of the United*
3484 *States of America* 2008; 105:985-990

- 3485 448. Chen Y, Hu Y, Lin M, Jenkins AJ, Keech AC, Mott R, Lyons TJ, Ma JX.
3486 Therapeutic effects of PPARalpha agonists on diabetic retinopathy in type 1
3487 diabetes models. *Diabetes* 2013; 62:261-272
- 3488 449. Hill MR, Clarke S, Rodgers K, Thornhill B, Peters JM, Gonzalez FJ, Gimble
3489 JM. Effect of peroxisome proliferator-activated receptor alpha activators on
3490 tumor necrosis factor expression in mice during endotoxemia. *Infection and
3491 immunity* 1999; 67:3488-3493
- 3492 450. Shurlygina AV, Dushkin MI, Mel'nikova EV, Panteleeva NG, Tenditnik MI,
3493 Khrapova MV, Trufakin VA. Bezafibrate causes depression of the immune
3494 response and increases the sensitivity to endotoxin in association with low
3495 level of HDL and PPARalpha activity in hypertensive ISIAH rats. *Bulletin of
3496 experimental biology and medicine* 2013; 155:724-728
- 3497 451. Chen T, Tibbitt CA, Feng X, Stark JM, Rohrbeck L, Rausch L, Sedimbi SK,
3498 Karlsson MCI, Lambrecht BN, Karlsson Hedestam GB, Hendriks RW,
3499 Chambers BJ, Nylen S, Coquet JM. PPAR-gamma promotes type 2 immune
3500 responses in allergy and nematode infection. *Science immunology* 2017; 2
- 3501 452. Nobs SP, Natali S, Pohlmeier L, Okreglicka K, Schneider C, Kurrer M,
3502 Sallusto F, Kopf M. PPARgamma in dendritic cells and T cells drives
3503 pathogenic type-2 effector responses in lung inflammation. *J Exp Med* 2017;
3504 214:3015-3035
- 3505 453. Standage SW, Caldwell CC, Zingarelli B, Wong HR. Reduced peroxisome
3506 proliferator-activated receptor alpha expression is associated with decreased
3507 survival and increased tissue bacterial load in sepsis. *Shock* 2012; 37:164-169
- 3508 454. Staels B, Maes M, Zambon A. Fibrates and future PPARalpha agonists in the
3509 treatment of cardiovascular disease. *Nature clinical practice Cardiovascular
3510 medicine* 2008; 5:542-553
- 3511 455. Montaigne D, Marechal X, Modine T, Coisne A, Mouton S, Fayad G, Ninni S,
3512 Klein C, Ortman S, Seunes C, Potelle C, Berthier A, Gheeraert C, Piveteau C,
3513 Deprez R, Eeckhoutte J, Duez H, Lacroix D, Deprez B, Jegou B, Koussa M,
3514 Edme JL, Lefebvre P, Staels B. Daytime variation of perioperative myocardial
3515 injury in cardiac surgery and its prevention by Rev-Erbalpha antagonism: a
3516 single-centre propensity-matched cohort study and a randomised study. *Lancet
3517 (London, England)* 2018; 391:59-69
- 3518 456. Durrington HJ, Farrow SN, Loudon AS, Ray DW. The circadian clock and
3519 asthma. *Thorax* 2014; 69:90-92
- 3520 457. Gibbs JE, Ray DW. The role of the circadian clock in rheumatoid arthritis.
3521 *Arthritis research & therapy* 2013; 15:205
- 3522
- 3523

3524 **Figure 1: Schematic presentation of the human PPAR α gene and protein domain**
3525 **structure-function relationship.** (A) The human PPAR α gene contains at least 8
3526 exons. Exons are shown in boxes with translated regions shaded. 5' UTR encoded by
3527 exons 1, 2 and the 5'-end of exon 3. The coding DNA sequence spans the 3' region of
3528 exon 3, exons 4–7 and the 5' extremity of exon 8. The 3' UTR consists of the last 232
3529 base pairs of exon 8. The splicing events S_{wt} and S_{tr} generating hPPAR α _{wt} and
3530 hPPAR α _{tr} transcripts respectively are depicted. The variant transcript lacks exon 6
3531 resulting in a frame shift generating a premature TGA termination codon. The
3532 corresponding protein products of the two splice isoforms are underlined. (B) PPAR α
3533 contains four distinct domains. The amino-terminal A/B domain contains the ligand-
3534 independent activation function-1 (AF-1), the C domain consists of a highly
3535 conserved DNA-binding domain (DBD), the D domain consists of a variable hinge
3536 region and the C terminal E domain includes ligand-binding domain (LBD) and a
3537 ligand-dependent activation function-2 (AF-2). Per domain, main functions are listed.
3538 Hsp90, Heat shock protein 90; PPRE, PPAR response element; UTR, untranslated
3539 region; wt, wild type; tr, truncated.

3540 **Figure 2: PPRE-dependent transcription regulation.** (A) PPRE-dependent
3541 activation. In the absence of specific ligands, PPAR α /RXR heterodimers bind to the
3542 PPRE located in the promoter of target genes, or elsewhere in the genome, and recruit
3543 corepressor complexes thereby maintaining PPAR α target genes in a silent state
3544 (ligand-independent repression). Upon ligand activation, the nuclear corepressors are
3545 released and the coactivator complexes are then recruited and bound to PPAR α /RXR α
3546 heterodimers, hence inducing expression of target genes involved in several biological
3547 processes including glucose and lipid metabolism. (B) PPRE-dependent inhibition of
3548 NF- κ B transcriptional activity. Upon ligand activation, PPRE-bound PPAR α directly

3549 interferes with the activity of p65 antagonizing thereby its binding to an NF- κ B-RE in
3550 the complement promoter. Sirt1; Silent information regulator 1; PPRE, PPAR-
3551 response element; RXR, Retinoid X receptor; DR1, Direct repeat1; NF- κ B-RE, NF-
3552 κ B response element.

3553 **Figure 3: Levels of modulating PPAR α activity.** PPAR α activity is controlled at
3554 several levels including gene expression, protein translation, ligand selectivity,
3555 posttranslational modifications affecting receptor stability and cofactor recruitment.
3556 Ub, Ubiquitinated; S, SUMOylated; P, Phosphorylated; PPRE, PPAR response
3557 element; GSK3, glycogen synthase kinase 3; AMPK, AMP kinase; PKC, protein
3558 kinase A; PKA, protein kinase A; PIASy, Protein inhibitor of activated STATy; RXR,
3559 retinoid X receptor.

3560 **Figure 4: Models of PPAR α transrepression activity.** (A) PPAR α directly interacts
3561 with pro-inflammatory transcription factors such as NF- κ B, AP-1 and STAT to
3562 negatively regulate their targets leading to anti-inflammatory effects through a DNA-
3563 independent mechanism. (B) Simultaneous ligand-activation of PPAR α and GR leads
3564 to the enhanced repression of TNF-induced IL-6 transcriptional activity, likely via a
3565 mechanism involving a direct physical interference between PPAR α and GR.

3566 Ub, Ubiquitinated; S, SUMOylated; P, Phosphorylated; PPRE, PPAR response
3567 element; GSK3, glycogen synthase kinase 3; AMPK, AMP kinase; PKC, protein
3568 kinase A; PKA, protein kinase A; PIASy, Protein inhibitor of activated STATy; RXR,
3569 retinoid X receptor; C/EBP- β , CAATT/enhancer-binding protein β ; STAT, signal
3570 transducer and activator of transcription; AP-1, activator protein-1; NF- κ B, nuclear
3571 factor- κ B.

3572 **Figure 5: Anti-inflammatory effects of PPAR α activation.** (A) Effect of human
3573 PPAR α activation, by various synthetical ligands on inflammatory mediators. (B)

3574 Effect of rodent PPAR α on inflammatory mediators. Note that for some of these
3575 effects, conclusions on an involvement of PPAR α were reached by using PPAR α -/
3576 mice, in which an aggravated inflammatory effect was observed. hASMCs, human
3577 aortic smooth muscle cells; hUVEC, human vascular endothelial cells; COX-2,
3578 cyclooxygenase; PG, prostaglandin; VCAM, vascular cell adhesion molecule; MCP-
3579 1, Monocyte chemotactic protein-1; VEGFR2, vascular endothelial growth factor
3580 receptor-2; CRP, C-reactive protein; IFN- γ , interferon- γ ; APP, acute phase response
3581 proteins; LPS, lipopolysaccharide; SAA, serum amyloid A; IL-1ra, IL-1 receptor
3582 antagonist; LTB₄, Leukotriene B₄; iNOS, inducible nitric oxide synthase.

3583 ***Figure 6: Stimulatory effects of human and murine PPAR α activation on***
3584 ***inflammatory mediators.*** Note here that mostly natural ligands seem able to trigger
3585 PPAR α -dependent pro- inflammatory effects. MCP-1, Monocyte chemotactic protein-
3586 1; LPS, lipopolysaccharide; 8(*S*)-HETE, 8(*S*)- hydroxyeicosatetraenoic acid; LTB₄,
3587 Leukotriene B₄; NOS, nitric oxide synthase.

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Table 1: PPARα functional domains		
<i>Domain</i>	<i>Functions</i>	<i>Ref</i>
N-Terminal (A/B domain)	Transactivation function AF-1 Phosphorylation sites Subtype-selective target gene expression	(35,40) (41-43) (38,44)
DBD (C domain)	Zinc-fingers binding motifs Phosphorylation sites Recognition PPRE Dimerization	(45) (46) (47,48) (49)
Hinge (D domain)	Nuclear localization signals Docking for Coactivators Phosphorylation sites SUMOylation sites Interacts with HSP90	(33,50) (51) (46,52) (53) (54)
C-Terminal LDB (E/F domain)	Transactivation function AF-2 / Cofactor recruitments SUMOylation sites Dimerization Interacts with HSP90	(55) (56) (51,57) (54)

Table 1: PPAR α functional domains and their relative functions. PPAR α displays a classical nuclear receptor canonical structure. Per domain, main PPAR α functions are listed (details in the text). Hsp90, Heat shock protein 90; PPRE, PPAR response element.

Table 2: Phosphorylation modifications affecting PPARα activity				
<i>Kinase involved</i>	<i>Residues phosphorylated</i>	<i>Effect on transcriptional activity</i>	<i>Physiological outcome</i>	<i>Ref</i>
ERK1/2 MAPK	Ser12 and Ser21 in A/B domain in hPPAR α	Increased ligand-dependent transactivation	Cross-talk between insulin signaling and PPAR α activity	(58,149)
P38 MAPK and JNK	Ser6, Ser12 and Ser21 in A/B domain in mPPAR α	Increased ligand-dependent transactivation	Increased cardiac mitochondrial fatty acid β -oxidation during periods of stress	(150)
ERK-MAPK	Ser6, Ser12 and Ser21 in A/B domain in mPPAR α	Decreased transactivation	Down-regulation of PPAR α and its target genes during cardiac myocyte hypertrophic growth.	(151)
PKC	Ser179, Ser230 in D domain in hPPAR α	Increased transactivation Decreased transrepression	Molecular switch dissociating the transactivation and transrepression functions of PPAR α	(52)
PKA	Mainly C domain	Increased ligand-dependent transactivation	Enhanced β -oxidation, production of glucose and ketone bodies under stress, fasting or exercise	(155)
AMPK	n.d.	Increased transactivation	Increased fatty acid oxidation and PPAR α gene expression in skeletal muscle	(113,156, 157)
GSK3	Predominantly at serine 73 in the A/B domain in rPPAR α	Decreased PPAR α stability	Links GSK3 signaling and PPAR α activity to metabolic regulation	(42)

Table 2: Phosphorylation modifications affecting PPAR α activity. PPAR α undergoes several phosphorylation modifications that markedly impact receptor function (details in the text).

Table 3: SUMOylation modifications affecting PPAR α activity

<i>SUMO Ligase (E3) identified</i>	<i>Residues SUMOylated</i>	<i>Effect on transcriptional activity</i>	<i>Physiological outcome</i>	<i>Ref</i>
PIASy	SUMO-1, Lys358 in the LBD region in mPPAR α	Transcriptional repression	Sex-specific gene repression and protective effect in estrogen-related liver diseases, including inflammation and cholestasis	(56)
	SUMO-1, Lys185 in the hinge region in hPPAR α	Downregulation of transactivation	Decrease in NCoR-specific hPPAR α target gene expression	(53)

Table 3: SUMOylation modifications affecting PPAR α activity. PPAR α undergoes several SUMOylation modifications that markedly impact receptor function (details in the text).

Table 4: PPAR α Natural and Synthetic Ligands

Natural Ligands				
<i>Type</i>	<i>Ligand</i>		<i>Biological & therapeutic outcome</i>	<i>Ref</i>
Fatty acids	Arachidonic Acid		PPAR α binding and activation.	(19,191)
Eicosanoids	8(S)-HETE		PPAR α -mediated transcription activation and induction of adipogenic differentiation of 3T3-L1 preadipocytes	(19,171)
	20-HETE		PPAR α target gene expression (APOA1) activation	(172)
	Leukotriene B4		LTB ₄ breakdown stimulation which may contribute to the resolution of inflammation.	(19,165,174,175)
Phospholipids	Oxidized phospholipids		PPAR α activation in a phospholipase A2-dependent manner in endothelial cells.	(176)
	Phosphatidylcholine (16:0/18:1-GPC)		Interaction with PPAR α -LBD and coactivator peptide motifs. PPAR α -dependent gene induction and hepatic steatosis decreased.	(179)
Polyphenols	Resveratrol		PPAR α activation in cell-based reporter assays. Brain protection against ischemic stroke in mice.	(180-183)
Synthetic Ligands				
<i>Ligand</i>	<i>EC50</i>	<i>Status of Clinical development</i>	<i>Biological & therapeutic outcome</i>	<i>Ref</i>
Clofibrate	50 (m)-55(h) μ M	In clinical use	Decreased the lipid levels in hypercholesterolemic patients, mainly as the results of a reduction in VLDL, and less in LDL fraction.	(192-194)
Fenofibrate	18(m)-30(h) μ M	In clinical use	Improved the plasma lipid profiles and lipoprotein profiles. Decreased atypical sphingolipids in plasma of dyslipidaemic patients.	(194-196)
Bezafibrate	20(m)-80(h) μ M	In clinical use	Decreased plasma TG levels and increased HDL-C levels in dyslipidaemic and diabetic patients.	(197)
Gemfibrozil	61(h) μ M	In clinical use	Increased HDL-C levels and lowered TG levels. Coronary heart disease and stroke prevention.	(196,198,199)

WY14643	0.63(m)-5(h) μ M	Used in basic research only	Agonist activity in functional assays. Inhibition of NF- κ B transcriptional activity and decreased inflammatory responses <i>in vitro</i> and <i>in vivo</i> .	(19,23,191,192,194)
GW9578	0.005(m)-0.05(h) μ M	Used in basic research only	Potent lipid lowering Activity. Decreased LDL-C in Sprague-Dawley rats. Improved insulin sensitivity in obese Zucker rats.	(194,200,201)
GW7647	0.001(m)-0.006(h) μ M	Used in basic research only	Agonist activity in GAL4-PPAR binding assay. Decreased TGs in fat-fed hamsters and rats.	(202)
Pemafibrate (K-877)	1 nM (h)	Phase 3 trials ongoing for treatment of dyslipidaemia.	Improved lipid profile in patients with dyslipidaemia. Enhances RCT and decreased inflammation and atherosclerosis.	(188,190,203)
<i>Dual PPARα/β(δ) agonists</i>				
Elafibranor (GFT505)	10-20 nM	Phase 3 trial ongoing for treatment of NASH	Improved hepatic steatosis, inflammation and fibrosis in NASH rodent models and in patients with NASH. Improved lipid profile and insulin sensitivity in patients with dyslipidaemia or prediabetes and in obese individuals.	(189,204-206)

Table 4: The natural and synthetic PPAR α ligands and their physiological roles.

(h), EC50 for human PPAR α ; (m), EC50 for murine PPAR α

Table 5: List of selected PPAR α target genes

Target gene	Official gene symbol	Gene functions	Comments	Fibrates		Ref
				WT	KO	
LIVER						
FA Transport Protein (FATP)	SLC27A1	Facilitates the uptake of long chain fatty acids by the liver Fatty acid transport	Direct PPAR α target with a functional PPRE in its promoter.	↑	=	(268-270)
Fatty acid translocase (FAT/CD36)	CD36	Uptake of long-chain fatty acids and oxidized LDL	Transcriptional mechanism remains unclear. Induction goes through the distal promoter region of the gene even though no PPRE could be identified.	↑	=	(270-272)
Acyl-coA synthetase	ACS	Catalyzes fatty acid metabolism by converting inactive fatty acids into active acyl CoA derivatives	Direct PPAR α target with a functional PPRE in its promoter.	↑	=	(208,223,269, 273,274)
Fatty acid binding protein	FABP	Intracellular lipid trafficking	Functional PPRE was identified. FABP2 and FABP1 have different effects on the ability of different agonists to promote PPAR α activation ligand-dependently.	↑	=	(275-277)
Acyl-CoA binding protein (ACBP)	DBI	Fatty acyl CoA esters transport	Functional PPRE was identified. ACBP expression is regulated by fasting/refeeding in rodents. A dual regulation by PPAR α and SREBP-1c might be considered.	↑	=	(278,279)
Carnitine palmitoyl-transferase 1	CPT1A	Catalyzes the transfer of a long-chain fatty acyl group from coenzyme A to carnitine.	Functional PPRE was identified.	↑	=	(280)
Carnitine palmitoyl-transferase 2	CPT2	Conjugates the fatty acid <i>back</i> to Coenzyme A for subsequent β -oxidation.	Functional PPRE was identified.	↑	=	(208,281)
Medium-chain acyl-CoA dehydrogenase (MCAD)	ACADM	Mitochondrial fatty acid β -oxidation	Functional PPRE was identified.	↑	=	(210,282-284)

Long-chain acyl-CoA dehydrogenase (LCAD)	ACADL	Mitochondrial fatty acid β -oxidation	No PPRE / unknown mechanism.	↑	=	(208,285)
Very long chain acyl-CoA dehydrogenase (VLCAD)	ACADVL	Mitochondrial fatty acid β -oxidation	No PPRE reported	↑	=	(208,286,287)
Dodecenoyl-CoA δ -isomerase	ECI1	Mitochondrial β -oxidation of unsaturated and saturated fatty acids	Using microarray, expression of ECI1 was found to be decreased in PPAR α -deficient mice but no PPRE has yet been identified.	↑	?	(288,289)
Acyl-CoA oxidase	ACOX	Peroxisomal β -oxidation	Functional PPRE was identified. The fasting-induced activation of ACOX expression was markedly blunted in PPAR α deficient mice.	↑	=	(71,165,210,288,290)
Bifunctional enzyme (BIEN)	EHHADH	Peroxisomal β -oxidation	Three different PPRES have been identified in the promoter sequence of the BIEN gene, yet only one allows for efficient transactivation of the BIEN gene by PPAR α .	↑	=	(276,288,290,291)
Peroxisomal 3-ketoacyl-CoA thiolase.	ACAA1	Peroxisomal β -oxidation	It is unclear whether the DR-1 sequence identified within its promoter mediates PPAR α transactivation. Differential gene regulation in human vs rodent hepatocytes.	↑	=	(71,291-293)
Peroxisomal membrane protein 11A PEX11 α	PEX11A	Peroxisome proliferation	A functional PPRES 8.4 kb downstream of the PEX11 α was identified by a gene transfection study.	↑	?	(294-296)
Cytochrome P450 4A	CYP4A	Microsomal FA ω -hydroxylation	In rodents, CYP4A1 upregulation through a functional PPRES. In humans, no PPRES detected in the 5'-flanking region of the CYP4A11 gene. Induction upon fasting or fenofibrate	↑	=	(288,297-299)

			treatment in transgenic mice.			
Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (mHMG-CoAS)	HMGCS2	Ketogenesis/condensation of acetyl-CoA and acetoacetyl-CoA to generate HMG-CoA	Functional PPRE identified in the rat and pig mHMG-CoAS gene. mHMG-CoAS proteins interact physically with PPAR α and act as a coactivator to up-regulate transcription from the PPRE of its own gene.	↑	=	(215,288)
Fibroblast growth factor 21	FGF21	Metabolic fuel homeostasis during ketosis	Functional PPRE identified. Induction upon fasting and PPAR α agonists treatment.	↑	=	(217,300,301)
FA desaturase 2 (Fads2)	FADS	Lipogenesis	DR-1 that functions in the regulation of human FADS2 gene transcription identified. An indirect regulatory mechanism involving SREBP-1c might be considered.	↑	=	(220,302-306)
Stearoyl-CoA desaturase (Scd1)	SCD	Lipogenesis	Functional PPRE identified. An indirect regulatory mechanism involving SREBP-1c might be considered.	↑	=	(302-304)
Malic enzyme (Mod1)	ME1	Lipogenesis	Functional PPRE identified. Decrease of ME1 expression in livers of PPAR α deficient mice.	↑	=	(272,288,307)
Phosphatidate phosphatase (Lpin2)	LPIN2	Lipogenesis	Dual target of PPAR α and PPAR β/δ . Induction by fasting and dietary FA maintained in PPAR α deficient mice.	↑	=	(232,308)
Acetyl-CoA carboxylase (ACC)	ACACA	Lipogenesis	PPAR α might indirectly influence ACC and FAS expression by controlling metabolic processes. In human primary	↑	?	(220-222)

Fatty acid synthase (FAS)	FASN	Lipogenesis	hepatocytes, PPAR α agonists, cooperatively with insulin and LXR agonists, induce FAS and ACC.	↑	?	
Liver X receptor alpha (LXR α)	NR1H3	Cholesterol metabolism	Induction in macrophages upon PPAR α treatment Decreased in livers upon fasting in PPAR α deficient mice.	↑	?	(309,310)
Cholesterol 7 α -hydroxylase (Cyp7a1)	CYP7A	Bile acid metabolism	Functional PPRE was identified. Murine Cyp7A1 species, harbors an additional PPRE. Indirect mechanism involving HNF4 α transactivation activity was also reported.	#	?	(228,231,311,312)
Cholesterol 27 α -hydroxylase (Cyp27a1)	CYP27A1	Bile acid metabolism	PPAR α affects the stability of Cyp27a1 mRNA. In rodents, fibrates suppress bile acid biosynthesis via PPAR α -mediated downregulation of Cyp27a.	↓	=	(231,310)
Sterol-12 α -hydroxylase	CYP8B1	Bile acid metabolism	Functional PPRE identified.	↑	=	(229)
Phosphoenolpyruvate carboxykinase (Pck1)	PKC1	Gluconeogenesis	Elusive regulation mechanism, although a functional PPRE was shown to be functional in adipocytes. PPAR α -mediated Pck1 regulation only observed in human hepatocytes. Induction during fasting reported.	?	?	(232,233,313)
Glycerol-3-phosphate dehydrogenase (GPDH)	GDP	Metabolic conversion of glycerol into glucose	PPAR α directly governs glycerol metabolic by directly upregulating expression of these genes. Upregulation by fasting only in wild-type mice.	↑	=	(233)
Glycerol kinase,	GK					
Glycerol transporters aquaporins 3&9	AQA3&9					
Pyruvate dehydrogenase kinase isoform 4 (Pdk4)	PDK4	Glucose oxidation	No PPRE yet identified. In wild type PPAR α mice, PDK4 expression	?	?	(314,315)

			increased in response to fasting with suppression by refeeding.			
Glycogen synthase 2 (Gys-2)	GYS2	Glycogen synthesis	Functional PPRE identified. Regulation mechanism involving competition between HNF4 α and PPAR α reported. Gys-2 mRNA reduction is PPAR α deficient mice and in fasted and refed state	↑	=	(238)
Lipoprotein lipase	LPL	Hydrolysis of TGs	Functional PPRE identified	↑	=	(48,249,270,289)
Angiopoietin-like protein 4	ANGPTL4	Inhibitor of LPL activity	Increased upon fasting.	↑	=	(256,316)
Rev-erba	NR1D1	Repressor of gene transcription	Functional PPRE identified. Negative interference with the activation of APOC3 gene promoter by HNF4	↑	?	(47,249,260)
Apolipoprotein AI	APOA1	Plasma HDL Metabolism	In humans, a functional PPRE was identified. In rodents, an indirect mechanism involving the PPAR α -dependent induction of the Rev-erba was reported.	↓	=	(259,260,317)
Apolipoprotein AII	APOA2	Plasma HDL Metabolism	Functional PPRE identified. Induced APOA2 plasma levels and hepatic mRNA expression in human. Both a marginal reduction and induction upon fibrate treatment observed in rodents.	↑	=	(258,318-320)
Apolipoprotein A-V	APOA5	Plasma TG Metabolism	Functional PPRE identified.	↑	?	(254,255)
Apolipoprotein C-III	APOC3	Plasma HDL Metabolism	Transcriptional suppression by fibrates involves HNF4.	↓	=	(250,253,321)

Heart

Acyl-CoA oxidase	ACOX	Peroxisomal β -oxidation	Reduced fasting-induced ACOX expression in PPAR α -deficient mice.	?	?	(71,210)
Carnitine palmitoyl-transferase 1	CPT1	Fatty acid transport/oxidation	Functional PPRE identified. Reduced fasting-induced CPT1 expression in PPAR α deficient mice.	↑	?	(210,322,323)
Carnitine palmitoyl-transferase 2 (CPT2)	CPT2	Fatty acid oxidation	Functional PPRE identified.	?	?	(281,324)
Long-chain acyl-CoA synthetase (LCAS)	ACADL	Fatty acid activation	Functional PPRE identified.	?	?	(273,324)
Medium-chain acyl-CoA dehydrogenase (MCAD)	ACADM	Mitochondrial fatty acid β -oxidation	The fasting-induced activation ACADM expression was abolished in PPAR α deficient mice.	?	?	(210,283,324)
Muscle						
Carnitine palmitoyl-transferase 1	CPT1	Fatty acid transport/oxidation	Functional PPRE identified	↑	?	(323,325)
Pyruvate dehydrogenase kinase isoform 4 (Pdk4) (soleus)	PDK4	Glucose oxidation	No PPRE has yet been identified	↑	?	(323,326)
White adipose tissue						
Fatty acid translocase (FAT/CD36)	CD36	Uptake of long-chain fatty acids and oxidized LDL	Transcriptional mechanism remains unclear.	↑	↑	(327)
Acyl-CoA oxidase	ACOX	Peroxisomal β -oxidation	Functional PPRE identified.	↑	↑	(71,327)
Lipoprotein lipase	LPL	Hydrolysis of TGs	Functional PPRE identified. Basal levels of LPL mRNA were higher in PPAR α deficient mice as compared to WT mice.	↑	=	(249,327)
Glycogen synthase 2 (Gys-2)	GYS2	Glycogen synthesis	Gys-2 mRNA is reduced in PPAR α deficient mice.	?	?	(238)
Small intestine						
Pyruvate dehydrogenase kinase isoform 4 (Pdk4)	PDK4	Glucose oxidation	Intestine-specific regulation of PDK gene transcription by LXR.	?	?	(328)
Carnitine palmitoyl-transferase 1	CPT1	FA transport/oxidation	Intestine-specific regulation of CPT1 gene transcription	?	?	(328)

			by LXR.			
Apolipoprotein C-III)	APOC3	Plasma HDL Metabolism	PPAR α -dependent gene repression by fibrates <i>in vivo</i> .	↓	?	(251,327)
Fatty acid binding protein	FABP	Intracellular lipid trafficking	Reduced FABP mRNA in PPAR α deficient mice.	↑	?	(275,327)

Table 5: Selected PPAR α target gene. PPAR α regulates the expression of its target genes involved in different biological process via distinct mechanisms (more details for some examples are discussed in the text). ↑, represents an increase upon fibrate treatment; ↓, represents a decrease upon fibrate treatment; =, represents no change upon fibrate treatment; ?, no information available on a change; #, represents conflicting results; WT, wild-type mouse; KO, knockout PPAR α mouse.

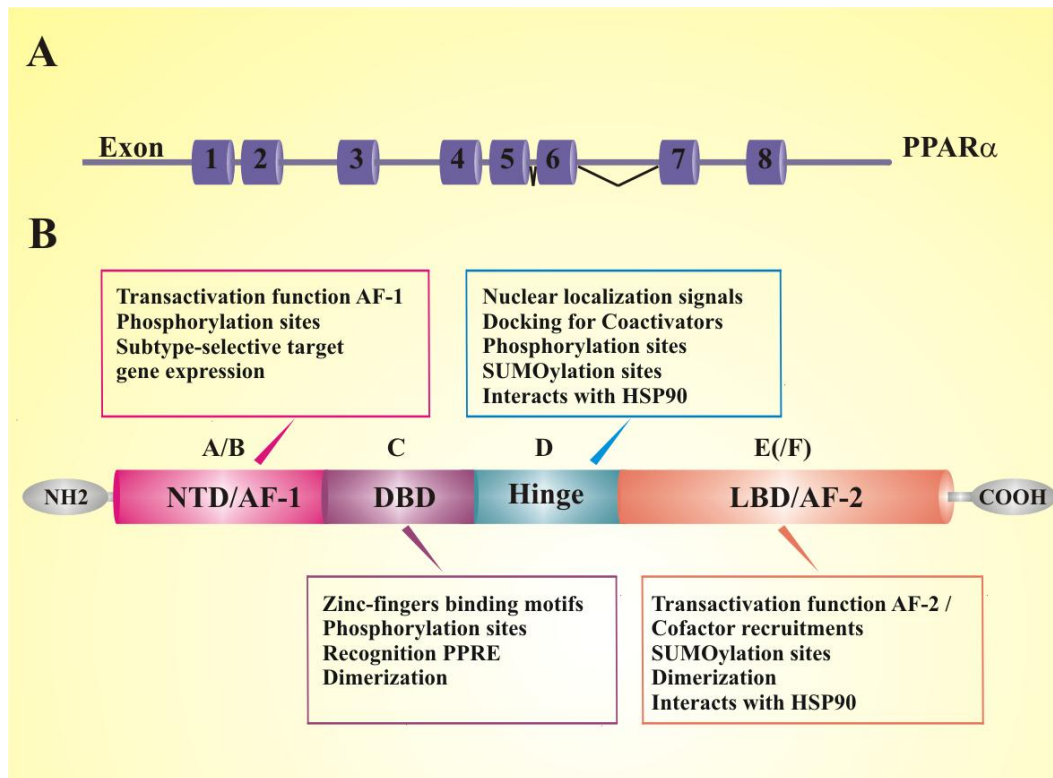


Figure 1: Schematic of PPAR α gene and protein domain structure-function relationship. (A) Schematic of the PPAR α gene showing 8 exons. (B) PPAR α contains four distinct domains. The amino-terminal A/B domain contains the ligand-independent activation function-1 (AF-1), the C domain consists of a highly conserved DNA-binding domain (DBD), the D domain consists of a variable hinge region and the C terminal E domain includes ligand-binding domain (LBD) and a ligand-dependent activation function-2 (AF-2). Per domain, main functions are listed. Hsp90, Heat shock protein 90; PPRE, PPAR response element.

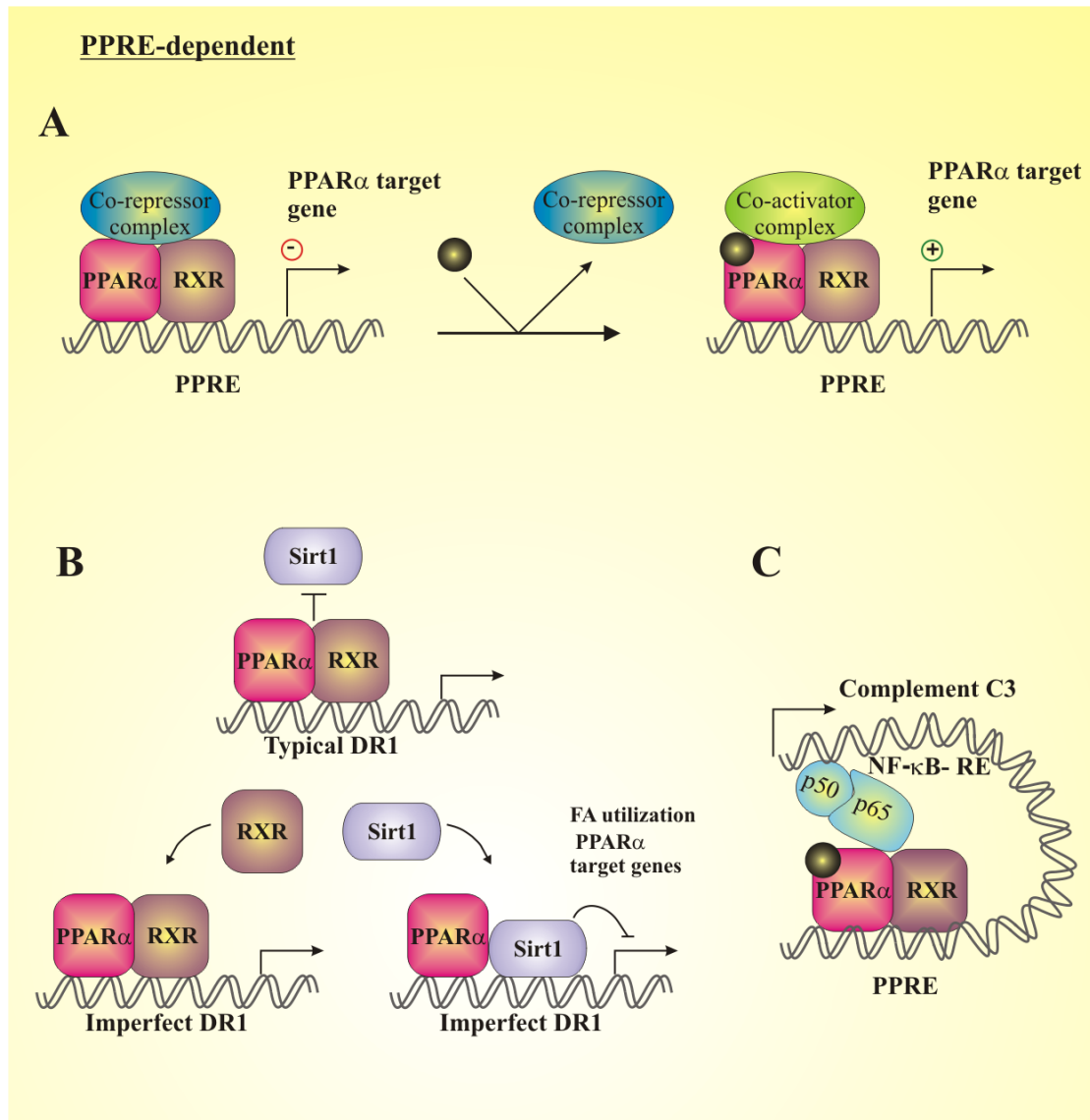


Figure 2: PPRE-dependent transcription regulation. (A) PPRE-dependent activation. In the absence of specific ligands, PPAR α /RXR heterodimers bind to the PPRE located in the promoter of target genes, or elsewhere in the genome, and recruit corepressor complexes thereby maintaining PPAR α target genes in a silent state (ligand-independent repression). Upon ligand activation, the nuclear corepressors are released and the coactivator complexes are then recruited and bound to PPAR α /RXR α heterodimers, hence inducing expression of target genes involved in several biological processes including glucose and lipid metabolism. (B) The typical DR1 sequence favors PPAR α /RXR α heterodimerization, whereas the switch from PPAR α /RXR to

PPAR α /Sirt1 takes place on imperfect DR1s, thereby causing downregulation of many known PPAR α target genes mediating FA utilization (56). (C) PPRE-dependent inhibition of NF- κ B transcriptional activity. Upon ligand activation, PPRE-bound PPAR α directly interferes with the activity of p65 antagonizing thereby its binding to an NF- κ B-RE in the complement promoter (56). Abbreviations used in the figure: Sirt1; Silent information regulator 1; PPRE, PPAR-response element; RXR, Retinoid X receptor; DR1, Direct repeat1; NF- κ B-RE, NF- κ B response element.

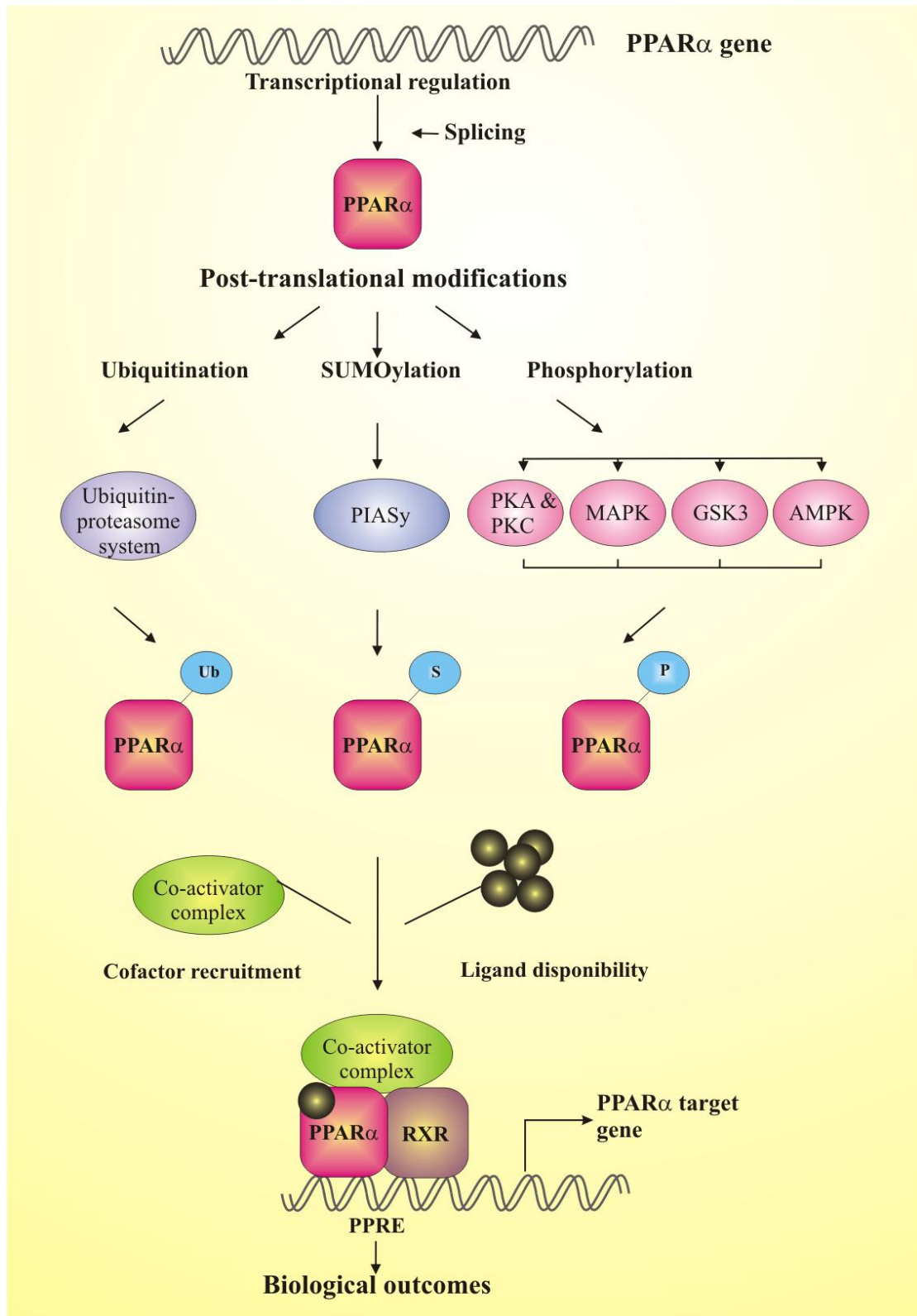


Figure 3: Levels of modulating PPAR α activity. PPAR α activity is controlled at several levels including gene expression, protein translation, ligand selectivity, posttranslational modifications affecting receptor stability and cofactor recruitment. Abbreviations used in the figure; Ub, Ubiquitinated; S, SUMOylated; P, Phosphorylated; PPRE, PPAR response element; GSK3, glycogen synthase kinase 3;

AMPK, adenosine monophosphate -activated protein kinase; PKC, protein kinase C;
PKA, protein kinase A; PIASy, Protein inhibitor of activated STATy; RXR, retinoid
X receptor.

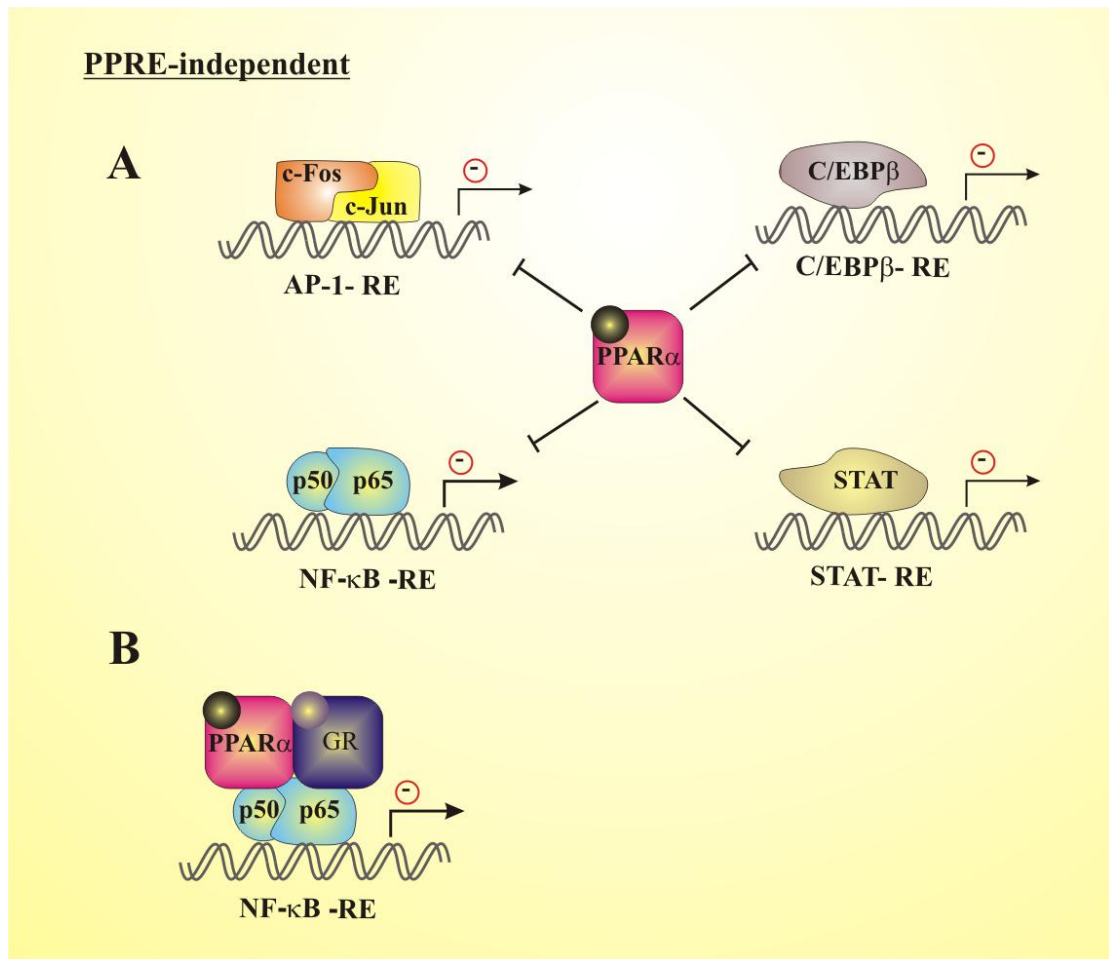


Figure 4: Models of PPAR α transrepression activity. (A) PPAR α directly interacts with pro-inflammatory transcription factors such as NF- κ B, AP-1 and STAT to negatively regulate their targets leading to anti-inflammatory effects through a DNA-independent mechanism. (B) Simultaneous ligand-activation of PPAR α and GR leads to the enhanced repression of TNF-induced IL-6 transcriptional activity, likely via a mechanism involving a direct physical interference between PPAR α and GR.

Abbreviations used in the figure; Ub, Ubiquitinated; S, SUMOylated; P, Phosphorylated; PPRE, PPAR response element; GSK3, glycogen synthase kinase 3; AMPK, adenosine monophosphate -activated protein kinase; PKC, protein kinase C; PKA, protein kinase A; PIASy, Protein inhibitor of activated STATy; RXR, retinoid X receptor; C/EBP- β , CAATT/enhancer-binding protein β ; STAT, signal transducer and activator of transcription; AP-1, activator protein-1; NF- κ B, nuclear factor- κ B.

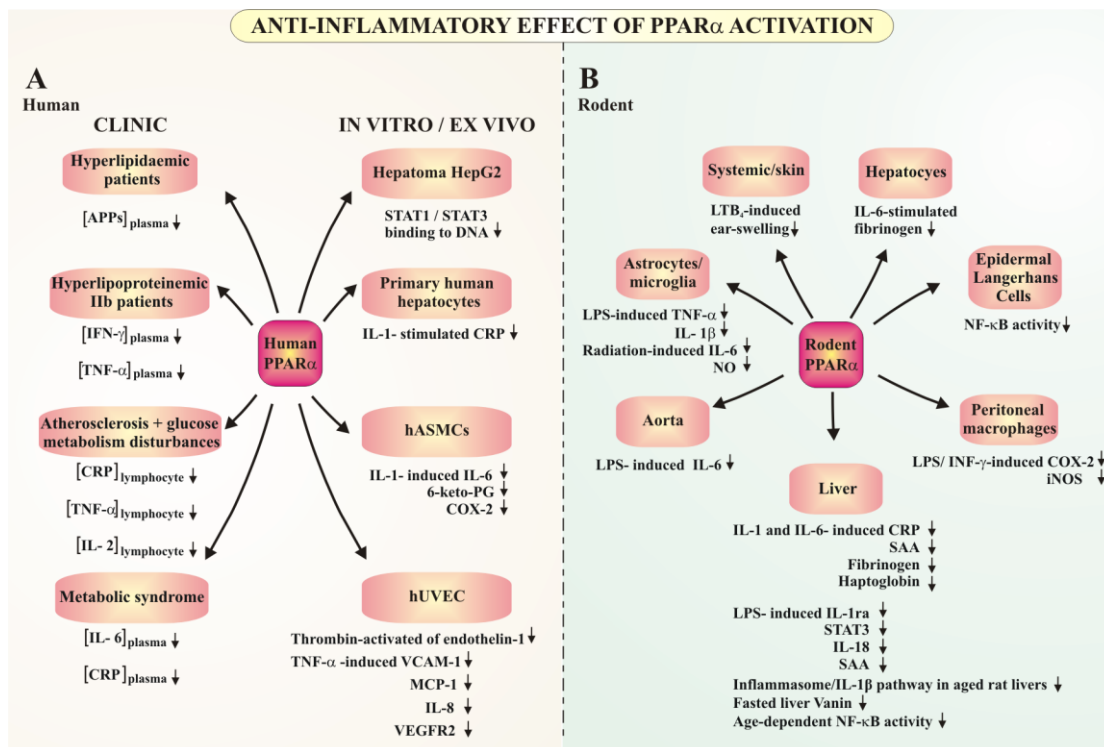


Figure 5: Anti-inflammatory effects of PPAR α activation. (A) Effect of human PPAR α activation, by various synthetical ligands on inflammatory mediators. (B) Effect of rodent PPAR α on inflammatory mediators. Note that for some of these effects, conclusions on an involvement of PPAR α were reached by using PPAR α $-/-$ mice, in which an aggravated inflammatory effect was observed. Abbreviations used in the figure; hASMCs, human aortic smooth muscle cells; hUVEC, human vascular endothelial cells; COX-2, cyclooxygenase; PG, prostaglandin; VCAM, vascular cell adhesion molecule; MCP-1, Monocyte chemotactic protein-1; VEGFR2, vascular endothelial growth factor receptor-2; CRP, C-reactive protein; IFN- γ , interferon- γ ; APP, acute phase response proteins; LPS, lipopolysaccharide; SAA, serum amyloid A; IL-1ra, IL-1 receptor antagonist; LTB₄, Leukotriene B₄; iNOS, inducible nitric oxide synthase.

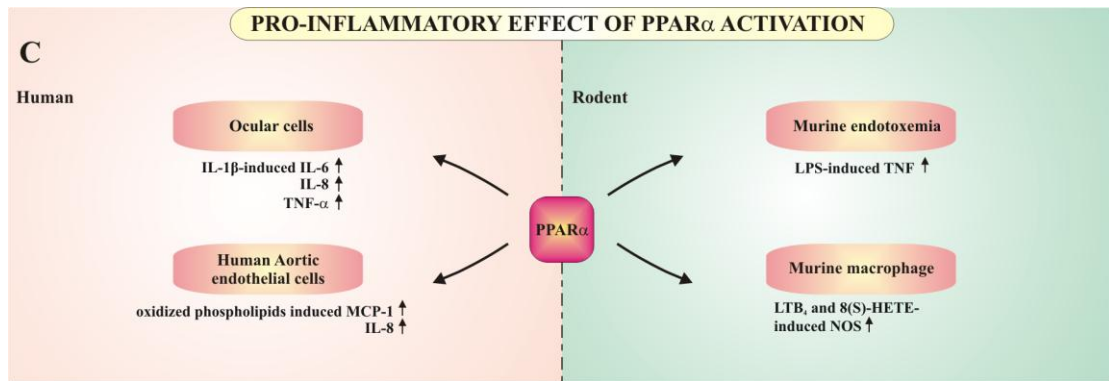


Figure 6: Stimulatory effects of human and murine PPAR α activation on inflammatory mediators. Note here that mostly natural ligands are able to trigger PPAR α -dependent pro-inflammatory effects. Abbreviations used in the figure; MCP-1, Monocyte chemotactic protein-1; LPS, lipopolysaccharide; 8(S)-HETE, 8(S)-hydroxyeicosatetraenoic acid; LTB₄, Leukotriene B₄; NOS, nitric oxide synthase.