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1 **DISTINCT BUT COMPLEMENTARY CONTRIBUTIONS OF PPAR ISOTYPES TO ENERGY HOMEOSTASIS**

2

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11

12 **Conflicts of interest:** BS is an advisor of Genfit SA.

13

14 **Abstract**

15

16 Peroxisome proliferator-activated receptors (PPARs) regulate energy metabolism and are, as such,  
17 therapeutic targets in metabolic diseases such as type 2 diabetes and non-alcoholic fatty liver  
18 disease. While they share anti-inflammatory activities, the PPAR isotypes distinguish themselves by  
19 differential actions on lipid and glucose homeostasis. In this review, we discuss the complementary  
20 and distinct metabolic effects of the PPAR isotypes together with the underlying cellular and  
21 molecular mechanisms, as well as the synthetic PPAR ligands used in the clinic or under  
22 development. We will highlight the potential of new PPAR ligands with improved efficacy and safety  
23 profiles in the treatment of complex metabolic disorders.

24

## 25 **Introduction**

26

27 Metabolic syndrome (MetS) is a pathophysiological condition characterized by increased visceral  
28 adiposity, dyslipidemia, prediabetes and hypertension. This cluster of risk factors predisposes to type  
29 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD) and increases the risk of microvascular  
30 complications and cardiovascular (CV) events. With the global increase in obesity, the prevalence of  
31 MetS has reached epidemic proportions. The pathophysiology of MetS and its co-morbidities is  
32 complex due to multiple alterations in lipid and glucose metabolism accompanied by inflammation  
33 occurring simultaneously in several tissues; therefore, current treatments address the individual  
34 components (1).

35 Over the last decades, the peroxisome proliferator-activated receptors (PPARs), which are members  
36 of the nuclear receptor superfamily of transcription factors (TFs), have been targeted to fight MetS  
37 and its complications. PPARs regulate many metabolic pathways upon activation by natural ligands,  
38 such as fatty acids (FA) and derivatives, or synthetic agonists, which bind to the ligand-binding  
39 domain of the receptor triggering a conformational change. Subsequent recruitment of coactivators  
40 to the PPAR/retinoid-X-receptor (RXR) heterodimer assembled at specific DNA response elements –  
41 PPAR response elements or PPREs – ultimately results in transactivation of target genes. In addition,  
42 PPAR activation attenuates the expression of pro-inflammatory genes, mostly through a  
43 transrepressive mechanism (2).

44 Three PPAR isotypes with different tissue distribution, ligand specificity and metabolic regulatory  
45 activities exist in mammals: PPAR $\alpha$  (NR1C1), PPAR $\beta/\delta$  (NR1C2), and PPAR $\gamma$  (NR1C3). Fibrates are  
46 synthetic PPAR $\alpha$  ligands used to treat dyslipidemia. Thiazolidinediones (TZDs) or glitazones, synthetic  
47 PPAR $\gamma$  ligands, are anti-diabetic drugs with potent insulin-sensitizing effects. There are currently no  
48 synthetic PPAR $\beta/\delta$  ligands in use clinically. Potency and safety issues have undermined the use of  
49 certain PPAR ligands, underscoring the need for new, safer, and more selective ways to target PPARs  
50 for combating metabolic diseases (2).

51 **Natural PPAR ligands**

52 PPARs are activated by FA and their derivatives, and the level of physiological receptor activation  
53 depends on the balance between ligand production and inactivation. Natural PPAR ligands originate  
54 from three main sources: diet, *de novo* lipogenesis (DNL) and lipolysis, alternating processes which  
55 depend on the integration of nutritional status and circadian rhythms (3). PPARs control these  
56 metabolic processes to maintain metabolic flexibility, a prerequisite for the preservation of health.  
57 Dietary lipids are important regulators of PPAR activity, as evidenced by the increased target gene  
58 expression of PPAR $\alpha$  in liver (4) and PPAR $\beta/\delta$  in skeletal muscle (SKM) (5) upon high-fat diet (HFD)  
59 feeding in mice. Tissue-specific deficiency of fatty acid synthase (FAS) – a key enzyme in FA synthesis  
60 – impairs PPAR $\alpha$  activity, identifying DNL as another source of PPAR ligands (6)(7). PPAR $\alpha$  ligands  
61 originating from DNL are not only simple FA but include more complex molecules, such as  
62 phosphatidylcholines (8). A third source of natural PPAR activators is through lipolysis. Angiotensin-  
63 like proteins are secreted glycoproteins which inhibit lipoprotein lipase (LPL), hence controlling the  
64 plasma lipid pool according to lipid availability and cellular fuel demand. Angptl4 expression is  
65 induced in several tissues including adipose tissue, liver and SKM by circulating FA via PPARs, leading  
66 to inhibition of LPL and decreasing plasma TG-derived FA uptake, thus forming a negative feedback  
67 loop (9). Intracellular lipolysis also provides PPAR ligands. Indeed, deficiency of adipose triglyceride  
68 lipase (ATGL), which lipolyzes TG in lipid droplets, decreases PPAR target gene expression in various  
69 tissues (10)(11)(12)(13). Ligand availability is also modulated by FA degradation in peroxisomes,  
70 whose genes are regulated by PPARs as part of a feedback mechanism (14). PPAR activity hence  
71 relies on a careful balance between ligand production and degradation in order to meet the  
72 fluctuating energy demand.

73

74 **Contrasting metabolic effects of ligand-activated PPAR $\alpha$  and PPAR $\gamma$**

75

76 Although they share some similarities in function and mechanism of action, it has become  
77 increasingly clear that both PPAR isotypes display important physiological and pharmacological  
78 differences. This section discusses the clinical and genetic evidence of contrasting PPAR $\alpha$  and PPAR $\gamma$   
79 effects, and sheds light on the cellular and molecular mechanisms underlying these differences.

80

### 81 *Clinical effects of PPAR $\alpha$ and PPAR $\gamma$ activation*

82

83 Except for the weak pan-agonist bezafibrate, all clinically used fibrates are specific activators of  
84 PPAR $\alpha$ . Fibrate outcome trials such as the Helsinki Heart Study (HHS) (15), Veterans Affairs-High  
85 density lipoprotein cholesterol Intervention Trial (VA-HIT) (16), Bezafibrate Infarction Prevention  
86 (BIP) (17), Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (18), and Action to  
87 Control Cardiovascular Risk in Diabetes (ACCORD) (19) consistently show beneficial effects on plasma  
88 lipids, particularly in normalizing the typical dyslipidemia of MetS characterized by the so-called  
89 ‘atherogenic lipid triad’ (high low density lipoprotein-cholesterol (LDL-C) and triglycerides (TG), low  
90 high density lipoprotein-cholesterol (HDL-C)). Fibrate therapy significantly decreases TG and increases  
91 HDL-C, whereas LDL-C generally decreases except in patients with severe hypertriglyceridemia and  
92 low baseline LDL-C. Fibrate therapy, however, does not change circulating FA concentrations (20).

93 Although both the FIELD and ACCORD trials showed a trend towards decreased CV risk (primary  
94 endpoint) in T2D, post-hoc and meta-analysis revealed that dyslipidemic patients (high TG and low  
95 HDL-C) show the highest CV reduction (21)(22). Fibrates do not improve glucose homeostasis in T2D  
96 patients (23)(18)(19); however, PPAR $\alpha$  activation improves glucose homeostasis in prediabetic  
97 patients (24), and may thus prevent conversion of prediabetes to overt T2D. Fibrates exert few  
98 adverse effects. Most compounds induce mild hypercreatininemia and hyperhomocysteinemia, but  
99 these effects appear to be pharmacodynamic markers of PPAR $\alpha$  activation rather than indicators of  
100 renal dysfunction (25). Hepatic carcinogenesis has been observed in rodents treated with fibrates but

101 not in humans and non-human primates likely due to lower levels of peroxisomes and peroxisomal  $\beta$ -  
102 oxidation in human liver (26).

103 TZDs are PPAR $\gamma$  ligands that exert strong insulin-sensitizing effects, resulting in long-term glycemic  
104 control in T2D patients (27). However, their clinical use has been challenged due to side effects  
105 including body weight gain, edema, and bone fractures (2). The increase in body weight upon TZD  
106 administration is due to PPAR $\gamma$ -dependent adipocyte expansion in WAT (28) as well as fluid retention  
107 caused by PPAR $\gamma$  activation in the collecting ducts of the kidney (29). The increased fracture risk in  
108 TZD-treated patients results from a PPAR $\gamma$ -driven rebalancing of bone remodelling in favour of net  
109 bone loss. Indeed, PPAR $\gamma$  activation in bone marrow stimulates mesenchymal progenitor  
110 differentiation into the adipocyte lineage, thereby reducing osteoblast production thus suppressing  
111 bone formation (30). In this context, protein phosphatase PP5 controls mesenchymal differentiation  
112 towards adipocytes and osteoblasts through reciprocal regulation of PPAR $\gamma$  and RUNX2, respectively  
113 (31). Conversely, pharmacological PPAR $\gamma$  activation promotes osteoclast formation thereby  
114 increasing bone resorption (32), although this effect may not occur in physiological conditions (33).

115 Rosiglitazone and pioglitazone increase plasma levels of the insulin-sensitizing adipokine adiponectin  
116 (2). They also increase HDL-C and reduce circulating FA levels (34), but have differential effects on TG  
117 and LDL-C as well as on CV risk. Pioglitazone, a full PPAR $\gamma$  agonist with moderate PPAR $\alpha$  activating  
118 properties (35), lowers TG, increases HDL-C and reduces CV outcomes in T2D (36) as well as insulin-  
119 resistant patients (37). In contrast, the pure PPAR $\gamma$  agonist rosiglitazone does not decrease CV risk in  
120 T2D, while increasing both HDL-C and LDL-C (38). Hence, the beneficial effects of pioglitazone on TG  
121 levels and CV events are likely due to combined PPAR $\alpha$  and PPAR $\gamma$  activation. A recent Mendelian  
122 randomization study refuted a causal role for adiponectin in CV disease (39), providing a plausible  
123 explanation for the neutral effect of rosiglitazone on CV outcome despite the rise in adiponectin.

124 In summary, activation of PPAR $\alpha$  improves the lipid profile, whereas activation of PPAR $\gamma$  rather  
125 improves glycemic control and insulin sensitivity.

126

127 *Genetic evidence of contrasting PPAR $\alpha$  and PPAR $\gamma$  functions*

128

129 The different phenotypes observed in patients carrying single nucleotide polymorphisms (SNPs) and  
130 mutations in PPAR $\alpha$  or PPAR $\gamma$  coding sequences further highlight the contrasting functions of the two  
131 isotypes. *PPARA* variants are associated with perturbations of lipid metabolism (40) and CV risk (41).  
132 The STOP-NIDDM trial revealed an association of *PPARA* SNPs with conversion from impaired glucose  
133 tolerance to T2D (42). These findings corroborate data showing that *PPARA* gene variation influences  
134 age of onset and progression of T2D (43). On the other hand, dominant-negative mutations in the  
135 ligand-binding domain of PPAR $\gamma$  result in severe insulin resistance (44). Accordingly, rare variants in  
136 *PPARG* with decreased adipogenic properties are associated with increased risk of T2D (45).  
137 Genome-wide association studies also revealed an association between *PPARG* SNPs and T2D,  
138 although not all studies concur (46)(47). A recently developed functional assay has permitted to  
139 identify new *PPARG* variants with altered PPAR $\gamma$  function (48). Moreover, SNPs found within DNA  
140 recognition motifs for PPAR $\gamma$  or cooperating factors and which alter PPAR $\gamma$  recruitment to chromatin  
141 modulate the response to anti-diabetic drugs (49). In addition, these SNPs in PPAR $\gamma$  binding sites are  
142 highly enriched among SNPs associated with TG and HDL-C levels in genome-wide association studies  
143 (49).

144 Altogether, these genetic data confirm the functional dichotomy between PPAR $\alpha$  and PPAR $\gamma$  in  
145 humans, underscoring PPAR $\alpha$ 's effects on lipid metabolism and conversion from impaired glucose  
146 tolerance to T2D, as opposed to the role of PPAR $\gamma$  in T2D and the regulation of glucose homeostasis.

147

148 *Cellular and molecular mechanisms underlying PPAR $\alpha$  and PPAR $\gamma$  functions*

149

150 PPAR $\alpha$ 's function (**Figure 1**) is best characterized in the liver, where it regulates genes involved in  
151 lipid and plasma lipoprotein metabolism during the nutritional transition phases (50)(51). During  
152 fasting, PPAR $\alpha$  increases hepatic uptake and transport to mitochondria of FA originating from

153 adipose tissue lipolysis through transcriptional upregulation of FA transport proteins and carnitine  
154 palmitoyltransferases. In the mitochondria, enhanced expression of acyl-CoA dehydrogenases by  
155 PPAR $\alpha$  stimulates hepatic FA oxidation (FAO), resulting in increased acetyl-CoA production which  
156 upon prolonged fasting is preferentially converted into ketone bodies to provide energy for extra-  
157 hepatic tissues. Mitochondrial HMGCS, a rate-limiting enzyme of ketogenesis, is also upregulated by  
158 PPAR $\alpha$  (52)(53). Moreover, glucagon receptor and PPAR $\alpha$ -signaling cooperate to control metabolic  
159 pathways during fasting (54). The hepatic IRE1 $\alpha$ /XBP1 pathway also participates in the adaptation to  
160 fasting by promoting FAO and ketogenesis through upregulation of PPAR $\alpha$  (55). In the fed state, on  
161 the other hand, PPAR $\alpha$  coordinates different pathways of DNL to supply FA which will be stored as  
162 hepatic TG for periods of starvation. A crucial step in DNL is the citrate-malate shuttle which controls  
163 the efflux of acetyl-CoA from the mitochondria to the cytosol, where it serves as a precursor for FA  
164 synthesis. Citrate carrier (CIC), an essential component of this shuttle system, is a direct PPAR $\alpha$  target  
165 gene in hepatocytes (56). In addition, PPAR $\alpha$  increases protein levels of the lipogenic factor SREBP1c  
166 by promoting proteolytic cleavage of its precursor (57), and stimulates transcription of SREBP1c  
167 target genes including *Fas*, *Scd1* and *Acc1* (58). In these postprandial conditions, mTORC1 is activated  
168 through the insulin-dependent PI3K pathway, resulting in NCoR1-dependent inhibition of PPAR $\alpha$ -  
169 mediated hepatic ketogenesis (59). Adjustment of PPAR $\alpha$  activity to nutritional status also involves  
170 phosphorylation of the receptor by several kinases (see next section). PPAR $\alpha$  thus contributes to the  
171 maintenance of metabolic flexibility by adapting fuel utilization to fuel availability, and its expression  
172 decreases in conditions of metabolic 'inflexibility', such as during NAFLD progression (60).  
173 Mechanisms contributing to dysregulated PPAR $\alpha$  signaling in NAFLD may include microRNA-10b (61),  
174 microRNA-21. (62) and JNK (63). Indeed, these pathways repress hepatic PPAR $\alpha$  signalling and are  
175 upregulated in NAFLD.

176 Reduction of plasma TG-rich lipoproteins upon PPAR $\alpha$  activation is linked to enhanced FA uptake and  
177 oxidation as well as increased activity of LPL which hydrolyses lipoprotein TG. PPAR $\alpha$  stimulation of  
178 LPL enzymatic activity is both direct through PPRE-dependent activation of the *LPL* gene (64) as well



179 as indirect through decreasing the levels of the LPL inhibitor and pro-atherogenic APO-CIII (65)(66)  
180 and increasing the levels of the LPL activator APO-AV (67). Reduced VLDL production contributes to  
181 the TG-lowering effects of PPAR $\alpha$  activation mainly in rodents and, likely to a lesser extent, in  
182 humans. Indeed, reduced VLDL production, as observed in patients carrying a SNP in the *TM6SF7*  
183 gene, is associated with lower circulating TG levels but more severe hepatic steatosis (68), an effect  
184 not observed in PPAR $\alpha$  agonist-treated patients (69). In MetS patients, fenofibrate treatment  
185 increases the fractional catabolic rate of VLDL-APOB, IDL-APOB and LDL-APOB, without affecting  
186 VLDL-APOB production (70). On the other hand, the rise in plasma HDL-C upon PPAR $\alpha$  activation is  
187 linked to increased synthesis of major HDL-C constituents, apolipoproteins APO-AI and APO-AII (71)  
188 as well as induction of PLTP (72). Of note, differences between rodents and humans with respect to  
189 apolipoprotein regulation exist, as APO-AI and APO-AV are direct positive PPAR $\alpha$  target genes in  
190 human but not murine liver (50). Through FAO, PPAR $\alpha$  activation leads to energy dissipation not only  
191 in the liver but also in SKM (73) and white adipose tissue (WAT) (74). In brown adipose tissue (BAT),  
192 PPAR $\alpha$  stimulates lipid oxidation as well as thermogenesis in synergy with PPAR $\gamma$  coactivator 1 $\alpha$   
193 (PGC1A) (75). Interestingly, while PPAR $\alpha$  activation reduces weight gain in rodents (74), there is no  
194 evidence of PPAR $\alpha$  effects on body mass in humans (18)(19).

195 The inability of fibrates to improve glucose homeostasis in T2D patients (18)(19) may result from  
196 several mechanisms. First, glucose handling in liver and peripheral tissues is reduced as a  
197 consequence of increased FAO (76). Next, PPAR $\alpha$  activation reduces PK expression and induces PDK4  
198 in the liver, leading to decreased glycolysis and enhanced gluconeogenesis (77). By contrast, as  
199 discussed above, clinical and genetic data revealed a role for PPAR $\alpha$  in preventing conversion from  
200 impaired glucose tolerance to overt T2D. This effect might stem from PPAR $\alpha$ -induced protection of  
201 pancreatic  $\beta$ -cells from lipotoxicity (78) as well as PPAR $\alpha$ -dependent decrease in insulin clearance  
202 through repression of CEACAM1, a membrane glycoprotein that promotes hepatic insulin  
203 endocytosis and targeting to the degradation process (79).

204 PPAR $\gamma$  is highly expressed in WAT, where it controls FA uptake and lipogenesis. Target genes  
205 contributing to this activity include fatty acid binding protein-4 (FABP4) and the fatty acid translocase  
206 CD36 (80). In addition, PPAR $\gamma$  is a master regulator of white adipocyte differentiation. Multiple TFs  
207 including the glucocorticoid receptor (GR) and STAT5A team up to induce PPAR $\gamma$  during adipogenesis  
208 (28), while other TFs such as C/EBP $\alpha$  cooperate with PPAR $\gamma$  to stimulate genomic binding and  
209 transcription of target genes (81), thereby regulating both house-keeping and adipocyte-specific  
210 functions (82). These PPAR $\gamma$ -mediated changes in gene expression are preceded by chromatin  
211 remodelling involving both adipocyte-specific TFs such as C/EBP $\beta$  (83) as well as ubiquitous TFs such  
212 as CCCTC-binding factor (CTCF) (84). Interestingly, promotion of adipogenesis by the mTORC1  
213 complex occurs through stimulation of PPAR $\gamma$  translation (85) and transcriptional activity (86), which  
214 contrasts with the inhibitory effect of mTORC1 on PPAR $\alpha$  discussed above (59).

215 In contrast to WAT, PPAR $\gamma$  target genes in BAT encode thermogenic proteins and inducers of  
216 mitochondrial biogenesis such as PGC1A and uncoupling protein 1 (UCP1, also known as  
217 thermogenin). PPAR $\gamma$  promotes differentiation of brown adipocytes, but activation of additional TFs  
218 including PPAR $\alpha$  is required to switch on their thermogenic program (75).

219 PPAR $\gamma$  enhances whole body insulin sensitivity through multiple mechanisms (**Figure 2**). By  
220 augmenting WAT expandability, PPAR $\gamma$  shifts lipids from liver and SKM to WAT, thereby indirectly  
221 increasing glucose utilization in liver and peripheral tissues. As a result of this 'lipid steal' process,  
222 lipotoxicity, which impairs insulin signalling, is alleviated. PPAR $\gamma$  also regulates the expression of  
223 adipocyte hormones such as adiponectin and leptin, which modulate liver and SKM insulin sensitivity  
224 (2). PPAR $\gamma$  induces adiponectin, an effect which likely contributes to PPAR $\gamma$ -mediated increase in  
225 glucose tolerance (87). Leptin expression is inhibited by PPAR $\gamma$  activation (88), which may contribute  
226 to TZD-induced appetite and body weight gain. Finally, PPAR $\gamma$  activation also improves pancreatic  $\beta$ -  
227 cell function and survival by preventing FA-induced impairment of insulin secretion (78) and  
228 enhancing the unfolded protein response (89). Thus, whereas PPAR $\alpha$  activation leads to energy

229 dissipation, activation of PPAR $\gamma$  stimulates energy storage in WAT, thereby sensitizing liver and  
230 peripheral tissues to insulin.

231 The contrasting mechanisms of action of PPAR $\alpha$  and PPAR $\gamma$  are also illustrated by their opposite  
232 function on hepatic lipid metabolism. Reduced hepatic steatosis due to increased FAO in hepatocytes  
233 occurs upon PPAR $\alpha$  activation in rodent models of NAFLD (90)(91). In contrast, PPAR $\gamma$  activation in  
234 rodents increases liver fat accumulation by enhancing hepatic expression of PPAR $\gamma$ -dependent genes  
235 involved in lipogenesis (80), as confirmed by liver-specific PPAR $\gamma$  deletion (92). Interestingly, hepatic  
236 PPAR $\gamma$  expression levels determine liver steatosis. Indeed, mice with low hepatic PPAR $\gamma$  expression  
237 are resistant to diet-induced development of fatty liver when treated with rosiglitazone, whereas  
238 liver steatosis is exacerbated in obese mice with high hepatic levels of PPAR $\gamma$  (93). The dimeric AP-1  
239 protein complex modulates NAFLD via differential regulation of hepatic PPAR $\gamma$  expression depending  
240 on the dimer composition. Whereas the FOS-like AP-1 transcription factor subunits FRA1 and FRA2  
241 inhibit the PPAR $\gamma$  pathway and reduce hepatic lipid content, other AP-1 proteins such as c-Fos and  
242 JunD induce hepatic PPAR $\gamma$  signalling and lipid accumulation (94). In NAFLD patients, PPAR $\gamma$   
243 expression is, however, unaltered (60) and TZD treatment rather lowers hepatic steatosis, likely due  
244 to decreased FA flux from WAT to liver (95)(96).

245 In addition to the 'classical' metabolic organs, energy homeostasis is also regulated by inter-organ  
246 communications involving the brain and the gut. Neuronal PPAR $\gamma$  deletion in mice diminishes food  
247 intake and energy expenditure resulting in reduced weight gain upon HFD feeding, suggesting that  
248 brain PPAR $\gamma$  exerts hyperphagic effects and promotes obesity (97). Similarly, central activation of  
249 PPAR $\alpha$  may also increase food intake (6), although not all studies concur (98). In the intestine, PPAR $\alpha$   
250 activation suppresses the transient postprandial hyperlipidemia by enhancing intestinal epithelial cell  
251 FAO (99). In addition, activation of intestinal PPAR $\alpha$  reduces cholesterol esterification, suppresses  
252 chylomicron production and increases HDL synthesis by enterocytes (100).

253

254 *Molecular basis for differential activities of PPAR $\alpha$  and PPAR $\gamma$*

255

256 The exact mechanisms via which the different PPAR isotypes – which share similar DNA binding  
257 motifs – bind and regulate different genes, remain to be fully established. Nevertheless, several  
258 explanations and hypotheses can be put forward. First, PPAR $\alpha$  is predominantly expressed in the  
259 liver, whereas PPAR $\gamma$  expression is highest in WAT (2). The different PPARs emerged during evolution  
260 from gene duplications, but subsequent sequence variations of their promoter and 3'UTR have  
261 contributed to acquisition of differential expression patterns and functions (101). Tissue-specific  
262 chromatin and TF environments also play a deterministic role by restricting PPAR recruitment to  
263 selective enhancers and therefore specifying PPAR target genes (28). This is illustrated by the tissue-  
264 specific PPAR $\gamma$  cistromes in white adipocytes and macrophages, both expressing high levels of PPAR $\gamma$ .  
265 The macrophage-specific PPAR $\gamma$  cistrome is defined by the pioneer TF PU.1 (102), which induces  
266 nucleosome remodelling and histone modifications, promoting the recruitment of additional TFs  
267 (103). In white adipocytes, however, these macrophage-specific binding regions are marked with  
268 repressive histone modifications, disabling PPAR $\gamma$  binding (104). Furthermore, PPAR $\gamma$  cistromes differ  
269 between different types of white adipocytes (epididymal vs. inguinal) and are associated with depot-  
270 specific gene expression patterns (105).

271 Nutritional status is another contributor to differential PPAR regulation. PPAR $\alpha$  is a metabolic sensor,  
272 switching its activity from coordination of lipogenesis in the fed state to promotion of FA uptake and  
273 oxidation during fasting (50). PPAR $\alpha$  activation during fasting involves the induction of the  
274 coactivator PGC1 $\alpha$  by the fasting-induced TF EB (TFEB) (106). In addition to PPAR $\alpha$  itself (107),  
275 circadian transcription of genes encoding acyl-CoA thioesterases coordinates cyclic intracellular  
276 production of FA ligands (108). The TF CREBH, a recently identified circadian regulator of hepatic lipid  
277 metabolism, rhythmically interacts with PPAR $\alpha$  and regulates its activity (109). Adjustment of PPAR $\alpha$   
278 transcriptional activity to nutritional status is also controlled by kinases phosphorylating PPAR $\alpha$  or its  
279 coregulators. In the fed state, PPAR $\alpha$  activity is enhanced through insulin-activated MAPK and  
280 glucose-activated PKC, while glucagon-activated PKA as well as AMPK increase PPAR $\alpha$  signaling in

281 fasting (50). Moreover, the fasting response is co-controlled by interaction of PPAR $\alpha$  with GR $\alpha$ , which  
282 show extensive chromatin colocalization and cooperate to induce lipid metabolism genes upon  
283 prolonged fasting through genomic recruitment of AMPK (110). By contrast, GR $\beta$  antagonizes  
284 glucocorticoid-induced signaling during fasting via inhibition of GR $\alpha$  and PPAR $\alpha$ , increasing  
285 inflammation and hepatic lipid accumulation (111).

286 PPAR $\gamma$  activity is higher in the fed state, in line with its major role in the regulation of lipid synthesis  
287 and storage. PPAR $\gamma$  activity in WAT is repressed during fasting via mechanisms involving SIRT1 (112)  
288 or AMPK (113). In mice, the amplitude of hepatic circadian clock gene expression is reduced by HFD  
289 feeding (114), whereas circadian rhythmicity of PPAR $\gamma$  and PPAR $\gamma$ -binding site-containing genes is  
290 induced (115). Thus, the HFD-induced transcriptional reprogramming relies at least in part on  
291 changes in expression, pattern of oscillation and chromatin recruitment of PPAR $\gamma$ . Gut microbiota,  
292 which also exhibit circadian activity (116), are drivers of this hepatic transcriptional reprogramming  
293 by PPAR $\gamma$  upon HFD in mice (117).

294 Nutritional status also links PPARs to FGF21 signaling. Indeed, fasting increases PPAR $\alpha$ -dependent  
295 FGF21 expression in liver, further enhancing FAO and ketogenesis (118). In WAT, PPAR $\gamma$  induces the  
296 expression of FGF21 (119), where it acts as an autocrine factor in the fed state, regulating PPAR $\gamma$   
297 activity through a feedforward loop mechanism (120). The related family member FGF1 is also  
298 induced by PPAR $\gamma$  in WAT, and this PPAR $\gamma$ -FGF1 axis is critical for maintaining metabolic homeostasis  
299 and insulin sensitization (121). In the pancreas, PPAR $\gamma$  agonism reverses the high glucose-induced  
300 impairment of islet function by enhancing FGF21 signaling (122).

301

### 302 **Combating inflammation: a shared function of PPAR $\alpha$ and PPAR $\gamma$**

303

304 Besides differentially regulating lipid and glucose metabolism, PPAR $\alpha$  and PPAR $\gamma$  also display a  
305 shared function, i.e. countering inflammation. However, the anti-inflammatory effects of PPAR $\alpha$  and  
306 PPAR $\gamma$  activation are likely distinct due to differences in tissue and cell-type expression.

307

308 *Anti-inflammatory effects*

309

310 MetS is accompanied by a low grade inflammatory state in different metabolic tissues – termed  
311 meta-inflammation – characterized by increased secretion of pro-inflammatory chemokines and  
312 cytokines, many of which (including TNF $\alpha$ , IL-1 and IL6) influence lipid metabolism and insulin  
313 resistance (123).

314 In WAT, fenofibrate as well as rosiglitazone reduce the expression of several pro-inflammatory  
315 mediators by white adipocytes, including IL-6 and the chemokines CXCL10 and MCP1 (124). PPAR $\gamma$   
316 also inhibits pro-inflammatory cytokine production by WAT-resident macrophages, and modulates  
317 macrophage polarization (125). Although innate immune cells such as macrophages have long been  
318 considered as the drivers of WAT inflammation and metabolic dysregulation, recent reports argue for  
319 an important role of the adaptive immune system, including WAT regulatory T cells (Tregs) (126).  
320 PPAR $\gamma$  acts as a crucial molecular orchestrator of WAT Treg accumulation, phenotype, and function  
321 (127)(128). Indeed, the WAT Treg transcriptome alterations in obese mice are dependent on PPAR $\gamma$   
322 phosphorylation by cyclin-dependent kinase 5 (CDK5) (127). In addition, PPAR $\gamma$  expression in WAT  
323 Tregs is necessary for complete restoration of insulin sensitivity in obese mice upon pioglitazone  
324 treatment (128). PPAR $\gamma$  is also implicated in the metabolic reprogramming of CD4 $^+$  T-cells. Indeed, T-  
325 cell activation leads to mTORC1-dependent PPAR $\gamma$  induction and increased expression of genes  
326 involved in FA uptake, enabling the rapid proliferation of these T-cells, a prerequisite for an optimal  
327 immune response (129).

328 In liver as well as isolated hepatocytes, IL-1-mediated induction of pro-inflammatory genes is  
329 repressed by pretreatment with PPAR $\alpha$  agonists (130). In the vascular wall, PPAR $\alpha$  and PPAR $\gamma$   
330 modulate the recruitment of leukocytes to endothelial cells, stimulate cholesterol efflux from  
331 macrophage-derived foam cells, and regulate inflammatory cytokine production by smooth muscle  
332 cells (131).

333

334 *Molecular mechanisms*

335

336 Inhibition of pro-inflammatory gene expression is the main process underlying the anti-inflammatory  
337 properties of PPAR $\alpha$  and PPAR $\gamma$ . Several mechanisms have been proposed for transcriptional  
338 repression by PPARs that are not mutually exclusive. These include direct physical interaction of  
339 PPAR $\alpha$  or PPAR $\gamma$  with several pro-inflammatory TFs including AP-1 and NF- $\kappa$ B (132)(133). Repression  
340 of inflammation independently of direct DNA binding of PPAR $\alpha$  results in anti-inflammatory and anti-  
341 fibrotic effects in a mouse model of non-alcoholic steatohepatitis (NASH) (134). In addition to this  
342 PPRE-independent transrepression mechanism, interaction between NF- $\kappa$ B and PPRE-bound PPAR $\alpha$   
343 also occurs, leading to repression of TNF- $\alpha$ -mediated upregulation of complement C3 gene  
344 expression and protein secretion during acute inflammation (135). Moreover, simultaneous  
345 activation of PPAR $\alpha$  and GR $\alpha$  increases the repression of NF- $\kappa$ B-driven genes, thereby decreasing  
346 cytokine production (136). Transcriptional repression of pro-inflammatory genes by PPAR $\gamma$  may  
347 include ligand-activated PPAR $\gamma$  sumoylation, which targets the receptor to corepressor complexes  
348 assembled at inflammatory gene promoters. This prevents promoter recruitment of the proteasome  
349 machinery that normally mediates the inflammatory signal-dependent removal of corepressor  
350 complexes required for gene activation. As a result, these complexes are not cleared from the  
351 promoters and inflammatory genes are maintained in a repressed state (137).

352 In addition to downregulating the expression of pro-inflammatory genes, PPAR $\alpha$  (138) as well as  
353 PPAR $\gamma$  (139) also suppress inflammation by direct upregulation of genes with anti-inflammatory  
354 properties such as IL-1Ra, suggesting a possible cooperation between PPAR-dependent  
355 transactivation and transrepression to counter inflammation.

356

357 **PPAR $\alpha$  and PPAR $\gamma$  in human NAFLD**

358

359 The anti-inflammatory properties of PPAR $\alpha$  likely contribute to the improved lobular inflammation  
360 and hepatocellular ballooning observed in NAFLD patients treated with pioglitazone (140) or  
361 elafibranor (141), a dual PPAR $\alpha$ / $\beta$ ( $\delta$ ) agonist. Pioglitazone reduces hepatic steatosis in NAFLD  
362 patients (140), likely due to PPAR $\gamma$  activation. In line, the pure PPAR $\gamma$  agonist rosiglitazone also  
363 lowers liver fat in humans (96), whereas the pure PPAR $\alpha$  agonist fenofibrate does not (69).  
364 Treatment of dyslipidemic patients with fenofibrate lowers plasma atypical deoxysphingolipids (142),  
365 whose levels increase upon transition of simple steatosis to NASH (143). Thus, both PPAR $\alpha$  and  
366 PPAR $\gamma$  activation appear beneficial in human NAFLD, although the underlying mechanisms clearly  
367 differ. Whereas effects of PPAR $\alpha$  agonism on inflammation and ballooning are due to direct PPAR $\alpha$   
368 activation in the liver, PPAR $\gamma$ 's effects on hepatic steatosis are likely mediated by indirect  
369 mechanisms, such as suppression of FA flux to the liver, in line with the low expression and absence  
370 of PPAR $\gamma$  induction in human fatty liver (60).

371

### 372 **PPAR $\beta$ / $\delta$ , the clinically enigmatic third PPAR**

373

374 Selective synthetic PPAR $\beta$ / $\delta$  agonists are not yet clinically available. However, beneficial effects of  
375 PPAR $\beta$ / $\delta$  activation on various components of the MetS, displaying both differences and similarities  
376 with PPAR $\alpha$  and PPAR $\gamma$ , have been reported.

377

378 *PPAR $\beta$ / $\delta$  shares metabolic effects with both PPAR $\alpha$  and PPAR $\gamma$*

379

380 *PPARD* variants are associated with cholesterol metabolism (144) as well as insulin sensitivity (145)  
381 and T2D risk (146). In addition, several SNPs in *PPARD* associate with CV risk (41). In obese men,  
382 administration of the synthetic PPAR $\beta$ / $\delta$  agonist GW501516 lowers liver fat content and plasma  
383 levels of insulin, FA, TG, and LDL-C (147). These beneficial effects on plasma lipids are also observed  
384 in overweight patients treated with MBX-8025, a novel PPAR $\beta$ / $\delta$  agonist (148). Thus, PPAR $\beta$ / $\delta$



385 agonism combines the metabolic effects of PPAR $\alpha$  and PPAR $\gamma$  activation on lipid metabolism and  
386 glucose homeostasis, respectively. Preclinical studies support this conclusion, as GW501516  
387 administration to overweight monkeys (149) or obese rats (150) lowers serum LDL-C and raises HDL-  
388 C, while improving insulin sensitivity.

389

#### 390 *Cellular and molecular mechanisms*

391

392 PPAR $\beta/\delta$  activation protects from diet- or genetically induced obesity in mice by increasing energy  
393 expenditure (151). In BAT, activation of PPAR $\beta/\delta$  induces the expression of thermogenic genes  
394 including UCP1 as well as genes involved in FAO (151). In addition, PPAR $\beta/\delta$  agonism promotes FAO  
395 in SKM (152), WAT (153), and liver (154). PPAR $\beta/\delta$  in brain also controls energy expenditure, since  
396 neuron-specific deletion of PPAR $\beta/\delta$  increases the susceptibility to diet-induced obesity (155). Thus,  
397 similar to PPAR $\alpha$ , activation of PPAR $\beta/\delta$  induces energy dissipation. Interestingly, both isotypes  
398 exhibit crosstalk in liver, where PPAR $\beta/\delta$  stimulates the production of the PPAR $\alpha$  ligand 16:0/18:0-  
399 phosphatidylcholine as well as PPAR $\alpha$  expression and DNA-binding activity, thereby increasing  
400 hepatic FAO (156). Enhanced FAO upon PPAR $\beta/\delta$  activation contributes to its plasma lipid-lowering  
401 effects, together with decreased cholesterol absorption (157) and increased trans-intestinal  
402 cholesterol efflux (158). PPAR $\beta/\delta$  also raises HDL-C by increasing hepatic expression of  
403 apolipoprotein AII (APO-AII) (159) and phospholipid transfer protein (PLTP) (160).

404 Countering inflammation is also a hallmark of PPAR $\beta/\delta$  agonism. Similar to PPAR $\alpha$  and PPAR $\gamma$ , ligand-  
405 activated PPAR $\beta/\delta$  inhibits pro-inflammatory cytokine production (161) and regulates macrophage  
406 polarization in WAT (162) and liver (163). Inhibition of NF- $\kappa$ B is one anti-inflammatory mode of action  
407 of PPAR $\beta/\delta$  (164).

408 PPAR $\beta/\delta$  agonism improves insulin sensitivity through several mechanisms (**Figure 3**). In SKM,  
409 PPAR $\beta/\delta$  activation favours fiber-type switching from type II fast-twitch glycolytic fibers towards type  
410 I slow-twitch oxidative fibers (165) via mechanisms involving PGC1 $\alpha$  (166) and an estrogen-related

411 receptor  $\gamma$  (ERR $\gamma$ )/miRNA regulatory circuit (167), thereby improving glucose handling (168). The type  
412 I fiber fraction is reduced in T2D patients (169), which may contribute to altered glucose  
413 homeostasis. Myocyte-selective PPAR $\beta/\delta$  knockout mice exhibit a fiber-type switching towards fewer  
414 type I fibers that precedes the development of a diabetic phenotype (166). PPAR $\beta/\delta$  also improves  
415 glucose handling and insulin sensitivity in the liver. GW501516 treatment suppresses hepatic glucose  
416 output and enhances glucose disposal by increasing glucose flux through the pentose phosphate  
417 pathway (170). Liver-restricted PPAR $\beta/\delta$  overexpression reduces fasting glucose levels and stimulates  
418 hepatic glycogen production via upregulation of glucose utilization pathways (171). In addition,  
419 stress-induced JNK signalling is reduced, contributing to improved hepatic insulin sensitivity (171).  
420 PPAR $\beta/\delta$  agonism promotes pancreatic  $\beta$ -cell mitochondrial function and ATP production, thus  
421 improving glucose-stimulated insulin secretion (172). In addition, PPAR $\beta/\delta$  increases intestinal  
422 production of the incretin glucagon-like peptide 1 (GLP1), an insulin secretagogue (173).  
423 In summary, the mechanisms underlying the metabolic effects of PPAR $\beta/\delta$  resemble those of PPAR $\alpha$ ,  
424 which promotes energy dissipation, as opposed to PPAR $\gamma$ , which promotes energy storage. PPAR $\beta/\delta$   
425 normalizes plasma lipids through enhanced FAO in several tissues, coupled to actions on hepatic  
426 apolipoprotein metabolism and intestinal cholesterol homeostasis. However, in contrast to PPAR $\alpha$   
427 and similar to PPAR $\gamma$ , activation of PPAR $\beta/\delta$  enhances insulin sensitivity. The mechanisms underlying  
428 PPAR $\beta/\delta$ -mediated improvement in glucose handling are not similar to PPAR $\gamma$ , but involve PPAR $\beta/\delta$ -  
429 specific actions on SKM fiber type distribution, hepatic glucose metabolism, and pancreatic islet  
430 function.

431

#### 432 **Where do we stand?**

433

434 Currently used PPAR agonists display weak potencies (PPAR $\alpha$ ) or are associated with important side  
435 effects (PPAR $\gamma$ ). Optimization of therapeutic efficacy may be achieved through the development of  
436 selective PPAR modulators that retain the beneficial effects of PPAR activation while diminishing

437 unwanted side effects (174). Pemafibrate (K-877), a promising candidate among the selective PPAR $\alpha$   
438 agonists (175), displayed greater lipid modifying efficacy than fenofibrate in a phase II trial, with little  
439 or no effect on serum creatinine and homocysteine levels (176). This compound is currently  
440 undergoing a phase III clinical cardiovascular prevention trial, PROMINENT, in patients with high TG  
441 and low HDL-C. Administration of LY518674, another potent and selective PPAR $\alpha$  agonist, to MetS  
442 patients increased cholesterol efflux capacity without changing steady-state HDL-C or APO-AI levels  
443 (177). Use of the PPAR $\gamma$  agonists rosiglitazone and pioglitazone is restricted due to safety concerns  
444 related to congestive heart failure and bone fracture. Better insights into the molecular mechanisms  
445 of PPAR $\gamma$  activity may lead to new compounds with fewer side effects. As an example, PPAR $\gamma$   
446 phosphorylation at serine 273 by CDK5 modifies interaction with thyroid hormone receptor-  
447 associated protein 3 (THRAP3) and alters regulation of a large number of genes whose expression is  
448 changed in obesity including adiponectin (178)(179). These findings spawned the development of a  
449 new class of anti-diabetic drugs that inhibit CDK5-mediated phosphorylation of PPAR $\gamma$  while lacking  
450 classical agonist activity. Along these lines, Gleevec blocks CDK5-mediated PPAR $\gamma$  phosphorylation,  
451 exhibiting potent anti-diabetic effects in obese mice without triggering fluid retention or weight gain  
452 (180). Whether this concept will eventually result in novel, clinically useful compounds is still unclear.  
453 The non-TZD PPAR $\gamma$  modulator INT131 improves glucose tolerance in T2D patients to a similar extent  
454 as rosiglitazone without adverse effects on body weight or hemodilution (181). The PPAR $\beta/\delta$  agonist  
455 GW501516, whose development has been abandoned because of preclinical safety issues (182), and  
456 MBX-8025 have shown efficacy in decreasing plasma TG and increasing HDL-C as well as improving  
457 insulin sensitivity and liver function (148).

458 Alternatives to selective agonists are dual (activating two PPAR isotypes) and pan-agonists (activating  
459 the three PPARs), aiming to combine the beneficial effects of each receptor isotype. The pan-agonist  
460 chiglitazar (CS038) improves the lipid profile and insulin sensitivity without increasing body weight in  
461 animal models of obesity, and is currently in phase III clinical development (183). IVA337, a pan-  
462 agonist which prevents and reverses fibrosis in skin (184), is currently entering phase II for the

463 treatment of NASH. Many dual PPAR $\alpha$ / $\gamma$  agonists, also termed glitazars, showed improved efficacy on  
464 glucose and lipid metabolism in clinical trials, although safety concerns have halted further  
465 development (185). Substantial preclinical and clinical evidence suggests that a large part of adverse  
466 events are drug-specific, off-target actions and hence PPAR-independent, although identifying the  
467 mechanisms is often challenging in the in vivo setting as off-target actions are superimposed on  
468 target-mediated effects (186). Two phase III trials with saroglitazar showed improved glucose and  
469 lipid profiles in patients with diabetic dyslipidemia compared to pioglitazone (187) or placebo (188).  
470 In contrast to the other PPAR $\gamma$ -dominant glitazars, saroglitazar predominantly activates PPAR $\alpha$  with  
471 only moderate PPAR $\gamma$  agonism, which may explain the lack of typical PPAR $\gamma$  side effects. The non-TZD  
472 dual PPAR $\alpha$ / $\gamma$  agonist DSP-8658, reportedly in phase I development, normalizes blood glucose and  
473 plasma lipids in obese mice without increasing adipogenesis (189). The dual PPAR $\beta$ ( $\delta$ )/ $\gamma$  agonist  
474 DB959 regulates glucose, TG, and HDL in preclinical models of T2D and dyslipidemia (190).  
475 Elafibranor (GFT505), a dual PPAR $\alpha$ / $\beta$ ( $\delta$ ) agonist, demonstrated protective effects against hepatic  
476 steatosis, inflammation, and fibrosis in animal models of NAFLD/NASH (90). In phase IIa trials,  
477 elafibranor improved the lipid profile and enhanced insulin sensitivity in dyslipidemic and prediabetic  
478 patients (191) as well as in obese individuals (192). The GOLDEN-505 phase IIb study in NASH  
479 patients showed that elafibranor treatment induces resolution of NASH without worsening fibrosis in  
480 a higher proportion of patients compared to placebo. The drug was well tolerated and improved  
481 glucose homeostasis and the patients' CV risk profile (141).

482

### 483 **PPARs are still valuable targets for metabolic diseases**

484

485 Over the last decades, market withdrawals and failed drug development programs have cast doubts  
486 on the clinical value of PPAR-activating compounds. However, this issue is not black and white. The  
487 pure PPAR $\gamma$  agonist rosiglitazone as well as dual PPAR agonists with predominant PPAR $\gamma$  activating  
488 properties all displayed important adverse effects, leading to restricted use or halted development.

489 However, most of these side effects were either drug-specific and hence off-target, or related to  
490 excessive PPAR $\gamma$  activation. Several fibrate trials, including FIELD and ACCORD, failed to meet the  
491 primary endpoint of reduced CV risk. However, such negative outcomes are likely linked to  
492 inappropriate patient selection, since subgroup analyses revealed significant CV risk reduction in  
493 those patients with marked dyslipidemia upon fenofibrate treatment (21). In addition, in several of  
494 these fibrate trials, including BIP and FIELD, the proportion of patients receiving statin therapy was  
495 unbalanced between the placebo and treatment groups. Correction for this non-randomized statin  
496 drop-in in the FIELD study estimated that fenofibrate induces a 19% relative CV risk reduction (193).  
497 To date, the mechanism of action of endogenous ligands is not fully elucidated. Therefore, one needs  
498 to rely on knockout mice and synthetic ligands to study PPAR functions, resulting in limitations in our  
499 understanding of the physiological functions of PPARs. Nevertheless, it has become increasingly clear  
500 that PPAR $\alpha$  and PPAR $\gamma$  agonism display contrasting metabolic effects with different mechanisms of  
501 action. Whereas PPAR $\beta/\delta$  agonism is more related to PPAR $\alpha$ , subtle differences exist (e.g. in  
502 regulation of glucose homeostasis). These findings are in line with the enhanced metabolic actions  
503 and improved safety profiles of novel compounds such as dual PPAR $\alpha/\beta(\delta)$  ligands, which target both  
504 the lipid abnormalities (via PPAR $\alpha$  and PPAR $\beta/\delta$ ), as well as the glucose alterations (via PPAR $\beta/\delta$ ) in  
505 MetS patients without displaying PPAR $\gamma$ -related adverse effects. Altogether, we are convinced that  
506 modulating PPARs in metabolic disorders remains a valuable and promising approach with a future  
507 ahead.

508

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515

516

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1035

1036 **Figure legends**

1037

1038 **Figure 1. PPAR $\alpha$  activation stimulates fatty acid and triglyceride metabolism.** During fasting  
1039 (yellow), fatty acids (FA) released from white adipose tissue (WAT) are taken up by the liver and  
1040 transported to mitochondria where FA oxidation (FAO) takes place to produce acetyl-CoA (AcCoA)  
1041 which can be further converted to ketone bodies serving as fuel for peripheral tissues. In the fed  
1042 state (green), AcCoA is shuttled to the cytosol where de novo lipogenesis (DNL) takes place. Effects of  
1043 PPAR $\alpha$  activation and PPAR $\alpha$  target genes are indicated in pink. FAO is also stimulated by PPAR $\alpha$  in  
1044 WAT and skeletal muscle (SKM). By regulating hepatic apolipoprotein synthesis, PPAR $\alpha$  activation  
1045 decreases plasma triglycerides (TG) and low density lipoprotein-cholesterol (LDL-C) and increases  
1046 high density lipoprotein-cholesterol (HDL-C) levels. PPAR $\alpha$  also acts on brown adipose tissue (BAT),  
1047 gut and pancreas, whereas central effects are unclear. Blue brackets indicate PPAR $\alpha$  actions  
1048 restricted to mice and not (peroxisome proliferation, reduced liver fat content) or to a lesser extent  
1049 (reduced APO-B production) seen in humans

1050

1051 **Figure 2. PPAR $\gamma$  activation increases whole body insulin sensitivity.** In white adipose tissue (WAT),  
1052 PPAR $\gamma$  activation (effects are indicated in pink) enhances fatty acid (FA) uptake and storage,  
1053 lipogenesis and adipogenesis (lipid steal action). PPAR $\gamma$  activation lowers circulating FA levels,  
1054 alleviating lipotoxicity and increasing insulin sensitivity. PPAR $\gamma$  agonism induces adiponectin  
1055 production by WAT further enhancing insulin sensitivity and lowering blood glucose. PPAR $\gamma$  also  
1056 exerts metabolic effects on brown adipose tissue (BAT), brain and pancreas. Increased hepatic  
1057 steatosis upon PPAR $\gamma$  activation occurs in mice but not in humans (blue brackets), who in contrast  
1058 display increased hepatic insulin sensitivity due to reduced FA flux from WAT.

1059

1060 **Figure 3. PPAR $\beta/\delta$  activation enhances glucose and lipid homeostasis.** In skeletal muscle (SKM),  
1061 PPAR $\beta/\delta$  activation (effects are indicated in pink) favours fiber-type switching towards type I

1062 oxidative fibers, which have a higher glucose-handling capacity compared to type II fibers. PPAR $\beta/\delta$   
1063 also augments fatty acid oxidation (FAO) in SKM, liver and white adipose tissue (WAT) and enhances  
1064 hepatic glucose metabolism and pancreatic  $\beta$ -cell function. PPAR $\beta/\delta$  activation decreases fatty acids  
1065 (FA), triglycerides (TG) and low density lipoprotein-cholesterol (LDL-C) and increases high density  
1066 lipoprotein-cholesterol (HDL-C) levels in blood. Metabolic effects of PPAR $\beta/\delta$  agonism also take place  
1067 in brain and gut.