PPAR control of metabolism and cardiovascular functions

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Abstract | Peroxisome proliferator-activated receptor-α (PPARα), PPARδ and PPARγ are transcription factors that regulate gene expression following ligand activation. PPARα increases cellular fatty acid uptake, esterification and trafficking and regulates lipoprotein metabolism genes. PPARδ stimulates lipid and glucose utilization by increasing mitochondrial function and fatty acid desaturation pathways. By contrast, PPARγ promotes fatty acid uptake, triglyceride formation and storage in lipid droplets, thereby improving insulin sensitivity and glucose metabolism. PPARs also exert anti-atherogenic and anti-inflammatory effects on the vascular wall and immune cells. Clinically, PPARγ activation by glitazones and PPARα activation by fibrates improve insulin resistance and dyslipidaemia, respectively. PPARs are also physiological master switches in the heart, steering cardiac energy metabolism in cardiomyocytes, thereby affecting pathological heart failure and diabetic cardiomyopathy. Novel PPAR agonists in clinical development are providing new opportunities in the management of metabolic and cardiovascular diseases.

Introduction

Cardiovascular diseases (CVD) are a leading cause of morbidity and mortality, representing 33% of deaths worldwide[1]. Obesity, diabetes mellitus, dyslipidaemia and hypertension are risk factors for CVD and can be targeted by pharmacological strategies. Although LDL-cholesterol lowering with statins reduces the risk of CVD, a residual risk persists[2], particularly in patients with diabetes and combined dyslipidaemia characterized by high triglyceride and low HDL-

cholesterol levels. The peroxisome proliferator-activated receptor (PPAR) transcription factors regulate genes that encode proteins controlling metabolic homeostasis and function in multiple organs, including the liver, adipose tissue, intestine, skeletal muscle, vascular wall and heart. PPAR agonists (such as fibrates for PPARα and glitazones for PPARγ) have been used for decades in the treatment of dyslipidaemia and diabetes. However, clinical trials of these agents have resulted in mixed results on reducing the risk of CVD.

In this Review, we discuss how PPARs regulate the atherogenic lipid profile, vascular atherosclerosis and cardiac remodelling. Given the abundant literature on their metabolic and vascular functions, we focus on findings published after 2017, whereas the cardiac functions of PPARs are covered in more detail, given the paucity of clinical pharmacological data in this field.

Overview of the PPAR family

PPARα (also known as nuclear receptor subfamily 1 group C member 1 (NR1C1)), PPARδ (also known as PPARβ or NR1C2) and PPARγ (also known as NR1C3) are nuclear receptors regulating numerous metabolic functions through intra-organ and inter-organ connections[3]. The genes encoding PPARα, PPARδ and PPARγ are located on human chromosomes 22, 6 and 3 and murine chromosomes 15, 17 and 6, respectively. The PPAR proteins are organized into domains. The N-terminal domain exerts activation functions and determines target-gene specificity. The DNA-binding domain contains two zinc-fingers that allow binding to DNA PPAR response elements (PPRE). The hinge region provides structural flexibility and docks several nuclear receptor cofactors. The C-terminal domain contains the ligand-binding domain and is involved in the interaction with its obligatory heterodimer partner, the retinoid X receptor and other co-regulators, such as nuclear receptor corepressor 1, PPARγ-coactivator 1α (PGC1α) or receptor-interacting protein 140[4,5]. PPARs also extensively crosstalk with other

regulatory factors, such as the Krüppel-like factors (KLFs), which modulate PPARγ-mediated adipogenesis[6–8], PPARα expression in cardiomyocytes[9,10] and PPARδ activity in skeletal muscle[11]. PPAR activity is also modulated by environmental factors, such as nutritional status and circadian timing, through multiple interactions and post-translational modifications[12].

PPARs are lipid sensors that modulate whole-body energy metabolism. PPARα promotes the adaptive response to fasting by controlling fatty acid transport, oxidation and ketogenesis. PPARγ is a master regulator of adipogenesis, which can increase lipid storage, improve insulin sensitivity and glucose metabolism through a lipid-steal action. PPARδ increases both lipid and glucose metabolism and participates in the response to exercise by regulating the switch from glycolytic to oxidative muscle fibres[3].

Ligand-activated PPARs bind to PPREs, consisting of a repetition of the AGG(A/T)CA sequence spaced by one or two nucleotides (direct repeat 1 or direct repeat 2) in the regulatory regions of target genes, a process called transactivation[5]. PPARs also exert anti-inflammatory effects by repressing pro-inflammatory pathways, a process termed transrepression[5,13]. However, the mechanisms mediating transrepression are not understood in detail.

Unsaturated fatty acid and derivatives provided by the diet, de novo lipogenesis and triglyceride lipolysis are natural PPAR ligands (Table 1). Synthetic PPAR agonists were serendipitously identified and comprise the fibrates and glitazones, which activate PPARα and PPARγ, respectively. The discovery of the PPAR isotypes allowed targeted screening for agonists with single, dual or pan-PPAR agonist profiles. Examples include the PPARα agonist pemafibrate[14], PPARδ agonist seladelpar[15], the dual PPARα and PPARγ agonist saroglitazar[16], the dual PPARα and PPARδ agonist elafibranor[17], and the pan-PPAR agonists lanifibranor[18] and chiglitazar[19], some of which are in development for the treatment of metabolic diseases and CVD[3,12]. Given that compounds with different chemical structures display distinct receptor-binding modalities, inducing specific conformational changes and cofactor

interactions, different regulatory responses might occur. Together with compound-specific pharmacokinetic characteristics, this situation results in selective PPAR modulator profiles, which might improve clinical efficacy (Table 1).

Metabolic control by PPARs

Liver

PPARα is the predominant PPAR isoform in the liver, where it regulates genes encoding proteins involved in lipid and lipoprotein metabolism. Activated by fatty acid released from triglyceride lipolysis, PPARα increases fatty acid uptake, lipogenesis, oxidation[3,12] and ketogenesis[20] depending on the nutritional status (that is, fed or fasted). In the post-prandial state, characterized by high circulating glucose and insulin levels, insulin-activated MAPK and glucose-activated protein kinase C induce PPARα activity, thereby favouring fatty acid synthesis, elongation and desaturation, simultaneously producing endogenous PPAR ligands. During prolonged fasting, glucagon-activated protein kinase A and induction of the AMPK pathway increase PPARα signalling through phosphorylation and interaction with the PGC1α coactivator[5], consequently switching fatty acid metabolism to oxidation and ketogenesis[5,12]. Therefore, fatty acid synthesis and oxidation display a circadian rhythmicity aligned with a circadian regulation of hepatic PPARα. Accordingly, lipid-lowering treatment with a PPARα agonist is more efficacious at the peak of liver PPARα expression[21]. PPARα also contributes to the adaptation in energy substrate utilization by increasing ketone body production during pathophysiological conditions such as sepsis and functioning with PPARγ to prevent sepsis-related cardiac dysfunction, thereby improving survival[22,23].

Well-known regulatory stimuli of PPARα expression are fasting, growth hormones, leptin and glucocorticoids[13]. Induction of hepatocyte PPARα expression upon fasting occurs through a complex autoregulatory loop that involves lysine-specific demethylase 6B (KDM6B), NAD-dependent protein deacetylase sirtuin 1 (SIRT1) and PPARα. Interference

with this complex by hepatocyte-specific *Kdm6b* deletion in mice lowers the expression of PPARα and its target genes[24]. Moreover, mice with hepatocyte-specific *Vps15* deletion (the gene encoding regulatory subunit 4 of phosphoinositide 3-kinase, a protein involved in autophagy) have a loss of autophagy, leading to the accumulation of the two PPARα co-repressors, histone deacetylase 3 and nuclear receptor corepressor 1 (NCOR1), thereby repressing PPARα transcription[25]. In addition, hepatic PPARα polyubiquitination and degradation are inhibited in fasted mice with hepatic *Paqr3* deletion[26].

Obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) increase the risk of CVD[27]. Visceral obesity and hepatic steatosis drive atherogenic dyslipidaemia, which is characterized by plasma hypertriglyceridaemia, increased concentrations of small dense LDL particles and decreased HDL-cholesterol levels, thereby increasing the risk of myocardial infarction, stroke or revascularization (Table 2). Hepatic *PPARA* mRNA levels and activity decrease with the progression of NAFLD, owing to elevated levels of G protein pathway suppressor 2, a subunit of the PPAR–NCOR1 complex, in non-alcoholic steatohepatitis (NASH) and liver fibrosis[28,29]. Hepatic PPARα-deficient mice have increased liver steatosis and inflammation, with increased levels of pro-inflammatory macrophages, hyperlipidaemia and hypercholesterolemia with ageing[30–32]. Impaired hepatic PPARα metabolism results in compensatory extrahepatic fatty acid oxidation (FAO), protecting against fasting-induced hepatosteatosis in mice[33]. Fibroblast growth factor 21 is a fasting-induced PPARα target with lipid-lowering[34] and hepato-protective properties and is currently under development for the treatment of NASH[35,36].

In patients with dyslipidaemia, fibrates lower plasma triglyceride levels and increase plasma levels of HDL cholesterol, apolipoprotein A-I (ApoA-I) and ApoA-II[13]. PPARα increases intravascular lipolysis by inducing PPRE-mediated expression and activity of the enzyme lipoprotein lipase (which hydrolyses triglycerides in lipoproteins) and expression of

its activator ApoA-V, while decreasing expression of its inhibitor ApoC-III[12] (Table 2). In mice, pemafibrate corrects dyslipidaemia by increasing reverse cholesterol transport and decreasing levels of systemic and hepatic inflammatory markers, thereby decreasing histological NASH and atherosclerosis[14,37,38].

PPARα activation also affects the levels of liver and plasma bioactive lipids. In patients with dyslipidaemia, fenofibrate decreases plasma levels of atypical deoxysphingolipids[39]. In non-obese diabetic mice, fenofibrate increases very-long-chain sphingolipids and exerts anti-inflammatory and anti-apoptotic actions in the endocrine pancreas[40]. Conversely, PPARα activation in humans with diabetes does not improve glucose metabolism[41,42]. Interestingly, in mice, NASH-induced myocardial steatosis, inflammation and fibrosis are prevented by PPARα activation[43].

Hepatic PPARδ induces FAO, increases lipogenesis (to supply fatty acids as skeletal muscle energy substrates), increases glucose uptake, glycogen storage and glycolysis, and decreases gluconeogenesis[3,12]. The differential functions of hepatic PPARα and PPARδ are not well understood. PPARα and PPARδ have similar effects on plasma lipoprotein metabolism (raising plasma HDL-cholesterol levels and lowering LDL-cholesterol and triglyceride levels), but can also lower levels of free fatty acids. PPARδ also lowers ApoC-III levels and increases ApoA-II levels[12] (Table 2). Moreover, PPARδ stimulates the expression of hepatic PPARα and its target genes[44]. Interestingly, PPARδ expression is reduced in the livers of patients with severe hepatic steatosis[45], but do not decrease further as the disease progresses to NASH[28]. PPARδ-mediated inhibition of VLDL receptor expression might protect against steatosis[45].

In mice, hepatocyte PPARγ activation induces steatosis[46], an effect not observed in humans[12,28]. However, PPARγ is expressed in rodent and human hepatic stellate cells, and PPARγ activation protects against hepatic stellate cells conversion to profibrogenic myofibroblasts[47].

Adipose tissue

Adipose tissue is composed of adipocytes and immune, endothelial and vascular cells. Adipose tissue is a secretory organ, which affects liver, vessel and heart function, secreting adipokines, microparticles and lipids. Body distribution, quality and level of expansion regulate the biological activity of adipose tissue.

In contrast to subcutaneous white adipose tissue, the amount of visceral white adipose tissue positively correlates with the risk of CVD[48], whereas brown and beige adipose tissue protects the cardiovascular system by promoting energy expenditure[48]. Remote adipose tissue depots exert endocrine cardiovascular regulatory actions by secreting bioactive substances, whereas epicardial and perivascular adipose tissue modulates cardiovascular functions through paracrine effects[48,49]. In obesity, diabetes or inflammation, the adipose secretome becomes pro-inflammatory and pro-atherogenic, thereby increasing the risk of CVD[48].

- *White adipose tissue.* PPARγ increases adipocyte differentiation, fatty acid uptake and storage into lipid droplets, thereby decreasing ectopic lipid deposition and improving systemic insulin sensitivity[3,12] (Table 2). Studies have shed further light on the molecular mechanisms that regulate PPARγ activity in adipose tissue. Deficiency of the mediator of RNA polymerase II transcription subunit 19 (MED19) in mouse adipocytes reduces PPARγ-induced adipogenesis[50]. Adipocyte-specific deletion of transcriptional coactivator with PDZ-binding motif improved glucose tolerance and insulin sensitivity and decreased adipose tissue inflammation by de-repressing PPARγ activity in mice[51]. PPARγ also interacts with the epigenetic modulator methylcytosine dioxygenase TET1 to control adipocyte DNA methylation, target-gene transcription and insulin sensitivity in vitro in 3T3-L1 adipocytes[52,53]. Moreover, heat shock protein 20 interacts with the ubiquitin ligase complex F-box only protein

4 to promote PPARγ degradation, and its deletion in mice mimicked PPARγ activation[54]. Adipose tissue-specific PPARγ$_2$ deficiency results in metabolic inflexibility in mice[55] (Table 3), reduces adipose tissue lipid storage and redirects lipids to muscle, causing triglyceride accumulation in skeletal muscle and increased insulin resistance[55]. Interestingly, a genetic mutation that prevents PPARγ SUMOylation of Lys107 improves insulin sensitivity in mice with diet-induced obesity without increasing adiposity[56].

PPARδ modulates preadipocyte differentiation in vitro[57]. Moreover, PPARδ drives the polarization of anti-inflammatory M2 macrophages in adipose tissue and exerts anti-inflammatory properties[58]. In mice, constitutive PPARδ activation in adipose tissue induce weight loss and protect against obesity[59,60]. However, this effect is not observed in individuals who are overweight, although an improved lipid profile and reduced waist circumference were observed[61].

- Brown adipose tissue and browning. In brown adipose tissue, PPARγ induces the expression of thermogenic and mitochondrial biogenesis proteins, including uncoupling protein 1, PR domain-containing zinc finger protein 16 (PRDM16) and PGC1α[3]. In addition, PPARγ can regulate brown adipocyte differentiation. Glitazone treatment activates white adipose tissue browning and increases expression of uncoupling protein 1 and cell death-inducing DNA fragmentation factor-α subunit-like effector A and SIRT1. In conditions of energy deficiency, SIRT1 is activated and deacetylates PPARγ on Lys268 and Lys293, which leads to the recruitment of PRDM16 and expression of brown adipose tissue genes[62]. Regulation of PPARγ through this pathway or by inhibition of Ser273 phosphorylation, which protects mice from insulin resistance induced by a high-fat diet[63], could be applied in the design of novel PPARγ agonists to dissociate insulin-sensitizing from the adverse effects of glitazone treatment (adiposity, reduced bone density, fluid retention and cardiac hypertrophy)[64].

PPARα is highly expressed in brown adipose tissue, where it regulates the expression of lipid oxidation and thermogenesis genes through interaction with PGC1α[65] following activation by ligands released by β-adrenergic stimulation of lipolysis. Although PPARα expression is low in white adipose tissue[3], activation of PPARα by adipose triglyceride ligase-mediated lipolysis-derived fatty acid ligands promotes mitochondrial activity, adipose tissue energy metabolism and a brown–beige adipose tissue-like phenotype[66–68]. PPARα agonist treatment reduces adiposity in male but not in female mice, probably owing to negative interference between PPARα and oestrogen receptor signalling leading to sex-specific regulatory responses of FAO genes in the liver[69]. In addition, the interaction between PPARδ and PGC1α also activates FAO and thermogenesis in mice[3] (Table 2).

- *Perivascular adipose tissue.* Perivascular adipose tissue has an important function in atherogenesis. *Pparg* deletion inhibited the development of brown-like perivascular adipose tissue, which resulted in larger atherosclerotic lesions with increased macrophage infiltration and increased local concentrations of IL-1β, IL-6 and tumour necrosis factor[70].

Intestine

The intestine provides the organism with energy through nutrient absorption and is also an active secretory organ, producing incretins, such as glucagon-like peptide 1 (GLP1), which, after binding to the GLP1 receptor, improves glucose homeostasis and can reduce the risk of CVD in patients with diabetes[71,72]. In the gut, the microbiota acts as an 'endocrine-like organ' producing bioactive metabolites affecting host homeostasis, such as short-chain fatty acids, secondary bile acids and trimethylamine (which is further oxidized to trimethylamine *N*-oxide in the liver). Gut microbiota dysbiosis affects the gut barrier, resulting in subclinical sepsis and

systemic inflammation, promoting metabolic conditions and CVDs, such as obesity, diabetes, atherosclerosis and heart failure[27,73] (Table 2).

Short-chain fatty acids produced by the gut microbiota protect against obesity and improve insulin sensitivity through the downregulation of adipose tissue and liver PPARγ expression, thereby favouring oxidative metabolism and reducing hepatic steatosis and lipogenesis[74]. Butyrate regulates metabolism by activating colonocyte PPARγ[75], thereby lowering the synthesis of inducible nitric oxide synthase, preserving epithelial hypoxia, preventing dysbiosis and improving mucosal defences in mice fed a high-fat diet[76,77].

Caloric restriction also induces duodenal PPARα expression[78]. Intestinal PPARα activation increases intestinal epithelial cell FAO and HDL production and reduces chylomicron secretion by enterocytes, thereby controlling postprandial hyperlipidaemia[12,79,80].

The improved glucose tolerance with PPARδ activation is partly due to its stimulatory effect on GLP1 release from enteroendocrine L cells[81]. Moreover, enterocyte deficiency of PPARδ prevents the PPARδ-agonist-inducted increase in plasma HDL-cholesterol levels[60]. Therefore, intestinal PPARδ protects against obesity, insulin resistance and dyslipidaemia[60] (Table 2).

Skeletal muscle

Physical exercise exerts beneficial effects on several risk factors for CVD, improving glucose and lipid metabolism and control of body weight. Exercise training promotes endurance by increasing skeletal muscle oxidative metabolism and delaying the depletion of carbohydrates stored as glycogen in the liver and muscle. PPARδ is highly expressed in skeletal muscle, where it induces a switch from glycolytic to oxidative muscle fibres. PPARδ overexpression in mouse skeletal muscle generates a ‘marathon-like’ phenotype[82,83]. PPARδ overexpression in vivo in rodent skeletal muscle promotes FAO and increases mitochondrial biogenesis by

protecting PGC1α from degradation and inducing nuclear respiratory factor 1 (NRF1) expression[84]. In cooperation with AMPK, PPARδ overexpression in vivo in rodent skeletal muscle and in vitro in C2C12 muscle cells increases glucose transporter type 4 (GLUT4) expression during exercise training via NRF1–MEF2A[85]. PPARδ agonist treatment also decreases visceral adipose tissue and skeletal muscle inflammation by increasing anti-inflammatory regulatory T cell numbers in lymph nodes of diet-induced obese mice[86]. Finally, by preserving systemic glucose levels, PPARδ activation with GW501516 in mice delays the onset of hypoglycaemia during exercise, resulting in increased running endurance[87] (Table 2).

PPARα overexpression in mouse skeletal muscle also increases FAO, but reduces insulin-stimulated glucose uptake owing to GLUT4 repression, resulting in glucose intolerance despite being protected from obesity[88]. PPARα agonists reverse palmitate-induced insulin resistance in myotubes by increasing FAO and limiting ceramide accumulation in vitro[89]. PPARγ improves skeletal muscle insulin sensitivity via the lipid-steal action to increase fatty acid storage in white adipose tissue lipid droplets[12].

PPARs in atherosclerosis

Vascular function and inflammation

Atherosclerosis is characterized by endothelial dysfunction leading to immune cell infiltration, cholesterol deposition and further atherosclerotic plaque development containing a necrotic core and regions of calcification[90]. Risk factors for atherosclerosis include dyslipidaemia, hypertension, obesity and smoking, which increase vascular permeability, inflammation and oxidative stress[91]. In the early 2000s, PPARs were shown to reduce endothelial cell activation and adhesion and vascular smooth muscle cell and trans-endothelial leukocyte migration[92]. PPARs exert anti-inflammatory and antioxidant effects in cells of the vascular wall and reduce

macrophage foam cell formation by inducing reverse cholesterol transport, thereby promoting plaque stability[92] (Table 2).

Data have shown that endothelial PPARγ deficiency also accelerates age-induced vascular dysfunction, inflammation and senescence via mechanisms involving increased NADPH oxidase and Rho-associated protein kinase activity[93]. In human primary endothelial cells, PPARγ promotes DNA repair by interacting with the E3 ubiquitin-protein ligase UBR5 and the DNA-damage sensor MRN complex-interacting protein, promoting serine-protein kinase ATM-mediated signalling, a pathway that is disrupted in patients with pulmonary arterial hypertension[94]. In mouse endothelial cells, the LDL-receptor-related protein 1 (LRP1) controls lipid, glucose and energy metabolism, functioning as a PPARγ coactivator to regulate the expression of PPARγ and its target genes[95]. These surprising findings identify a role for the endothelial LRP1–PPARγ complex in vascular function and systemic energy metabolism[95]. PPARγ mediates bone morphogenetic protein 2 inhibition of vascular smooth muscle cell proliferation by transforming growth factor-β1 (TGFβ1)-induced interference through the STAT3–FOXO1 and TGFβ1–SMAD3/4 pathways and by regulating the glycolytic enzymes phosphofructokinase (PFK) and protein phosphatase 1 regulatory subunit 3G[96]. The methylation status of the *Pparg* promoter region is regulated by DNA (cytosine-5)-methyltransferase 1 (DNMT1) in murine macrophages[97]. Increased DNMT1 levels in transgenic mouse macrophages resulted in decreased PPARγ expression and increased pro-inflammatory cytokine production, leading to aggravation of atherosclerosis in mice[97]. PPARγ activation counteracted the pro-inflammatory profile promoted by DNMT1 overexpression in macrophages[97]. Finally, PPARγ induces anti-inflammatory M2 macrophage polarization by facilitating intracellular glutamine metabolism[98,99].

The anti-inflammatory actions of PPARα have also been extensively discussed[92]. Interestingly, circulating monocyte numbers decrease with short-term fasting in humans,

through a mechanism involving AMPK–PPARα suppression of systemic CC-chemokine ligand 2 production that reduces bone marrow monocyte mobilization, as observed in fasted wild-type but not PPARα-deficient mice[100]. As a consequence, chronic inflammatory diseases are improved through dietary intervention[100].

PPARδ reduces atherosclerotic lesion progression through increasing plasma levels of HDL and exerting anti-inflammatory activity within the vessel wall in *Apoe*$^{-/-}$ mice[101]. Another study showed that PPARδ increases endothelial relaxation in diabetic mice[102] and prevents accumulation of reactive oxygen species by increasing mitochondrial uncoupling protein 2 expression in mouse aortic endothelial cells[103]. PPARδ also induces microRNA-100, leading to VLDL-receptor inhibition in endothelial cells in vitro[104] and inhibition of vascular smooth muscle cell proliferation through SIRT1 activation[105].

Regulation of ischaemic events

Several studies on animal models of ischaemia–reperfusion injury that mimicked an acute myocardial infarction demonstrated cardioprotective effects, with reduced infarct size after PPARγ[106], PPARα[107] or PPARδ[108] activation in rodent hearts. The underlying mechanisms mediating this cardioprotection probably involve decreased oxidative stress, apoptosis[109] and inflammation[107]. Interestingly, treatment with the PPARγ agonist rosiglitazone decreased ischaemia–reperfusion injury in diabetic mice[110] and in non-diabetic mice[111], indicating a mechanism of action that is independent of glucose control.

PPAR agonists in CVD clinical studies

Overall, PPARs exert favourable anti-inflammatory and anti-atherogenic effects in atherosclerosis, which can lower the risk of CVD. Moreover, glitazones prevent the progression to diabetes in Hispanic women with prior gestational diabetes[112]. In the secondary prevention

PROactive trial[113] in patients with type 2 diabetes, pioglitazone significantly decreased the secondary end point of all-cause mortality, non-fatal myocardial infarction and stroke. However, the primary end point was not achieved owing to an increase in peripheral revascularization[113]. In the IRIS study[114], pioglitazone administered to insulin-resistant individuals after ischaemic stroke or transient ischaemic attack reduced the risk of stroke and myocardial infarction. Unfortunately, glitazone treatment increases the risk of bone fractures, weight gain and oedema, which might precipitate heart failure. Although tesaglitazar induces cardiac mitochondrial dysfunction in mice by inhibiting the SIRT1–PGC1α pathway[115], no data have reported direct deleterious effects of glitazones on heart function. Studies on cardiomyocyte-specific PPARγ-deficient mice revealed that the effects of glitazones on cardiac dysfunction primarily occur through extracardiac actions, such as via the induction of peripheral oedema[116–118]. Therefore, the development of oedema should be monitored during glitazone treatment, especially in patients at risk of heart failure.

Whereas both the FIELD[41] and ACCORD[42] clinical trials did not achieve statistically significant reductions in cardiovascular events in patients with type 2 diabetes treated with fenofibrate, subgroups analysis suggested that fibrates might benefit patients with high plasma triglyceride (≥200 mg/dl) and low plasma HDL-cholesterol levels[41,42]. This hypothesis is now being tested in the PROMINENT trial[119], which is enrolling 10,000 patients with type 2 diabetes, mild-to-moderate hypertriglyceridaemia (200–499 mg/dl) and low plasma HDL-cholesterol levels (≤40 mg/dl), who will be randomly assigned to pemafibrate treatment (0.2 mg twice daily) or placebo. The primary end point is a composite of non-fatal myocardial infarction, ischaemic stroke, hospitalization for angina that requires urgent coronary revascularization and cardiovascular death (results expected in 2022)[120]. Previous phase II and phase III trials revealed that pemafibrate treatment in patients with type 2 diabetes improves lipid profiles and decreases risk factors for CVD. Pemafibrate therapy is more efficient in

lowering plasma triglyceride levels and does not increase alanine aminotransferase nor γ-glutamyltransferase levels compared with fenofibrate therapy[121,122]. This novel, selective PPARα modulator seems promising in lowering the risk of CVD in patients with diabetes and dyslipidaemia.

PPARs in healthy hearts

Physiology

The heart utilizes different carbon substrates to produce energy. Although the adult heart primarily consumes fatty acids, it shows fuel flexibility and can metabolize glucose, lactate, fatty acid and ketone bodies (Box 1). Nutrients are used by the heart to maintain muscle activity and for anabolic reactions, such as physiological cardiac growth (cardiomyocyte multiplication) in the fetus and pathological cardiac remodelling (cardiomyocyte hypertrophy). Cardiac metabolism is flexible and can switch to preferred nutrients by the action of upstream regulators. PPARs are master switches, which fine tune the cardiomyocyte enzymatic machinery[123,124](Box 1; Figs 1,2).

During development, the changing environment induces alterations in cardiac metabolism via upstream master switches (Box 1). The fetal metabolic phenotype is characterized by high hypoxia-inducible factor (HIF) and low PPARα–PGC1α activity[125], which results in high expression of glycolytic genes and low expression of genes associated with fatty acid catabolism and mitochondrial energy production. This fetal metabolic phenotype of cardiomyocytes provides high quantities of glycolytic intermediates, necessary for nucleotide, amino-acid and lipid biosynthesis[126], thereby promoting cardiomyocyte multiplication by supporting growth and anabolism[127]. Cardiomyocyte depletion of the mitochondrial pyruvate carrier induces early hypertrophy and maladaptation to myocardial stress[128,129], with increased glycolysis in the heart, suggesting a crucial role of the pyruvate–

lactate axis in cardiomyocyte biosynthesis and potentially cell proliferation[128]. Moreover, low mitochondrial FAO protects against DNA damage induced by reactive oxygen species and subsequent cell cycle arrest[130].

Although a direct role of PPARs in this physiological metabolic switch has not yet been proven, PPARs are thought to be involved in this switch. Indeed, a switch in the HIF and PPARα–PGC1α signalling balance occurs within a few days after birth in the neonatal heart into an 'adult phenotype', which relies on fatty acid catabolism and strong mitochondrial oxidative phosphorylation[131,132] (Box 1). It is tempting to speculate that PPARα or PPARδ activation might also reduce pathological cardiac hypertrophy through their stimulatory actions on FAO (see below).

Adult hearts

All PPARs are found in the adult heart, with varying levels of expression: PPARα and PPARδ are highly expressed in the heart at levels similar to those in other metabolically active tissues, such as the liver and skeletal muscle[123]. PPARγ is expressed at very low levels in the adult heart, particularly compared with levels in adipose tissue (cardiac levels of PPARγ are approximately 2% of those in adipose tissue)[133].

Studies using mice with genetic deletion or overexpression of PPARs (mostly in cardiomyocytes) have shown differential roles for these proteins in the regulation of the 'normal' adult metabolic phenotype, that is, the production of large amounts of ATP via mitochondrial FAO. Although a cardiomyocyte-specific *Ppara*-deletion model has not yet been generated, hearts from ubiquitously PPARα-deficient mice have low expression levels of genes encoding proteins involved in sarcolemmal transport (fatty acid translocase (FAT; also known as CD36) and fatty acid transport protein 1 (FATP1)), mitochondrial transport (carnitine *O*-palmitoyltransferase 1 (CPT1) and malonyl-CoA decarboxylase (MCD)), and mitochondrial

(long-chain specific acyl-CoA dehydrogenase (LCAD), medium-chain specific acyl-CoA dehydrogenase (MCAD) and short-chain specific acyl-CoA dehydrogenase) and peroxisomal (acyl-CoA oxidase) oxidation of fatty acids[134,135] (Fig. 2). These alterations, which are insensitive to long-term fasting[136], translate to a switch from fatty acid to glucose and lactate oxidation to maintain sufficient baseline ATP production and cardiac function[137]. However, the metabolic reserve in the hearts of these mice is lower and insufficient to maintain cardiomyocyte levels of high-energy phosphate under high workloads[137]. In addition, deficiency of adipose triglyceride lipase, the enzyme catalysing the first step of triglyceride lipolysis that generates endogenous PPARα and PPARδ ligands, resulted in disrupted mitochondrial oxidation, excessive lipid accumulation, cardiac insufficiency and lethal cardiomyopathy[138].

Cardiac-restricted PPARα overexpression results in increased expression levels of genes encoding proteins involved in fatty acid uptake transport and mitochondrial oxidation, at baseline and after short-term fasting in mice[139]. This increased gene expression translated into high myocardial FAO rates and low glucose uptake and oxidation. Moreover, PPARα overexpression induced myocardial expression of glycerol-3-phosphate acyltransferase (GPAT)) and diacylglycerol acyltransferase, two enzymes involved in the esterification of fatty acids to triglycerides, and adipophilin (also known as perilipin 2), a lipid droplet fatty acid-binding protein[139] (Fig. 2). Cardiomyocyte lipid droplets accumulated excessively after 24 h fasting in mice[139], indicating an imbalance between the increased fatty acid uptake and mitochondrial oxidative capacity. At 2–4 months of age, hearts from PPARα-overexpressing mice developed ventricular hypertrophy (with elevated hypertrophic gene marker expression), left ventricular dilatation and systolic ventricular dysfunction.

Using cardiac-specific *Ppara*-overexpressing or *Ppard*-overexpressing transgenic mice, Burkart and colleagues studied the distinct metabolic programmes governed by these

PPARs[140]. Although both PPARs activate the expression of genes encoding proteins involved in mitochondrial fatty acid transport (CPT1), mitochondrial oxidation (MCAD, LCAD, very long-chain specific acyl-CoA dehydrogenase (VLCAD) and acyl-CoA thioesterase 1) and peroxisomal oxidation (acyl-CoA oxidase), the expression of genes encoding proteins involved in cellular fatty acid transport and activation (FATP1, CD36 and acyl-CoA synthetase 1) and lipogenesis (GPAT and fatty acid synthase) were activated only by PPARα. Genes encoding proteins involved in glucose transport (GLUT4) and glycolysis (PFK and hexokinase) were induced by PPARδ, but unchanged or decreased by PPARα[140] (Fig. 2). In parallel to these distinct metabolic regulatory programmes, diet-induced myocardial triglyceride accumulation occurred in myosin heavy chain (MHC)–PPARα mice that have cardiac-specific expression of PPARα[140]. By contrast, MHC–PPARδ mice did not have diet-induced myocardial triglyceride accumulation. Cardiomyopathy developed in 2-month-old, cardiac-specific *Ppara*-transgenic mice receiving either a chow or a high-fat diet. However, MHC–PPARδ mice did not develop cardiac hypertrophy or dysfunction even after mice were subjected to a high-fat diet[140].

Liu and colleagues developed a tamoxifen-inducible transgenic mouse model to allow cardiomyocyte-specific PPARδ induction in adult mice[141]. In addition to an increased expression of genes encoding proteins involved in fatty acid and glucose metabolism, the expression of genes encoding proteins involved in mitogenesis, oxidative phosphorylation and scavenging of reactive oxygen species were also increased after short-term induction of cardiomyocyte-specific PPARδ expression[141]. This increased expression translated into increased myocardial oxidative catabolism of both fatty acid and glucose, decreased glycogen content and AMPK activity and increased cardiac performance in an isolated working heart model[141]. Cardiomyocyte-specific PPARδ deletion resulted in the downregulation of genes encoding proteins involved in mitochondrial fatty acid transport (CPT1 and MCD) and oxidation (VLCAD and LCAD), peroxisomal oxidation (acyl-CoA oxidase) and pyruvate

dehydrogenase kinase 4[142]. These hearts had reduced basal myocardial FAO and ATP starvation, demonstrated by increased AMPK activity, despite elevated glucose uptake. These mice had progressive myocardial lipid droplet accumulation, followed by cardiac hypertrophy and dysfunction, which resulted in increased lethality caused by heart failure.

Cardiomyocyte-specific PPARγ deficiency in mice leads to cardiac hypertrophy with preserved systolic function owing to oxidative stress associated with mitochondrial damage[116,143]. Whereas cardiac-specific *Pparg*-overexpressing transgenic mice have increased expression of GLUT1 and GLUT4 and genes encoding proteins involved in lipid uptake, synthesis and storage[133] (Fig. 2). This overexpression translated into increased cardiac uptake of both lipids and glucose and storage of fatty acid, triglyceride and glycogen within cardiomyocytes. Consequently, cardiac hypertrophy, dilatation and dysfunction developed within a few months of life[133]. Intriguingly, cardiomyocyte-specific PPARγ overexpression in PPARα-deficient mice increased fatty acid uptake and lipid droplet size, but heart function was preserved[144]. In vitro studies showed that PPARγ, while increasing neutral lipid accumulation, reduces endoplasmic reticulum stress[145]. These results suggest that partitioning of lipids to storage and oxidation is cardioprotective.

Altogether, PPARα and PPARδ signalling is activated in adult hearts and drives a normal metabolic phenotype to maintain high-energy phosphate content through mitochondrial oxidation of both fatty acid and glucose. PPARα signalling activates the cellular fatty acid transport, lipogenesis, mitochondrial and peroxisomal oxidation pathways. By contrast, PPARδ signalling activates both cellular fatty acid and glucose transport, mitochondrial oxidation, mitochondrial biogenesis and reactive oxygen species-scavenging systems. The physiological role of PPARγ is probably related to specific intracellular lipid trafficking, determining the balance of lipid signalling species with cardiotoxic potential and the storage of energy-providing triglycerides in droplets in adult cardiomyocytes.

PPARs in diseased hearts

Reversal to the fetal metabolic phenotype in heart failure

Heart failure is a condition of cardiac contractile dysfunction, reducing the ability of the heart to supply sufficient blood to the tissues. The failing heart cannot maintain normal cardiac output and arterial blood pressure without an increase in the cardiac preload, in the first stage of heart failure only during exercise and in end-stage heart disease even at rest (Fig. 1). Two major adaptations that have a large effect on cardiac energy metabolism occur during heart failure[146]. First, heart mass progressively increases secondary to cardiomyocyte hypertrophy associated with de novo sarcomeric protein synthesis (cardiac hypertrophic remodelling). This remodelling allows the cardiac chambers to cope with their increased load and is mandatory to prevent rupture of the heart, as predicted by Laplace's law. This remodelling requires a substantial and persistent anabolism, since heart mass can often increase by more than twofold in end-stage heart failure. Second, low cardiac output and arterial pressure chronically activate the renin–angiotensin–aldosterone system (RAAS) and sympathetic system, which alters cardiac nutrient supply by activating liver gluconeogenesis and ketogenesis, adipose tissue lipolysis and skeletal muscle protein degradation[147]. Moreover, increased RAAS signalling and adrenergic tonus lead to the activation of HIF, mTOR and NF-κB signalling[126,148,149], which can repress PPARα[150,151] and PPARδ[152] expression and activity, and activate PPARγ expression[148] (Fig. 2). These modified expression levels of genes encoding proteins involved in cardiac metabolism are reminiscent of the 'fetal cardiac phenotype'. This phenotype is characterized by low expression of genes encoding proteins involved in fatty acid uptake and mitochondrial catabolism and high expression of genes encoding proteins involved in glucose uptake, glycolysis, and glycogen and lipid storage, accompanied by high glucose-6-phosphate and aspartate concentrations[127,153], which feed anabolic reactions for hypertrophy. The return

to a fetal-like phenotype is also characterized by re-expression of specific contractile protein isoforms (α-actin and β-MHC) and natriuretic peptides and decreased sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2 expression[148]. Overall, the failing heart prefers glucose[154], lactate and ketone bodies[155] for energy supply, while fatty acid uptake and mitochondrial oxidation proportionally decrease, which might lead to the accumulation of mitochondrial (mito)-toxic lipids (diacylglycerol and ceramides)[156]. Finally, the low oxidative phosphorylation capacity, combined with PPARα and PPARδ repression, results in a poor metabolic reserve with decreased cardiomyocyte high-energy phosphate content and poor contractile performance during exercise[157].

Importantly, the current paradigm of energy metabolism disruption in heart failure is based on clinical studies involving patients with compensated chronic heart failure secondary to either hypertrophic cardiomyopathy[158] or idiopathic dilated[159] or ischaemic[155] cardiomyopathy with reduced left ventricular ejection fraction (~30%). According to rodent studies, a progressive worsening of cardiac metabolism occurs from early to end-stage heart failure[160]. Further studies to determine whether this progressive worsening of cardiac metabolism occurs in patients with heart failure are warranted. Moreover, specific studies exploring myocardial metabolism in acute heart failure or in the growing phenogroup of chronic heart failure with preserved left ventricular ejection fraction have not yet been performed.

Diabetic cardiomyopathy

Even in the absence of overt clinical heart failure, patients with diabetes have alterations in myocardial structure, metabolism and energetics. These alterations include low glucose uptake and elevated FAO that is not suppressed by insulin[159,161], intra-cardiomyocyte lipid droplet accumulation[158], mitochondrial network fission and dysfunction[162], low high-energy phosphate

content that further decreases during exercise[163], concentric left ventricular remodelling and subtle contractile dysfunction[158]. This specific phenotype, referred to as diabetic cardiomyopathy, is thought to underlie the increased risk of heart failure in patients with diabetes, even after adjustment for other classic risk factors (such as coronary artery disease and hypertension).

Consistent with the observation that cardiac-restricted PPARα overexpression mimics the diabetic heart phenotype, chronic activation of cardiomyocyte PPARα by high circulating levels of free fatty acids, in combination with other non-PPAR related mechanisms (such as protein *O*-GlcNAcylation, protein kinase C and AMPK signalling), is probably a master switch in diabetic cardiomyopathy[164]. PPARα-mediated induction of genes encoding proteins involved in fatty acid uptake and oxidation, together with low expression of genes encoding proteins involved in glucose transport and glycolysis, promotes a vicious cycle of imbalance between fatty acid uptake and oxidation, accumulation of mitotoxic lipids, mitochondrial fatty acid (versus pyruvate) oxidation with high levels reactive oxygen species production, mitochondrial uncoupling and mitochondrial fission[130,162]. These events cause an inability to maintain high-energy phosphate content, that is, ATP starvation, despite nutrient overflow. PPARγ overexpression in combination with intra-myocardial lipid accumulation has been observed in left ventricular biopsy samples from patients with metabolic syndrome, which might also contribute to diabetic cardiomyopathy[165].

Importantly, these alterations largely reflect the early metabolic changes related to systemic insulin resistance. Whether high rates of FAO are maintained or decreased in later stages of cardiac dysfunction related to diabetes, as occurs in the ischaemic heart, remains to be determined.

PPARs: targets in heart failure?

Failing heart are characterized by high levels of glucose uptake dedicated to anabolism rather than fuelling mitochondria with pyruvate and cytotoxic fatty acid accumulation (triglyceride, diacylglycerol and ceramides) secondary to an imbalance between fatty acid uptake and catabolism by dysfunctional mitochondria. Despite being favourable for the biosynthesis of cardiomyocyte material, this fetal-like metabolism, driven partly by low PPARα and PPARδ activity, also induces ATP starvation and a low metabolic reserve. Furthermore, increasing FAO by deleting *Acacb*, encoding acetyl-CoA-carboxylase 2, prevented cardiac remodelling, owing to glucose-induced aspartate synthesis, in phenylephrine-stimulated cardiomyocytes in vitro and in a pressure overload-induced cardiac hypertrophy model in vivo[127]. Moreover, preservation of FAO prevented the shift of metabolic flux to the anabolic pathway, promoting catabolic metabolism for energy production, thereby preventing cardiac hypertrophy and improving myocardial energetics[127,166]. Interestingly, induction of high levels of cardiac FAO in adult mice with tamoxifen-induced cardiac-specific *Acacb* deletion did not cause cardiac dysfunction but protected against cardiomyopathy in chronically obese mice, in part by maintaining mitochondrial function through regulating parkin-mediated mitophagy[166]. Therefore, it is tempting to hypothesize that increasing PPARδ signalling, alone or in combination with PPARα signalling, would rescue the failing heart by increasing mitochondrial oxidative phosphorylation capacity and specifically FAO.

However, very few studies have addressed this issue so far. Treatment with the PPARδ agonist L-165041 prevented phenylephrine-induced hypertrophy of neonatal rat cardiomyocytes and its related fetal-like gene expression pattern in vitro, owing to PPARδ transrepression of NF-κB[167]. Constitutive activation of cardiac PPARδ partially protected mice against pressure-overload mechanical stress induced by transaortic constriction, whereas constitutive PPARδ activation did not modify heart mass or expression of molecular cardiac hypertrophy markers, such as atrial natriuretic factor, in the transaortic constriction mouse

model[141]. Instead, constitutive PPARδ activation resulted in a less pronounced decrease in left ventricular ejection fraction and less pronounced myocardial fibrosis than in wild-type mice[141].

By contrast, persistent PPARα activation induces insulin resistance and causes lipid accumulation and lipotoxicity, a situation that mimics the diabetic heart[168]. However, with the use of an inducible transgenic mouse model and the PPARα agonist WY-14643, Kaimoto and colleagues showed that short-term PPARα activation early (2 weeks) after transaortic constriction maintained cardiac FAO, improved myocardial energetics and partially prevented cardiac remodelling in pressure-overload heart failure[169]. Agonist-mediated PPARα activation in hypertrophied hearts resulted in severe impairment of cardiac function despite preventing the substrate switch in a rat model of cardiac pressure overload[170]. Long-term treatment with fenofibrate prevented the metabolic switch observed in pacing-induced heart failure in dogs, without altering the development of heart failure[171].

Future directions

PPARs control various pathways at the systemic, vascular and cardiac levels, affecting risk factors for CVD and heart failure. PPARα activation, primarily in the liver, reduces atherogenic dyslipidaemia and thereby has the potential to decrease post-statin residual risk in patients with dyslipidaemia. This hypothesis, generated by post-hoc analysis of several fibrate trials, is currently being tested in the PROMINENT trial[119]. PPARγ improves glucose metabolism by increasing insulin sensitivity and vascular function. Although glitazones might precipitate heart failure in high-risk patients by putting an increased preload on the failing heart, these drugs decrease the risk of myocardial infarction and stroke in secondary prevention patients with insulin-resistance, according to data from the IRIS trial[114]. Although PPARδ agonists have not yet been tested in outcome trials, all PPARs might affect CVD and heart failure through complex systemic actions that modulate cardiovascular risk factors and improve NASH, which

is an increasing health problem and a cardiovascular risk factor[172]. Interestingly, several dual-PPAR and pan-PPAR agonists are being tested in clinical trials, currently mainly in patients with NAFLD[173].

Whether lipid accumulation in the failing heart is caused by increased fatty acid uptake, increased triglyceride synthesis or decreased lipid degradation is currently uncertain. Whereas the accumulation of selective bioactive lipids, such as diacylglycerol and ceramides, might provoke cardiomyocyte toxicity, the dynamic shuttling of fatty acid in cardiomyocytes between cellular uptake, lipid droplet triglyceride accumulation and mitochondrial oxidation is necessary for proper cardiac function[156,174]. Moreover, fatty acids released by triglyceride lipolysis are natural PPAR ligands, and their turnover also maintains the expression of PPAR target genes in the failing heart[175,176].

Evidence suggests that the healthy heart consumes ketone bodies in direct proportionality to their circulating levels and that the failing heart becomes more reliant on ketone bodies as a fuel[155,177]. Moreover, increasing the delivery of ketone bodies to the heart can prevent or reduce heart failure in preclinical models[178]. The beneficial effect of sodium–glucose cotransporter 2 inhibitors on the incidence of heart failure might be explained, at least in part, by their effect on cardiac substrate utilization[179], that is, their promotion of ketogenesis and ketone body utilization[180,181]. Given that hepatic ketogenesis is driven by PPARα, the activation of PPARα in the liver might be hypothesized to be beneficial in heart failure and warrants further study.

Although the differential functions of PPARα and PPARδ require further investigation, downregulation of cardiac PPARα and PPARδ activity seems to be a ‘necessary evil’ during heart failure to allow the heart to adapt to the increased myocardial wall stress by promoting anabolic hypertrophic response pathways necessary for cardiac protection. Although sustained, cardiac-restricted PPARα activation seems inappropriate, treatment with a selective PPARδ

agonist or a dual PPARα–PPARδ agonist might be a promising method to boost cardiac mitochondrial function. Rescuing PPARδ, possibly with PPARα, particularly in the early stages of cardiac remodelling, could be a promising therapeutic strategy that warrants clinical testing.

Conclusions

The biology of the PPARs has proven to be complex and exciting. Several areas of research, such as PPAR regulation of inter-organ crosstalk, sex-specific PPAR actions and circadian control of PPAR activity, warrant further attention. These areas might be major determinants of optimal pharmacological responses to treatment with PPAR agonists. Further studies on the PPAR transcription factors in relation to heart disease are therefore warranted.

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Competing interests

B.S. is a consultant for Genfit. D.M. and L.B and declare no competing interests.

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Review criteria

We have focused on original research articles published after 2017 covering the topics of cardiovascular risk factors, metabolism and new mechanisms of regulation by PPARs, because exhaustive reviews on PPARs functions covering the period before 2017 have previously been published. For the section on the role of PPARs in heart metabolism, we focus on studies showing the function of the PPARs in the heart.

Key points

Peroxisome proliferator-activated receptors (PPARs) are fatty acid sensors regulating whole-body metabolism.

Activation of PPARγ (for example, by glitazones) improves the management of diabetes mellitus by increasing insulin-sensitivity.

Activation of PPARα (for example, by fibrates) normalizes atherogenic dyslipidaemia, thereby lowering the risk of cardiovascular disease.

PPARs are expressed in the heart, where they modulate lipid and glucose metabolism.

Failing or stressed hearts switch from the preferential use of fatty acids as energy substrates to glucose oxidation, with repression of the PPARα and PPARδ pathways.

Rescuing PPARδ or both PPARα and PPARδ signalling, particularly in early stages of cardiac remodelling, might be a promising therapeutic strategy for heart failure.

Table 1 | **Single, dual and pan PPAR agonists**

Targets	Agonists	Reported biological effects	Refs
PPARα	Unsaturated fatty acids, phospholipids, leukotriene B4, 8(*S*)-hydroxyeicosatetraenoic acid, pemafibrate (K-877), fenofibrate, WY14643	Improved lipid profile in patients with dyslipidaemia	[14,41,42]
PPARδ	Unsaturated fatty acids, components of VLDL, prostacyclin I, 13(*S*)-hydroxyoctadecadienoic acid, GW501516, seladelpar (MBX-8025), L-165041	Improved lipid profile and insulin sensitivity in patients and rodents	[15,182]
PPARγ	Unsaturated fatty acids, 15(*S*)-hydroxyeicosatetraenoic acid, 9(*S*)-hydroxyoctadecadienoic acid and 13(*S*)-hydroxyoctadecadienoic acid, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, pioglitazone, rosiglitazone	Improved glucose tolerance in patients with type 2 diabetes mellitus	[113,114,183]
PPARα and PPARγ	Saroglitazar and tesaglitazar	Improved glucose and lipid profile in patients with dyslipidaemia	[16]
PPARα and PPARδ	Elafibranor (GFT505)	Decreased severity of non-alcoholic steatohepatitis, improved lipid profile in patients	[17]
PPARα, PPARδ and PPARγ	Lanifibranor	Decreased severity of non-alcoholic fatty liver disease in rodents	[18]
	Chiglitazar	Improved lipid profile and decreased insulin resistance in obese mice	[19]

PPAR, peroxisome proliferator-activated receptor.

Table 2 | **PPAR-mediated control of cardiac function and risk factors for CVD**

Target	Risk factors	PPAR actions	Refs
Liver	Obesity, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, atherogenic plasma lipid profile (high triglyceride, high LDL-cholesterol and low HDL-cholesterol levels)	PPARα expression decreases with non-alcoholic steatohepatitis progression PPARα increases FAO and ApoA-I, ApoA-II and lipoprotein lipase levels (directly and indirectly by decreasing ApoC-III and increasing ApoA-V levels) PPARδ increases FAO and ApoA-II levels and decreases ApoC-III levels	12,13,28
White adipose tissue	The expansion of visceral adipose tissue in obesity and diabetes mellitus increases the risk of CVD; the adipose tissue secretome exerts pro-inflammatory and pro-atherogenic actions, which increases the risk of CVD	PPARγ increases insulin sensitivity by a lipid-steal action PPARγ and PPARδ decrease inflammation	12,98,101
Brown adipose tissue	High energy expenditure, which decreases the risk of CVD	PPARγ increases brown adipocyte differentiation PPARα and PPARγ increase white adipose tissue browning PPARα and PPARδ increase FAO and energy expenditure	3,62,65
Intestine	Altered epithelial barrier function and gut microbiota can increase the levels of pro-inflammatory cytokines in the plasma, thereby increasing the risk of CVD and non-alcoholic fatty liver disease	PPARα increases FAO in intestinal epithelial cells and HDL production and decreases chylomicron secretion PPARγ protects gut microbiota and the epithelial barrier PPARδ decreases dyslipidaemia and increases glucagon-like peptide 1 secretion	12,60,76,77,79–81
Skeletal muscle	Beneficial effects on glucose and lipid metabolism and body weight control	PPARα increases FAO PPARγ increases insulin sensitivity PPARδ increases exercise endurance, FAO and the glycolytic-to-oxidative muscle fibre switch, delays carbohydrate depletion during exercise and increases mitochondrial biogenesis	12,83,87,88
Vascular wall and immune system	Atherogenic profile, atherosclerosis and cardiovascular events	PPARα, PPARγ and PPARδ increase vasomotricity and decrease production of reactive oxygen species PPARα and PPARγ decrease the expression of adhesion molecules, immune cell infiltration and foam cell formation PPARγ and PPARδ decrease vascular smooth muscle cell proliferation	92,98,99,101
Heart	Altered cardiac metabolism in heart failure	PPARα and PPARδ increase FAO PPARγ increases lipid uptake and storage as lipid droplets PPARδ increases glycolysis	140,141,145

Apo, apolipoprotein; CVD, cardiovascular disease; FAO, fatty acid oxidation; PPAR, peroxisome proliferator-activated receptor.

Table 3 | **Genetic mouse models to study PPAR functions**

Tissue	Model	Phenotype	Refs
Liver	Hepatocyte PPARα deficiency	Increased liver steatosis and inflammation, hyperlipidaemia, hypercholesterolemia and increased extrahepatic FAO	30–32,33
White adipose tissue	Adipocyte PPARγ_2 deficiency	Metabolic inflexibility of adipose tissue	55
Perivascular adipose tissue	Brown adipocyte PPARγ deficiency	Larger atherosclerotic lesions than in wild-type mice	70
Intestine	Enterocyte PPARδ deficiency	Increased dyslipidaemia and insulin resistance	60
Endothelium	Endothelial cell PPARγ deficiency	Accelerated age-induced vascular dysfunction, inflammation and senescence	93
Skeletal muscle	PPARδ overexpression	'Marathon runner-like' phenotype	82,83
	PPARα overexpression	Increased FAO and protection against obesity but glucose intolerance	88
Whole body	PPARα deficiency	Switch from fatty acid to glucose and lactate metabolism in the heart; disrupted mitochondrial function and lipid accumulation in cardiomyocytes	134,135
Heart	Cardiomyocyte PPARα deficiency	Not described	–
	Cardiomyocyte PPARδ deficiency	Decreased fatty acid transport and FAO; lipid accumulation in cardiomyocytes; cardiac hypertrophy and dysfunction	142
	Cardiomyocyte PPARα overexpression	Increased fatty acid uptake and FAO; cardiomyocyte lipid accumulation; cardiomyopathy; mimics the diabetic heart phenotype	139,140
	Cardiomyocyte inducible PPARα overexpression	Short-term PPARα activation early after transaortic constriction procedure maintained cardiac fatty acid oxidation	169
	Cardiomyocyte PPARγ overexpression	Increased lipid uptake, synthesis and storage; increased glucose uptake; cardiac hypertrophy, dilatation and dysfunction	133
	Cardiomyocyte PPARδ overexpression	Increased FAO without increased expression of proteins involved in fatty acid transport; increased expression of proteins involved in glucose transport; increased glycolysis; no lipid accumulation; no cardiac hypertrophy or dysfunction in mice fed a high-fat diet	140
	Inducible cardiomyocyte PPARδ overexpression	Increased cardiac fatty acid and glucose metabolism, mitogenesis, oxidative phosphorylation and scavenging of reactive oxygen species	141

FAO, fatty acid oxidation; PPAR, peroxisome proliferator-activated receptor.

Fig. 1 | **Metabolic switches driven by the PPAR and HIF–mTOR pathways during heart failure.** The diameter of the pie charts is proportional to the absolute oxygen consumption and, therefore, the mechanical energy produced by the heart under each condition. The failing heart is characterized by low oxygen consumption capacity at rest and little metabolic reserve. Moreover, a return to a 'fetal-like' phenotype occurs, with an increased activity of hypoxia-inducible factor (HIF) and mechanistic target of rapamycin (mTOR) instead of peroxisome proliferator-activated receptor-α (PPARα) and PPARδ dominance, leading to a metabolic switch to the use of carbohydrates as preferential substrates. This switch further favours anabolism and cardiomyocyte hypertrophy.

Fig. 2 | **PPAR regulation of cardiomyocyte metabolism.** The 'omnivorous' heart catabolizes all types of energy sources, including fatty acids (FAs), glucose, ketone bodies and branched-chain amino acids (BCAAs) to deliver constant mechanical work. Peroxisome proliferator-activated receptors (PPARs) are major regulators of cardiomyocyte metabolism that regulate proteins and enzymes involved in energy substrate degradation pathways. In brief, PPARα regulates FA transport and mitochondrial β-oxidation (β-Ox) in cardiomyocytes. PPARα also stimulates triglyceride (TG) synthesis and lipid droplet (LD) formation in an environment with an excess of FAs. PPARδ increases fatty acid oxidation and glycolysis and promotes mitochondrial biogenesis. PPARγ regulates LD formation and TG lipolysis, increasing neutral lipid accumulation in LDs, thereby limiting the accumulation of cardiac cytotoxic lipids. Upstream pathways, including hypoxia-inducible factor (HIF) and mammalian target of rapamycin (mTOR), participate actively in the regulation of cardiac metabolism by modulating PPAR expression. Direct effects are illustrated in full lines and indirect effects in dashed lines. ATGL, adipose triacylglycerol lipase; CPT, carnitine *O*-palmitoyltransferase; DAG, diacylglycerol; DGAT, diacylglycerol acyltransferase; FAT, fatty acid translocase; FATP1,

fatty acid transport protein 1; G6P, glucose-6-phosphate; GLUT, glucose transporter; GPAT, glycerol-3-phosphate acyltransferase; HK, hexokinase; HSL, hormone-sensitive lipase; LAT, L-type amino acid transporter; LCAD, long-chain specific acyl-CoA dehydrogenase; LDH, lactate dehydrogenase; MCAD, medium-chain specific acyl-CoA dehydrogenase; MCT, monocarboxylate transporter; MPC, mitochondrial pyruvate carrier; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PFK, phosphofructokinase; TCA, tricarboxylic acid; RAAS, renin–angiotensin–aldosterone system; RXR, retinoid X receptor.

Box 1 | **Metabolic activity of the heart throughout development**

The 'omnivorous heart'

The heart needs to deliver constant mechanical work while facing a life-long changing environment. The diameter of the pie chart (see the figure) is quantitatively proportional to the absolute oxygen consumption and, therefore, the mechanical energy produced by the heart. The nutritional energy supply of the heart changes during different periods of life, from fetal to adult, and during the day (fasting versus post-prandial versus exercise periods). As illustrated, at maximal exercise, a fourfold to fivefold increase in energy metabolism fluxes matches the increase in cardiac stroke work to maintain the high-energy phosphate content at a constant level.

To cope with this high metabolic challenge, the heart is equipped with the necessary enzymatic machinery that, theoretically, enables the heart to catabolize all types of energy nutrients, including fatty acids, carbohydrates (such as glucose and lactate), ketone bodies and branched-chain amino acids[184]. Therefore, the heart is 'omnivorous', and its energy metabolism is flexible to utilize the nutrients delivered by the coronary circulation, such as glucose in the post-prandial period, lactate during exercise, and fatty acids and ketone bodies during overnight fasting[155,185,186].

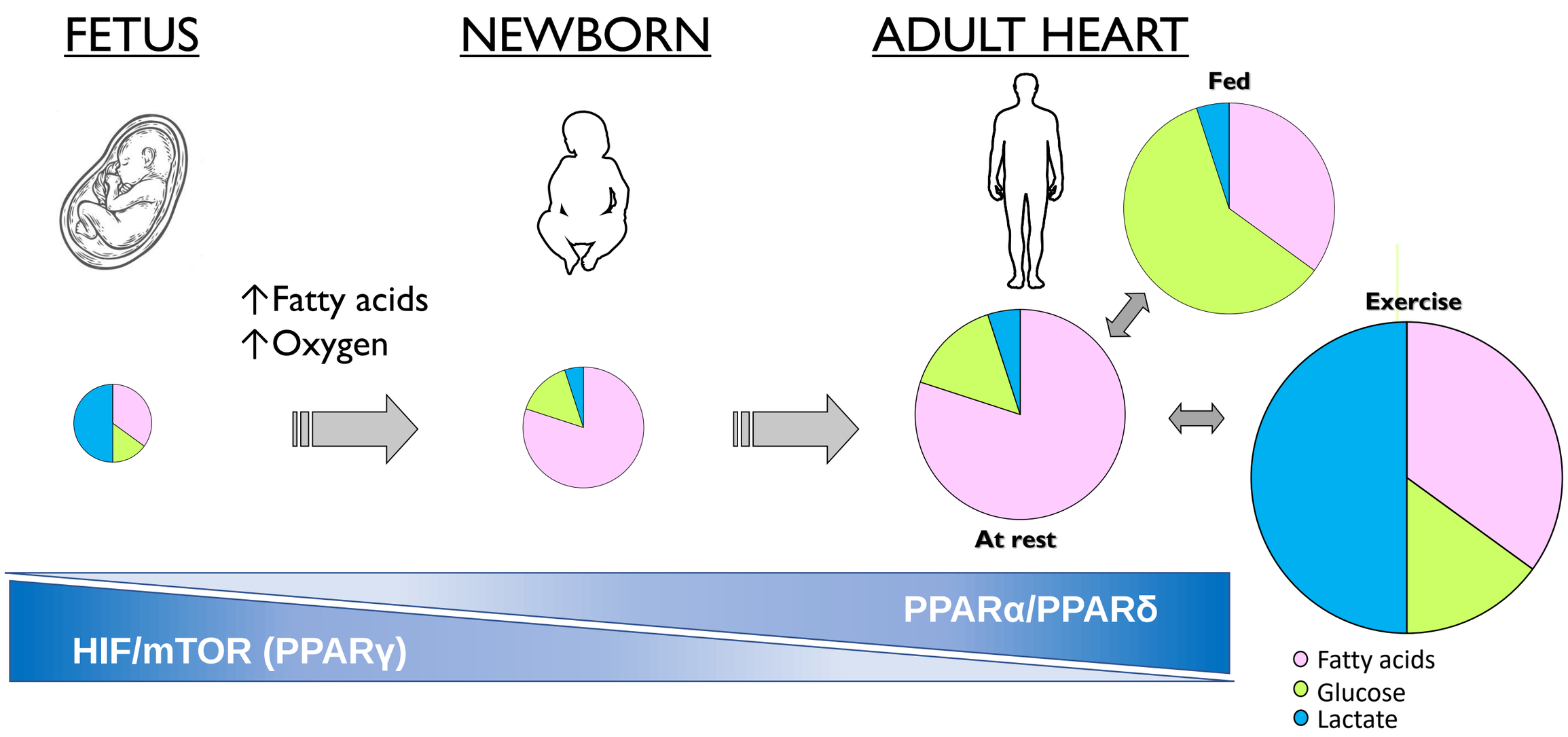
PPARs in the fetal-to-adult maturation of cardiac metabolism

The fetal heart is exposed to low oxygen and fatty acid levels, whereas the levels of blood lactate are high and glucose concentrations are similar to those in adults[187] (see the figure, fetus section). This fetal cardiomyocyte metabolic phenotype has high quantities of glycolysis intermediates, such as glucose-6-phosphate, necessary for nucleotide, amino-acid and lipid biosynthesis[126], and necessary to support the growth and anabolism required for cardiomyocyte multiplication[127]. This metabolism is associated with low levels of peroxisome proliferator-activated receptor-α (PPARα) and PPARδ activity and high levels of hypoxia-inducible factor

(HIF) and mechanistic target of rapamycin (mTOR) activity. Within the first days of life, the metabolic phenotype of cardiomyocytes switches in response to two major environmental changes: the increase in arterial oxygen partial pressure (from approximately 35 mmHg to 100 mmHg in humans) and the delivery of fatty acids from breast milk. This environment induces a switch in cardiac metabolism to fatty acid oxidation to produce energy as a result of low activity of HIF and high activity of PPARα and PPARδ–PPARγ-coactivator 1α[125]. This state is maintained throughout adult life.

ToC

Novel PPAR agonists are providing new opportunities in the management of metabolic and cardiovascular diseases. In this Review, Staels and colleagues discuss the physiological regulation and actions of the PPAR family and their modulation of the atherogenic lipid profile, atherosclerosis and cardiac remodelling.



Into Box1: Metabolic switches driven by the PPAR and HIF/mTOR pathways during physiological cardiac development

The fetal heart mainly uses carbohydrates as energy substrates, associated with low PPARα/PPARδ activity and highly active HIF and mTOR regulatory pathways. At birth, due to the change to an environment enriched in oxygen and fatty acids from milk, a metabolic switch occurs : fatty acids become the preferential energy substrates and the PPARα and PPARδ regulatory pathways are activated to degrade the fatty acids. This is maintained in adult life. The diameter of the pie charts is quantitatively proportional to the absolute oxygen consumption, and thus the mechanical energy produced by the heart, under that given condition. The energy produced by the heart increases throughout life and is enhanced during exercise.

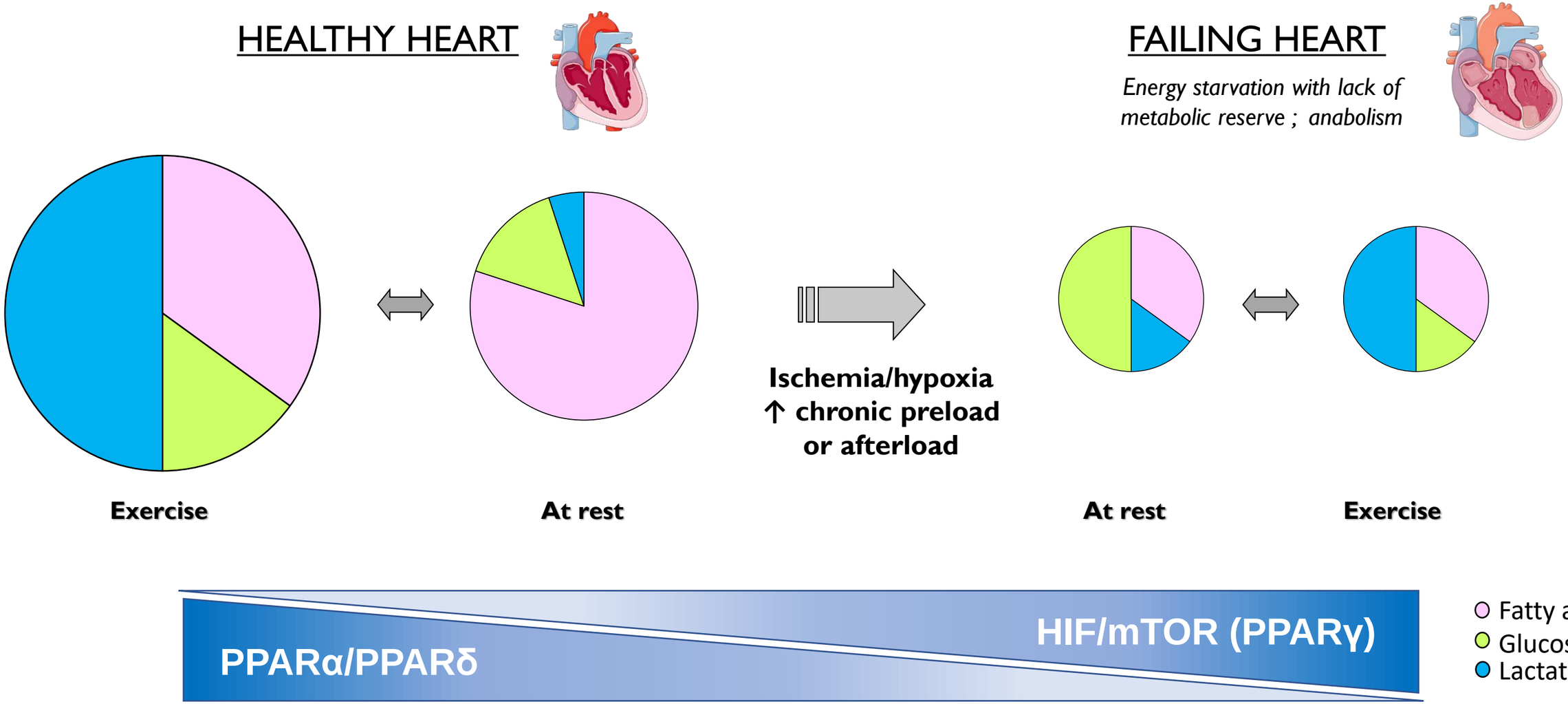


Fig 1: Metabolic switches driven by the PPAR and HIF/mTOR pathways during heart failure

The diameter of the pie charts is quantitatively proportional to the absolute oxygen consumption, and thus the mechanical energy produced by the heart, under that given condition. The failing heart is characterized by low oxygen consumption capacity at rest and little metabolic reserve. Moreover, a return to a “fetal-like” phenotype occurs, with an increased activity of HIF and mTOR instead of PPARα and PPARδ dominance, leading to a metabolic switch with carbohydrates as preferential substrates. This switch further favors anabolism and cardiomyocyte hypertrophy.

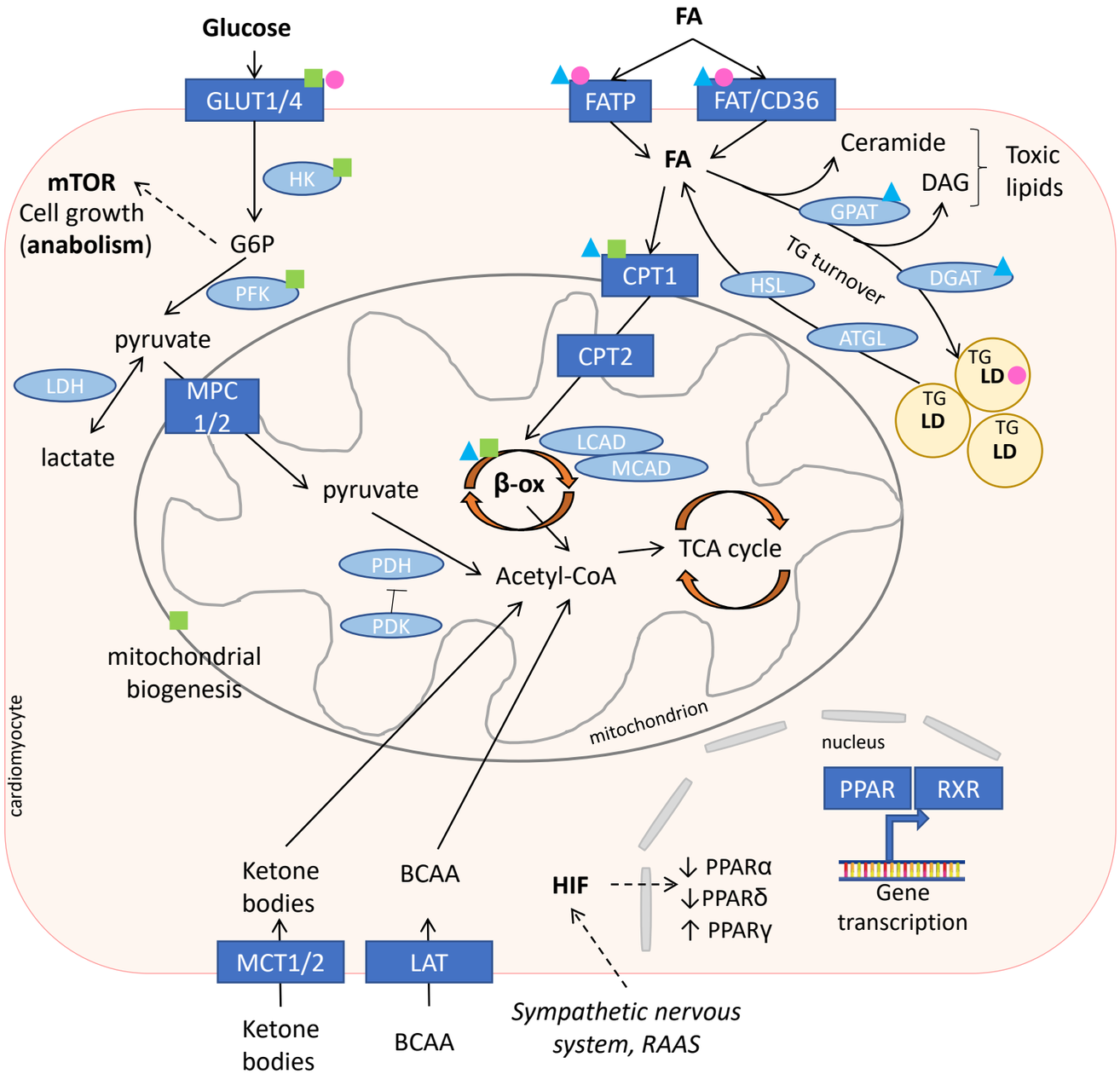


Fig 2: PPAR regulation of cardiomyocyte metabolism

The "omnivorous" heart catabolizes all types of energy sources: fatty acids (FA), glucose, ketone bodies and branched-chain amino-acids to deliver a constant mechanical work. PPARs are major regulators of cardiomyocyte metabolism regulating proteins and enzymes involved in energy substrate degradation pathways. (Regulated by: ▲PPARα ■PPARδ ●PPARγ)

PPAR: peroxisome proliferator-activated receptor, GLUT: glucose transporter, HK: hexokinase, PFK: phosphofructokinase, LDH: lactate dehydrogenase, MPC: mitochondrial pyruvate carrier, PDH: pyruvate dehydrogenase, PDK: pyruvate dehydrogenase kinase, ATGL: adipose triacylglycerol lipase, HSL, hormone sensitive lipase, MGL: monoacylglycerol lipase, TG: triglycerides, FATP: fatty acid transport protein, FAT/CD36: fatty acid translocase/cluster of differentiation 36, GPAT: glycerol-3-phosphate acyltransferase, DGAT: diacylglycerol acyltransferase, CPT: carnitine-palmitoyl transferase, β-ox: beta-oxydation, LCAD: long-chain acyl-CoA dehydrogenase, MCAD: medium-chain acyl-CoA dehydrogenase, TCA: tricarboxylic acid cycle, mTOR: mammalian target of rapamycin, HIF: hypoxia inducible factor, MCT: monocarboxylate transporter, BCAA: branched-chain amino acids, LAT: L-type amino acid transporter, RXR: retinoid X receptor, RAAS, renin angiotensin aldosterone system, G6P, glucose-6-phosphate, LD: Lipid droplet. Direct effects are schematized in full lines and indirect effects in stippled line.