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Transcriptional control of physiological and pathological processes by the nuclear receptor PPARβ/δ

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1. Introduction

Peroxisome proliferator-activated receptors (PPARs) are a class of transcription factors that belong to the nuclear hormone receptor superfamily, and their activities are dependent on their respective ligands. Since the discovery of PPARα (NR1C1) as a receptor that mediates peroxisome proliferation in rodent hepatocytes in 1990 [1], two other isotypes, PPARβ/δ (NR1C2) and PPARγ (NR1C3), were subsequently identified and characterized [2,3]. Members of the PPAR family have been extensively linked to numerous systemic and cellular activities that range far beyond simply mediating peroxisome proliferation in rodents [4]. Dependent on isotype-specific or shared tissue expression, all three PPARs regulate different or, in some cases, overlapping functions [5]. PPARα and PPARγ have established roles in fatty acid (FA) catabolism and in adipocyte differentiation and lipid storage, respectively, and both are pharmacological targets of FDA-approved drugs for the treatment of numerous metabolic diseases [6,7]. In contrast, no PPARβ/δ ligands are currently used in the treatment of any disease, although small studies on human subjects have used PPARβ/δ ligands to treat metabolic syndrome [8,9]. PPARβ/δ is expressed in numerous tissues [10,11], and many important functions have been attributed to PPARβ/δ in skeletal muscle, adipose tissue, the cardiovascular system, uterine implantation, the gut, the brain, and skin [12]. These factors make PPARβ/δ a very attractive and challenging target, as it is involved in numerous key functions, such as energy metabolism, cellular differentiation and proliferation, tissue repair, and cancer progression.

As is the case for all other members of the nuclear receptor superfamily, PPARβ/δ is structurally organized into functional modular domains. The DNA- and ligand-binding domains (DBD and LBD, respectively) are the most conserved regions among all members of the nuclear receptor superfamily. The DBD consists of α-helical DNA-binding motifs together with two zinc

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finger-like motifs. The structure of the DBD allows PPARβ/δ, as a heterodimer with a retinoid X receptor (RXR), to bind to peroxisome proliferator response elements (PPREs) in the regulatory domains of PPARβ/δ target genes. The LBD is composed of 13 α-helices and a 4-stranded β-sheet. As a member of the PPAR family, PPARβ/δ also possesses a relatively large ligand-binding pocket (~1300 $Å^3$), which allows PPARβ/δ to interact with a broad spectrum of ligands, including natural FAs, eicosanoids, and synthetic agonists or antagonists. In addition to the presence of a ligand, transcriptional activity is dependent on and regulated by a tight balance between the levels of binding with coactivators and corepressors. Ligands are able to allosterically alter the conformation of the helical structure (helix 12) at the C-terminal end of the LBD of PPARβ/δ. When no ligand is present, helix 12 exists in its open conformation, which allows for corepressor molecules to bind and repress its transcriptional activities. Ligand binding induces a conformational change at helix 12, exposing a binding domain that allows for coactivator molecules to bind to the LBD of PPARβ/δ and consequently promote the transcription of downstream target genes [13].

In this review, we will discuss studies related to the functions of the less-well known PPAR, PPARβ/δ as well as the status of this nuclear receptor as a potential therapeutic target for many of the metabolic diseases caused by the dysregulation of PPARβ/δ expression and activity.

2. Molecular mechanisms of transcriptional regulation by PPARβ/δ

2.1 Cellular localization

As a nuclear receptor, PPARβ/δ is localized in the nucleus of cells. For ligands to bind to PPARβ/δ, they must be transported from the cytoplasm into the nucleus [14]. The intracellular lipid-binding protein FA-binding protein 5 (FABP5) selectively performs this transport function

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to enhance the transcriptional activity of PPARβ/δ [15] (Figure 1). Since the characterization of FABP5 in keratinocytes nearly two decades ago, numerous studies have demonstrated the expression of FABP5 in many tissues and organs, such as the epidermis, adipose tissue, mammary glands, brain, kidneys, liver, lungs, heart, skeletal muscles, and testes, as well as in specific cell types such as macrophages [16]. This expression pattern of FABP5 parallels that of PPARβ/δ in many of these tissues, and the interaction of FABP5 with PPARβ/δ is thought to affect many functions of PPARβ/δ, including those involving cellular glucose and lipid homeostasis, cell differentiation, and apoptotic resistance [15,17,18]. Indeed, cooperative activities between FABP5 and PPARβ/δ have been reported to be involved in neurogenesis [19] and in pathological conditions such as cancer [20,21], metabolic syndrome [22,23], and atherosclerosis [24].

2.2 Transactivation and repression

The transactivation of PPARβ/δ involves the binding of an agonist to the LBD of PPARβ/δ monomers or heterodimers with RXRs and the recruitment of coactivator molecules, such as CBP/p300 and other histone acetyltransferases [25-27] (Figure 1). However, in contrast to PPARα and PPARγ, PPARβ/δ functions as a transcriptional repressor in its unliganded state (Figure 1). This function of PPARβ/δ is attributed to two interrelated properties: unliganded PPARβ/δ is able to repress basal transcription as well as PPARα- and PPARγ-mediated transcription [28]. In that report, the authors demonstrated that unliganded PPARβ/δ suppressed basal transcription via the recruitment of corepressor molecules. They also demonstrated that PPARβ/δ induced isotype-specific repression of PPARα and PPARγ target genes through competition for the PPRE sites of those genes. It has also previously been shown that PPARβ/δ-

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mediated repression involves potent corepressor molecules including nuclear receptor corepressor (NCoR) and silencing mediator for retinoid and thyroid hormone receptor (SMRT) [29,30], which can fine-tune receptor activity according to the expression levels of corepressors and coactivators [25,27,31,32] (Figure 1). Interestingly, PPARβ/δ alone is also regulated by another transcription factor, NF-κB. It has been shown that the p65/RelA subunit of NF-κB is able to exert a potent repressive effect on the PPARβ/δ-mediated transactivation of target genes in human keratinocytes and that this repression occurs only on PPARβ/δ bound to a PPRE via the recruitment of histone deacetylases (Figure 1) [26].

2.3 Transrepression

In addition to regulating cellular functions via the direct induction of target genes, PPARβ/δ is able to perform certain activities in concert with the PPARβ/δ-associated transcriptional repressor B-cell lymphoma-6 (BCL-6) (Figure 1). PPARβ/δ is expressed in vascular smooth muscle cells and endothelial cells together with BCL-6 [28,33], and in these cells, PPARβ/δ plays critical roles in modulating the survival and proliferation of endothelial cells [29,34,35] (Figure 1). In the latter process, the anti-inflammatory activity of PPARβ/δ is triggered by interaction with its ligands, which causes the dissociation of BCL-6 from PPARβ/δ. This dissociation allows BCL-6 to relocate to the promoter regions of pro-inflammatory genes such as VCAM-1 and E-selectin to repress their transcription, thereby protecting the vasculature [35,36]. Such anti-inflammatory effects of PPARβ/δ activation have also been reported for the BCL-6-mediated suppression of monocyte chemoattractant protein-1 and osteopontin, exerting anti-atherosclerotic effects, in angiotensin II-accelerated atherosclerosis [37,38] and in diabetic

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nephropathy [39]. In addition, unliganded PPARβ/δ has been found to be associated with BCL-6 in macrophages, where it may play a role in regulating chemokine and cytokine release [2].

2.4 Natural and synthetic ligands of PPARβ/δ

Over the years, many independent groups have reported various findings related to PPARβ/δ and its association with different diseases. Across these studies, controversies regarding the role of PPARβ/δ in certain diseases have been reported, and many of these discrepancies are likely due to differences in the experimental conditions. Despite these controversies, the development of synthetic ligands of PPARβ/δ, including both agonists and antagonists, has greatly contributed to meeting the goal of fully understanding the structure and functions of PPARβ/δ. In this review, we will discuss studies related to less well-known functions of PPARβ/δ as well as the status of this nuclear receptor as a potential therapeutic target for many of the metabolic diseases caused by the dysregulation of its expression and activity.

As a member of the PPAR family, PPARβ/δ is responsive to naturally occurring free FAs and their metabolites, such as monounsaturated and polyunsaturated FAs, carbaprostacyclin, and components of very-low-density lipoprotein (VLDL). Arachidonic acid metabolites, or eicosanoids, are also natural ligands that can activate PPARβ/δ [40–42]. One such example is the lipoxygenation product 8(*S*) hydroxyeicosatetraenoic acid [8(*S*)-HETE] [43,44]. The peroxidation products of polyunsaturated FAs 4-hydroxynonenal (4-HNE) and 4-hydroxydodecadienal (4-HDDE) were reported to activate PPARβ/δ in cultured endothelial cells and pancreatic β-cells [45,46]. However, the mechanism by which these two 4-hydroxyalkenals activate PPARβ/δ remains unclear. It has been proposed that these chemically reactive aldehydes may form covalent bonds with nucleophilic groups of certain amino acids (i.e. histidine, lysine,

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arginine or cysteine). However, it has also been reported that steric hindrance prevented covalent interaction of 4-HNE with histidine residues in the ligand binding domain of PPARβ/δ [47]. Very interestingly, it was also previously reported that the vitamin A metabolite all-*trans*-retinoic acid (RA) binds to and activates PPARβ/δ with nanomolar affinity [17,48,49]. As RA is a known ligand for the retinoic acid receptors (RARs), it was uncertain how RA could play a dual, simultaneous role in inhibiting and promoting cellular growth. The same group subsequently reported that the activation of RARs and PPARβ/δ by RA is regulated by a partitioning of RA itself between the two receptors by the intracellular FA transporters CRABP2 (also called CRABP-II) and FABP5, respectively. It has been demonstrated that FABP5 and CRABP2 translocate to the nucleus in response to PPARβ/δ and RAR agonists, respectively, and that these transporters directly bind to their corresponding receptors, enabling direct transfer of their ligands to their cognate receptors [15,17,50–52]. The structural features that allow these proteins to translocate to the nucleus only upon binding of agonists to their cognate receptors and not upon association with other ligands have been identified [51,53]. Moreover, it was demonstrated that the FABP5/CRABP2 expression ratio is critical to the efficient activation of PPARβ/δ and RARs in cultured cells and *in vivo* [15,17,49,54,55]. RAR activation by RA occurs in cells with a low FABP5:CRABP2 ratio, resulting in a pro-apoptotic effect. On the other hand, PPARβ/δ activation by RA was found to promote the survival of cells with higher FABP5 expression [17]. Thus, the relative expression levels of FABP5 and CRABP2 under different physiological circumstances have important functional consequences. For example, numerous reports have documented that the FABP5:CRABP2 ratio is increased in many human tumors as a result of upregulation of FABP5, silencing of CRABP2, or both. These tumor types include glioblastoma, astrocytic gliomas, oral and head-and-neck squamous cell carcinomas, and cancers

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of the pancreas, bladder, prostate, breast, skin, colon, and esophagus [56,57]. High levels of FABP5 in tumors are associated with poor patient prognosis in various cancer types (Oncomine, Compedia Bioscience database) [58,59]. Moreover, it has been documented that elevated levels of FABP5 promote cancer cell proliferation, migration, and invasion and tumor development and that in line with the role of FABP5 in enabling the activation of PPARβ/δ, FABP5 exerts these oncogenic effects by enhancing the transcriptional activity of PPARβ/δ, thereby inducing the expression of oncogenic PPARβ/δ target genes [17,20,49,60–62]. However, Rieck et al. (2008) argued against this proposition of PPARβ/δ activation by RA based on a comparative analysis between RA and other PPARβ/δ selective agonists. In their study, RA failed to activate PPARβ/δ, as shown by their reporter assays, and to recruit coactivators to bind to PPARβ/δ [63]. Hence, it is also possible that the effects of RA observed by previous studies may involve a currently undiscovered indirect mechanism. Interestingly, PPARβ/δ and FABP5 are downregulated in adipose tissue of obese subjects [64] but are upregulated in neural stem/progenitor cells during postnatal hippocampal neurogenesis [65]. In addition to the desire to identify naturally occurring ligands, the need to discover therapeutic agents for metabolic diseases resulted in the development of highly specific synthetic PPARβ/δ ligands as potential hypolipidemic drugs. These ligands include agonists and antagonists; the potential benefits of these ligands in the healthcare setting have previously been reviewed and will not be discussed further here [66]. Although none of these compounds have been approved for clinical use, studies of these ligands demonstrated the central role of PPARβ/δ in metabolism. Suitable drug therapies targeting PPARβ/δ could provide multiple benefits against a diverse range of metabolic disorders.

Interestingly, a nucleocytoplasmic shuttling mechanism between FABP4 and PPARγ similar to that between FABP5 and PPARβ/δ has been proposed [67,68]. Despite numerous

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studies, many questions remain to be answered. Using its relatively large ligand-binding pocket, PPARβ/δ interacts with a broad spectrum of ligands, including a variety of natural FAs, eicosanoids, and synthetic agonists or antagonists. However, whether intracellular FA transporters accommodate and shuttle these various ligands to PPARβ/δ remains to be determined, and the selectivity of the various FABPs, such as FABP4 and FABP5, for particular PPAR agonists is uncertain. It is of particular interest that this shuttling mechanism has never been demonstrated for antagonist- or inverse agonist-mediated inhibition of PPARβ/δ. Interestingly, an antagonist of one nuclear receptor family member can function as an agonist of another. For example, Ro 41-5253 is a potent antagonist of RARα but is able to activate PPARγ [69]. In this context, the interplay among the various effectors implicated in the selective partitioning of agonists or antagonists of different nuclear receptors further underscores the importance of nucleocytoplasmic shuttling.

3. PPARβ/δ in early fetal development.

In adults, PPARβ/δ regulates cellular processes that are also key for development [70]. PPARβ/δ is highly expressed in early-stage *Xenopus laevis* embryos, in which PPARα is weakly expressed and PPARγ is not expressed at detectable levels [2,39]. The PPARβ/δ protein is present in all cell nuclei of the embryo and is strongly upregulated during gastrulation, which suggests a prominent function of this receptor at this developmental stage [38]. In support of this hypothesis, a PPARβ/δ loss-of-function experiment using an antisense morpholino (MO) demonstrated disrupted gastrulation movement. These results are supported by reduced expression of marker genes reflective of defects in muscle (*actc1*, *myod1*) and brain (*krox20*) differentiation at the neurula stage in the absence of PPARβ/δ. By combining the loss-of-

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function approach with high-throughput RNA-seq transcript expression analyses and chromatin immunoprecipitation experiments, an important cooperation between epigenetic marks and PPARβ/δ was unveiled. During gastrulation, PPARβ/δ recognizes H3K27me3 marks previously deposited at the pluripotent stage to activate the transcription of early differentiation genes. Importantly, PPARβ/δ is the first identified transcription factor to drive an epigenetic signature of pluripotency *in vivo* during embryonic development [70]. These findings open the door for the development of a greater mechanistic understanding of how the activation of many genes might be coordinated during early development. In mammals, PPARβ/δ also plays a major role later in development during the formation of the placenta, in which PPARγ is also involved [71–73].

Despite its discovery as early as 1992 and the numerous studies underscoring the important roles of PPARβ/δ in the transcriptional control of energy homeostasis and various pathological processes, surprisingly little is known about its expression during human fetal development. The mRNA and protein expression of PPARβ/δ in human various fetal tissues was examined by a few groups [74,75]. Based on an analysis of nine human fetal tissues, specifically intestinal, liver, lung, heart, kidney, adrenal, thymus, stomach and spleen tissues, ranging in age from embryonic day (ED) 54 to 125, PPARβ/δ mRNA expression in fetal lung, adrenal, stomach (ED54–120), kidney (ED54–125), spleen (ED67–125) and thymus tissues (ED74–120) did not change with age, as determined by real-time PCR using β2-microglobulin as the internal control gene [75]. Human fetal liver expressed PPARβ/δ mRNA from ED54–125, and its expression increased significantly across the age range; in contrast, its expression decreased in fetal heart (between ED54 and 125) and intestinal tissues (ED54–120). Except for adrenal tissue, in which PPARβ/δ protein expression decreased with fetal age, no tissue showed a significant change in the PPARβ/δ protein level as determined by western blot analysis. The spatiotemporal

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distribution of PPARβ/δ during development (from 7 to 22 weeks of gestation, WD; ~ED49-154) of the human fetal digestive tract was further examined via immunohistochemistry using specific polyclonal antibodies [74]. PPARβ/δ was detected throughout the gastric epithelium at all the developmental stages examined. PPARβ/δ expression in the cytoplasm and nucleus of human esophageal epithelial cells was detectable between 7WD and 14WD, peaked at 15WD, and then markedly decreased at 20WD. At later stages, PPARβ/δ staining was more restricted to nuclei. In the small intestine, stronger PPARβ/δ staining was observed in the ileum than in the jejunum at all stages studied. At 22WD, the PPARβ/δ staining signal was stronger in the ileal crypt epithelial cells than in the differentiated villous cells. PPARβ/δ was expressed in the different layers of the human fetal colon at 8-20WD. The PPARβ/δ signal was primarily localized to the nuclei in epithelial and mesenchymal cells. Compared to PPARβ/δ staining in the ileum, stronger PPARβ/δ staining was observed in the crypt regions of the colon. However, PPARβ/δ staining was barely detected in these regions at 14WD [74]. The distinct expression profiles of PPARβ/δ in various human fetal tissues and regions of the fetal digestive tract suggest that PPARβ/δ may play major roles in tissue morphogenesis, development and/or physiology.

4. PPARβ/δ in gametes and preimplantation embryos and in placentation

All three PPAR isotypes are expressed in somatic and germ cells of the testis. In rats, PPARβ/δ is expressed in Leydig cells and Sertoli cells [76]. In mice, PPARβ/δ is expressed in spermatids and spermatocytes [10]. The expression of PPARβ/δ in mouse spermatids and spermatocytes is further supported by the observed expression of *Ssm*, a novel PPAR target gene, in mouse testes [77]. Preimplantation mouse embryos show PPARβ/δ expression, which is already detectable by immunohistochemistry at the two-cell stage [78] or the eight-cell stage [79]

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and remains detectable throughout the preimplantation period. Mouse blastocysts also express PPARβ/δ in the inner cell mass and the trophectoderm [79,80]. These observations suggest that PPARβ/δ plays an important role in early development.

To understand the functions of PPARβ/δ in an *in vivo* and physiologically relevant context in rodents, three independent groups have used different strategies to generate PPARβ/δ knockout mice. The observations from these groups reveal an apparent discrepancy in the role of PPARβ/δ in placentation. In 2000, Peters et al. disrupted the mouse PPARβ/δ gene by inserting a 1.14-kb phosphoribosyltransferase II gene into the last exon in the same direction of transcription in the genomic clone, herein referred to as PPARβ/δ^{ex8}. This insertion truncated only the C-terminal 60 amino acids of PPARβ/δ [81]. Northern blot analysis of RNA from brain, adipose and liver tissues revealed an mRNA transcript 1 kb larger than the wild-type mRNA in the PPARβ/δ^{ex8} mouse, and the expression of this mutant transcript was lower than that of the wild-type transcript in non-mutant mice. Neither the larger nor a truncated mRNA was detected in the skin of PPARβ/δ^{ex8} mice, and this result was explained by a later study that revealed that PPARβ/δ was undetectable in adult mouse skin cells [82]. However, despite the presence of these mRNA species, the PPARβ/δ protein was not detected in hepatic nuclear extracts from PPARβ/δ^{ex8} mice. The breeding of heterozygous offspring of mixed genetic backgrounds (C57BL/6N x Sv/129) produced fewer homozygous PPARβ/δ^{ex8} mice than expected. An analysis of E10 embryos and E18 fetuses revealed that the absence of PPARβ/δ was not lethal during intrauterine development, and the gross morphology of the concepti appeared normal [81]. Subsequent backcrosses produced PPARβ/δ^{ex8} mice, ~75% of which were in the C57BL/6N genetic background. The colony of PPARβ/δ^{ex8} mice reproduced successfully, and normal Mendelian genotype distributions were found in subsequent heterozygous matings.

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Barak et al. (2002) used a Cre/lox-mediated recombination strategy to delete exon 4 of the PPARβ/δ gene, which harbors the N-terminal half of the DBD, herein referred to as PPARβ/δ^{ex4} [72]. In contrast to the approach by Peters et al. (2000), this disruption strategy eliminated nearly the entire PPARβ/δ gene product. PPARβ/δ^{ex4} pups were rarely obtained from heterozygous crosses, suggesting that the homozygous loss of PPARβ/δ frequently resulted in lethality to embryos, which appeared to occur at E10.5. In contrast to PPARβ/δ^{ex8} mice, PPARβ/δ^{ex4} embryos showed no increase in survival rate despite the performance of up to six backcrosses of the original knockout strain (129sv/Jae) with isogenic C57BL/6J breeders. This result indicates that the lethality of PPARβ/δ^{ex4} is not alleviated by either a heritable component or a specific genetic background [72,81]. Surviving PPARβ/δ-deficient progeny showed markedly stunted growth at term, and most PPARβ/δ^{ex4} pups were smaller than their wild-type counterparts. Histological examination of PPARβ/δ^{ex4} concepti at E9.5 revealed abnormally loose placental-decidual connections. By E12.5, three of four PPARβ/δ^{ex4} embryos surviving the major E10.5 lethality point exhibited extensive maternal hemorrhages into the labyrinthine zone.

Nadra et al. (2006) confirmed that deletion of the PPARβ/δ gene results in a severe failure of the placenta to undergo proper morphogenesis, leading to embryonic lethality between E9.5 and E10.5 [73]. This independent group used a homologous recombination strategy to delete exon 4 and most of exon 5 from the PPARβ/δ gene (i.e., PPARβ/δ^{ex4}). Heterozygote mating (mixed background, C57BL6/Sv129) did not produce the expected Mendelian ratio of mutant animals, and live PPARβ/δ^{ex4} offspring were rare, although no instances of perinatal death were observed. Further investigation revealed that the trophoblast giant cell layer of the placenta was the most severely affected by this mutation. The authors showed a direct role of PPARβ/δ in promoting trophoblast cell differentiation towards giant cells. This function of

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PPARβ/δ depended on phosphatidylinositol 3-kinase (PI3K) and Akt1 (also referred to as protein kinase B) and was at least partly associated with high expression levels of two kinases involved in Akt activation, specifically 3-phosphoinositide-dependent kinase 1 (PDK1; also referred to as PDPK1) and integrin-linked kinase (ILK). In addition, PPARβ/δ caused an increase in the expression of I-mfa, a non-helix-loop-helix (HLH) inhibitor of the myogenic basic HLH (bHLH) subfamily that is involved in the differentiation process. Maternal PPARβ/δ is critical to implantation and decidualization, and embryonic PPARβ/δ is crucial for placentation. Moreover, Wang et al. (2007) showed a reciprocal relationship between the PPARβ/δ-AKT and leukemia inhibitory factor- signal transducer and activator of transcription 3 (STAT3) signaling pathways, which serve as cell lineage sensors to direct trophoblast cell fates during placentation. This finding of stage-specific integration of maternal and embryonic PPARβ/δ signaling provides further evidence that PPARβ/δ is a molecular link that coordinates implantation, decidualization, and placentation, all of which are crucial to a successful pregnancy [83].

In fact, PPARβ/δ^{ex4} embryos can be lost prior to E9.5 at any stage, including ovulation, fertilization, preimplantation, implantation, and postimplantation [80]. PPARβ/δ^{ex4} ablation adversely affected embryo development during the preimplantation stage and consequently hampered implantation [79]. Compared with wild-type embryos, PPARβ/δ^{ex4} embryos show developmental delay as early as 48 hours after harvest of two-cell stage embryos. At 96 hours after harvest of two-cell embryos, only 65% of PPARβ/δ^{ex4} embryos had reached or passed the blastocyst stage, and 28% subsequently underwent hatching or had hatched completely, compared with 100% and 85% of wild-type embryos, respectively [79]. PPARβ/δ^{ex4} embryos also exhibit decreased embryonic cell proliferation compared with wild-type embryos. Investigators have proposed that activation of PPARβ/δ by an endogenous PPAR ligand, such as

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prostaglandin I2 (also known as prostacyclin) [84] or retinoic acid [17], may be necessary for biological processes in embryos during preimplantation and subsequent stages of development.

Although genetic approaches support a beneficial role of PPARβ/δ in placentation, pharmacological approaches have yielded varying outcomes at different stages of gestation. PPARβ/δ activation by the synthetic agonist L-165041 or iloprost (a stable PGI2 analogue) enhanced the development and implantation of cultured embryos in a concentration-dependent manner [85–87]. Embryos preconditioned with L-165041 or iloprost showed higher implantation rates when transferred to gestational carriers [79,86]. Administration of the more selective PPARβ/δ agonist GW501516 to pregnant rats resulted in malformations of the endometrium and placenta. Histopathologically, a single oral administration of GW501516 induced cystic degeneration associated with lysis of glycogen cells [88], unexpectedly leading to significant developmental toxicity. These results suggest that a transrepression mechanism may dominate the activity of PPARβ/δ during development.

This role of PPARβ/δ in preimplantation and placentation clearly warrants further investigation. The reason for the stark contrast in the role of PPARβ/δ in placentation between PPARβ/δ^{ex8} [81] and PPARβ/δ^{ex4} [72,73] mice remains unclear, and determining the mechanisms underlying these differences would require comparative analysis of these two models of PPARβ/δ disruption in a congenic background. It has been proposed that the different disruption strategies employed may be responsible for these discrepancies. Disruption of the DBD, as performed by Barak et al. (2002) and Nadra et al. (2006), eliminated nearly the entire PPARβ/δ gene product [72,73], whereas the approach employed by Peters et al. (2000) disrupted only the last 60 amino acids of the LBD of PPARβ/δ [81]. In the latter approach, the limited deletion might not completely abolish PPARβ/δ activity and could theoretically produce a hypomorphic

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allele that retains some aporeceptor function [88–90]. Importantly, either PPARβ/δ^{ex4} or PPARβ/δ^{ex8} mice may be applicable to studies of various diseases, such as tumorigenesis and neurological diseases. As elaborated in subsequent sections of this review, opposing roles of PPARβ/δ have been reported, particularly in relation to tumorigenesis; however, the conclusions of these studies have been roughly concordant when using PPARβ/δ^{ex4} mice derived by two independent laboratories [72,73].

5. Tissue repair

We have previously reviewed the involvement of all three PPARs in tissue injury and wound repair [91]. Below, we focus on recent findings related to the specific roles of PPARβ/δ in the tissue repair process.

5.1 Inflammatory response during tissue repair

A cardinal feature of poorly healing wounds is a persistent inflammatory response at the wound site [92]. This can lead to unbalanced proteolytic activity, which overwhelms the protective mechanisms of the local tissue and leads to a dysfunctional wound microenvironment that cannot support healing. PPARs are central effectors in the induction and modulation of several inflammatory reactions. These inflammatory processes serve purposes that range from protection against external microbial infections to promotion of pathological inflammation-related disorders such as atherosclerosis and type 2 diabetes [93]. The expression of PPARα is transiently elevated after adult mouse injury and has been implicated in the promotion of anti-inflammatory effects [82,94]. In comparison, PPARγ activation leads to reduced production of pro-inflammatory cytokines, including TNFα, IL-6 and nitric oxide (NO) [95]. In contrast, the role of PPARβ/δ in the modulation of inflammation during wound repair is poorly understood.

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However, one current model exists; this model suggests that the role of PPARβ/δ involves the switching of macrophage functions from pro- to anti-inflammatory. This switching mechanism involves the ligand-mediated activation of PPARβ/δ and the subsequent promotion of the release of BCL-6 to repress the transcriptional activities of pro-inflammatory genes (Figure 1). In agreement with these observations, other reports have suggested that PPARβ/δ agonists are able to downregulate lipopolysaccharide-induced pro-inflammatory genes, including inducible NO synthase (iNOS) and COX2, via NF-κB [96,97]. Interestingly, PPAR-mediated inflammatory crosstalk has also been implicated in the maintenance of tissue homeostasis, particularly in skin. While PPARα is important in the early inflammatory phases of wound healing for the recruitment of immune cells to the wound bed, PPARβ/δ plays a crucial role in reducing these inflammatory activities as the wound closes and heals.

5.2 Skin repair

Of all the human tissues in which the role of PPARβ/δ has been studied, skin tissue repair has been particularly well studied in terms of the functions of PPARβ/δ at various stages of tissue repair (Figure 2). Cutaneous wound repair is classified as a high-priority survival response to skin injuries. Upon formation of a cutaneous wound, the primary goal of the body is to reconstruct a new and effective epidermal barrier that covers the wound, thereby preventing tissue dehydration and any opportunistic microbial infections [98,99]. Normal wound healing is composed of three major phases – inflammation, cell proliferation and migration (re-epithelialization), and extracellular matrix (ECM) remodeling. These three phases occur in a partially overlapping pattern via the production of cytokines and growth factors in a temporally and spatially regulated manner [98]. The inflammation phase begins immediately after skin

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injury. Damaged blood vessels in the vicinity of the injury release signals that initiate localized blood clotting and influx of inflammatory cells.

PPARβ/δ is the dominant PPAR subtype in the human epidermis. In mice, the expression of PPARβ/δ in the interfollicular epidermis declines as the animal develops from the fetal stage to adulthood. However, upon cutaneous injury, PPARβ/δ expression is rapidly upregulated in the epidermis at the wound edges, and PPARβ/δ-activating ligands are produced [82]. Upon the influx of inflammatory cells during skin injury, the expression levels of pro-inflammatory cytokines, such as TNFα, have been found to be associated with *Pparβ/δ* gene stimulation via the SAPK/AP-1 pathway. Consequently, induction of PPARβ/δ expression leads to increased production of ILK and PDK1 (or PDPK1), both of which have been reported to be direct targets of PPARβ/δ-mediated activation. In addition, PPARβ/δ activation coordinates the downregulation of the expression of phosphatase and tensin homologue deleted on chromosome 10 (PTEN). These activities lead to an increase in AKT1 activation, which suppresses keratinocyte apoptosis by modulating both the death-receptor and mitochondrial apoptotic pathways. This process ensures the recruitment of a sufficient quantity of viable keratinocytes at the wound edge for re-epithelialization to occur [82,99]. Furthermore, *in vivo* wound studies have shown that PPARβ/δ activation exerts an anti-apoptotic effect on keratinocytes in wounded tissues [100]. In addition to its anti-apoptotic effects during wound healing, PPARβ/δ upregulates the activity of NF-κB, which leads to increased matrix metalloproteinase-9 (MMP-9) production [100]. This increased production of MMP-9 was subsequently found to play a role in the regulation of keratinocyte migration during wound healing [101] (Figure 2).

Wound repair involves epithelial-mesenchymal interactions that require communication among different cell types in a temporal manner. The signals that are communicated within the

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wounded tissue are mediated by key effectors such as growth factors secreted by cells in the epithelium and mesenchyme. Therefore, in addition to studying the functions of keratinocytes in the process of wound healing, our group has previously identified a novel and critical role of fibroblast-derived PPARβ/δ in modulating skin homeostasis in a paracrine fashion in the adjacent epithelium [102]. Keratinocyte-derived interleukin-1 (IL-1) promotes the upregulation of PPARβ/δ expression in neighboring fibroblasts [102]. Fibroblast-derived PPARβ/δ subsequently stimulates the production of secreted IL-1 receptor antagonist (sIL-1ra), thereby inhibiting further IL-1-induced production of mitogenic factors by fibroblasts. This regulated decrease in mitogenic factor production leads to tight regulation of keratinocyte proliferation during wound healing, thereby ensuring homeostasis in the epidermal layer of the skin [102] (Figure 2). Such control over homeostasis during normal wound healing highlights the importance of tight regulation of the complex epithelial-mesenchymal interactions. When this tight control becomes dysregulated, mechanisms of epithelial-mesenchymal crosstalk may become defective, leading to disorders such as poor wound healing in diabetes patients.

The importance of PPARβ/δ as a potential therapeutic target for promoting proper wound healing, particularly healing of chronic diabetic wounds, has also been recently demonstrated [103]. Diabetic wounds are imbued with early, excessive and protracted reactive oxygen species (ROS) production. Wang et al. (2015) underscored a novel role of PPARβ/δ in fibroblasts in the modulation of oxidative stress levels in a diabetic wound microenvironment. They demonstrated that *catalase* and *glutathione peroxidase 1* (*Gpx1*) were novel target genes of PPARβ/δ in fibroblasts. Both catalase and GPx1 are antioxidants that function to scavenge the excessive hydrogen peroxide (H_2O_2) that accumulates in diabetic wound beds. In addition, these authors showed that excessive levels of H_2O_2 modified the ECM, which subsequently impaired

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keratinocyte migration, leading to the formation of poorly healed or unhealed wounds in diabetic patients. To demonstrate the therapeutic potential of fibroblast-derived PPARβ/δ for promoting diabetic wound closure, wounds in diabetic mice were treated with a microencapsulated form of the PPARβ/δ agonist GW501516. The microencapsulation approach provided early and sustained release of GW501516 into the wound bed, increasing its bioavailability. When translated clinically, the concept of drug microencapsulation would help maintain patient compliance with treatment. Importantly, diabetic wounds treated with GW501516 healed much more rapidly than vehicle-treated wounds due to reduced levels of H_2O_2 production by fibroblasts in the diabetic wound microenvironment, leading to enhanced keratinocyte migration and, therefore, improved wound closure [103] (Figure 2). The importance of PPARβ/δ in fibroblasts is also well supported by other previous studies. A separate report demonstrated its importance in downregulating the UVB-induced secretion of MMP-2, along with upregulating elastin and decreasing ROS levels. Such processes may contribute to the maintenance of skin integrity [104]. In another study, the expression of PPARβ/δ in fibroblasts was increased upon heat-induced injury, which subsequently initiated processes that led to cellular protection from heat injury-induced morphological changes and to increased keratinocyte proliferation [105]. Another report has shown that activation of PPARβ/δ in fibroblasts induced the upregulation of *Ski* in a rat model, thereby leading to increased fibroblast proliferation and improved wound repair [106,107]. *Ski* encodes the nuclear proto-oncogene protein homologue of the avian sarcoma viral (v-ski) oncogene. Ski functions as a repressor of TGFβ signaling [108]. Recently, PPARβ/δ activation was implicated in α-smooth muscle actin (α-SMA) upregulation [109], which was shown to be caused by a dual binding mechanism involving the interaction of activated PPARβ/δ with a direct repeat-1 (DR1) site in the α-SMA promoter and the interaction

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of Smad3 with a Smad-binding element (SBE) in another region of the α-SMA promoter. Elevated α-SMA levels correlate with increased fibroblast-to-myofibroblast differentiation, concomitant with enhanced fibroblast migration and contractility. While this report demonstrated the beneficial role of PPARβ/δ in wound healing via the upregulation of α-SMA in fibroblasts, the study was performed in the presence of serum in the culture. The presence of serum could have contributed to non-specific activation of PPARβ/δ in the cultured fibroblasts. Nonetheless, all of these studies suggest that PPARβ/δ plays crucial roles in promoting appropriate cutaneous wound repair.

In addition to their crosstalk with fibroblasts, keratinocytes communicate with endothelial cells during wound repair. In order for the skin to have proper and efficient nourishment, waste removal, inflammatory responses, and temperature regulation, a functional vascular circulation is essential. In contrast, dysfunctional vascular circulation severely impairs the tissue repair process [106,110–112]. This dysfunction is one of the main impediments to the proper healing of diabetic wounds [113]. Previously, it has been shown that angiopoietin-like protein 4 (ANGPTL4) is a direct target of PPARβ/δ [112,114]. The C-terminal form of the post-processed ANGPTL4 protein (cANGPTL4) was shown to weaken cell-cell tight junctions and to induce NO production through the integrin/JAK/STAT3-mediated upregulation of iNOS in the epithelial layer of the wound. This finding reveals a novel mechanism in which ligand-mediated activation of PPARβ/δ participates in upregulating the expression and secretion of keratinocyte-derived cANGPTL4 to promote the angiogenic process via keratinocyte-endothelial cell crosstalk, leading to accelerated wound healing [115,116] (Figure 2).

In addition to cell-cell communication, PPARβ/δ modulates the interactions between cells and the ECM. Similar to its observed activities in normal keratinocytes, the PPARβ/δ target

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cANGPTL4 was found to be primarily produced by wound keratinocytes at the wound site [117,118]. As a matricellular protein, cANGPTL4 can associate with the myriad of proteins that are located in the ECM reservoir and, therefore, with various cell surface receptors to act as a possible mediator of paracrine signaling during the wound healing process and as a component of various regulatory networks [114,119]. Wound keratinocyte-derived cANGPTL4 has previously been shown to modulate cell migration by regulating both integrin-mediated signaling and cell-ECM crosstalk via the control of matrix protein integrity. In addition, cANGPTL4 has been shown to interact with integrin α1β5, thereby activating the integrin-FAK-Src-PAK1 signaling pathway and leading to selective integrin internalization to promote cell migration [120,121] (Figure 2). Considering these observations, it is possible that exogenous administration of PPARβ/δ agonists could aid in wound healing via cANGPTL4-mediated regulation of cell-ECM communication.

5.3 Tissue repair in other organs

In addition to the skin, tissues from other organs are also known to undergo repair via processes involving the activation of PPARβ/δ. Corneal stromal fibrosis, which occurs as a result of poor wound healing in the cornea, is characterized by an increased abundance of myofibroblasts and excess ECM deposition. Corneal scarring occurs naturally following trauma, infection, or refractive surgery and could result in loss of vision [122]. One study showed that activation of PPARβ/δ using GW501516 after excimer laser keratectomy provided antifibrotic effects by targeting different phases of wound healing. For example, GW501516 was shown to promote angiogenesis in the early phase of healing, resulting in increased nutrient supply. However, at the beginning of the remodeling phase of wound healing, GW501516 deregulated

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the activation and proliferation of keratinocytes and subsequently prevented their transdifferentiation into myofibroblasts, which caused aberrant ECM deposition and, hence, the appearance of corneal haze [122].

PPARβ/δ is also known to play a role in maintaining endothelial homeostasis. In the presence of GW501516 and its co-activator PPARγ co-activator 1 α (PGC1α), PPARβ/δ has been shown to induce the production and activity of heme oxygenase-1, which in turn has a vasculoprotective effect against H_2O_2-induced vascular injury by increasing the production of bilirubin and heavy-chain ferritin and promoting the opening of Fe^{2+} export channels [123]. These end products have significant anti-inflammatory, anti-apoptotic, and anti-oxidant effects.

In the liver, chronic alcohol consumption can impair liver regeneration as a result of attenuated insulin signaling and oxidative injury. In the rat liver, PPARβ/δ agonist administration reduces the severity of ethanol-induced injury and attenuates the effects of ethanol on liver repair by restoring insulin responsiveness. Interestingly, this beneficial effect of PPARβ/δ agonist administration persists even when ethanol consumption is continued at a high level [124].

6. PPARβ/δ in cardiovascular disease

Several reports have shown that PPARβ/δ is involved in vascular processes, suggesting its role in cardiovascular disease (CVD) [125].

6.1 Endothelial dysfunction

Perturbation of endothelial function due to conditions such as hypertension or dyslipidemia can provoke vasospasms, thrombosis, intimal growth, inflammation, and plaque rupture, leading to the development and progression of cardiovascular diseases [126]. PPARβ/δ activation may protect blood vessels through direct and indirect effects. In the vascular

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endothelium, PPARβ/δ activation directly causes endothelium-dependent vasodilatation, increased eNOS phosphorylation, and elevated NO production in rat aortae through activation of the PI3K/Akt pathway [127] (Figure 3). Indirect effects of PPARβ/δ agonists include the prevention of dyslipidemia and beneficial effects on insulin resistance and glucose homeostasis, which protect the vascular endothelium from well-established risk factors for the initiation and progression of vascular disease. Both the direct and indirect effects of PPARβ/δ agonists might contribute to restoration of endothelial function in streptozotocin-induced animal models of type 1 [127] and type 2 diabetes [128] by increasing NO bioavailability as a result of reduced NADPH oxidase-mediated superoxide production and preserved PI3K/Akt pathway function. In a more recent study [129], PPARβ/δ activation was confirmed to reduce endothelial dysfunction in aortae from mice fed a high-fat diet (HFD), and this reduction was found to be associated with reduced levels of vascular ROS, decreased activity of NADPH, and upregulated expression of antioxidant genes. Lipids cause endothelial dysfunction through an ROS-mediated reduction in NO bioavailability, and PPARβ/δ activation ameliorates FA-induced endothelial dysfunction by upregulating carnitine palmitoyltransferase 1 (CPT-1), which controls an essential step in mitochondrial FA β-oxidation, thus reducing diacylglycerol (DAG) accumulation and subsequent protein kinase C (PKC)-mediated ROS production as well as causing endothelial NO synthase (eNOS) inhibition. In another animal model of spontaneous hypertension in rats, PPARβ/δ activation has been shown to reduce blood pressure, ameliorate endothelial dysfunction, and reduce the vascular pro-inflammatory and pro-atherogenic status of animals [130]. These changes were associated with increased eNOS protein levels, antioxidant gene upregulation, reduced NADPH oxidase-driven superoxide production and increased expression of regulator of G protein–coupled signaling protein (RGS)4 and RGS5. RGSs play important roles in the

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regulation of G protein signaling by binding to active G subunits and stimulating GTP hydrolysis, thus switching off G protein signaling [131]. Therefore, RGS upregulation may attenuate the effects of vasoconstrictors such as endothelin and angiotensin II [132]. Similar findings were obtained in a renin-independent hypertension model induced using deoxycorticosterone acetate (DOCA) salt. Upregulation of RGS5 by PPARβ/δ agonists appears to be an essential underlying their antihypertensive and antioxidant properties and their protective effects on endothelial function. Interestingly, the antidiabetic drug metformin has been shown to reverse impaired endothelium-dependent relaxation through the inhibition of endoplasmic reticulum (ER) stress-induced ROS generation, thereby increasing NO availability in the aortae of diet-induced obese wild-type mice but not their diet-induced obese PPARβ/δ^{ex8} knockout littermates [133]. These findings suggest that the vasoprotective effects of the commonly used drug metformin require PPARβ/δ. Finally, some evidence suggests that PPARβ/δ activation *in vivo* might increase angiogenesis [30].

6.2 Atherosclerosis

Dyslipidemia and macrophage-mediated inflammation are key factors in the development of atherosclerosis. PPARβ/δ may retard the development and progression of atherosclerosis by modulating lipid metabolism and exerting anti-inflammatory effects on macrophages. Regarding dyslipidemia, one study reported that PPARβ/δ^{ex8} knockout mice exhibited elevated levels of plasma triglycerides (TGs) compared to wild-type littermates [134], while another report showed no differences in plasma lipid profiles between PPARβ/δ^{ex4} mice and wild-type mice [35,72]. When PPARβ/δ^{ex8} knockout mice were fed an HFD, they displayed elevated plasma levels of TGs, primarily in association with increased hepatic VLDL production and reduced lipoprotein

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lipase-mediated TG catabolism, although these animals showed no change in cholesterol levels [134]. Treatment of animal models of obesity and diabetes with PPARβ/δ ligands has been shown to have beneficial effects on plasma lipoprotein levels, including reductions in plasma VLDL-TG, low-density lipoprotein (LDL)-cholesterol and non-esterified FA (NEFA) levels as well as an increase in high-density lipoprotein (HDL)-cholesterol levels [135,136] (Figure 3). In addition, PPARβ/δ activators can reduce plasma TG levels by increasing hepatic FA oxidation (FAO), which reduces the availability of FAs for VLDL synthesis, via amplification of the PGC-1α-lipin 1-PPARα pathway [137]. The PPARβ/δ-mediated modulation of hepatic expression of genes involved in lipoprotein metabolism, including *ApoA4*, *ApoA5*, *ApoC1* and the VLDL receptor (*Vldlr*), may also contribute to the hypotriglyceridemic effect of PPARβ/δ *in vivo* [138]. The increase in plasma HDL-cholesterol levels following PPARβ/δ activation has been linked to an increase in the hepatic expression of *ApoA1* and *ApoA2* [139]. A recent study demonstrated that PPARβ/δ activation also regulates the expression of the hepatic phospholipid transfer protein (*Pltp*), which contributes to the maintenance of HDL levels in plasma and generates preβ-HDL [140]. Regarding its reduction of LDL-cholesterol levels, PPARβ/δ activation decreases intestinal cholesterol absorption, which has been associated with significant downregulation of the Niemann-Pick C1-like gene [141] and with the stimulation of fecal cholesterol excretion, primarily by increasing transintestinal cholesterol efflux [142]. The findings of pre-clinical studies prompted the examination of PPARβ/δ ligands in small-scale clinical trials, primarily for the treatment of atherogenic dyslipidemia. This type of dyslipidemia is an important risk factor for myocardial infarction and cardiovascular disease and is a typical feature of obesity, insulin resistance, metabolic syndrome and type 2 diabetes mellitus (T2DM). Atherogenic dyslipidemia manifests as three characteristic features: increased blood concentrations of small, dense LDL

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particles, decreased levels of HDL particles, and increased levels of TGs. In the first relevant study, performed on healthy volunteers, GW501516 administration increased plasma HDL-cholesterol levels and improved postprandial TG clearance [8]. In abdominally obese men with moderate dyslipidemia, GW501516 reduced plasma TG, ApoB, LDL-cholesterol and insulin levels but did not alter HDL-cholesterol levels [9]. Moreover, treatment with this drug reduced liver fat content by 20%. To elucidate the mechanism of action of GW501516, Ooi et al. (2011) studied the effects of this drug on the kinetics of lipoproteins in subjects with central obesity together with dyslipidemia [143]. GW501516 reduced plasma TG, NEFA, ApoB100, and ApoB48 concentrations. Additionally, treatment with this drug increased the hepatic catabolism of VLDL particles, which may have resulted from decreased ApoC3 levels, and increased plasma HDL-cholesterol and ApoA2 levels. In another study, performed on patients with fasting plasma HDL-cholesterol levels below 45 mg/dl (1.16 mmol/L), GW501516 produced significant increases in the level of HDL-cholesterol and reductions in the levels of NEFAs, ApoA1, ApoB and LDL-cholesterol [144]. Furthermore, plasma LDL particle levels decreased as a result of a reduction in the number of small LDL particles, which are more atherogenic, whereas an increase in the number of large LDL particles was observed. Overall, these changes suggest a transition towards lipoprotein profiles that are less atherogenic following GW501516 treatment. The efficacy of the novel PPARβ/δ agonist MBX-8025 has also been evaluated alone and in combination with atorvastatin to treat overweight patients with mixed dyslipidemia. The effects of MBX-8025 monotherapy were very similar to those reported for GW501516 treatment (significant reductions in plasma LDL-cholesterol, ApoB100, TG and NEFA levels). Administration of MBX-8025 in combination with atorvastatin led to a greater reduction in LDL-cholesterol and ApoB levels than MBX-8025 monotherapy, but the combination of MBX-

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8025 and atorvastatin was not more effective in reducing LDL-cholesterol or ApoB levels than atorvastatin alone [145,146]. Similarly, the combination of MBX-8025 and atorvastatin caused a greater reduction in TG levels and increase in HDL-cholesterol levels than atorvastatin monotherapy but not MBX-8025 monotherapy [146]. When lipoprotein subfractions were analyzed, MBX-8025 treatment was observed to provoke a shift in LDLs from smaller to larger particles in approximately 90% of the subjects, and this effect of MBX-8025 was greater than that of atorvastatin [146]. MBX-8025 administration also enhanced insulin sensitivity and increased the levels of markers of liver function [146]. Recently, CER-002, a new PPARβ/δ agonist that has been shown to increase HDL-cholesterol levels and halt the progression of atherosclerosis in pre-clinical studies, has been studied in a completed Phase I clinical trial for the treatment of cardiovascular disease (http://www.cerenis.com/en/).

In addition to dyslipidemia, maladaptive immune responses driven by the accumulation of cholesterol-laden macrophages in arterial walls, which can result in vascular inflammation, are central to atherosclerosis. PPARβ/δ agonists have been found to reduce the area of atherosclerotic lesions through anti-inflammatory mechanisms in ApoE$^{-/-}$ and LDLR$^{-/-}$ mice [29,147–149]; however, some studies have reported no such reduction in atherosclerotic lesion size [150]. While PPARβ/δ agonists provoke anti-inflammatory effects in macrophages *in vitro*, surprisingly, selective deletion of PPARβ/δ from macrophages attenuates atherosclerosis in LDLR$^{-/-}$ mice [35]. This observation suggests that PPARβ/δ can also have pro-inflammatory effects. The mechanism underlying these contradictory findings involves the interaction between PPARβ/δ and the inflammatory suppressor protein BCL-6 [144] (Figure 1). This interaction explains the apparent contradiction that both PPARβ/δ deficiency and PPARβ/δ activation exert

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anti-inflammatory effects in macrophages due to the release of BCL-6 bound to PPARβ/δ [29,35,148].

6.3 Cardiac disease

Genes involved in FAO are transcriptionally controlled by PPARβ/δ. Consequently, the Cre/loxP-mediated cardiomyocyte-restricted deletion of PPARβ/δ in mice (αMyHC-Cre PPARβ/δ^{ex4}) downregulates the constitutive expression of key FAO genes and decreases basal myocardial FAO, resulting in progressive myocardial lipid accumulation. This is accompanied by cardiac dysfunction, cardiac hypertrophy and congestive heart failure, leading to reduced survival [151]. Another study found that PPARβ/δ^{ex4} knockout in the adult mouse heart caused a reduction in lipid and glucose oxidation and attenuated the cardiac expression of endogenous antioxidants, and these effects were accompanied by increased oxidative damage to the heart [152]. In addition, expression of the key mitochondrial biogenesis gene *Pgc-1α* was substantially decreased, together with a decrease in the number of mitochondria. Moreover, the PPARβ/δ^{ex4} conditional knockout mice showed a decrease in cardiac performance and developed cardiac hypertrophy. The constitutive cardiomyocyte-specific expression of PPARβ/δ (driven by the myosin heavy chain promoter in MHC-PPARβ/δ mice) has been shown to increase the expression of FAO-associated genes but was not found to induce lipid accumulation or cardiac dysfunction; this observation contrasted with the findings in MHC-PPARα mice [153]. Liu et al. (2008, 2011) generated a transgenic mouse model that expressed a constitutively active form of PPARβ/δ upon tamoxifen administration in a tissue-specific manner [154,155]. In this model, the expression of genes involved in FAO, the levels of endogenous antioxidants, the *Pgc-1α* levels, the mitochondrial DNA copy numbers, and cardiac performance were increased (Figure 3).

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Moreover, activation of PPARβ/δ in the adult heart improved cardiac function and impeded the development of pathological characteristics under conditions of pressure overload [154].

Given the important role of PPARβ/δ in cardiac FAO, a reduction in PPARβ/δ expression or activity might contribute to the exacerbation of the pathological processes involved in cardiac dysfunction. It has been reported that myocardial hypoxia, a characteristic of heart failure, provokes an increase in the expression of the miRNA cluster miR-199a~214, which decreases PPARβ/δ protein levels and mitochondrial FAO [156]. These changes facilitate a metabolic shift from a predominant reliance on FAO in the healthy myocardium towards increased reliance on glucose metabolism at the onset of heart failure. Moreover, cardiomyopathy in streptozotocin-induced diabetic rats was found to be associated with a marked decrease in cardiac PPARβ/δ levels [157]. Activation of PPARβ/δ can ameliorate certain cardiac pathologies linked to reductions in FAO. Thus, PPARβ/δ activation in the adult heart improves cardiac performance and reduces fibrosis and mitochondrial abnormalities in mice subjected to pressure-overload-induced cardiac hypertrophy [155]. Moreover, activation of PPARβ/δ protects the heart from ischemia-reperfusion injury in Zucker diabetic fatty rats through several mechanisms, including attenuation of the lipotoxicity caused by ischemia-reperfusion injury by increasing cardiac FAO and upregulating pro-survival signaling in the heart [155]. Similarly, PPARβ/δ activation might alleviate lipid-induced ER stress and inflammation in the heart [158,159]. In contrast, a recent study showed that treatment with the PPARβ/δ agonist GW610742 had only a temporary effect on early fibrosis in the infarcted myocardium and that the functional and structural beneficial effects of GW610742 might not be sustained [160]. Park et al. (2016) showed that PPARβ/δ expression was highest 3 days after myocardial infarction and began to decrease by day 14 [160]. While investigating the potential therapeutic effects of GW610742 on cardiac healing in rats

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after myocardial infarction, the authors showed that the degrees of angiogenesis and fibrosis after myocardial infarction were significantly higher in the GW610742-treated rats than in the untreated rats at 1 week following myocardial infarction, although no significant difference in angiogenesis or fibrosis was observed at 2 weeks after myocardial infarction. Notably, GW610742 increased myofibroblast differentiation and TGFβ2 expression in the infarct zone at 7 days after myocardial infarction. GW610742 also increased bone marrow-derived mesenchymal stem cell recruitment in the whole myocardium and increased serum platelet-derived growth factor B, stromal-derived factor-1α, and MMP9 levels at day 3 after myocardial infarction [160].

Cardiovascular diseases are a group of disorders of the heart and blood vessels, including events such as hypertension, heart attack, stroke, atherosclerosis, and chronic comorbidities such as kidney disease. It is well established that complications of CVD may develop over a considerable period after onset of the original disease. Most studies of PPARβ/δ in the setting of CVD have focused on the relatively short-term impact of PPARβ/δ; however, the long-term functions of PPARβ/δ in CVD must also be investigated to determine the therapeutic potential of drugs targeting PPARβ/δ.

7. PPARβ/δ in insulin resistance and T2DM

Over the years, PPARβ/δ has been found to be involved in many processes in insulin-responsive organs and tissues. Its roles in such organs are summarized below.

7.1. Adipose tissue

As adipose tissue expands during obesity, there is an increase in chronic, systemic low-grade inflammation, mainly due to greater macrophage infiltration and polarization towards the

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pro-inflammatory M1 phenotype. This chronic inflammatory process is thought to play a major role in the development of insulin resistance and diabetes [161]. PPARβ/δ has been identified as a potential drug target for modulating tissue macrophage activation and insulin sensitivity. Kang et al. (2008) demonstrated in mice that Th2 cytokines secreted by adipocytes, including IL-13 and, to a lesser extent, IL-4, induce PPARβ/δ expression in macrophages through a signal transducer and activator of transcription 6 (STAT6) binding site on the PPARβ/δ promoter, which triggers alternative M2 activation (Figure 4) [162]. Consequently, HFD-fed myeloid-specific PPARβ/δ^{ex4} knockout mice showed increased levels of M1 markers and decreased levels of markers of the alternative anti-inflammatory M2 phenotype, which is believed to improve insulin sensitivity. Increased adipose tissue inflammation, lipolysis and insulin resistance accompanied these changes.

Moreover, specifically overexpressing PPARβ/δ in white adipose tissue renders mice resistant to both HFD-induced and genetically predisposed obesity, in association with a reduction in triglyceride accumulation in adipocytes and circulating NEFA and TG levels [163]. These effects might be the result of the PPARβ/δ-mediated activation of overall oxidative metabolism in white adipose tissue [164]. In contrast, PPARβ/δ^{ex4} knockout mice fed an HFD were prone to weight gain [165]. In a different study, the adipose tissue of PPARβ/δ^{ex4} knockout mice displayed increased STAT3 phosphorylation and elevated suppressor of cytokine signaling (SOCS)3 protein levels than their wild-type littermates [165]. These findings suggest that PPARβ/δ activation might prevent the activation of STAT3 and the subsequent increase in SOCS3 expression, thus inhibiting insulin signaling by preventing the coupling of insulin receptor substrate (IRS)-1 to the insulin receptor and by promoting the proteasome-mediated degradation of IRS-1 [166]. Moreover, adipose tissue inflammation and glucose intolerance were

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shown to be exacerbated in fructose-fed PPARβ/δ^{ex4} knockout mice via nuclear factor E2-related factor 2 (Nrf2), a transcription factor that has been reported to impair insulin signaling [163].

A reduction in dietary salt intake is recommended for many diabetic patients, although the potential benefits of sodium reduction remain debatable. Furthermore, the relationship between sodium intake and glucose homeostasis remains unclear in diabetes. Using adipose-specific PPARβ/δ knockout mice (Fabp4-PPARβ/δ^{ex4}), Zhao et al. (2016) recently showed that a high-salt diet (HSD, high sodium) reduced fasting blood glucose levels in wild-type control mice compared with Fabp4-PPARβ/δ^{ex4} mice, suggesting that PPARβ/δ in adipocytes improves glucose tolerance and enhances natriuresis [167]. The HSD selectively elevated the expression of PPARβ/δ in perirenal fat by increasing osmotic pressure, leading to an increase in adiponectin production. Adipose-derived adiponectin suppressed the kidney expression of sodium-glucose cotransporter 2 (SGLT2), which plays a crucial role in the regulation of renal glucose transport and sodium reabsorption. Adiponectin reduced the levels of the transcription factors HNF-1α and SP-1 bound to the promoter of the gene encoding SGLT2 (*SLC5A2)*, leading to reduced SGLT2 expression. These findings reveal an interesting mode of communication between adipose tissue and the kidney that links sodium intake to glucose homeostasis. Notably, the expression of PPARβ/δ is lower in morbidly obese patients than in non-obese subjects [64]. Overall, these findings suggest that reduced PPARβ/δ expression in adipose tissue might contribute to metabolic alterations.

7.2 Skeletal muscle

Lipid-induced insulin resistance in skeletal muscle is of paramount interest because myocytes are responsible for approximately 80% of insulin-stimulated glucose uptake and thus

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greatly affect the whole-body rate of glucose clearance [168]. In addition, skeletal muscle is an important consumer of FAs, and muscle-specific PPARβ/δ overexpression results in a switch to more oxidative fibers [169], probably through an estrogen-related receptor γ (ERRγ)/miRNA circuit [170]. This alteration is accompanied by an increase in the expression of genes involved in oxidative metabolism, leading to a reduction in body fat mass [169]. Conversely, mice with selective PPARβ/δ^{ex4} ablation in skeletal muscle myocytes exhibit a shift in skeletal muscle fiber type towards muscle fibers with lower oxidative capacity, leading to obesity and T2DM [171]. The genes involved in FA metabolism that are upregulated by PPARβ/δ *in vivo* include genes involved in cellular FA uptake, such as FAT/CD36; FA activation, such as acyl-CoA synthase (ACS); mitochondrial FA uptake, such as carnitine palmitoyl transferase (CPT); and FA β-oxidation, such as hydroxyacyl-CoA dehydrogenase. PPARβ/δ activation also upregulates the expression of pyruvate dehydrogenase kinase 4 (PDK4), which inhibits the pyruvate dehydrogenase complex, leading to FA oxidation [136,169,172]. The increase in FAO caused by PPARβ/δ appears to be dependent on PGC-1α [172], which itself is a PPARβ/δ target gene [171]. This evidence reveals that PPARβ/δ in skeletal muscle promotes a metabolic switch favoring FAO, reducing the availability of FAs to be accumulated in skeletal muscle and other tissues such as the liver, ultimately preventing obesity and insulin resistance [173]. Recent findings indicate that PPARβ/δ-mediated increases in skeletal muscle FA uptake are also coupled to diurnal hepatic PPARβ/δ activity through the synthesis of the phosphatidylcholine 18:0/18:1, an endogenous ligand of PPARα [174].

Altogether, these findings suggest that PPARβ/δ activation increases the oxidation of FAs, reducing their availability to be accumulated as FA derivatives such as diacylglycerol or ceramides, which promote inflammation and insulin resistance. This PPARβ/δ-mediated

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elevation in oxidative FA metabolism might explain why ligands of this receptor prevent lipid-induced ER stress, a process that induces inflammation and insulin resistance, and may explain the observed increase in the levels of ER stress markers in the skeletal muscles of PPARβ/δ^{ex4} knockout mice [175]. Moreover, PPARβ/δ acts as a FA sensor in skeletal muscle by regulating the expression of several genes, including *Angptl4* [176,177], which affects lipid metabolism by inhibiting lipoprotein lipase [178] and activating lipolysis in adipose tissue [112,179,180]. The increase in skeletal muscle ANGPTL4 secretion caused by FAs-activated PPARβ/δ has been proposed to enhance adipose tissue lipolysis, ensuring the supply of FAs to skeletal muscle during states of increased FA β-oxidation, such as fasting and exercise [176]. In contrast, stimulation of cardiac *Angptl4* expression by FAs via PPARβ/δ has been considered part of a feedback mechanism aimed at protecting the heart against lipid overload by reducing lipoprotein lipase activity [177], which is responsible for hydrolyzing plasma TGs to release FAs. Another PPARβ/δ target gene is adipocyte differentiation-related protein (ADRP, also referred to as adipophilin or perilipin2), a lipid droplet-associated protein that binds to and sequesters intracellular FAs. ADRP is involved in intramuscular lipid accumulation and T2DM [173,181]. ADRP protein expression is muscle fiber type specific in humans and rats, with the highest protein content in fibers containing the most intramyocellular lipids. The muscle ADRP protein content was 2- to 3-fold higher in Zucker diabetic fatty rats during the progression of type 2 diabetes than in lean normoglycemic control rats, and this elevation in ADRP protein levels was paralleled by high intramyocellular lipid levels in diabetic animals [182]. In humans, ADRP is highly expressed in the vastus lateralis muscle, the largest and most powerful component of the quadriceps, of obese non-diabetic and obese diabetic patients in the fasting state [183]. Consistent with the proposed role of ADRP in the progression of T2DM, ADRP expression is

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upregulated under circumstances of improved glucose tolerance. The upregulation of ADRP may act to sequester FAs as TGs in discrete lipid droplets that could protect muscle from the detrimental effects of FAs on insulin activity and glucose tolerance. Clearly, in addition to controlling muscle FA metabolism, PPARβ/δ is involved in glucose metabolism in muscles. Transgenic mice overexpressing PPARβ/δ specifically in muscle exhibited increased capacity for glucose oxidation by skeletal muscles through the cooperation of AMP kinase (AMPK) and the muscle-enriched transcription factor myocyte enhancer factor 2 (MEF2) [184]. Interestingly, this pattern of changes induced by PPARβ/δ resembles that following exercise. Additional protective effects of PPARβ/δ on fructose-induced insulin resistance may involve increased skeletal muscle expression of fibroblast growth factor 21 (*Fgf21*) [185], a hormone with a wide range of endocrine and autocrine effects on carbohydrate and lipid metabolism. Consistent with this hypothesis, circulating FGF21 levels are increased in humans in response to pharmacological activation of PPARβ/δ [186].

7.3 Liver

Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease and is considered to be the hepatic manifestation of metabolic syndrome [187]. The hallmark of NAFLD is persistent and excessive neutral lipid accumulation within hepatocytes. NAFLD can be benign, but it predisposes individuals to non-alcoholic steatohepatitis (NASH), which may result in fibrosis and/or cancer [188]. While the etiology of NASH is not well understood, the transition from NAFLD to NASH is considered a critical point in the progression of NASH pathology. Interestingly, the dual PPARα/γ agonist Saroglitazar (Lipaglyn) [189],

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which was launched in India for the treatment of hypertriglyceridemia and diabetic dyslipidemia in patients with T2DM not controllable by statins, is now also under examination in Phase III clinical trials evaluating its effect in adult NASH patients. Furthermore, recent evidence from pre-clinical [190] and clinical [191] studies has highlighted the potential of the dual-agonistic GFT505 (Elafibranor) targeting of both PPARα and PPARβ/δ in the treatment of NASH. Lipids that accumulate in association with NAFLD may originate from increased uptake from chylomicrons, *de novo* lipogenesis and/or decreased lipid degradation [192,193]. Therefore, the ability of PPARβ/δ to modulate the activity of components important in lipogenesis and FAO may be responsible for the beneficial effects of PPARβ/δ activation in relation to NAFLD and NASH.

Lipogenesis is an enzymatic pathway that allows the cell to produce saturated and mono-unsaturated FAs, which can be used to replace TG energy stores, to generate lipid-based membranes or to produce lipid-dependent signaling molecules. *De novo* lipogenesis is very active in murine liver tissue after feeding but is repressed in response to fasting [194]. The mechanism by which feeding regulates the activity of lipogenic enzymes is largely transcriptional [195]. Numerous transcription factors have been shown to play a significant role in this process. Among these transcription factors, both SREBP-1c [196] and ChREBP [192] appear to integrate hormonal (insulin) and nutritional (glucose) signals, respectively, that coordinate the transcription of genes encoding lipogenic enzymes. Importantly, both SREBP-1c and ChREBP are regulated by LXR [193], a nuclear receptor that is activated by oxysterols [197]. Interestingly, SREBP-1c [198], ChREBP [199], LXR [200,201] and PPARβ/δ [202] appear to be involved in coordinating gene regulation in response to exogenous FAs (Figure 5). In fact, one article reported that PPARβ/δ suppresses lipogenesis by reducing SREBP-1c levels and

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consequently ameliorating hepatic steatosis in obese diabetic *db/db* mice [203]. The mechanism by which PPARβ/δ reduces SREBP-1c activation might involve the induction of the insulin-induced gene (Insig)-1 protein, which blocks SREBP-1c activity by slowing the release of the SREBP cleavage-activating protein (SCAP)/SREBP complex from the ER. In one study, *Ldlr*$^{-/-}$ mice fed a high-fat diet and treated with GW501516 showed reduced lipogenesis and increased insulin sensitivity [204]. However, several other studies have suggested that PPARβ/δ may promote *de novo* lipogenesis. The increase in hepatic steatosis following treatment with a PPARβ/δ agonist has been reported to be strictly time-dependent and evident only after 4 weeks of treatment, whereas longer treatments were ultimately protective against liver steatosis [204,205]. Comparisons of the gene expression profiles of livers between control and GW501516-treated *db/db* mice suggest that PPARβ/δ activation reduces hepatic glucose production by increasing glycolysis and the activity of the pentose phosphate shunt as well as by enhancing lipogenesis in the liver [206]. Moreover, a recent study performing adenovirus-mediated liver-restricted PPARβ/δ activation confirmed that PPARβ/δ activation increases hepatic *de novo* lipogenesis [207]. However, during hepatic lipid accumulation, PPARβ/δ activation has been shown to increase the production of monounsaturated FAs and reduce the formation of saturated FAs, leading to reduced hepatic damage and JNK-mediated stress signaling. These findings suggest that hepatic PPARβ/δ-regulated lipogenesis protects against lipotoxicity. Finally, one unique and recent report describing experiments performed in mice specifically lacking PPARβ/δ in hepatocytes provides evidence that PPARβ/δ is involved in the circadian control of lipogenesis [174]. Importantly, this work also indicated that this diurnal control by PPARβ/δ significantly influences whole-body physiology. Specifically, PPARβ/δ from hepatocytes regulates the production of FAs required to produce phosphatidylcholine

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18:0/18:1 PC (18:0/18:1), which acts as a hepatic lipokine for communication with skeletal muscles, thus influencing FAO in myocytes. Administration of GW501516 to wild-type [137] or LDLR$^{-/-}$ mice [204] enhanced hepatic FAO and AMPK activity, probably by increasing the AMP:ATP ratio in the liver [137]. As a result of PPARβ/δ activation, a reduction in substrate availability indirectly activates AMPK, and this effect also contributes to the glucose-lowering effect of this nuclear receptor [207]. Additionally, it has recently been shown that PPARα is required for the effect of PPARβ/δ agonists on steatosis [205]. A recent report identified PPARα from hepatocytes as a critical transcription factor for FA degradation in hepatocytes and in protection against NAFLD [208]. How PPARβ/δ may influence PPARα activity in hepatocytes remains to be established, and whether this process occurs though a cell-autonomous pathway remains to be investigated.

One key issue in understanding the role of PPARβ/δ in the liver is elucidating its respective roles in different cell types because PPARβ/δ is highly expressed in Kupffer and stellate cells. These cell types are involved in the control of inflammation and fibrosis, which develops in the most severe stages of NAFLD. PPARβ/δ controls the expression of the alternative anti-inflammatory phenotype of Kupffer cells, the resident macrophages in the liver; additionally, transplantation of PPARβ/δ$^{-/-}$ bone marrow into wild-type mice reduces the alternative activation of Kupffer cells, leading to mitochondrial dysfunction and insulin resistance in hepatocytes [209,210]. In wounded areas of the liver, stellate cells are stimulated by factors that promote their proliferation and transition from a quiescent, vitamin A-storing phenotype towards an activated, proliferative myofibroblast-like phenotype. In turn, these cells contribute to the production of abnormally high levels of ECM proteins and remodeling factors, which ultimately results in ECM accumulation [211]. PPARβ/δ is highly expressed in hepatic

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stellate cells and contributes to the enhancement of their proliferation [212]. PPARβ/δ is also involved in the control of vitamin A metabolism during the activation of stellate cells [213]. Pre-clinical studies have shown contrasting results regarding the protective [209,214] and detrimental effects [215] of PPARβ/δ agonists on liver fibrosis.

7.4 Pancreas

The clinical onset of T2DM develops when pancreatic β-cells fail to compensate for the decrease in insulin sensitivity due to insulin resistance. Incretins, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are intestinal postprandial hormones that stimulate insulin release from the pancreas in response to nutrients. In addition, incretins can preserve the morphology and function of pancreatic β-cells [216]. Treatment of wild-type or *ob/ob* mice with a PPARβ/δ agonist potentiates GLP-1 production by the small intestine, leading to increased plasma levels of this incretin after an oral glucose load and improved glucose tolerance [217] Moreover, PPARβ/δ is required for the expression of genes involved in mitochondrial function and, thus, the production of ATP, which is required for glucose-stimulated insulin secretion (GSIS). Activation of PPARβ/δ in β-cells is triggered by the lipolytic activity of the major triacylglycerol hydrolase desnutrin [218]. Thus, PPARβ/δ agonists restore GSIS and the expression of mitochondrial oxidative genes in mice in which desnutrin is ablated in β-cells. Because desnutrin levels are reduced in obesity, these findings suggest a mechanism by which prolonged treatment of obese and diabetic *db/db* mice with a PPARβ/δ agonist reduces blood glucose levels in association with improved insulin sensitivity and pancreatic islet function [219]. Interestingly, specific deletion of *Pparβ/δ* (PPARβ/δ^{ex4} knockout) in the epithelial compartment of the mouse pancreas led to increased numbers of islets and

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enhanced insulin secretion, resulting in hyperinsulinemia [220]. The broad repressive role of PPARβ/δ in pancreatic β-cells also affects the vesicular and granular compartment and the actin cytoskeleton. Studies of insulin release from isolated PPARβ/δ-deficient islets revealed an accelerated second phase of GSIS that parallels an increase in filamentous actin (F-actin) disassembly and correlates with elevated protein kinase D activity, resulting in alterations in Golgi organization. This evidence shed new light on the metabolic function of PPARβ/δ by indicating a repressive effect of PPARβ/δ on β-cell mass and insulin exocytosis. Together, these results underscore a possible dual function of PPARβ/δ in β-cells, combining gene activation and gene repression/derepression.

8. PPARβ/δ and cancer

Among the different physiological and pathological functions attributed to PPARβ/δ, its involvement in cancer is certainly the topic in which studies of PPARβ/δ have shown most discrepancies. Overall, PPARβ/δ has been shown to be involved in carcinomas, in which it appears to have opposing effects. In this section, we discuss findings from *in vivo* studies of mouse cancer models and human tumors to characterize the advances in research on the biological functions of PPARβ/δ in cancer.

The *in vivo* involvement of PPARβ/δ in the development and progression of colorectal cancer and skin cancer has been well documented in different studies; however, the precise functions of PPARβ/δ remain controversial.

8.1 Function in colorectal carcinoma (CRC) development

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PPARβ/δ is highly expressed in the small and large intestines in rodents and humans, and *in situ* hybridization studies have shown that this nuclear receptor is expressed throughout the intestinal epithelium, with higher expression at the bottom of the crypts. Function of PPARβ/δ has been proposed in Paneth cells, enteroendocrine cells and enterocytes [221]. Two models are classically used for *in vivo* studies of CRC development. One of these models is the multiple intestinal neoplasia (Min) mouse strain, which carries a heterozygous nonsense mutation in the adenomatous polyposis coli (Apc) gene ($Apc^{min/+}$). This mutation predisposes mice to developing cancer, and examination of this mouse strain facilitates the identification of factors that regulate the transition between normal and neoplastic cell growth. However, adenoma formation requires the inactivation of both *Apc* alleles. Of note, *Apc* has been found to be mutated in both sporadic CRC and hereditary familial adenomatous polyposis (FAP) in humans [222–224]. The second model involves chemically induced colon cancer using the mutagenic agent azoxymethane (AOM), which exerts colonotropic carcinogenicity. Repeated intraperitoneal administration of AOM results in the spontaneous development of tumors within 30 weeks. As an alternative approach, inflammation-dependent tumor growth can be investigated by administering a combination of AOM and the inflammatory agent dextran sodium sulfate (DSS) in drinking water, which causes rapid growth of multiple colon tumors within 10 weeks [225].

The first study investigating PPARβ/δ function in CRC showed that *Pparb/d* is induced by β-catenin/T-cell factor 4, which in turn induces the well-characterized proto-oncogenes cyclin D1 and c-Myc, suggesting that PPARβ/δ could play a role in CRC development [226]. To investigate PPARβ/δ function in intestinal carcinogenesis, total and intestine-specific KO of PPARβ/δ have been performed. In mice in an $Apc^{min/+}$ genetic background, PPARβ/δ^{ex4} deletion decreased intestinal adenoma growth and inhibited the tumor-promoting effects of the PPARβ/δ

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agonist GW501516 [227]. Consistent with this finding, intestine-specific PPARβ/δ^{ex4} deletion in mice subjected to AOM treatment resulted in resistance to the chemical induction of CRC [89]. In both studies, these effects were attributed to the stimulatory effects of PPARβ/δ on *Vegf* expression, and it was suggested that PPARβ/δ acts as a pro-tumorigenic factor in CRC development [227–229]. Another study conducted using the PPARβ/δ^{ex4} *Apc*$^{min/+}$ model supports these findings [230]. These observations support earlier findings that PPARβ/δ stimulates *Vegf* expression in bladder cancer cells [229]. Other studies have shown that PPARβ/δ exerts a protective effect against genetic and chemically induced intestinal tumorigenesis. AOM administration to PPARβ/δ^{ex8}- mice, with or without GW0742 co-administration, resulted in an enhanced number of colon polyps compared to AOM administration to wild-type mice [72,227]. When crossed with mice in an *Apc*$^{min/+}$ genetic background, PPARβ/δ^{ex8}-deleted mice displayed a sex-specific difference in tumor susceptibility. PPARβ/δ^{ex8} deletion also differentially affected tumor size and location depending on the study, which hinders a clear understanding of the anti-tumor activities of PPARβ/δ. Indeed, some studies have shown that PPARβ/δ deletion enhances the formation of polyps in the colons of male and female mice but that polyps in the small intestine appeared only in female mice [231]. However, other studies have shown that PPARβ/δ^{ex8} deletion combined with the *Apc*$^{min/+}$ genotype led to an increase in colon polyp count only in females and that the polyp sizes were increased in both sexes. In the small intestine, polyp count did not differ between sexes [231]. This result is in accordance with another study, which showed that PPARβ/δ^{ex8} specifically leads to an increase in the size and number of small intestinal polyps, without affecting the colon polyp count [229,232]. Taken together, these studies highlight the complexity of the role of PPARβ/δ in CRC formation, in which sex is a determining factor. Highly contrasting results emerged from studies using two different specific

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pharmacological agonists of PPARβ/δ. While *Apc*$^{min/+}$ mice treated with GW501516 for 6 weeks displayed an increase in the total number of polyps and in polyp size [227,233], long-term (22 weeks) activation of PPARβ/δ with its ligand GW0742 attenuated chemically induced colon carcinogenesis, and no effects on polyp number and size were observed in *Apc*$^{min/+}$ mice treated with GW0742 for 6 weeks [229,232].

Consistent with a pro-tumorigenic role of PPARβ/δ, a recent elegant study by Beyaz et al. (2016) showed that dietary fat (60% fat) activated PPARβ/δ and promoted the proliferation of intestinal Lgr5^{+} stem and progenitor cells [230]. Treating mice with the PPARβ/δ agonist GW501516 produced similar tissue remodeling and regeneration. The mechanism underlying these effects involved the Wnt-β-catenin signaling pathways. Importantly, HFD- and agonist-activated PPARβ/δ signaling endowed an organoid-initiating capacity to progenitor cells, and enforced PPARβ/δ signaling permitted these progenitor cells to form *in vivo* tumors after loss of the tumor suppressor *Apc*. These findings highlight how diet-modulated PPARβ/δ activation alters not only the function of intestinal stem and progenitor cells but also their capacity to initiate tumors [230,234].

In humans, PPARβ/δ mRNA expression was found to be strongly upregulated in colorectal tumor samples compared to paired, adjacent, normal tissue samples in some studies [226,235], although other studies showed only a modest [236] or no difference in PPARβ/δ gene expression between CRC and normal tissue [237,238]. However, there appears to be massive heterogeneity between CRC samples [239], which could be due to the heterogeneity of tumor tissues, the tumor stage analyzed, and treatments applied to the tissues after surgical ablation.

Immunohistological and protein quantification analyses have been also performed to examine the involvement of PPARβ/δ in human CRC; these studies have been reviewed

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extensively by Neels and Grimaldi [240]. The results obtained from these analyses should be considered with caution due to the lack of specificity of commercially available anti-PPARβ/δ antibodies [241]. Moreover, the activity level of PPARβ/δ based on the mRNA expression levels of its target genes could be a better marker of PPARβ/δ activity in CRC and, more generally, in cancer development.

Altogether, the studies of animal cancer models or human tumors conducted to date have failed to clearly characterize the function of PPARβ/δ in CRC development. Several hypotheses have been proposed to explain the disparities between studies [242]. Interestingly, the genetic background of the *Apc*$^{min/+}$ PPARβ/δ mice used in various studies can greatly impact CRC development [243]. Indeed, some studies have been performed using PPARβ/δ-deficient mice in a mixed genetic background, while others used mice in the pure C57Bl/6 background. These differences become important when the animals are crossed with C57Bl/6 *Apc*$^{min/+}$ mice, as the genetic background could strongly influence the penetrance of the Min phenotype due to strain-specific impacts of the loci, termed modifiers of the Min phenotype (Mom). Indeed, *Apc*$^{min/+}$ mice in the C57Bl/6 background are more prone to develop intestinal tumors than *Apc*$^{min/+}$ mice in a mixed genetic background [243,245]. Moms are likely the cause of this variation, and there is considerable evidence that the genetic background is responsible for major differences in adenoma counts. The different strategies used to ablate PPARβ/δ could be another major reason for the discrepancies in the findings between studies (see **PPARβ/δ in placentation**). In addition, animal housing conditions might influence other processes involved in intestinal tumorigenesis, such as inflammatory status or the COX2 enzymatic pathway [246,247], which could also explain the disparities among the diverse studies using these animal models. Moreover, recent results from studies of CRC tumorigenesis showed that both the gut microbiome, which differs

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between animal facilities and diets administered, and the circadian rhythm, which could influence the expression of genes encoding proteins involved in DNA repair and the cell cycle such as the proto-oncogene c-Myc, are critical for the initiation and progression of CRC, as supported by clinical and epidemiological data [247–252]. Although the evidence from many studies favors a pro-tumorigenic role of PPARβ/δ, its precise role may be stage- and tumor-specific and requires further investigation. We propose that future reports also indicate the genetic models of PPARβ/δ used, such as PPARβ/δ^{ex8} or PPARβ/δ^{ex4}, as well as the genetic background, housing conditions, and dietary intake in which these mutations are studied.

8.2 PPARβ/δ function in skin carcinoma development

Squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs), both of which are derived from keratinocytes, are the most common types of non-melanoma skin cancer (NMSC). Although NMSCs are rarely fatal, they can be highly disfiguring and can result in a heavy personal burden and an enormous cost to society. Approximately 90% of NMSC cases are associated with excessive and/or chronic exposure to ultraviolet (UV) radiation from the sun; in particular, UVB radiation (290–320 nm, sunburn rays) shows low skin penetration and therefore predominantly affects keratinocytes [253,254]. The role of PPARβ/δ in skin carcinoma development has been investigated *in vivo* using two different experimental models: chronic UVB radiation and a two-stage model based on the chemical induction of tumors via topical application of 7,12-dimethylbenz[*a*]anthracene/12-O-tetradecanoylphorbol 13-acetate (DMBA/TPA), in which DMBA is used as a carcinogen to generate *H-Ras* mutations, followed by 20 weekly applications of the nonmutagenic agent TPA, which provides a microenvironment and proliferative stimuli that favors the clonal outgrowth of initiated keratinocytes. These two

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methodological approaches have shown contradictory results. Chronic UV exposure to wild-type and PPARβ/δ^{ex4} mice showed that PPARβ/δ promotes UV-induced skin tumorigenesis *in vivo* by upregulating the Src gene and protein expression as well as Src activity, which in turn enhances the EGFR/Erk1/2 signaling pathway in response to UVB radiation [249,255]. In this mouse model, PPARβ/δ sensitizes keratinocytes to UV radiation and promotes the development of actinic keratosis and progression of tumors by stimulating the expression of epithelial-mesenchymal transition (EMT) markers that affect basement membrane integrity. Interestingly, *PPARβ/δ* expression directly correlates with *SRC*, *MMP19* and *SNAI1* expression in SCC samples from human skin, and these relationships suggest a direct effect of PPARβ/δ on EMT initiation in human SCC. Furthermore, a meta-analysis of PPARβ/δ activity in various epithelial tumors, including human SCC, revealed a positive interaction between the expression levels of *PPARβ/δ* and those of two of its targets, *SRC* and *TGFB1*. The identification of these relationships in large, independent datasets of various tumor types, particularly in lung, colon and ovarian cancers known to have high levels of Src expression and activity, strongly supports a pro-carcinogenic role of PPARβ/δ in human carcinomas [255]. One can speculate that early in the process of UV-induced skin actinic keratosis formation, PPARβ/δ regulates Src and may act in concert with genetic mutations resulting from UV exposure to promote tumor progression by increasing the migratory and proliferative properties of keratinocytes. These data help to define the pro-tumorigenic properties of PPARβ/δ in skin carcinoma and most likely in carcinomas originating from other tissues. Inflammation is increasingly recognized as an essential component of tumor development [256,257]. Recently, a novel PPARβ/δ-miR-21-3p axis was reported to be involved in UV radiation-induced skin inflammation [258]. This PPARβ/δ-dependent molecular cascade involving TGFβ1 and the passenger strand of the miRNA miR-21-

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3p was activated in the epidermis in response to UV exposure. miR-21-3p performs a pro-inflammatory function in keratinocytes, and a high level of miR-21-3p expression in human skin was associated with psoriasis and SCC. Importantly, inhibiting miR-21-3p reduced UV radiation-induced cutaneous inflammation in *ex vivo* human skin biopsies, underscoring the clinical relevance of this signaling axis to inflammatory cutaneous disorders [258]. In contrast, Kim et al. (2004) showed anti-cancer properties of PPARβ/δ in skin carcinoma using a DMBA/TPA-induced model of carcinogenesis, in which tumor development was more severe in PPARβ/δ^{ex8} mice than in wild-type animals. Their results suggest that PPARβ/δ attenuates the development of chemically induced skin cancer by inhibiting keratinocyte proliferation *via* PKCα [259]. However, in mice, susceptibility for DMBA/TPA-induced skin tumorigenesis was not affected by transgenic overexpression of PKCα [250,251]. Using the same model of DMBA/TPA-induced tumorigenesis, topical treatment of wild-type and PPARβ/δ^{ex8} mice with a PPARβ/δ agonist (GW0742) inhibited chemically induced skin tumorigenesis only in wild-type mice by reducing skin tumor formation and multiplicity [260].

The discrepancies in the results obtained using these two models could be explained by the fact that induction of skin cancer using DMBA/TPA involves different molecular mechanisms and creates different genetic mutations than those associated with skin cancer caused by chronic UV radiation exposure [261,262]. Notably, tumor initiation via administration of a single topical sub-carcinogenic dose of a genotoxic carcinogen (DMBA) primarily induces activating mutations in *H-Ras*. The frequency of *H-Ras* mutations of only 10–20% in human SCC and BCC reflects a minor contribution of this oncogene to the development of human skin carcinomas [263–265]. In this context, the pro-carcinogenic function of PPARβ/δ via the EGFR/Src pathway could be masked by activating *H-Ras* mutations, rendering activation of the

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downstream MAPK Erk1/2 independent of Src/EGFR pathway activation. These differences in results between studies also highlight that the mutational status of the tumor cell and the tumor environment could modulate the activities of PPARβ/δ in cancer development. This dual function of PPARβ/δ as a pro- or anti-carcinogenic effector parallels the dual function of TGFβ1 in skin carcinoma, which has been defined as a PPARβ/δ target gene [266]. Indeed, TGFβ1 acts as both a tumor suppressor and an oncogene in skin carcinoma, a dual specificity that appears to depend on the stage of the cancer [267,268]. The generally accepted paradigm for TGFβ1 is that it acts as a tumor suppressor during the early stage of tumor formation but as a promoter of malignant conversion and metastasis in the later stages of skin carcinoma development in the DMBA/TPA model [269,270]. However, pharmacological inhibition of TGFβ1 signaling during the tumor promotion phase (TPA application) leads to a reduction in benign tumor formation. However, once formed, these tumors display an increased frequency of conversion to SCC [267]. Moreover, in a model of UVB radiation-induced skin carcinoma, TGFβ1 has been shown to exert a pro-tumorigenic effect that enforces PPARβ/δ function [249,271]. Regarding TGFβ1, it has been proposed that the conversion from its tumor-suppressing activities to its oncogenic activities reflects genetic or epigenetic alterations in the signaling pathways in tumor cells that alter the downstream effects of the TGFβ1 pathway [267,272,273]. This evidence clearly highlights the importance of the genetic configuration of the tumor cell in managing the TGFβ1 response, which could also be the case for PPARβ/δ. Intriguingly, studies from independent laboratories have clearly demonstrated PPARβ/δ as a pro-differentiating factor in keratinocytes after skin injury [274–276]. Similarly, a pro-differentiation function has been attributed to TGFβ1 [277] and the MAPK Erk1/2 pathway in keratinocytes during skin renewal, which is a pathway that is clearly pro-carcinogenic during skin tumor formation [278,279]

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Together, these studies highlight the dual function of PPARβ/δ in tumor development, as its function is likely modulated by the genetic alterations and epigenetic modifications that occur during tumor formation. However, this hypothesis must be tested to clearly address the putative cellular context-dependent specificities of the effects of PPARβ/δ on tumor cell responses. These findings also illustrate the crucial role of the tumor environment, which could regulate and/or be regulated by PPARβ/δ in tumor cells, as PPARβ/δ is able to drive the expression of circulating factors that can affect tumor development, such as VEGF, ANGPTL4 and TGFβ1.

9. PPARβ/δ in neurological diseases

The spatial expression of PPARβ/δ has been examined in the central nervous system (CNS) of rats and mice. All the PPAR isotypes are coexpressed in the nervous system during rat embryogenesis, and PPARβ/δ is the predominant isotype [76,280]. PPARβ/δ can be detected in the rat CNS beginning from E13.5 of gestation and remains highly expressed in the CNS postnatally [76]. Immunolocalization studies showed high levels of PPARβ/δ in the hippocampus, telencephalic cortex and cerebellar cortex of rats. In the rat spinal cord, PPARβ/δ is the most abundant PPAR isotype and is expressed in every cell layer [281]. A detailed analysis of mouse brains revealed that PPARβ/δ mRNA and protein are expressed throughout the brain, with particularly high levels in the entorhinal cortex, hypothalamus and hippocampus and lower levels in the corpus callosum and caudate-putamen. At the cellular level, PPARβ/δ was found to be expressed in oligodendrocytes and neurons but not in astrocytes [282]. However, PPARβ/δ expression has been reported in *in vitro* cultures of rat and mouse astrocytes [281,283]. These observations suggest a role of PPARβ/δ in neuronal function within the CNS. Despite the comparatively low expression of PPARβ/δ in the corpus callosum, histological examinations of

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PPARβ/δ^{ex8} knockout mice have revealed alterations in the extent of myelination [81]. This deficiency in myelination was not observed in other brain regions, including the cerebellum and brainstem. However, the levels of mRNAs encoding for proteins important for myelination, such as myelin basic protein (MBP), proteolipid protein (PLP), and two brain-specific acyl-CoA synthases (ASC2 and ASC3), in the corpus callosum were similar between PPARβ/δ^{ex8} mice and their wild-type counterparts. Whether this region-specific defect in myelination also occurs in PPARβ/δ^{ex4} mice remains to be investigated [72,73]. Neuron-specific deletion of PPARβ/δ (Nestin-PPARβ/δ^{ex4}) in mice did not cause any apparent developmental abnormalities in comparison to floxed littermate control mice. Nissl staining of coronal sections of the hippocampus and hypothalamus revealed no evident differences in the structure of nuclei in the hippocampus, hypothalamus, or any other forebrain structure between Nestin-PPARβ/δ^{ex4} mice and corresponding control mice [279]. In summary, although these observations suggest that deletion of PPARβ/δ from neurons does not cause gross anatomical malformations, functional alterations have been reported in mice deficient in PPARβ/δ [81,283–285].

9.1 Neuroprotective role in neurological injuries

Cerebral ischemia (also known as cerebrovascular ischemia) is a condition in which there is insufficient blood flow to the brain to meet metabolic demand. This leads to poor oxygen supply, or cerebral hypoxia, and thus results in the death of brain tissue or cerebral infarction/ischemic stroke. In mice and rats, agonist-activated PPARβ/δ has been shown to reduce ischemic brain injury [280,286]. In a model of ischemic brain injury based on middle cerebral artery occlusion (MCAO) in rats, intracerebroventricular infusion of the PPARβ/δ agonist L-165041 or GW501516 significantly attenuated ischemic brain damage. Lending

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support for a neuroprotective role of PPARβ/δ, the results from this model showed that ischemic damage was doubled and the hyperphagic response was absent in PPARβ/δ^{ex4} mice compared with wild-type mice [287]. Hyperphagia is the abnormal increase in appetite associated with hypothalamic injury. Indeed, increased malondialdehyde (MDA) and interferon γ (IFN-γ) levels as well as reduced glutathione and manganese superoxide dismutase (MnSOD) levels after MCAO in PPARβ/δ^{ex4} knockout mice are indicative of hypothalamic injury. Oxidative stress in the brain was dramatically enhanced in these PPARβ/δ^{ex4} mice. Enhanced oxidative stress and inflammatory responses in the ischemic brain contribute to neuronal death. The neuroprotective role of PPARβ/δ was associated with its anti-inflammatory and antioxidant properties, as demonstrated by an increased content of MDA and decreased expression levels of antioxidant genes, such as glutathione, MnSOD and catalase, in PPARβ/δ^{ex4} mice [280,281,286].

Apoptosis in neurons and oligodendrocytes is a prominent feature after spinal cord injury (SCI) and may greatly contribute to patient paralysis [288]. *In vivo* animal studies have shown that administration of the PPARβ/δ agonist GW0742 to mice after SCI improves their limb functions. Conversely, the PPARβ/δ antagonist GW0660 has been shown to block the effect of GW0742 on motor function, suggesting that the neuroprotective effects of GW0742 are dependent on ligand-activated PPARβ/δ [283,289]. PPARβ/δ is also involved in the neuroprotective activities of palmitoylethanolamide (PEA) after SCI. PEA is an endogenous FA amide that displays anti-inflammatory and analgesic activities [283,289]. Similarly, the effects of GW0742 are associated with reduced oxidative stress and pro-inflammatory responses. Ligand-activated PPARβ/δ has been shown to reduce neutrophil infiltration, pro-inflammatory cytokine expression, and oxidative damage, including nitrotyrosine formation and lipid peroxidation [283].

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Multiple sclerosis (MS) is a potentially disabling disease of the brain and spinal cord. In MS, the immune system attacks the myelin that covers nerve fibers and causes communication deficiencies between the brain and the remainder of the body. Ultimately, MS causes the nerves themselves to deteriorate or become permanently damaged. There is currently no cure for MS. However, treatments can help speed recovery from attacks and modify the course of the disease. Experimental autoimmune encephalomyelitis (EAE), in which mice are immunized with the encephalitogenic peptide myelin oligodendrocyte glycoprotein, is a well-recognized model of MS. Interestingly, treatment with the selective PPARβ/δ agonist GW0742 exerts a notable effect on clinical outcome [290]. Oral administration of GW0742 in this mouse model of EAE only modestly attenuated clinical symptoms when the drug was administered simultaneously with immunization. A further reduction in clinical symptoms accompanied by a reduction in the appearance of new cortical lesions was observed when GW0742 was administered during EAE progression. Additionally, Polak et al. (2005) showed that IFN-γ production by T cells was not affected by GW0742, although GW0742 reduced astroglial and microglial inflammatory activation and IL-1β levels in the brains of mice subjected to EAE [290]. This result is interesting because numerous studies using this animal model of MS have provided convincing evidence that T cells specific for self-antigens mediate the disease pathology. T helper type 1 (Th1) cells were previously thought to be the main effector T cells responsible for autoimmune inflammation [291]. However, recent studies have highlighted an important pathogenic role of CD4(+) T cells that secrete interleukin (IL)-17, termed Th17 cells, and IL-17-secreting γδ T cells in EAE as well as other autoimmune and chronic inflammatory conditions. In contrast to the findings of Polak et al. (2005), two studies have shown that PPARβ/δ ameliorates EAE in C57BL/6 mice by blocking IFN-γ and IL-17 production by T helper type 1 (Th1) and Th17 cells

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[286,292]. The inhibition of EAE by the PPARβ/δ agonists GW501516 and L165041 was also associated with the reduction of IL-12 and IL-23 levels in antigen-presenting cells and the inhibition of Th1 and Th17 polarization [292]. Independently, Dunn et al. (2010) showed that PPARβ/δ^{ex8} mice exhibited a more severe course of classical EAE, characterized by persistent hindlimb weakness and a reduced frequency of recovery after the initial acute phase of EAE [286]. The more severe EAE that developed in PPARβ/δ^{ex8} mice was due to immune-mediated myelin and axon damage. PPARβ/δ^{ex8} mice also displayed more inflammatory foci in the CNS during the course of EAE, in association with preferential expansion of CD4(+) and CD19(+) cells [286]. The molecular mechanisms involved in the regulation of Th1 and Th17 responses in EAE by PPARβ/δ agonists remain unclear. In brief, analogous to the anti-apoptotic, anti-inflammatory and anti-oxidative activities of PPARβ/δ during skin wound repair (see **Tissue repair**), PPARβ/δ activation in the CNS has been shown to confer neuroprotective effects, thus attenuating neuro-inflammation, in many neurological injuries.

9.2 Function in neurological diseases

Many research groups have begun to explore the possible benefit of targeting PPARβ/δ in neurological diseases, such as Alzheimer's disease (AD). AD is a neurodegenerative disorder characterized by cognitive deterioration, memory loss, progressive functional impairment, and multiple behavioral and psychological disturbances. The formation of amyloid fibrils and neurofibrillary tangles is thought to contribute to the degradation of neurons in the brain and the subsequent symptoms of AD [293]. Amyloid plaques primarily composed of β-amyloid (Aβ) peptide progressively form in the brains of AD patients, and mutations in three genes (amyloid precursor protein [APP], presenilin 1 and presenilin 2) cause early-onset familial AD by directly

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increasing production of the toxic, plaque-promoting Aβ peptide [293]. Aβ peptide, the product of the large type 1 trans-membrane protein APP, is produced in a two-step proteolytic process initiated by the β-secretase BACE1 and followed by the γ-secretase presenilin 1 or 2. Due to its apparent rate-limiting activity, BACE1 appears to be a prime target for prevent Aβ peptide generation in AD [294,295]. In the healthy brain, these protein fragments are degraded and eliminated. In AD, these fragments aggregate to form insoluble plaques. The receptor for advanced glycation end-products (RAGE) is a multiligand receptor that transports circulating Aβ peptides across the blood-brain barrier (BBB) into the brain. The RAGE-Aβ peptide interaction at the BBB leads to oxidative stress, inflammatory responses and reduced cerebral blood flow. Thus, regulating RAGE activity at the BBB and/or within the brain could be beneficial to AD patients [296–298]. Aβ peptide interacts with the signaling pathways that regulate the phosphorylation of the microtubule-associated protein tau. Hyperphosphorylation of tau disrupts its normal function in regulating axonal transport and leads to the accumulation of insoluble, twisted fibers termed neurofibrillary tangles within neurons. Furthermore, degradation of hyperphosphorylated tau by the proteasome is inhibited by the actions of Aβ peptide. These two proteins and their associated signaling pathways therefore represent important therapeutic targets for AD [295,298].

PPARβ/δ^{ex4} mice showed cognitive impairment in an object recognition task in association with increased IL-6 expression, tau phosphorylation, and levels of BACE1 and RAGE, which are involved in Aβ peptide synthesis and deposition. The protein levels of glial fibrillary acidic protein (GFAP) were increased in the cortex of PPARβ/δ^{ex4} mice, suggesting the presence of reactive astrogliosis [299,300]. Astrocyte activation and the release of pro-inflammatory cytokines that regulate astrocytic hypertrophy and proliferation, collectively referred to as

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reactive astrogliosis, is a ubiquitous but poorly understood hallmark of all CNS pathologies, including AD. The increases in the levels of GFAP, inflammatory cytokines such as IL-6 and TNFα, BACE1 and RAGE were proposed to increase NF-κB DNA-binding activity in the cortex of PPARβ/δ^{ex4} mice [300]. The expression of RAGE and BACE1 is regulated by the transcription factor NF-κB. The ability of the PPARβ/δ agonist GW0742 to reduce the amyloid burden and suppress neuroinflammation in 5XFAD mice, a transgenic mouse model of AD, has been reported by two independent groups [299,301]. PPARβ/δ activation decreased Aβ peptide levels in the subiculum, hippocampus and cortical layer V. Notably, Malm et al. (2015) showed that these reductions were specific to extracellular deposits because the number of APP/Aβ peptide-positive neurons remained unchanged by PPARβ/δ activation [301]. Different mechanisms of action of PPARβ/δ have been proposed. In a study by Kalinin et al. (2009), the investigators found that the GW0742-mediated change in the plaque burden was accompanied by increased expression of the amyloid-degrading enzymes neprilysin and insulin-degrading enzyme [299]. GW0742 also reduced astrocyte activation, suggesting its anti-inflammatory effects on glia. In contrast, Malm et al. (2015) proposed that the Aβ reduction was due to enhanced microglial-mediated clearance of Aβ peptides. The authors also suggested that differences in GW0742 treatment regimens and in the age of the mice used between the two studies might have resulted in the disparate outcomes [301]. Clearly, additional investigations are needed to clarify the precise reason for these discrepancies, and such clarity would help in evaluating PPARβ/δ ligands as potential treatments for AD.

AD has been described as “Type 3 diabetes” that selectively involves the brain, as AD has molecular and biochemical features that overlap with both type 1 diabetes mellitus and T2DM [302–304]. Insulin and IGF-1 receptors in the brain begin to disappear early in Alzheimer's

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disease and continue to be downregulated as the disease progresses. The progressive breakdown of insulin signaling results in increased oxidative stress, impaired metabolism and cell death, all of which lead to neurodegeneration. Intracerebral administration of streptozotocin to rats or mice depletes the brain of insulin and mimics the neurodegeneration observed in AD (i.e., plaque deposits, neurofibrillary tangles, diminished brain size, impaired cognitive function, cell loss and overall brain deterioration) [302,303,305]. Thus, it has been proposed that AD may be treatable, preventable and curable using anti-diabetic drugs. In phase I/II trials, the PPARβ/δ and PPARγ agonist T3D-959 (www.t3dtherapeutics.com) has been shown to possess striking activities in preserving the hypothalamus and the temporal lobes, areas of the brain responsible for memory, learning, and behavior [306,307]. These activities were found to be mediated by increased binding of insulin to insulin receptors, reduced levels of oxidative stress and tau phosphorylation, and increased choline acetyltransferase expression in the brain [308]. AD appears to be caused by parallel abnormalities, impaired insulin signaling and oxidative stress, which is regulated by the NOS and NOX protein families [309]. PPARβ/δ showed the greatest function in reducing oxidative stress and improving learning and memory.

Parkinson's disease (PD) is a degenerative disorder of the CNS that mainly affects the motor system. The pathologic hallmark of PD is the loss of dopaminergic neurons in the *substantia nigra*, a region of the midbrain, and the presence of intracytoplasmic inclusions termed Lewy bodies, which are aggregates of α-synuclein and ubiquitin [310]. The causes of cell death in PD are poorly understood. The progression of PD has been attributed to the enzymatic and non-enzymatic oxidation of dopamine, which generates ROS that induce apoptotic cell death in dopaminergic neurons. Experimental models for dopaminergic neurodegeneration associated with PD can be established using neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

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(MPTP) [311,312]. The connection between PD and MPTP was traced to the illicit use of an analog of the narcotic meperidine tainted with MPTP by several drug abusers [309]. MPTP induces most of the biochemical, pathological and clinical features related to PD in nonhuman primates. MPTP, which is lipid soluble, readily penetrates the BBB and enters brain cells. MPTP itself is not toxic, but its oxidation by monoamine oxidase B in astrocytes and serotonergic neurons produces a toxic cation 1-methyl-4-phenylpyridinium (MPP+). MPP+ primarily kills dopamine-producing neurons by interfering with complex I of the electron transport chain, a component of mitochondrial metabolism, which leads to cell death and causes the buildup of free radicals, toxic molecules that further contribute to cell destruction [280,311,313,314]. In this model, the PPARβ/δ levels in mice were shown to be increased immediately after MPTP treatment compared with saline treatment [280,314], and heterozygous PPARβ/δ^{ex4} mice were not protected from MPTP toxicity. However, intra-striatal infusion of the PPARβ/δ agonist GW0742 reduced the MPTP-induced loss of dopaminergic neurons in mice compared to vehicle infusion [314]. In contrast, a recent study using another PD animal model established via injection of 6-hydroxydopamine (6-OHDA) into the *substantia nigra* to selectively cause ROS-mediated destruction of dopaminergic neurons suggested that PPARβ/δ activation leads to a decrease in expression of full-length tropomyosin receptor kinase B, which consequently increases neuronal death, thereby contributing to the progression of PD [304]. The levels of PPARβ/δ and the oxidative stress mediator 4-hydroxynonenal, an endogenous ligand of PPARβ/δ, were increased in the damaged *substantia nigra* [47]. One reason for this discrepancy in the involvement of PPARβ/δ in PD may be due to the use of different animal models of PD. Particularly, distinct 6-OHDA models of PD have been developed by injecting the toxin into different parts of the nigrostriatal pathway to induce degeneration of dopaminergic neurons,

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which is a hallmark characteristic of PD. Although injection of 6-OHDA into the *substantia nigra pars compacta* leads to more specific and moderate DA depletion, subsequent evaluation of DA depletion and behavioral deficits that mimic PD indicated that specific DA depletion in the subregions of the caudate–putamen complex was the most appropriate model for studying the early and late stages of PD [315]. Clearly, further mechanistic investigation of the involvement of PPARβ/δ in the development and progression of PD is required.

To date, the biological roles of PPARβ/δ have been attributed to its mechanistic functions as a ligand-activated transcriptional factor (see **Introduction**). Transrepression, involving the interaction of PPARβ/δ with the transcriptional repressor BCL-6, is thought to underlie the anti-inflammatory effects of PPARβ/δ. Recently, PPARβ/δ was implicated in Huntington's disease (HD). HD is an autosomal dominant neurodegenerative disorder that causes the progressive breakdown of neurons in the brain, affecting muscle coordination and resulting in mental decline. HD is caused by a CAG trinucleotide repeat expansion in the huntingtin (HTT) gene, which encodes a polyglutamine tract in the HTT protein. Notably, PPARβ/δ can directly interact with the HTT protein, and mutant HTT represses PPARβ/δ-mediated transactivation [316]. Consistent with a neuroprotective role of PPARβ/δ, increased PPARβ/δ activity is associated with reduced mitochondrial dysfunction and increased survival of neurons in mouse models of HD. Neuron-specific expression of the dominant-negative mutant PPARβ/δ^{E411P} (Nestin-Cre:PPARβ/δ^{E411P}) protein in mice results in a markedly reduced adult brain size and a decreased neuronal count compared with the wild-type genotype. PPARβ/δ^{E411P} expression in the CNS of mice was sufficient to induce motor dysfunction, neurodegeneration, mitochondrial abnormalities and transcriptional alterations that recapitulated HD-like phenotypes. In mouse models of HD, pharmacologic activation of PPARβ/δ using the agonist KD3010 has been shown to improve

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motor function, reduce neurodegeneration and increase survival. Thus, these observations suggest that PPARβ/δ activation may be beneficial in HD and related disorders [316].

All the above studies using *in vivo* models underscore the relevance of the biological functions of PPARβ/δ to the development of therapies for multiple neurodegenerative diseases and injuries. Additionally, further investigation of the mechanisms of PPARβ/δ function and the use of other experimental animal models of disease are clearly needed to realize the therapeutic potential of PPARβ/δ modulators.

10. Conclusions

Since the discovery of PPARβ/δ in 1992 [2,39], its wide expression along with its promiscuous ligand binding capability has hampered our understanding of the pathophysiological roles of this nuclear receptor. Over the past two decades, numerous studies have revealed pleotropic and unexpected roles of PPARβ/δ in various diseases, underscoring PPARβ/δ as a potential therapeutic target. As summarized in this review, PPARβ/δ has been implicated in various physiological and pathophysiological conditions. It is clear that PPARβ/δ, similar to the other two PPARs, regulates numerous cellular and physiological functions. As a ligand-activated transcription factor, PPARβ/δ is capable of altering gene expression in response to the metabolic status of the cellular environment. This function enables PPARβ/δ to be involved in the coordination of tissue development, tissue repair, and metabolism-related conditions. Global knockout animal models have greatly increased our understanding of the biological roles of PPARβ/δ under normal physiological conditions and in the context of diseases.

Looking forward, it is clear that much more information is needed to understand the molecular mechanisms by which PPARβ/δ participates in the etiology of various diseases. In

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many of the processes summarized in this review, the mechanism of PPARβ/δ function remains unclear. Although PPARβ/δ primarily regulates gene expression in a ligand-dependent manner, increasing evidence suggests additional mechanisms of PPARβ/δ function, such as transrepression. Mechanistically, the activity of PPARβ/δ involves dynamic switching between co-activator and corepressor molecules in the presence or absence of its cognate ligands. A major knowledge gap concerning PPARβ/δ function is our lack of understanding of the nature of endogenous PPARβ/δ ligands, including their origin, types and levels, at sites of pathology. Despite the diverse nature and size of PPARβ/δ ligands (agonists and antagonists), the transcriptional activation or repression activity of PPARβ/δ may depend on critical interactions between its ligands and specific amino side chains of its LBD, which subsequently facilitate the recruitment of coregulators. To date, no crystal structure of the entire monomeric PPARβ/δ protein or its heterodimer with an RXR has been reported. With advances in protein expression, instrumentation and methods for protein structure resolution, such as single-particle cryoelectron microscopy [317–320], we envisage that future effort may be directed to solve the protein structure of nuclear hormone receptors, a clinically important group of transcription factors. Moreover, new computational tools may be useful in the search for natural and synthetic agonists of PPARβ/δ. Guided by 16 crystal structures of synthetic PPARβ/δ ligands bound to the PPARβ/δ LBD, Kahremany et al. (2015) recently created an *in silico* model that helped in analyzing the binding pocket in the LBD and in determining the obligatory interactions between various synthetic PPARβ/δ agonists and amino acid side chains in the LBD of PPARβ/δ [321]. This model also tests the assumption that both large (e.g., long FAs and their metabolites) and small PPARβ/δ ligands (e.g., hydroxyalkenals and RA) may enter and interact with the bulky cavity in the LBD of PPARβ/δ. Although *in vitro* investigations have suggested that unliganded

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PPARβ/δ is bound to chromatin, whether this interaction occurs *in vivo* remains unclear. Importantly, the transcriptional potential of unliganded PPARβ/δ, if present on chromatin, and the effect of the summation of the post-translational modifications of PPARβ/δ on its transactivation activity remain to be determined.

A theme that has continually surfaced in this review is the effect of different PPARβ/δ treatment regimens on disease prognosis. In diabetic wound healing, early controlled release of the PPARβ/δ agonist GW501516 influenced the oxidative wound microenvironment and consequently impacted the wound healing rate. Similarly, in EAE, an experimental model of MS, improved clinical outcomes were observed when oral treatment of the PPARβ/δ agonist GW0742 was administered during disease progression compared with upon disease initiation. Differential effects of PPARβ/δ agonists on the clearance of Aβ peptide, a pathological hallmark of AD, were also reported. From a different perspective, determining the effects of PPARβ/δ agonists in a particular disease requires us to understand the dynamic host response and the pharmacokinetic profile of the agonist. For instance, the relative PPARβ/δ expression pattern in the major cellular components and the relative contributions of cellular and non-cellular PPARβ/δ to the initiation, development and progression of disease are uncertain. Although recent studies have begun to explore the function of PPARβ/δ during wound healing and atherosclerosis, relatively little is known about the roles of PPARβ/δ in other diseases. In addition to a better understanding of PPARβ/δ in disease development, one will need to appreciate the pharmacokinetic profile, including the bioavailability and stability, of the various PPARβ/δ drugs. Along these lines, it is noteworthy that very few studies exploring various controlled drug delivery systems have focused on our understanding of the PPARβ/δ expression profile and PPARβ/δ drug pharmacokinetics.

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The role of PPARβ/δ has been well established for some conditions, such as wound healing and lipid metabolism, while its role in others conditions, such as cancer and neurological diseases, remains controversial. Currently published studies have used different mouse models (e.g., PPARβ/δ^{ex4} or PPARβ/δ^{ex8}) and experimental regimes, which may confound our understanding of the role of PPARβ/δ. We do not believe that it is currently possible to declare any of these models to be most relevant, as each model fails to faithfully recapitulate all aspects of human disease development, particularly tumorigenesis. For example, *APC*^{min} mice, the most widely used mouse model of colon cancer, only harbor polyps that do not progress to colon tumors. Furthermore, most studies did not examine the role of PPARβ/δ in tumor stromal cells. The tumor microenvironment contains numerous different cell types, such as the predominant cancer-associated fibroblasts (CAFs), tumor associated macrophages (TAMs), tumor-infiltrating lymphocytes (TILs) and pericytes. Despite the well-established impact of these cell types on tumorigenesis, the role of PPARβ/δ in these tumor-associated stromal cells remains unclear and conceivably may be specific to the tumor type, tissue, and cancer stage. Nonetheless, knowledge gathered from all disease models has been useful to some extent, in that the results provide mechanistic insights that have collectively advanced our understanding of different aspects of tumorigenesis. Combining the results from different murine models with data obtained from human tumors will help clarify the role of PPARβ/δ and its associated machinery in CRC and other cancers.

We predict that the use of genetic and pharmacological approaches, such as tissue- and/or cell-type specific conditional knockout animal models along with specific PPARβ/δ agonists and antagonists, will prove to be useful in clarifying the role of PPARβ/δ in various diseases. Such approaches may also reveal novel roles of PPARβ/δ in the initiation and progression of particular

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diseases, and such studies could aid in the future design of novel and efficient pharmacological agents that target PPARβ/δ for the treatment of many diseases. Realizing this goal will require multidisciplinary collaborative efforts of various scientists and clinicians.

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Figure 1. Overall mechanism of PPARβ/δ function. Similar to other nuclear receptors, PPARβ/δ is structurally composed of an N-terminal domain (NTD), a DNA-binding domain (DBD), and a ligand-binding domain (LBD). PPARβ/δ ligands are currently understood to be transported from the cytoplasm into the nucleus by fatty-acid binding protein 5 (FABP5). In macrophages, the absence of a PPARβ/δ agonist allows for the scavenging of BCL-6, a PPARβ/δ-associated transcriptional repressor. This allows for transcription factors (TFs) to bind to their respective TF-binding sites (TFBSs) and activate the transcription of BCL-6-repressed genes (*b6rg*) encoding for macrophage-associated chemokines or cytokines. In the presence of a PPARβ/δ ligand, an anti-inflammatory effect of PPARβ/δ activation is observed, as BCL-6 is released from PPARβ/δ, leading to transrepression of *b6rg* with the aid of a corepressor complex. In other tissues, the presence of either a PPARβ/δ agonist or antagonist leads to heterodimerization of PPARβ/δ with a retinoid X receptor (RXR), another type of nuclear receptor, as well as the binding of the heterodimer complex to PPAR response elements (PPREs) found in the promoter regions of PPARβ/δ target genes. Depending on whether an agonist or antagonist is bound to PPARβ/δ, either a co-activator or corepressor complex is recruited, thus leading to the transactivation or transrepression of PPARβ/δ target genes, respectively.

Figure 2. PPARβ/δ in wound repair. Skin injury-induced inflammatory signals (e.g., TNFα) activate PPARβ/δ via the SAPK/AP-1 pathway. PPARβ/δ activation concurrently upregulates the transcriptional activation of direct targets, such as integrin-linked kinase (ILK) and 3-phosphoinositide-dependent kinase-1 (PDK1, also known as PDPK1), and downregulates phosphatase and tensin homologue deleted on chromosome 10 (PTEN). These events increase protein kinase B (AKT1) activation, which suppresses keratinocyte apoptosis via modulation of

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the death receptor and mitochondrial apoptosis pathways. Keratinocyte-derived interleukin-1 (IL-1) also upregulates PPARβ/δ in fibroblasts, stimulating the production of secreted IL-1 receptor antagonist (sIL-1ra). sIL-1ra inhibits further IL-1-induced production of mitogenic factors by fibroblasts, thereby tightly regulating keratinocyte proliferation during wound healing. PPARβ/δ-enhanced, and subsequently cleaved, angiopoietin-like protein 4 (cANGPTL4) also plays a role in the modulation of vascular leakiness via the JAK/STAT/iNOS pathway. Keratinocyte migration is coregulated by MMP-9 production and the cANGPTL4/JAK/STAT/iNOS pathway. In diabetic patients, PPARβ/δ activation in fibroblasts upregulates the expression of H_2O_2-scavenging catalase and glutathione peroxidase 1 (GPx1), thereby rescuing oxidatively modified ECM proteins to enhance keratinocyte migration during wound healing.

Figure 3. PPARβ/δ in cardiovascular disease. In the vascular endothelium, PPARβ/δ activation directly causes endothelium-dependent vasodilatation by increasing NO production through the PI3K/Akt pathway. PPARβ/δ activation also upregulates the expression of antioxidant genes and reduces NADPH activity, leading to reduced vascular levels of ROS and increased NO bioavailability. PPARβ/δ activation also reduces DAG-PKC-mediated ROS production by enhancing mitochondrial FA oxidation. PPARβ/δ ligands have beneficial effects on plasma lipoproteins, causing reductions in plasma VLDL-TG and LDL-cholesterol levels and increases in HDL-cholesterol levels. In addition, PPARβ/δ activation decreases the abundance of small, dense LDL particles, which are more atherogenic than larger LDL particles. In macrophages, PPARβ/δ agonists elicit anti-inflammatory effects by modulating the activity of the inflammatory suppressor protein BCL-6. In cardiomyocytes, PPARβ/δ controls the

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expression of antioxidant genes, genes involved in FA oxidation and the transcriptional co-activator PGC-1α. As a result of these activities, PPARβ/δ plays a key role in many physiological and pathological processes in the heart. BCL-6: B-cell lymphoma-6. CPT-1: carnitine palmitoyltransferase 1. DAG: diacylglycerol. HDL: high-density lipoprotein. LDL: low-density lipoprotein. NO: nitric oxide. PGC-1α: PPARγ co-activator 1α. PI3K: phosphatidylinositol 3-kinase. PKC: protein kinase C. ROS: reactive oxygen species. TG: triglyceride. VLDL: very-low-density lipoprotein.

Figure 4. Effects of PPARβ/δ on adipocytes and macrophages in adipose tissue. The Th2 cytokines IL-13 and IL-4 secreted by adipocytes induce the expression of PPARβ/δ in macrophages, which in turn polarizes macrophages towards the alternatively activated, anti-inflammatory M2 phenotype, promoting insulin sensitivity in adipose tissue. PPARβ/δ may also increase insulin sensitivity by preventing cytokine-induced STAT3 activation and the subsequent upregulation of SOCS3, which inhibits insulin signaling by interfering with IRS function. PPARβ/δ also activates the overall level of oxidative metabolism in white adipose tissue, and this effect may reduce triglyceride accumulation in adipocytes and the circulating NEFA levels. IRS: insulin receptor substrate. JAK: Janus kinase. NEFAs: non-esterified FAs. SOCS3: suppressor of cytokine signaling 3. STAT3: signal transducer and activator of transcription 3.

Figure 5. PPARβ/δ in hepatocytes influences the diurnal expression of lipogenic genes in the liver and thereby regulates inter-organ communication between the liver and muscle. In contrast to hepatic PPARα, which is active during fasting and which controls FA degradation in response to adipose tissue lipolysis, PPARβ/δ shows diurnal expression that peaks during the

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night, when lipogenesis is high, in fed mice. Disruption of PPARβ/δ in hepatocytes influences the diurnal expression of acetyl-CoA carboxylase (ACC), a key lipogenic enzyme, via a mechanism that remains unknown. This effect shifts the lipogenic flux and influences the rhythmic synthesis of FAs such as stearic acid (C18:0) and oleic acid (C18:1n-9), which are essential for the synthesis of phosphatidylcholine 18:0/18:1 (PC(18:0/18:1)). PC(18:0/18:1) activates PPARα and thereby increases FA uptake in muscle, reducing circulating free FA and TG levels.

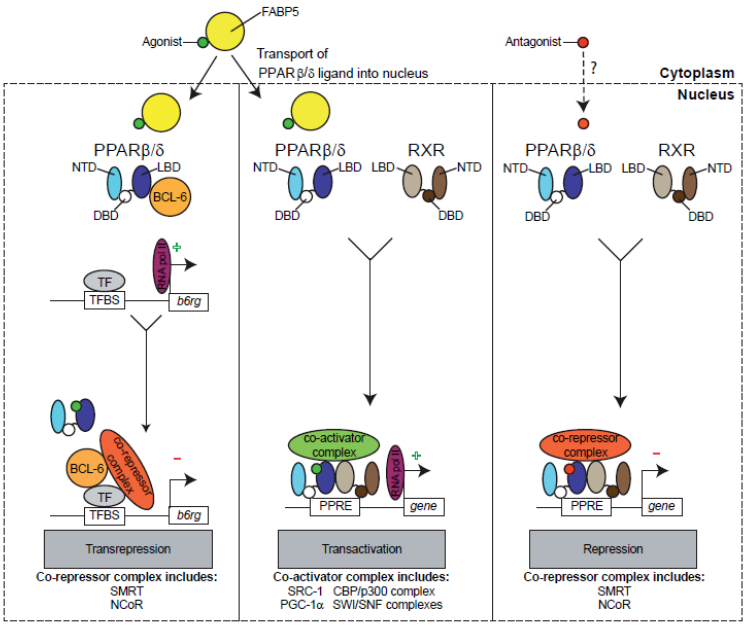

Figure 1

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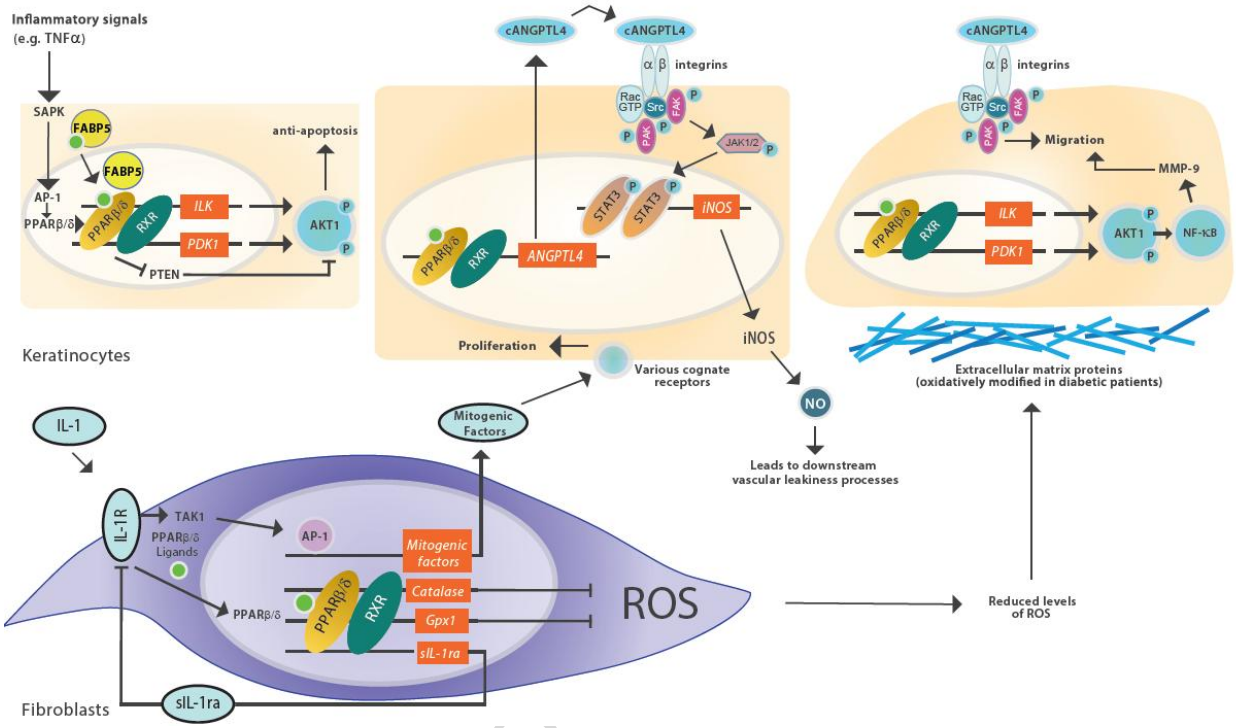

Figure 2

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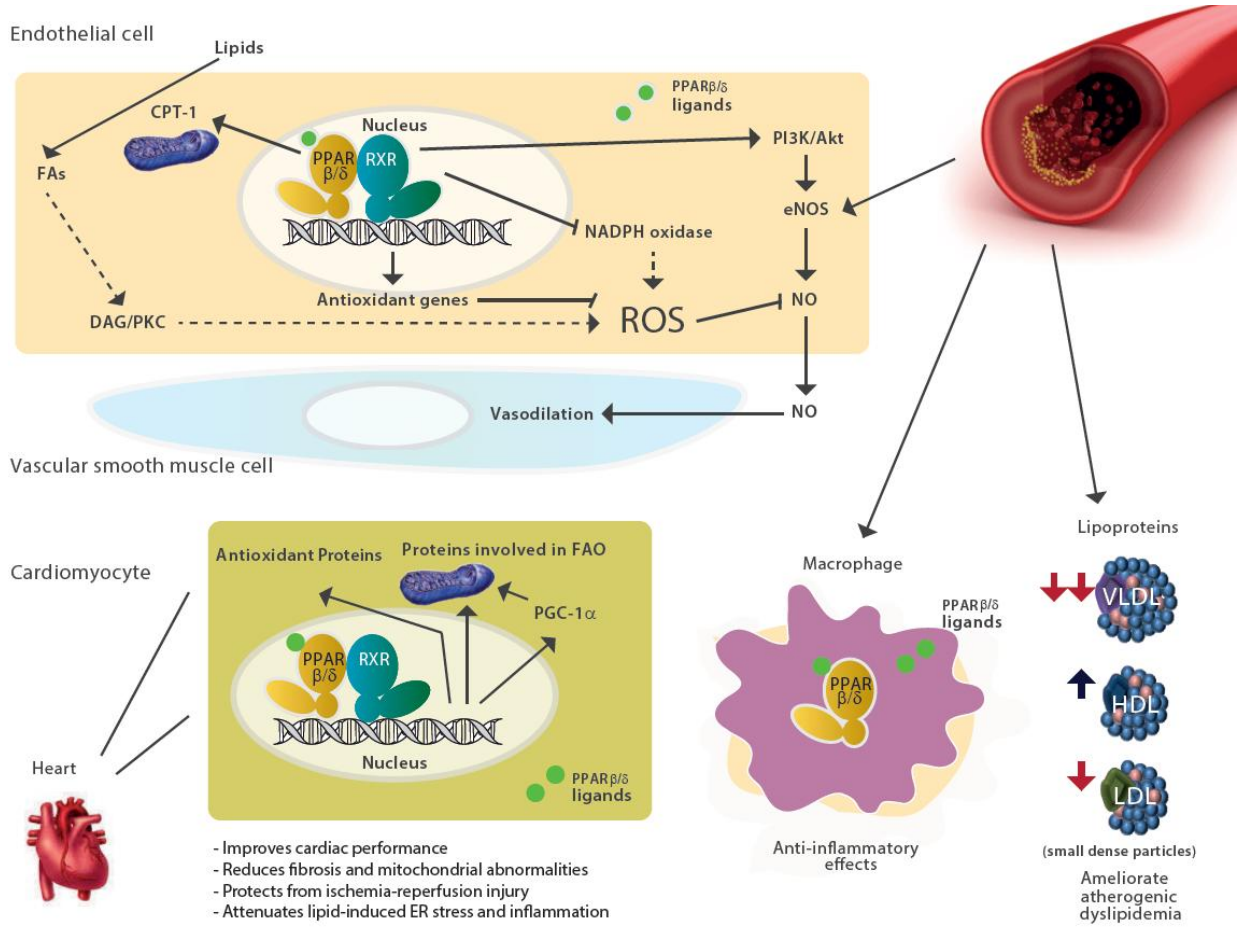

Figure 3

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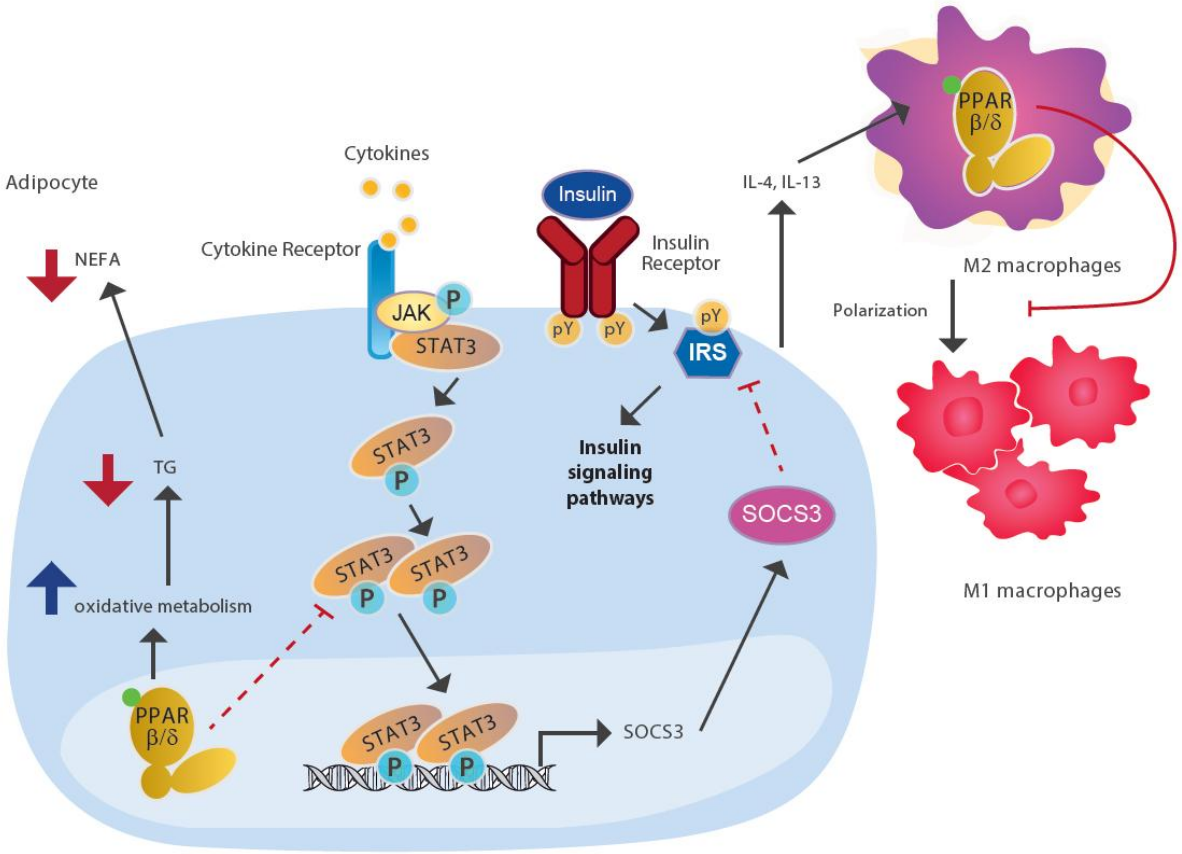

Figure 4

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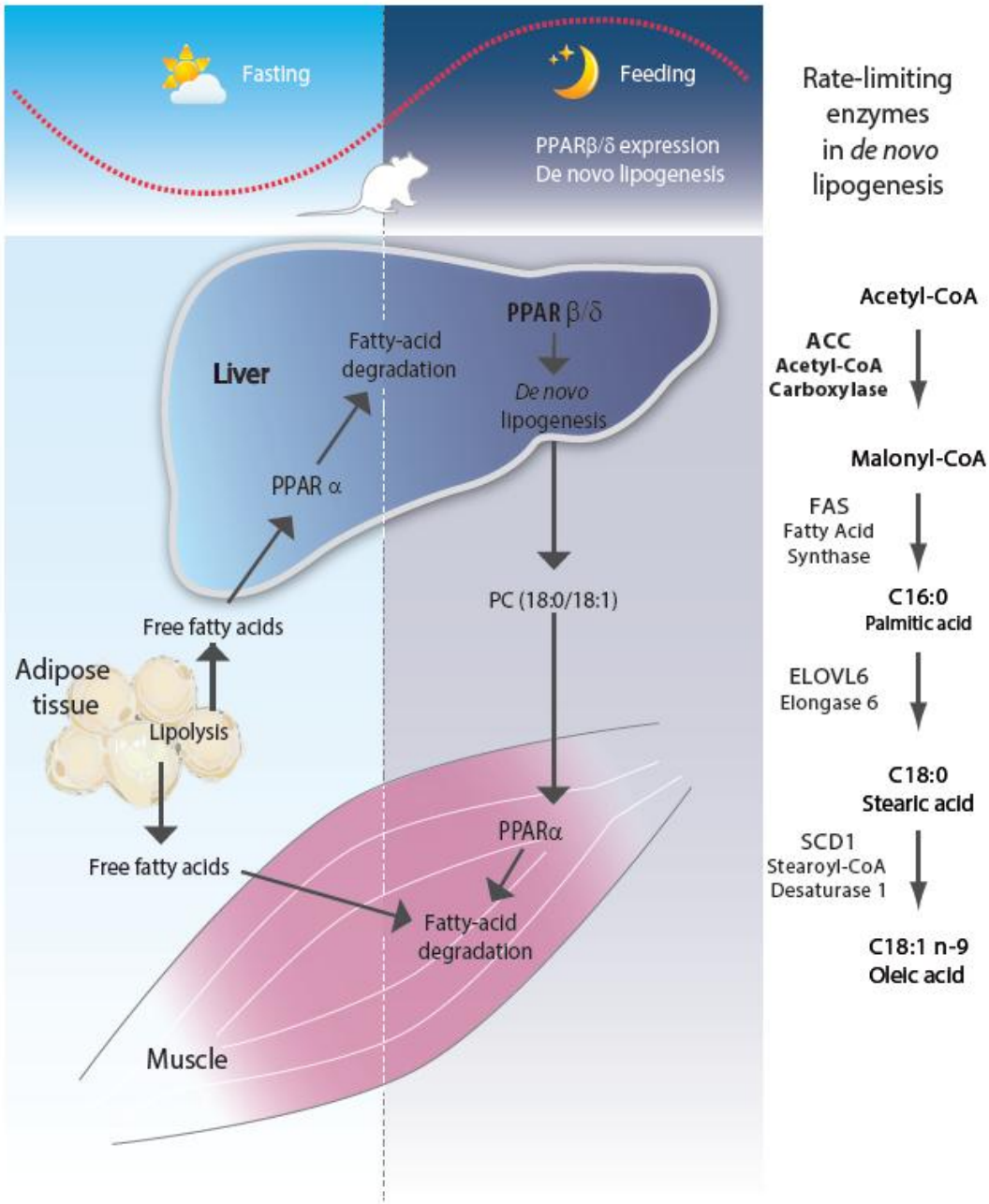

Figure 5

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