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*Review Article*

# The Emerging Role of PPAR Beta/Delta in Tumor Angiogenesis

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PPARs are ligand-activated transcriptional factors that belong to the nuclear receptor superfamily. Among them, PPAR alpha and PPAR gamma are prone to exert an antiangiogenic effect, whereas PPAR beta/delta has an opposite effect in physiological and pathological conditions. Angiogenesis has been known as a hallmark of cancer, and our recent works also demonstrate that vascular-specific PPAR beta/delta overexpression promotes tumor angiogenesis and progression in vivo. In this review, we will mainly focus on the role of PPAR beta/delta in tumor angiogenesis linked to the tumor microenvironment to further facilitate tumor progression and metastasis. Moreover, the crosstalk between PPAR beta/delta and its downstream key signal molecules involved in tumor angiogenesis will also be discussed, and the network of interplay between them will further be established in the review.

## 1. Introduction

Peroxisome proliferator-activated receptors (PPARs) as ligand-activated transcription factors belong to the steroid receptor superfamily, which includes three isoforms, PPAR alpha, PPAR beta/delta, and PPAR gamma [1]. PPARs form heterodimers with retinoic X receptors and regulate the expression of various genes upon ligand binding. PPARs also interact with corepressors or coactivators to modulate the transcription of its downstream target genes. PPARs as important transcriptional regulators have been suggested to be involved in lipid metabolism and multiple cellular functions. For instance, PPAR alpha also functions in fatty acid beta-oxidation and vascular inflammation [2]. PPAR gamma acts as a regulator in adipocyte differentiation and type 2 diabetes [3]. PPAR beta/delta is a key player in cardiac energy production, angiogenesis, and particularly in cancer progression [4].

PPAR alpha and PPAR gamma exert predominantly an antiangiogenic effect [5–10], but there still exist conflicting studies showing opposite results [11, 12]. On the contrary, PPAR beta/delta produces more obviously proangiogenic effects [13–18]. In this review, we will focus on the promoting role of PPAR beta/delta in angiogenesis, especially in tumor angiogenesis. The network of interplay between PPAR beta/-delta and its various downstream signal molecules, and also between those key molecules, will be further discussed and established. Remarkably, diverse important signal molecules involved in tumor angiogenesis and progression, and cancer cell metabolism have been identified as direct PPAR beta/-delta target genes.

## 2. Angiogenesis

Angiogenesis is the physiological process through which a new capillary network forms from the preexisting vasculature [19, 20], whereas vasculogenesis denotes de novo blood vessel formation mostly during embryogenesis in which endothelial progenitor cells (EPC) migrate to sites of vascularization, then differentiate into endothelial cells (EC), and coalesce into the initial vascular plexus [21, 22]. Besides the interaction between proangiogenic factors and antiangiogenic factors, angiogenesis is also a multiple step biological process during which a variety of molecules cooperate including cell adhesion molecules, matrix metalloproteinases

(MMPs), extracellular matrix (ECM), and basement membrane components.

Angiogenesis is a physiological and vital process in development and growth. An imbalance of proangiogenic and antiangiogenic factors causes angiogenesis in pathological conditions such as diabetic retinopathy and tumor growth. Thus, when the imbalance comes to a point at which angiogenesis is triggered by tumor cells, then an "angiogenic switch" of tumor cells is turned on; during tumor progression, the "angiogenic switch" is often activated and remains on [23–25]. Inducing angiogenesis is known as a hallmark of cancer [26], and angiogenesis is also a fundamental step by which most benign tumors transition into malignant ones.

*2.1. Tumor Angiogenesis.* Tumor needs to sprout new vessels and further develop a vascular network in order to supply nutrients and oxygen, remove waste products, support a continually high proliferative rate, and ultimately expand neoplastic growth [23, 27]. Hence, angiogenesis is essential for helping sustain tumor growth and facilitate tumor progression. Besides being a requirement for angiogenesis, an abnormal vasculature also helps to promote tumor progression and metastasis. The tumor vascular wall is imperfect and prone to leakage, so it is much easier for tumor cells to directly penetrate into the blood vessels or lymphatic vessels and then proliferate at another distant site to form metastasis [28].

Due to intensive abnormal neovascularization in tumor tissues, most malignant tumors grow rapidly and acquire the ability to spread to adjacent and distant organs, which makes them more malignant and even life threatening. Therefore, angiogenesis indeed plays an important role in tumor progression and metastasis, and to intervene with this process would obviously prevent tumor development and spread. Thus, this has been regarded as a critical target for antitumor therapy.

## 3. PPAR Alpha and Angiogenesis

It was reported firstly that a selective PPAR alpha agonist WY14643 did not show any effect on angiogenesis or EC proliferation [29]. But some subsequent studies showed that the activation of PPAR alpha inhibited angiogenesis in vitro by using fenofibrate, a clinically used PPAR alpha agonist [30]. Moreover, fenofibrate suppressed EC proliferation, migration, and tube formation through inhibition of protein kinase B (Akt) and disruption of the cytoskeleton [31]. Furthermore, PPAR alpha activation was shown to inhibit vascular endothelial growth factor- (VEGF-) induced EC migration and basic fibroblast growth factor- (bFGF/FGF2-) induced corneal angiogenesis in vitro and in vivo [5]. Especially, in vivo, reduced tumor growth and microvessel numbers were observed in mice implanted with melanoma, Lewis lung carcinoma (LLC), fibrosarcoma, and glioblastoma due to a systemic treatment of PPAR alpha ligand, and the antiangiogenic state induced through activation of PPAR alpha with elevated thrombospondin-1 (TSP1) and endostatin expression [5].

However, in that same year, it was demonstrated in another observation that activation of PPAR alpha stimulated neovascularization in vivo with increased phosphorylation of endothelial nitric oxide synthase (eNOS) and Akt via a VEGF-dependent manner [32]. Furthermore, Zhang and Ward also suggested that PPAR alpha activation induced proangiogenic responses in human ocular cells [33]. In another study, it was shown that a new PPAR alpha agonist (R)-K-13675 had no effect on angiogenesis [34]. Recently, PPAR alpha activation is further shown to have antineovascularization effects with downregulation of VEGF and angiopoietin expression in a rat alkali burn model [35].

In summary, the role of PPAR alpha in angiogenesis is still controversial. Some observations showed that ligand activation of PPAR alpha had antiangiogenic effects mediated either through upregulation of antiangiogenic factors such as TSP1 and endostatin, or downregulation of proangiogenic factors including VEGF, FGF2, AKT, and angiopoietins. Others also reported opposite results showing a proangiogenic role upon PPAR alpha activation. Thus, the specific molecular mechanism is still unclear and needs to be further studied.

## 4. PPAR Gamma and Angiogenesis

Ligand activation of PPAR gamma was previously shown to inhibit human umbilical vein endothelial cell (HUVEC) tube formation in collagen gels [36] and VEGF-induced choroidal neovascularization in vitro and in vivo [37]. Another study also demonstrated that EC apoptosis was induced through treatment with the PPAR gamma ligand 15d-PGJ2 [38]. Furthermore, rosiglitazone, a potent PPAR gamma agonist, was shown to inhibit primary tumor growth and metastasis through both direct and indirect antiangiogenic effects in vitro, and bFGF-induced corneal neovascularization in vivo [8]. Moreover, a similar observation also displayed the inhibition of VEGF-induced angiogenesis in a chick chorioallantonic membrane model [39]. In a mouse model with ischemia-induced retinopathy, pioglitazone, a PPAR gamma agonist, also showed a protective effect against pathological neoangiogenesis through upregulation of anti-inflammatory adipokine adiponectin [40]. Additionally, the PPAR gamma antagonist GW9662 was shown to reverse Omega-3 polyunsaturated fatty acid-induced reduction of E-Selectin, angiopoietin-2, vascular cell adhesion molecule-1, and intracellular adhesion molecule-1 [41], implicating an antiangiogenic potential of PPAR gamma itself. However, opposite results also showed that pioglitazone enhanced neovascularization and inhibited apoptosis of EPC in vitro and in vivo via a Phosphoinositide-3-Kinase- (PI3K-) dependent manner [42].

Nadra et al. observed that PPAR gamma-null embryos displayed a vascular structural defect at E9.5. Moreover, disorganized placental layers and an altered placental microvasculature were observed in pregnant wild-type mice treated with the PPAR gamma agonist rosiglitazone, as well as reduced expression of proangiogenic factors including VEGF, proliferin, and platelet-endothelial cell adhesion molecule-1 (PECAM1/CD31) [43], suggesting a crucial role of PPAR gamma in placental vascular development. The

major antiangiogenic properties on PPAR gamma activation were also reviewed here [44].

Notably, in most cancers, the canonical Wnt/beta-catenin pathway is upregulated, while on the contrary, PPAR gamma is downregulated. Interestingly, in numerous tissues, the activation of PPAR gamma inhibits the beta-catenin pathway, whereas the stimulation of the canonical Wnt/beta-catenin signal cascade also inactivates PPAR gamma [45], implicating a negative regulatory role of PPAR gamma in carcinogenesis where tumor angiogenesis might be a fundamental step.

In summary, PPAR gamma predominantly displays an antiangiogenic effect that may be mediated through the inhibition of VEGF or bFGF-induced neovascularization and reduction of the expression level of some proangiogenic factors.

## 5. PPAR Beta/Delta and Angiogenesis

Unlike PPAR alpha and PPAR gamma, on the contrary, many studies have explicitly shown the proangiogenic effects of PPAR beta/delta on physiological and pathological angiogenesis. The first evidence provided in a study is that activation of PPAR beta/delta with GW501516, a highly selective PPAR beta/delta agonist, induces HUVEC proliferation and an increased expression of VEGF and its receptor VEGFR1 (FLT1) [46]. Besides inducing EC proliferation, PPAR beta/delta activation by its ligand prostacyclin (PGI2) also stimulates upregulation of 14-3-3 alpha expression, an antiapoptotic and anti-inflammatory protein, which thereby protects ECs from $H_2O_2$-induced apoptosis and oxidant injury [47]. Moreover, a subsequent study further provides evidence that activation of PPAR beta/delta with GW501516 induces angiogenesis during which VEGF release is considered as a major trigger factor [48], firstly suggesting the promotion for angiogenesis upon PPAR beta/delta activation.

Müller-Brüsselbach et al. show that PPAR beta/delta -/- mice implanted with LLC and B16 melanoma exhibit diminished blood flow and immature microvascular structures compared with wild-type mice. Moreover, reexpression of PPAR beta/delta into the matrigel-invading cells triggers microvessel maturation and restores normal vascularization [17], indicating a crucial role of PPAR beta/delta in tumor vascularization. Additionally, another study also observed reduced levels of calcium intracellular channel protein 4 (CLIC4), but it observed enhanced expression of cellular retinol binding protein 1 (CRBP1) in migrating ECs from PPAR beta/delta-null mice [49], both of which play a role in tumor vascularization [50, 51]. It was reported that PPAR beta/delta was required for placentation [52], and most of the PPAR beta/delta-null mutant embryos died at E9.5 to E10.5 due to abnormal cell-to-cell communication at the placental-decidual interface [53]. However, in these studies [52–54], a defect in angiogenesis was not observed during normal development in PPAR beta/delta-knockout mice.

Some observations also show the important role of PPAR beta/delta in physiological angiogenesis. For instance, skeletal muscle-specific PPAR beta/delta overexpression leads to an increase in the number of oxidative muscle fibers and running endurance in adult mice [55–57]. Moreover, PPAR beta/delta activation promotes a rapid muscle remodeling via a calcineurin-dependent manner, and induces muscle angiogenesis in highly selective PPAR beta/delta agonist GW0742-treated animals [58]. Furthermore, in the heart, pharmacological PPAR beta/delta stimulation with GW0742 induces rapid cardiac growth and cardiac angiogenesis through direct transcriptional activation of calcineurin [15]. Interestingly, the same cardiac phenotype was also observed after treatment with the PPAR beta/delta agonist GW501516, implicating a response specificity for PPAR beta/delta stimulation [15]. Calcineurin activation further leads to the stimulation of nuclear factor-activated T cell c3 (NFATc3) and an enhanced expression of hypoxia inducible factor 1 alpha (HIF-1alpha) and cyclin-dependent kinase 9 (CDK9) [15]. Overall, the remodeling in skeletal muscle and heart is perfectly the same as the phenotype observed with exercise, and both of them are mediated through activation of calcineurin.

PPAR beta/delta may act as a key regulator in mediating pathological angiogenesis. For instance, PPAR beta/delta was shown to regulate retinal angiogenesis in vitro and in vivo, and its inhibition reduced preretinal neovascularization possibly via an Angiopoietin-like protein 4- (Angptl4-) dependent manner [59], implicating the potential of PPAR beta/delta in modulating pathological ocular angiogenesis. Recently, an observation reported that PPAR beta/delta knockdown in both retinal pigment epithelial and choroidal endothelial cells caused an antiangiogenic phenotype, and PPAR beta/delta promoted laser-induced choroidal neovascular (CNV) lesions in PPAR beta/delta +/+ mice [60]. Moreover, pharmacological inhibition of PPAR beta/delta with the antagonist GSK0660 also resulted in a significantly decreased CNV lesion size in vivo, suggesting a functional role of PPAR beta/delta in the development of CNV lesions [60]. This indicates that PPAR beta/delta has an important association with pathological angiogenesis.

Angiotensin II (Ang II), the biologically active peptide of the renin-angiotensin system (RAS), is a major blood pressure and cardiovascular homeostasis regulator and is also recognized as a potent mitogen. Angiotensin-converting enzyme inhibitors were introduced approximately 30 years ago as antihypertensive agents and have since become a successful therapeutic approach for high blood pressure, congestive heart failure, and postmyocardial infarction. In experimental systems, the antitumor effects of diverse ACE inhibitors show that these inhibit cell proliferation and possess antiangiogenic, antimetastatic, and anti-inflammatory effects [61–63]. It has been shown recently that activation of PPAR beta/delta inhibits Ang II-stimulated protein synthesis in a concentration-dependent manner and suppresses Ang II-induced generation of reactive oxygen species (ROS) in vascular smooth muscle cells [64]. PPAR beta/delta was further shown to inhibit Ang II-mediated atherosclerosis [65]. However, it is not clear until now if PPAR beta/delta activation can be considered as an ACE inhibitor-mimicking approach as it is for example the case for PPAR gamma activators [66].

Furthermore, the relevance of this hypothetical PPAR beta/delta feature might be limited for tumor angiogenesis where vascular smooth muscle hypertrophy and atherosclerosis do not contribute to the major pathology.

Besides inducing angiogenesis, it has been demonstrated that PPAR beta/delta directly acts on early EPC through activation of the AKT pathway and induces an enhanced vasculogenesis [67]. Similarly, the PPAR beta/delta-mediated provasculogenic effects are also observed on late EPC [68]. He et al. showed that PPAR beta/delta activation with GW501516 induced EPC proliferation and tube formation, whereas EPC treated with an inhibitor of cyclooxygenase (COX) or PGI2 synthase, or with PPAR beta/delta-specific siRNA also displayed an opposite effect [68]. Furthermore, it has been demonstrated that PPAR beta/delta induces angiogenesis and skeletal muscle regeneration through matrix metalloproteinase- (MMP-) 9-mediated insulin-like growth factor-1 paracrine networks upon EPC activation [69]. Han et al. also observed that PPAR beta/delta activation promoted a rapid wound healing with enhanced angiogenesis in a mouse model with skin punch wound [69]. Overall, in addition to EC, PPAR beta/delta is also a key regulator of EPC, or even may act as an initiator of activation of EPC to further induce vasculogenesis.

## 6. PPAR Beta/Delta and Tumor Angiogenesis Linked to Tumor Microenvironment

PPAR beta/delta expression is often upregulated and promotes cancer progression in many major human cancers such as colon, lung, breast, and gastric cancers [70–73], which suggests a crucial role of PPAR beta/delta in cancer cells even though there exist some conflicting studies indicating that the functional role of PPAR beta/delta in tumorigenesis or carcinogenesis still remains highly controversial [74–77] and dependent on specific tumor or cancer cell types. Thus, here we discuss the promotion of PPAR beta/delta in tumor progression through facilitating tumor angiogenesis.

PPAR beta/delta has been suggested as a critical "hub node" transcriptional factor which governs a tumor "angiogenic switch" [13, 78–80]. In the transcriptional network analysis, it was reported that tumor growth and tumor angiogenesis were markedly inhibited in PPAR beta/delta-null mice in comparison with wild-type mice [13]. Moreover, the elevated PPAR beta/delta expression level was also considered to be highly correlated to pathologically advanced tumor stage and increased cancer risk for recurrence and distant metastasis in patients with pancreatic cancer [13], indicating the crucial association of PPAR beta/delta with tumor angiogenesis, progression, and cancer invasiveness.

PPAR beta/delta may indirectly facilitate tumor angiogenesis and progression through its function on the tumor microenvironment (TME) where tumor angiogenesis is fostered. Moreover, a tumor also releases some extracellular signals to closely communicate and constantly collaborate with TME to facilitate tumor angiogenesis, in order to further enable tumor growth and progression. For instance, it was shown that colon cancer cells with PPAR beta/delta knockout failed to stimulate EC vascularization in response to hypoxic stress, whereas wild-type cells exposed to hypoxia were able to induce angiogenesis [81, 82], suggesting that PPAR beta/-delta is required for the promotion of angiogenesis in hypoxic stress-mediated TME. Moreover, in the TME, tumor-infiltrating myeloid cells are considered as the most important cells for fostering tumor angiogenesis among the multiple different kinds of stromal cells [82]. Besides stimulating tumor angiogenesis, tumor myeloid cells also support tumor growth by suppressing tumor immunity and promoting tumor metastasis to distinct sites [83]. Interestingly, it has been demonstrated that PPAR beta/delta activation in tumor-infiltrating myeloid cells stimulates cancer cell invasion and facilitates tumor angiogenesis via an Interleukin 10- (IL10-) dependent manner [84]. Moreover, impaired tumor growth and angiogenesis were observed in PPAR beta/delta KO BMT mice due to PPAR beta/delta deficiency in tumor myeloid cells [84], suggesting that PPAR beta/delta plays a key role in tumor angiogenesis and progression in tumor myeloid cells of TME.

Furthermore, the endoplasmic reticulum (ER), an essential organelle involved in many cellular functions, is implicated in TME. In cancer, stressors like hypoxia, nutrient deprivation, and acidosis disrupt ER function and lead to accumulation of unfolded proteins in ER, a condition known as ER stress. Cells adapt to ER stress by activating an integrated signal transduction pathway called the unfolded protein response (UPR). UPR represents a survival response by the cells to restore ER homeostasis and has both survival and cell death effects. The mechanisms that determine cell fate during ER stress are not well understood. For instance, short exposure to ER stress initially increases AKT signaling, but long-term ER stress suppresses AKT signaling [85]. PPAR beta/delta activation has been shown to reduce endoplasmic reticulum (ER) stress-associated inflammation in skeletal muscle through an AMPK-dependent mechanism [86] and to reduce inflammation in response to chronic ER stress in cardiac cells [87]. Furthermore, it has been nicely shown that PPAR beta/delta can repress RAS-oncogene-induced ER stress to promote senescence in tumors [88] This is mediated through the decrease of p-AKT activity promoting cellular senescence through upregulation of p53 and p27 expression [89]. It would be interesting to investigate the direct effects of PPAR beta/delta on senescence of tumor endothelial cells in an in vivo setting. We recently showed that senescent endothelial cells are indispensable for a healthy lifespan and that removal of senescent endothelium disrupts vascular function leading to diminished vessel densities and fibrotic lesions [90]. If PPAR beta/delta mediates senescence of tumor endothelium thereby protecting vessel integrity, this might explain the enhanced tumor growth and vascularization upon PPAR beta/delta activation observed by us and others [13, 16, 77].

Most recently, Zuo et al. demonstrated that PPAR beta/delta in cancer cells regulates tumor angiogenesis in vivo and in vitro by promoting the secretion of proangiogenic factors including VEGF and Interleukin 8 (IL8) [18]. Most importantly, in our recent works, it has been shown that conditional inducible vascular endothelium-specific PPAR beta/delta overexpression in vivo leads to

enhanced tumor angiogenesis, tumor growth, and metastasis formation, further indicating a vascular EC-specific PPAR beta/delta action mechanism in tumor progression, independent of some controversial observations of PPAR beta/delta in specific tumor or cancer cell types [16]. Wagner et al. also firstly reported the mouse model in which rapid induction of cardiac angiogenesis and cardiac hypertrophy were observed [91, 92].

*6.1. Crosstalk between PPAR Beta/Delta and Signal Molecules.* PPAR beta/delta activation or overexpression may upregulate the expression of its various downstream signal molecules involved in tumor angiogenesis including proangiogenic factors (such as VEGF, PDGF, and FGF), proinvasive matrix-degrading enzymes (such as MMP9), proinflammatory mediators (such as COX2), and cytokines and chemokines (such as IL1 and CXCL8), even some of which have been further identified as PPAR beta/delta direct target genes. Besides a leading role of PPAR beta/delta among the signal molecules, PPAR beta/delta may function in TME linked to diverse kinds of cells through direct or indirect modulation of its downstream molecules.

*6.1.1. Interplay between PPAR Beta/Delta and Inflammatory Angiogenesis.* Inflammatory angiogenesis is a crucial process in tumor progression. For instance, the proinflammatory mediator cyclooxygenase-2 (COX2) is considered as a key regulator of angiogenesis and tumor growth through multiple downstream proangiogenic mechanisms such as production of VEGF and induction of MMPs. Moreover, selective inhibition of COX2 has also been shown to suppress angiogenesis in vivo and in vitro [93]. It is well known that VEGFA plays a critical role in both angiogenesis and vasculogenesis [94], and it leads the directional migration of tip cells and stalk cell proliferation in microtubule branches [95, 96]. It has also been demonstrated that MMP9 triggers the "angiogenic switch" during carcinogenesis and enhances the availability of VEGF to its receptors [97]. Furthermore, it has been reported that inflammatory cell MMP9 initiates the onset of tumor neovascularization during which there exists functional links between VEGF and MMPs including MMP9 [98]. LEPTIN is shown to mediate angiogenesis in vivo and in vitro through induction of EC proliferation and expression of MMP2 and MMP9 [99], and to further promote EC differentiation and directional migration through enhancement of COX2 activity [100]. LEPTIN could also induce angiogenesis via transactivation of VEGFR in ECs [101]. Additionally, besides inducing angiogenesis, PPAR beta/delta also functions in chronic inflammation-facilitating tumorigenesis through induction of COX2 and its product prostaglandin E2 (PGE2) in vivo [102, 103]. Interestingly, COX2, VEGF, MMP9, and LEPTIN have been identified as PPAR beta/delta target genes via a direct transcriptional activation mechanism in hepatocellular carcinoma cells [104], colorectal cancer cells [105, 106], EPCs [67, 69], and liposarcoma cells [107], respectively.

In TME, tumor-infiltrating inflammatory cells also help to induce and sustain tumor angiogenesis, and further to facilitate tissue invasion and tumor metastatic spread by releasing some signal molecules such as proinvasive MMP9 and inflammatory chemokines [108–110]. Chemotaxis is also a crucial process for inducing angiogenesis in tumors, either directly by attracting ECs towards tumor cells to form new vessels, or indirectly by mediating immune inflammatory cells to infiltrate, eventually promoting tumor angiogenesis [111]. Chemotaxis of tumor cells and stromal cells in TME is also required for tumor dissemination during tumor progression and metastasis [110, 111].

CXC chemokines such as CXCL8 (encoding IL8) and CXCL5 are also involved in COX2-associated angiogenesis to contribute to non-small-cell lung cancer progression [111, 112]. It is further shown that IL8 directly regulates angiogenesis via recruitment of neutrophils [112], which further drives VEGF activation [113]. Moreover, IL8-responding neutrophils are considered as the major source of angiogenesis-inducing MMP9 [98, 114]. Chemokine C-C motif ligand 2 (CCL2), in addition to the promotion of angiogenesis [115, 116], also enhances tumor metastasis [117]. Furthermore, myeloid monocytic cells such as myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and dendritic cells are recruited to the tumor site mainly by CCL2 and produce many proangiogenic factors such as VEGF, CXCL8, platelet-derived growth factor (PDGF), and transforming growth factor beta (TGF beta) [118–120]. In fact, both TGF beta and hypoxia are potent inducers of VEGF expression in tumor cells and collaborate with TME to provide the foundation of tumor angiogenesis and cancer cell invasion [121]. Importantly, IL8 has been reported as a key target gene of PPAR beta/delta to promote angiogenesis in vivo and in vitro [18], and CCL2 expression is also significantly upregulated upon vascular PPAR beta/-delta overexpression in vivo [16].

COX2 also mediates IL1 beta-induced angiogenesis in vitro and in vivo [122, 123]. IL1 beta supports neovascularization through the regulation of the expression of VEGF and its receptor VEGFR2 (FLK1/KDR) on ECs [124]. IL1 acts as an upstream proinflammatory mediator that initiates and disseminates the inflammatory state by inducing a local interactive network and increasing adhesion molecule expression on ECs and leukocytes, which facilitates tumor-associated angiogenesis [125]. In TME, inflammatory IL1 beta recruits myeloid cells from bone marrow and activates them to produce proangiogenic factors such as VEGF; VEGF further activates ECs and myeloid cells, promoting tumor invasiveness and fostering tumor angiogenesis [125]. In addition, IL6 also stimulates angiogenesis and vasculogenesis [126, 127]. However, Gopinathan et al. observed an IL6-induced newly forming vascular structure with defective pericyte (PC) coverage ex vivo [128], thus facilitating cancer cell infiltration and tumor metastasis through vascular leakage. Interestingly, IL1 and IL6 expression levels are significantly upregulated in the PPAR beta/delta overexpression mouse model reported recently [16].

In summary, PPAR beta/delta seems to act as a key leader in inflammatory mediator-driven tumor angiogenesis linked to TME in which many proinflammatory mediators, chemokines, and proangiogenic factors closely communicate with

each other, and also associate with tumor-infiltrating myeloid cells such as neutrophils, TAMs, and MDSCs.

*6.1.2. Other Key PPAR Beta/Delta-Mediated Proangiogenic Factors.* It has been demonstrated that Wilms' tumor suppressor WT1 is a major regulator of tumor neovascularization and tumor progression [129]. E26 avian leukemia oncogene 1 (ETS1) also plays a key role in regulating vascular development and haemopoiesis, particularly in angiogenesis [130]. In addition, ETS1 promotes cancer cell invasion through upregulation of MMPs [131]. Consistent with this, silencing of ETS1 in highly invasive breast cancer cells also reduces the expression of MMP9 and MMP1 [132].

ETS1 also acts as a key regulator of MMPs such as MMP1, MMP3, and MMP9 in human cancer-associated fibroblasts (CAFs) [133, 134]. CAFs support tumor growth by secreting growth factors such as VEGF, FGF, PDGF, and chemokines to stimulate angiogenesis and thereby promote cancer cell invasion and metastasis formation [135, 136]. CAFs, as metastatic tumor stroma, are a crucial component in tumor progression through the remodeling of the ECM structure, thus helping a tumor to acquire an aggressive phenotype [136, 137]. PPAR beta/delta in CAFs also exhibits a protumorigenic effect. It was reported that ablation of PPAR beta/delta in CAFs attenuated tumor growth by altering the redox balance in TME [138], suggesting that PPAR beta/delta in CAFs is also an important player in tumor development. ETS1 induces the expression of VEGF, VEGFR1, and VEGFR2 in ECs [139–141]. In turn, VEGF is also a major inducer of ETS1 in ECs through the activation of either the PI3K/AKT pathway or the MEK/ERK/1/2 signal cascade [142, 143]. WT1 is also reported to regulate tumor angiogenesis via direct transactivation of ETS1 [144].

SRY-related HMG-box 18 (SOX18) has also been reported previously to induce angiogenesis during tissue repair and wound healing [145] and cancer progression [146]. And most recently, it was further shown that specific EC-derived endovascular progenitors initiated a vasculogenic process and differentiated into more mature endothelial phenotypes within the core of the growing tumors through reactivation of SOX18 [147]. Interestingly, these important proangiogenic molecules including WT1, ETS1, and SOX18 are also significantly upregulated in the vascular PPAR beta/delta overexpression model in vivo [16]. And, WT1 is also identified as a target gene of PPAR beta/delta in melanoma cells [148].

*6.1.3. PPAR Beta/Delta May Facilitate Cancer Progression at Diverse Cellular Levels in TME.* PPAR beta/delta activation is shown to induce colonic cancer stem cell (CSC) expansion and to promote the liver metastasis of colorectal cancer in vivo via direct transactivation of the Nanog gene [149]. NANOG as a key transcriptional factor governs the self-renewal and pluripotency of stem cells [150], and cancer cells expressing NANOG also often exhibit stem cell properties [151]. Protooncogene c-KIT/CD117 is known as the mast/-stem cell factor receptor and receptor tyrosine kinase, and its activation in CSCs may regulate the stemness to control tumor progression and drug resistance to tyrosine kinase inhibitors. Moreover, c-KIT has been identified as a potential marker of the cancer stem-like cells [152]. In addition, c-KIT not only functions on ECs [153, 154] but also belongs to the tumor angiogenesis-promoting molecule [155–158]. Studies also suggested that activation of c-KIT enhances the expression of VEGF that can be suppressed by imatinib, an inhibitor of c-KIT in gastrointestinal stromal tumor cells, which thereby has an impact on tumor angiogenesis [159, 160]. c-KIT is also involved in pathological ocular neovascularization [161] and is regulated transcriptionally by WT1 [129] and PPAR beta/delta [16].

PDGFB and its receptor PDGFR beta, also known as angiogenic factors, are suggested to enhance angiogenesis and vasculogenesis via their function in ECs [162–164] and EPCs [165], and to regulate vascular permeability and vessel maturation through recruitment of pericytes (PCs) [166, 167] and smooth muscle cells (SMCs) [168] in newly forming vessels. Moreover, PDGFB and PDGFR beta also interact with other proangiogenic factors such as FGF2 [169, 170], VEGFA, and its receptor VEGFR2 [163]. Furthermore, PDGFB and PDGFR beta may also affect cancer growth and progression by directly acting on TME. Besides the crosstalk with CAFs [171–173], PDGFR beta in stromal fibroblasts may mediate PDGFB-induced TAM recruitment [174], thus implicating a role of PDGFR beta in tumor stroma to facilitate tumor progression. Most recently, it was further shown that specific targeting of PDGFR beta kinase activity in TME inhibited cancer growth and vascularization in cancers with high PDGFB expression such as LLC [175]. Therefore, this indicates the diverse role of PDGFB and PDGFR beta in facilitating tumor angiogenesis and progression at different cellular levels in TME. PDGFR beta is demonstrated as a target of telomeric repeat binding factor 2 (TRF2) that is further activated transcriptionally by WT1 [176]. PDGFB and PDGFR beta have further been identified as critical targets of PPAR beta/delta via a direct transactivation mechanism in vivo [16].

In conclusion, a variety of key signal molecules involved in tumor angiogenesis and tumor progression and metastasis have either been identified as PPAR beta/delta direct targets or largely upregulated in the vascular PPAR beta/delta overexpression model in vivo reported recently [16]. Thus, PPAR beta/delta activation seems to give rise to a highly angiogenic phenotype, and even plays a "hallmark" role in promoting tumor angiogenesis and progression. Interestingly, it appears that there could also exist a widely interactive network between the downstream protumor-angiogenic molecules as described above. Therefore, the crosstalk network is established between PPAR beta/delta and the various signal molecules, and also between those molecules (Figure 1(a)).

Moreover, in addition to cancer cells, PPAR beta/delta may also produce pleiotropic effects in TME by modulating downstream key molecules to act on ECs, EPCs, PCs, SMCs, CSCs, CAFs, and tumor-infiltrating inflammatory cells, indirectly facilitating tumor angiogenesis and further promoting cancer development (Figure 1(b)).

*6.2. Other PPAR Beta/Delta Target Genes.* PPAR beta/delta regulates the transcription of target genes via a direct

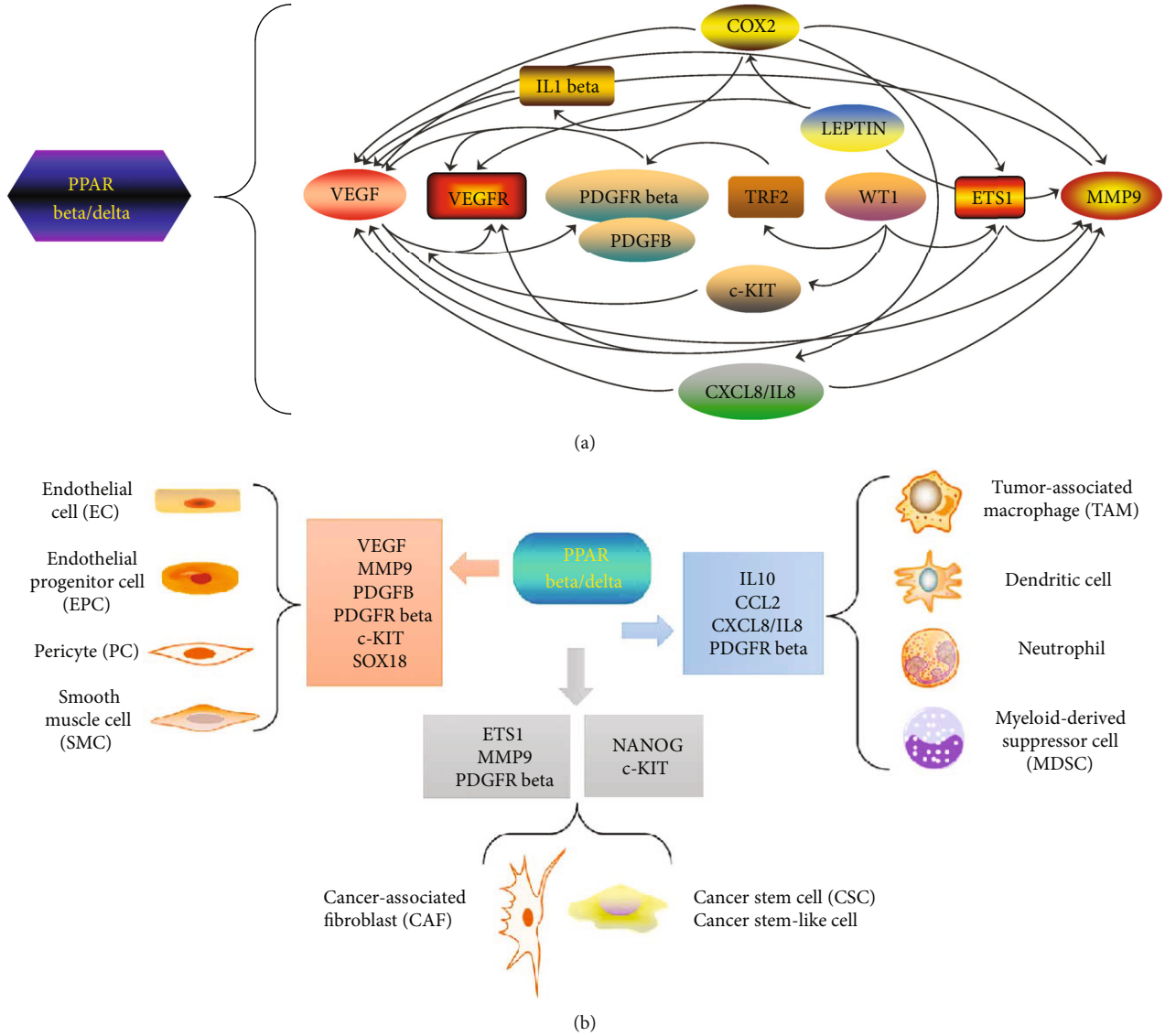


Figure 1: The "hallmark" role of PPAR beta/delta in tumor angiogenesis and progression. (a) Interplay between PPAR beta/delta and downstream key signal molecules. In the signal network of proangiogenic molecules, COX2 promotes the secretion of VEGF and MMPs including MMP9; COX2 infiltration also mediates IL1 beta-induced angiogenesis, which further activates VEGF; COX2 also contributes to cancer progression through the enhancement of the angiogenic chemokine CXCL8 (IL8) expression. IL8 drives VEGF activation and induces MMP9 expression. LEPTIN induces MMP9 expression, enhances COX2 activity, or transactivates VEGFR to facilitate angiogenesis. WT1 transactivates ETS1, TRF2, and c-KIT. ETS1 further upregulates the MMP9, VEGF, and VEGFR expression. In turn, VEGF is also a major inducer of ETS1. TRF2 transactivates PDGFR beta, and c-KIT may affect angiogenesis through the promotion of VEGF production. There exists a crosstalk between VEGF and MMP9 and between VEGF, VEGFR, and PDGFB and PDGFR beta. Oval shape: they represent those molecules that have been identified as direct target genes of PPAR beta/delta; rectangle shape: they represent those molecules that are significantly upregulated upon PPAR beta/delta overexpression. (b) Function of PPAR beta/delta at diverse cellular levels in TME. In TME, multiple distinct cells communicate and collaborate to enable tumor growth and progression. These cells include cancer cells, CSCs, ECs, EPCs, PCs, SMCs, CAFs, and tumor-infiltrating inflammatory cells. PPAR beta/delta can directly function on ECs and EPCs, or directly take action on them by regulating downstream signal molecules such as VEGF, MMP9, PDGFB, PDGFR beta, and SOX18. PDGFB and PDGFR beta regulate vascular permeability and maturation through the recruitment of PCs and SMCs. c-KIT also functions on ECs, c-KIT, and NANOG and may regulate the stemness to control cancer progression. ETS1 regulates MMP9 expression in CAFs; the crosstalk between CAFs and PDGFR beta also exists. PPAR beta/delta may act on tumor-infiltrating myeloid cells through the modulation of the IL10, IL8, CCL2, and PDGFR beta expression. As mentioned above, PPAR beta/delta stimulates cancer cell invasion and facilitates tumor angiogenesis in an IL10-dependent manner in tumor-infiltrating myeloid cells. IL8 can directly regulate angiogenesis via the recruitment of neutrophils. CCL2 is also a major regulator of recruitment of the myeloid monocytic cells such as MDSCs, TAMs, and dendritic cells. Also, PDGFR beta in stromal fibroblasts may mediate PDGFB-induced TAM recruitment. Among these molecules, SOX18, IL10, CCL2, and ETS1 are overexpressed upon PPAR beta/delta activation, and the others have been reported as direct targets of PPAR beta/delta.

Table 1: List of target genes of PPAR beta/delta.

| PPAR beta/delta target genes | Cellular biological function | References (for target genes) |
|---|---|---|
| Calcineurin A | Induction of cardiac vascularization, cardiac growth, and skeletal muscle remodeling [47, 48] | [15] |
| COX2 | An inflammatory angiogenic mediator and a key regulator of tumor angiogenesis [93, 122, 123] | [104] |
| VEGF | A key regulator of vasculogenesis and angiogenesis [74, 75, 76] | [105, 106] |
| MMP9 | A proinvasive matrix-degrading enzyme and a key regulator of tumor angiogenesis and metastasis [77, 78] | [69] |
| LEPTIN | Regulation of endothelial cell behavior and angiogenesis [79, 80, 81] | [107] |
| IL8 | A key angiogenic chemokine, a proinflammatory mediator, and a key regulator of tumor angiogenesis and progression [98, 111, 112, 114] | [18] |
| WT1 | An important regulator of tumor angiogenesis and progression [129] | [148] |
| NANOG | Regulation of self-renewal of cancer stem cells or cancer stem-like cells [149–151] | [149] |
| c-KIT | A potential marker of cancer stem-like cells [152]; promotion of tumor angiogenesis [155–158] and pathological ocular neovascularization [161] | [16] |
| PDGFB | A key regulator of angiogenesis and vasculogenesis [162–165] and vascular permeability and maturation [166–168] | [16] |
| PDGFR beta | A key regulator of angiogenesis and vasculogenesis [162–165], vascular permeability and maturation [166–168], and tumor progression [174, 175] | [16] |
| ANGPTL4 | Promotion of angiogenesis, tumor progression, and metastasis [178–182] | [183, 184] |
| PDK4 | Regulation of EMT and cell metabolism, and cancer progression [185–188] | [189] |
| FABP4 | Regulation of glucose and lipid metabolism; cell proliferation and apoptosis [190, 191] | [192] |
| CDKN1C | A prognostic factor for many types of cancer; regulation of angiogenesis and cancer hallmarks [193] | [17, 46] |
| SRC | Promotion of angiogenesis, cancer invasion, and tumor progression [194] | [194] |
| EDG2 | Enhancement of endothelial cell differentiation and vasculogenesis [195] | [195] |
| FOXO1 | Involvement of physiological, pathological, and developmental angiogenesis [196–198] | [199] |
| GLUT1 | Promotion of cancer cell metabolism and tumor growth [200, 201] | [202] |
| SLC1-A5 | Promotion of cancer cell metabolism and tumor progression [203, 204] | [202] |

PPRE-dependent transactivation mechanism. The peroxisome proliferator response element (PPRE) comprises a direct repeat (DR) of AGGTCA separated by one nucleotide (DR1) as AGGTCA (N) AGGTCA [177]. But currently, it was shown that only PPAR alpha binds to this sequence; whether ligand activation has an impact on PPARs binding to DNA response elements is still controversial [4]. A variety of genes have been identified as direct targets of PPAR beta/-delta and are known to be involved in various cellular biological processes such as fatty acid oxidation, cell survival, inflammation, angiogenesis, cancer cell metabolism, and tumor progression. Direct target genes of PPAR beta/delta identified to date already include Calcineurin A, COX2, VEGF, MMP9, LEPTIN, IL8, WT1, NANOG, c-KIT, PDGFB, PDGFRB, ANGPTL4, PDK4, FABP4, CDKN1C, SRC, EDG2, FOXO1, GLUT1, and SLC1-A5 (Table 1).

As mentioned above, most of these PPAR beta/delta target genes have been suggested to be involved in tumor angiogenesis and progression. ANGPTL4 is a well-known target gene of PPAR beta/delta [183, 184], and it promotes angiogenesis [178, 179], cancer cell invasion [180], and tumor progression and metastasis [181, 182]. Pyruvate dehydrogenase kinase 4 (PDK4) may promote cancer progression by regulating epithelial-mesenchymal transition (EMT) [185, 186] and cancer cell metabolism [186–188]. Fatty acid binding protein 4 (FABP4) may affect cell proliferation and apoptosis by regulating glucose and lipid metabolism [190, 191]. Both PDK4 and FABP4 are the established targets of PPAR beta/delta respectively [189, 192].

Cyclin-dependent kinase inhibitor 1C (CDKN1C) gene, which encodes the cell cycle inhibitor $p57^{KIP2}$, has been suggested to be involved in the regulation of several cancer hallmarks such as inducing angiogenesis, and it has been tested as a prognostic factor for various cancers [17, 193], as well as a target of PPAR beta/delta [17]. Oncogene SRC has been reported to be a direct PPAR beta/delta target, and its tyrosine kinase activity triggers the EGFR/ERK1/2 signal cascade, which promotes the development of ultraviolet radiation-induced skin cancer [194]. Endothelial differentiation gene 2 (EDG2) is also transactivated directly by PPAR beta/delta in late EPCs and leads to enhanced vasculogenesis [195]. Forkhead box protein O1 (FOXO1) is required for EC proliferation and vascular growth [196, 198], and directly regulates VEGFA expression during wound healing [197]. In addition to the physiological angiogenesis, FOXO1 is suggested to be involved in developmental and pathological angiogenesis

[198], which is also activated transcriptionally by PPAR beta/delta [199].

Finally, glucose transporter 1 (GLUT1/SLC2A1), as a member of the GLUT family, is widely expressed in many types of cancer cells and plays a key role in glucose uptake for cancer cell metabolism to enable tumor cell growth and proliferation [200, 201]. Neutral amino acid transporter B (SLC1-A5) is an important glutamine transporter in the regulation of essential amino acid influx [203]; and importantly, depletion of SLC1-A5 is demonstrated to abolish tumor progression [204]. Both GLUT1 and SLC1-A5 have been suggested to facilitate tumor progression and are transactivated directly by PPAR beta/delta [202].

For further information, PPARbeta/delta-related signaling pathways are covered by KEGG (Kyoto Encyclopedia of Genes and Genomes) (PATHWAY: map 03320), by the REACTOME pathway database (R-HSA-446176), and by the Protein-Protein Interaction Networks Functional Enrichment Analysis in STRING functional protein association network database (https://string-db.org/cgi/network.pl?taskId=OUdxEiHw19dW).

## 7. Conclusion

PPAR alpha and PPAR gamma seem to have an antiangiogenic role, but there are still conflicting observations. Unlike them, PPAR beta/delta exerts proangiogenic effects. Especially, there exists an intensive crosstalk between PPAR beta/delta and various signal molecules including the identified target genes, and also between those molecules. PPAR beta/delta plays a leading role in the network of interplay by directly and indirectly modulating the downstream proinflammatory or protumorigenic angiogenic molecules which further act on multiple different cell types in TME, thus indicating a potent "hallmark" role of PPAR beta/delta in tumor angiogenesis, cancer progression, and metastasis.

## Conflicts of Interest

The authors declare no conflict of interest.

## Authors' Contributions

S.D. conceived the idea. S.D., N.W., and K.-D.W. searched the literature and wrote the manuscript. S.D. performed the schematic visualization. Nicole Wagner and Kay-Dietrich Wagner contributed equally to this work.

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