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The role of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, an endogenous ligand of peroxisome proliferator-activated receptor γ, in tumor angiogenesis

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ABSTRACT

Peroxisome proliferator-activated receptor γ (PPARγ), a nuclear hormone receptor, is a ligand-activated transcription factor involved in adipogenesis, glucose homeostasis and lipid metabolism. 15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), an endogenous ligand of PPARγ, has multifaceted cellular functions. Angiogenesis plays an important role in the pathophysiology of ischemic and neoplastic disorders, especially cancer. 15d-PGJ_2 is involved in regulation of angiogenic mediators including vascular endothelial growth factor and hence participates in the blood vessel formation by means of angiogenesis. However, depending on the experimental conditions, this cyclopentenone prostaglandin can exert opposite effects on angiogenesis. 15d-PGJ_2 inhibits angiogenesis via suppression of pro-inflammatory enzymes and cytokines, while it also stimulates angiogenesis via induction of heme oxygenase-1, endothelial nitric-oxide synthase, and hypoxia inducible factor-1α. The aim of this review is to highlight such dual effects of 15d-PGJ_2 on angiogenesis and underlying molecular mechanisms.

1. Introduction

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that catalyze and coordinate distinct biochemical events required for maintaining lipid homeostasis, such as differentiation of adipocytes and regulation of lipoprotein metabolism [1]. They form heterodimers with the retinoid X receptor (RXR) and mediate transcriptional activation by binding to a specific DNA element termed the PPAR response element (PPRE) [2]. Binding of agonists within the ligand-binding site causes a conformational change which facilitates the recruitment of coactivators. By contrast, binding

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Abbreviations: AP-1, activator protein-1; CO, carbon monoxide; COX, cyclooxygenase; 15d-PGJ_2, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2; ERK, extracellular signal-regulated kinase; HIF, hypoxia inducible factor; HO-1, heme oxygenase-1; HRE, hypoxia response element; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NO, nitric oxide; PPARγ, peroxisome proliferator-activated receptor γ; PPRE, PPAR response elements; ROS/RNS, reactive oxygen/nitrogen species; RXR, receptor for 9 *cis*-retinoid; TGZ, troglitazone; TZD, thiazolidinedione; VEGF, vascular endothelial growth factor; ZnPP, zinc protoporphyrin; SnPP, tin protoporphyrin.

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of antagonists results in a conformation that favors interaction with corepressors [3]. The PPAR family consists of three different subtypes, namely PPARα, PPARγ, and PPARβ/δ. Among these isoforms, PPARγ has been known to be implicated in inflammation, immune response, and pathogenesis of some disorders including atherosclerosis, obesity, diabetes, Alzheimer's disease, cancer, etc. [1,4]. There are a variety of potential endogenous ligands for the PPARγ, including long-chain polyunsaturated fatty acids, arachidonic acid metabolites derived from the cycloxygenase and lipoxygenase pathways, and fatty acid derived components of oxidized low density lipoproteins (OxLDL) (e.g., 9-hydroxyoctadecadienoic acid and 13-hydroxyoctadecadienoic acid) [5]. The anti-diabetic thiazolidinedione (TZD) class of drugs including troglitazone (TGZ), rosiglitazone (BRL49653), pioglitazone and ciglitazone are synthetic ligands of PPARγ. Other synthetic compounds that can function as ligands include certain non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, ibuprofen, flufenamic acid and fenoprofen. In addition, non-thiazolidinedione derivatives, such as 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), CDDO-imidazolide (CDDO-Im), GW-7845, JTT-501, KPR-297, KPR-297, L-764406, MCC-555, GW-0072 and GW-0207 are also synthetic ligands of PPARγ [5]. Besides these synthetic ligands, there are some endogenous ligands for PPARγ. Among these, the cyclopentenone prostaglandin 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2; Fig. 1) was found to be the most potent [6,7]. 15d-PGJ_2 up-regulates the expression, transcriptional activity, and DNA binding activity of PPARγ, and many of the cellular events mediated by 15d-PGJ_2 have been shown to be PPARγ-dependent (reviewed in Ref. [8]).

Angiogenesis is the process of new vessel formation from preexisting capillaries. Physiological angiogenesis in adults is necessary during the female reproductive cycle [9], wound healing [10], hair growth [11], and bone formation [12]. However, dysregulated angiogenesis can cause many abnormal disorders such as cancer, obesity, arthritis, blindness and so on (Fig. 2) (reviewed in Refs. [13,14] and see references therein). Angiogenesis has been reported to be regulated by numerous angiogenic factors and mediators. As a prime mediator of angiogenesis, vascular endothelial growth factor (VEGF) induces angiogenesis in ischemic or inflamed tissues, wound healing, rheumatoid arthritis or diabetic retinopathy as well as during carcinogenesis (reviewed in Ref. [15]). It is well documented that some PPARγ ligands modulate angiogenesis. Interestingly, 15d-PGJ_2, a naturally occurring PPARγ ligand, is reported to have both angiogenesis-promoting and anti-angiogenic effects in a variety of cell types. Table 1 summarizes the mechanisms by which 15d-PGJ_2 modulates angiogenic processes.

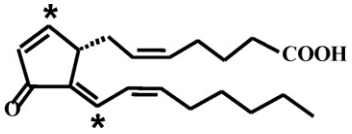

Fig. 1 – The chemical structure of 15d-PGJ_2. Asterisks (*) indicate the positions of electrophilic carbon atoms.

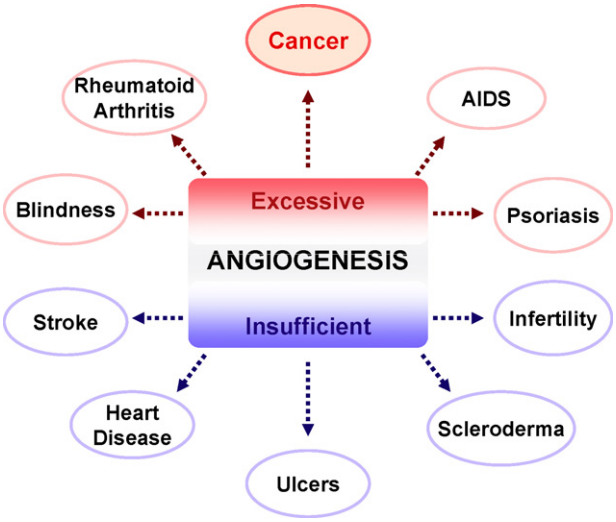

Fig. 2 – Schematic representation of human disorders characterized by abnormal angiogenesis.

2. Inhibition of angiogenesis by 15d-PGJ_2

15d-PGJ_2 as an endogenous ligand of PPARγ has been known to display several unique characteristics associated with carcinogenesis [16,17]. On the other hand, however, 15d-PGJ_2 induces growth inhibition, apoptosis, and terminal differentiation of several types of cancerous and transformed cells. The anti-proliferative effects of 15d-PGJ_2 are associated with *de novo* synthesis of proteins involved in regulating the cell cycle and cell survival/death. Anti-inflammatory effects of 15d-PGJ_2 are mainly attributable to interruption of nuclear factor-κB (NF-κB) signaling and subsequent blockade of pro-inflammatory gene expression [18,19].

The anti-tumerigenic effects of 15d-PGJ_2 are also manifested by its inhibition of invasiveness and angiogenesis [20–25]. 15d-PGJ_2 significantly inhibited the invasiveness of human breast and pancreatic cancer cells [22,26]. 15d-PGJ_2 reduced the protein levels and activity of matrix metalloproteinase (MMP)-2 and MMP-9, thereby abrogating the invasiveness of pancreatic cancer cells [21]. Moreover, 15d-PGJ_2 has been reported to have inhibitory effects on the proliferation and invasiveness of colon cancer cell lines which are associated with G1 cell cycle arrest and down-regulation of MMP-7 synthesis, respectively [27]. In addition, 15d-PGJ_2 suppressed the production of angiogenic factors, such as angiopoietin-1 and basic fibroblast growth factor (bFGF) in gastric cancer (MKN45) [28] and renal cell carcinoma (RCC) [24] cells, respectively. 15d-PGJ_2 also diminished the production of VEGF in RCC cells [24] and reduced the mRNA levels of VEGF receptor 1 (Flt-1) and 2 (Flk/KDR) in human umbilical vascular endothelial cells (HUVEC) [20,25]. In bladder tumor xenografts, 15d-PGJ_2 synergistically potentiated anti-tumor effects of the anti-angiogenic thrombospondin-1 peptide derivative ABT510 via targeted up-regulation of the endothelial receptor [23]. The induction of cell growth inhibition and apoptosis, and suppression of invasiveness and angiogenesis in various cancer cells by 15d-PGJ_2 suggest this cyclopentenone prostaglandin as a potential target in anti-cancer therapy.

Table 1 – Regulation of angiogenesis by 15d-PGJ_2

	Cell types	References
Angiogenesis inhibition		
↓ VEGF receptor 1 (Flt-1) and 2(Flk/KDR)	Human umbilical vein endothelial cells	[20,25]
↑ CD36, a receptor of antiangiogenic thrombospondin-1	Human microvascular endothelial cells	[23]
↓ bFGF	Renal cell carcinoma	[24]
↓ VEGF	Renal cell carcinoma	[24]
↓ Angiopoietin-1	Gastric cancer (MKN45)	[28]
Angiogenesis induction		
↑ VEGF	Vascular smooth muscle cells	[45,48]
	Human histiocytic lymphoma	[46]
	Human androgen-independent PC 3 prostate carcinoma	[47]
	5637 urinary bladder carcinoma	[47]
	Human monocytic leukemia	[50]
	Human coronary artery endothelial cells	[50]
	Human microvascular endothelial cells	[49]
	Macrophages	[48]
	Human breast cancer (MCF-7)	[69]
	Human microvascular endothelial cells	[106]
↑ VEGF receptor 1 (Flt-1) and 2(Flk/KDR)	Myofibroblasts	[51]
↑ HGF	Human and rat mesangial cells	[52]
↑ HO-1	Human microvascular endothelial cells	[49]
	Human breast cancer (MCF-7)	[69]
↑ CO	Human microvascular endothelial cells	[86]
↑ NO	Human umbilical vein endothelial cells	[97–99]
↑ Stabilization, nuclear accumulation and activiation of HIF-1α	Human proximal tubular cells HK-2	[107]

15d-PGJ_2 down-regulates inducible nitric oxide synthase (iNOS) [18,29,30] and cyclooxygenase-2 (COX-2) [31–33], which are typical pro-inflammatory enzymes. It has been reported that both COX-2 and iNOS are overexpressed in a variety of human malignant tumors which is associated with altered expression of important modulators of angiogenesis [34]. The expression of COX-2 and iNOS is regulated by transcription factors, especially NF-κB. Recently, several studies have demonstrated that 15d-PGJ_2 can act as a negative modulator of pro-inflammatory signaling by blocking the NF-κB activation pathway at multiple levels via covalent modification of NF-κB or its regulators [8]. Therefore, anti-angiogenic effects of 15d-PGJ_2 might be associated with disruption of NF-κB and subsequent blockade of inflammatory gene expression [18,19]. Another possibility of angiogenesis inhibition by 15d-PGJ_2 may involve down-regulation of pro-inflammatory mediators. 15d-PGJ_2 inhibited the production and secretion of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, in 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-treated monocytes [35] and IL-10 and IL-12 in lipopolysaccharide (LPS)-treated macrophages [36]. Pro-inflammatory cytokines, such as IL-1 and TNF-α, are known to be major pro-angiogenic stimuli of both physiological and pathological angiogenesis. Certain cytokines (e.g., IL-6 and CSF-1) can influence the phenotype and the function of tumor-associated macrophages and indirectly boost tumor invasiveness and angiogenesis [37]. Tumor-associated macrophages play an important role in tumor progression because they produce several angiogenic factors, such as VEGF, IL-8, inflammatory cytokines (IL-1 and IL-10) and proteases (MMP-2 and MMP-9) [37]. 15d-PGJ_2 inhibits angiogenesis through suppression of such pro-inflammatory cytokines. Induction of iNOS and COX-2 expression is mainly regulated by catabolic cytokines, such as IL-β and TNF-α. Besides iNOS and COX-2, induction of various pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-8, is transcriptionally regulated by NF-κB [38]. It is currently unclear whether 15d-PGJ_2 exerts an anti-angiogenic effect via blockade of NF-κB-driven induction of pro-inflammatory mediators or through down-regulation of cancer cell-derived pro-inflammatory cytokine release which is NF-κB independent. Hence, further investigations are necessary to unravel the signaling pathways that delineate the anti-angiogenic effects of 15d-PGJ_2.

3. Induction of angiogenesis by 15d-PGJ_2

Although the majority of the published studies imply the inhibitory effects of 15d-PGJ_2 on angiogenesis, there are some reports describing the opposite effect of 15d-PGJ_2 on the development of blood vessels formation. Thus, 15d-PGJ_2 given topically together with 7,12-dimethylbenz[*a*]anthracene (DMBA) significantly enhanced the rate of formation, the size and vascularization of the papillomas in the DMBA-initiated and TPA-promoted mouse skin carcinogenesis model [39]. Moreover, skin sections from mice treated with DMBA and 15d-PGJ_2 exhibited a markedly elevated VEGF expression as well as a reduced proportion of apoptotic cells [39]. Chinery et al. [40] showed that PGJ_2 and 15d-PGJ_2 induced the proliferation of COX-2-depleted colorectal cancer (HCA-7) cells at a nanomolar concentration. 15d-PGJ_2 elicited cytoprotective effects against pro-apoptotic agents such as BAY11-7085 (NF-κB inhibitor) and the peroxynitrite donor, 3-morpholinosydnonimine hydrochloride (SIN-1) [41,42]. Recently, Kim et al. [43] reported the positive feedback regulation by 15d-PGJ_2 of COX-2 expression in human breast cancer cells. Other studies also demonstrated the similar effect of 15d-PGJ_2 on COX-2 production [32,44]. COX-2 has been shown to contribute

to carcinogenesis by promoting cell proliferation and angiogenesis as well as by protecting premalignant or cancerous cells from apoptosis. Since abnormal overexpression of COX-2 is implicated in the pathogenesis of various human malignancies, it can be speculated that increased 15d-PGJ_2 synthesis as a consequence of COX-2 overexpression can facilitate angiogenesis.

15d-PGJ_2 has been reported to induce angiogenesis in various cell lines. Thus, 15d-PGJ_2 was found to stimulate the expression of VEGF in endothelial cells, human histiocytic lymphoma U937 cells, human androgen-independent PC3 prostate cancer cells and the 5637 urinary bladder carcinoma cell line [45–47]. Yamakawa et al. [45] have examined the VEGF secretion from vascular smooth muscle cells (VSMC) treated with different PPARγ ligands, including 15d-PGJ_2, TGZ, pioglitazone, LY171883, bezafibrate and Wy14643. TGZ, pioglitazone, LY171883 and 15d-PGJ_2 increased VEGF mRNA levels and protein secretion in the culture medium in a time- and dose-dependent manner, while bezafibrate and Wy14643 had no such effect. In rat VSMC, 15d-PGJ_2 significantly increased the expression of VEGF mRNA and protein in both the resting state and in IL-1β-stimulated cultures [48]. Similar effects of 15d-PGJ_2 were also observed in either resting or LPS-stimulated murine macrophages (RAW264.7) [48]. The up-regulation of VEGF by 15d-PGJ_2 was accompanied by activation of PPARγ [49]. The involvement of PPARγ activation in the up-regulation of VEGF synthesis was also suggested in the human macrophages [46]. The mRNA expression of VEGF was augmented not only by 15d-PGJ_2 but also the synthetic PPARγ activator TGZ in VSMC, human monocytes/macrophages, human acute monocytic leukemia (THP-1) cells and human coronary artery endothelial cells (HCAECs) [45,50]. Incubation of VSMC and RAW264.7 with ciglitazone also significantly enhanced the release of VEGF protein into the media, both in resting and in IL-1β- or LPS-stimulated cultures [48]. More recently, 15d-PGJ_2 and TGZ have been reported to increase the expression of VEGF and its receptors (Flt-1 and KDR) in myofibroblasts [51]. In addition, 15d-PGJ_2, TGZ and ciglitazone induced secretion as well as mRNA expression of hepatocyte growth factor (HGF), capable of promoting angiogenesis [52]. The following sections address the plausible mechanisms responsible for modulation of angiogenesis by 15d-PGJ_2.

4. The potential mechanisms of angiogenesis regulation by 15d-PGJ_2

4.1. *Heme oxygenase-1 (HO-1)*

Heme oxygenase (HO) catalyzes the conversion of heme to carbon monoxide (CO) and bilirubin with a concurrent release of iron. Two HO isoforms, HO-1 and HO-2, are encoded by different genes. HO-1 is barely expressed under basal conditions and can be induced by oxidative stress-causing agents such as UV, heavy metals, LPS and reactive oxygen/nitrogen species (ROS/RNS) [53,54]. HO-2 is constitutively expressed in most tissues, and its levels are relatively unaffected by factors inducing HO-1 [53,55]. HO-1 expression is mainly mediated via antioxidant response elements (ARE) present in the promoter regions of many antioxidant or detoxifying enzymes, which are under the control of NF-E2 related factor 2 (Nrf2) [56]. The biological functions of HO-1 are believed to be associated with a fundamental adaptive and defensive response to oxidative stress and other cellular injuries [57]. Inhibitors of HO-1 including zinc protoporphyrin (ZnPP) and tin protoporphyrin-IX (SnPPIX) often exacerbate some experimentally induced pathogenesis, such as graft rejection [58] and ischemia-reperfusion injury [59]. In contrast, pharmacological HO-1 inducers and selective over-expression of HO-1 by genetic manipulation confer cytoprotective or health beneficial effects [57]. However, several reports also demonstrate that HO-1 participates in the pathogenesis and progression of certain types of malignancies. HO-1 is extensively expressed in various tumor cells including melanoma [60], renal adenocarcinoma [61], lymphosarcoma [62], benign prostatic hyperplasia and prostate cancer [63], and acute hepatitis and hepatoma [64]. In addition, administration of the HO-1 inhibitor ZnPP significantly suppressed the growth of Sarcoma 180 tumors implanted in the dorsal skin of ddY mice [65]. Up-regulation of HO-1 has been shown to contribute to the angiogenesis of pancreatic carcinoma [66] and resistance to apoptotic stimuli in gastric cancer cells [67]. Furthermore, HO-1 overexpression increased viability, proliferation, and angiogenic potential of melanoma cells and augmented metastasis in the tumor-bearing mice [60]. Induction of HO-1 is hence likely to be associated with carcinogenesis under certain conditions. Fang et al. [57] have proposed that the anti-apoptotic action of HO-1 in cancerous cells is mostly attributable to its heme degradation products.

Relatively high levels of HO-1 observed in various tumors may play a role in stimulating cancer cell growth because of its anti-oxidative and anti-apoptotic effects (reviewed in Ref. [57]). Induction of HO-1 expression is also associated with VEGF expression (reviewed in Ref. [68]). HO-1 protects endothelial cells from apoptosis, is involved in blood vessel relaxation regulating vascular tone, attenuates inflammatory response in vessel wall and participates in the blood vessel formation by means of angiogenesis and vasculogenesis. Interestingly, the afore-mentioned angiogenic activity of 15d-PGJ_2 has been proposed to be dependent on HO-1 activity. The up-regulation of VEGF by 15d-PGJ_2 was accompanied by increased HO-1 promoter activity [49]. The induction of HO-1 expression preceded the up-regulation of VEGF in MCF-7 cells stimulated with 15d-PGJ_2 [69]. It is well known that 15d-PGJ_2 is a potent inducer of the expression and activity of HO-1 in several cell types [49,70–73]. HO-1 has been shown to be a link between 15d-PGJ_2 and VEGF, since 15d-PGJ_2-stimulated VEGF synthesis was inhibited by SnPPIX, an inhibitor of HO-1 [49]. The role of HO-1 in the up-regulation of VEGF expression was corroborated by results of experiments utilizing HO-1 gene transfer in VSMC and microvascular endothelial cells [49,74].

As 15d-PGJ_2 is an endogenous ligand of PPARγ while capable of inducing HO-1, it can be speculated that the PPARγ activation is associated with induction of HO-1. It has been reported that activation of PPARγ up-regulates HO-1 expression [75–78]. NS-398, a COX-2 inhibitor, increased both PPARγ luciferase reporter gene activity and HO-1 expression, suggesting that induction of HO-1 by NS-398 may be mediated through activation of PPARγ [75]. Similarly, PPARγ knock down abolished expression of COX-2 and HO-1 protein induced by

NO, which was mimicked by use of T0070907, a PPARγ inhibitor [76]. Several studies have indicated that HO-1 is a direct target gene product whose expression is under the control of PPAR via PPREs. The HO-1 promoter contains at least one PPRE motif, located at −623 bp relative to the transcription start site, which is transcriptionally activated by PPARγ agonists [79]. Kronke et al. have demonstrated that the ARE-containing enhancer region of the human HO-1 promoter was dispensable for the PPAR-induced transcriptional regulation of the HO-1 promoter, because the 3.8-kb and 2.2-kb HO-1 promoter constructs, which lack this enhancer but include the PPREs, were still PPAR-responsive [77]. Mutation of the AREs did not affect PPAR-induced HO-1 promoter activity, which implies that expression of HO-1 is directly regulated by PPAR. Moreover, adenoviral transfer of cyclooxygenase-1 (Adv-COX-1) gene increased the level of 15d-PGJ_2 in ischemic brain accompanied by reduced infarct volume, and enhanced expression of HO-1 and PPARγ [78]. In this study, 15d-PGJ_2 and rosiglitazone inhibited neuronal apoptosis and necrosis via induction of HO-1 in a PPARγ-dependent manner [78]. Likewise, another synthetic PPAR ligand TZDs can also induce HO-1 mRNA expression and prevent neuronal damage after spinal cord injury [75]. Therefore, up-regulation of HO-1 by 15d-PGJ_2 is one of the possible mechanisms by which 15d-PGJ_2 enhances carcinogenesis through angiogenesis as well as confers survival advantage in existing cancer cells. Moreover, 15d-PGJ_2-induced transcription of glutathione S-transferase involves synergistic activation of Nrf2 and PPARγ [80]. In contrast, 15d-PGJ_2, has also been shown to induce HO-1 expression via AREs in an PPARγ-independent manner [69,71,81–85].

4.2. *Carbon monoxide (CO), the end product of HO-1*

A recent study by Kim et al. postulated the possible involvement of HO-1 in angiogenesis induced by 15d-PGJ_2 [69]. 15d-PGJ_2 activates ERK1/2 signaling and subsequently induces VEGF expression via up-regulation of HO-1 in human breast cancer MCF-7 cells. Inhibition of ERK1/2 diminished the 15d-PGJ_2-induced expression of VEGF, whereas it barely affected HO-1 induction by 15d-PGJ_2. Treatment of MCF-7 cells with the HO-1 inhibitor ZnPP reduced 15d-PGJ_2-induced phosphorylation of ERK. These findings indicate that phosphorylation of ERK1/2 by 15d-PGJ_2 is downstream of HO-1 expression [69]. Among the different end-products of HO-1 activity, CO was proposed to be involved in angiogenesis induction. CO plays a key role in the induction of VEGF [86] and stromal cell-derived factor 1 by HO-1 activity in endothelial cells [87]. CO stimulates endothelial cell proliferation [86,88], suppresses their apoptosis [89,90], and induces VEGF synthesis in VSMC, macrophages and microvascular endothelial cells [49,74]. In endothelial cells, addition of CO-releasing molecule (CORM) or induction of HO-1 by hemin resulted in not only an elevation in CO production but also an increase in VEGF synthesis and capillary sprouting [49,74]. Interestingly, much higher levels of CO and a further increase in VEGF production were achieved in cells treated with 15d-PGJ_2, a potent inducer of HO-1 [86]. In contrast, inhibition of HO-1 activity with SnPPIX prevented the induction of CO generation and reduced the VEGF synthesis [86]. Therefore, it is likely that CO generated via induction of HO-1 by 15d-PGJ_2 stimulates the production of VEGF. Recently, Bilban et al. have reported that CO alone induces the generation of mitochondrial ROS which, in turn, play a role as signaling molecules in activating PPARγ, and that PPARγ activation accounts for the anti-inflammatory effects of CO [91].

4.3. *Nitric oxide (NO)*

NO has a key role in promoting angiogenesis by increasing vasodilation, vascular permeability, endothelial cell proliferation and migration, and also by modifying the activities of angiogenic mediators. NO is a highly diffusive hydrophobic gas and is a key signaling molecule in inflammation-driven diseases, including cancer [92]. NO is produced by a group of enzymes called nitric-oxide synthases (NOS): neuronal NOS, endothelial NOS (eNOS), inducible NOS (iNOS), and more recently, mitochondrial NOS [93]. iNOS is known to regulate VEGF expression, and thereby tumor angiogenesis. Targeting iNOS for cancer prevention and treatment has been extensively investigated, with conflicting or paradoxical outcomes due to variability in NO production, heterogeneity in NO chemistry and biology and differential cellular responses as well as cellular adaptation/selection in the cytotoxic action of NO [94].

Multiple clinical observational studies have revealed a dysregulation of eNOS expression in vascular cells of tumors. Genetic comparison studies with healthy people and cancer patients have shown that polymorphisms in *eNOS* are associated with the development of multiple cancers [95,96]. NO produced by eNOS can be modulated by cellular redox status. Interestingly, it has been reported that 15d-PGJ_2 increased cultured endothelial cell NO release without increasing the expression of eNOS in porcine pulmonary artery endothelial cells and HUVEC [97]. Hwang et al. have reported that PPARγ ligands including 15d-PGJ_2 increase NO release which alters the vascular endothelial function through regulation of redox stage [98]. This study suggests that PPARγ ligands coordinately regulate the balance between $^{\bullet}NO$ and $O_2^{\bullet-}$ production in vascular endothelial cells, and that PPARγ ligands might directly activate a program of gene expression in vascular endothelial cells, resulting in increased NO bioavailability. The enhanced NO bioavailability may ameliorate endothelial dysfunction and vascular diseases. In addition, 15d-PGJ_2, ciglitazone, and rosiglitazone increased NO production via distinct signaling pathways that are PPARγ-dependent in HUVEC [99]. These results provide further evidence that PPARγ ligands have the ability to directly modify vascular endothelial function and to modulate the production of NO.

4.4. *HIF-1*

Analysis of the VEGF promoter region revealed the presence of several potential binding sites for transcription factors including AP-1/2, SP-1, and hypoxia inducible factor (HIF)-1 [100]. As a key transcription factor responsible for hypoxia-induced generation of VEGF [101], HIF-1 is induced in hypoxic cells and bound to the hypoxia response element (HRE). HIF-1 is known to mediate the transcriptional activation of several genes that promote angiogenesis, a response at the systemic level to increase oxygen supply to the hypoxic region. HIF-1 is a

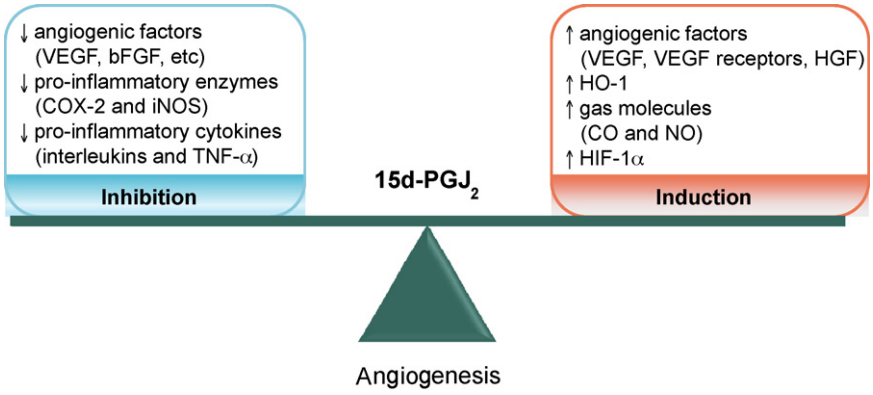

Fig. 3 – Bifunctional roles of 15d-PGJ$_2$ in angiogenesis. 15d-PGJ$_2$ has been suggested to exert an anti-angiogenic effect by suppressing pro-angiogenic mediators, such as angiopoietin-1, bFGF, VEGF, and VEGF receptors. However, 15d-PGJ$_2$ can also induce angiogenesis through up-regulation of angiogenic factors, induction of HO-1, release of CO or NO, and/or activation of HIF-1α which are either PPARγ-dependent or -independent.

heterodimeric transcription factor composed of HIF-1α and HIF-1β subunits. In mammals, three genes have been shown to encode HIF-1α subunits that appear to be regulated in a similar manner (reviewed in Ref. [102]). Interestingly, a few recent studies reported the link between hypoxia and regulation of PPARγ [103–105]. Li et al. reported that hypoxia-activated signals other than the HIF-1 pathway might be partly associated with the reduced PPARγ expression in confluent human proximal renal tubular epithelial cells [103]. On the contrary, the administration of PPARγ agonists or adenovirus carrying PPARγ cDNA resulted in a significant reduction of the nuclear HIF-1α level as well as expression of VEGF [104]. In addition, it has been reported that hypoxia and overexpressing HIF-1α induce expression of VEGF and PPARγ angiopoietin related gene (PGAR) which is a target gene of PPARγ and potential modulator of angiogenesis in cardiomyocytes [105]. These results suggest that hypoxia-induced up-regulation of PGAR expression is mediated by HIF-1α.

On the other hand, 15d-PGJ$_2$ has been demonstrated to inhibit HIF-1α activity in both normoxia and hypoxia [106]. The effect of 15d-PGJ$_2$ on HIF-1α activity seems to be attributed to the electrophilic interaction of an α,β-unsaturated carbonyl moiety present in this cyclopentenone prostaglandin with thiol groups of HIF-1α. It has been suggested that 15d-PGJ$_2$ regulates HIF-1α transcriptional activity either by covalent modifying or indirectly oxidizing the critical sulfhydryl group [8]. A recent paper has shown that the electrophilic activity residing in the cyclopentenone structure of 15d-PGJ$_2$ is likely to be responsible for the induction of HIF-1α accumulation through modification of thiols in cellular proteins or GSH [107]. Although the evidence for the role of 15d-PGJ$_2$ in the activation of HIF-1α is insufficient, HIF-1α appears to be one of most plausible signaling molecules which may link 15d-PGJ$_2$ or PPARγ activation to the stimulation of angiogenesis.

5. Conclusion

PPARγ has been known to be implicated in inflammation, immune response, and pathogenesis of some disorders including atherosclerosis, obesity, diabetes, Alzheimer's disease, cancer, etc. Recent data confirm that the PPARγ pathway may be a therapeutic target for cancer and several other disorders, in which excessive angiogenesis is implicated. Some PPARγ ligands inhibit angiogenesis through their action on the endothelium. In particular, 15d-PGJ$_2$ has been shown to display an anti-tumorigenic effect by inhibiting tumor angiogenesis via different molecular mechanisms. However, 15d-PGJ$_2$ can also exhibit pro-angiogenic activity through up-regulation of HGF, VEGF and Flt-1 (VEGF receptor-1) and Flk/KDR (VEGF receptor-2). The induction of angiogenesis by 15d-PGJ$_2$ has been suggested to be mediated through up-regulation of HO-1 expression, release of CO and NO, and/or activation of HIF-1α in a PPARγ-dependent or -independent fashion (Fig. 3). Therefore, continuing efforts will be necessary to better understand the dual functions of 15d-PGJ$_2$ on tumor angiogenesis.

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