

Review Article

Anticancer Role of PPAR γ Agonists in Hematological Malignancies Found in the Vasculature, Marrow, and Eyes

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The use of targeted cancer therapies in combination with conventional chemotherapeutic agents and/or radiation treatment has increased overall survival of cancer patients. However, longer survival is accompanied by increased incidence of comorbidities due, in part, to drug side effects and toxicities. It is well accepted that inflammation and tumorigenesis are linked. Because peroxisome proliferator-activated receptor (PPAR)- γ agonists are potent mediators of anti-inflammatory responses, it was a logical extension to examine the role of PPAR γ agonists in the treatment and prevention of cancer. This paper has two objectives: first to highlight the potential uses for PPAR γ agonists in anticancer therapy with special emphasis on their role when used as adjuvant or combined therapy in the treatment of hematological malignancies found in the vasculature, marrow, and eyes, and second, to review the potential role PPAR γ and/or its ligands may have in modulating cancer-associated angiogenesis and tumor-stromal microenvironment crosstalk in bone marrow.

1. Introduction

Peroxisome proliferator activated receptors (PPARs) are a subfamily of the larger nuclear hormone receptor superfamily of transcription factors [1, 2]. Three distinct but closely related isoforms designated PPAR α , PPAR β/δ , and PPAR γ make up the family. PPAR γ functions are further delineated by two isoforms PPAR γ 1 and PPAR γ 2, which arise due to alternative promoter usage accompanied by alternative splicing and/or polyadenylation of the primary transcript (recently reviewed in [3]). PPARs are best known for their roles in lipid homeostasis and energy metabolism including cholesterol and triglyceride turnover [4], obesity [5], metabolic syndrome [6–9], and diabetes [5, 10, 11];

however, since their discovery, the PPARs and/or PPAR agonists have been implicated in a broader spectrum of biological processes playing protective and homeostatic roles such as promoting wound healing [12, 13] and, for the most part, countering the effects of aging [14], cardiovascular disease [15, 16], inflammation and immune responses [17–19], thrombosis and hemostasis [7, 8, 17–21], pathological angiogenesis [22–32], and cancer [24, 25, 31–41].

A number of naturally occurring ligands activate PPAR γ (Table 1), such as unsaturated fatty acids and eicosanoids [42], 15-deoxy- Δ -12-14-prostaglandin J₂ (15d-PGJ₂), and components of oxidized low density lipoproteins (LDLs) [43]. The affinity of PPAR γ for many of the endogenous ligands is low and, in some cases the physiological relevance

TABLE 1: PPAR- γ ligands.

Natural ligands	Ref.
lysophosphatidic acid	[349]
nitrolinoleic acid	[350]
9-hydroxyoctadecadienoic acid	[351, 352]
13-hydroxyoctadecadienoic acid	[351, 352]
15-hydroxyeicosatetraenoic acid	[353]
prostaglandin D2	[351, 353–357]
15-deoxy- Δ 12,14-prostaglandin J ₂ (15d-PGJ ₂)	[351, 353–357]
Synthetic Ligands	Ref
Thiazolidinedione family (TZDs)	[18, 44, 313, 353, 354, 358, 359]
ciglitazone	
pioglitazone	
rosiglitazone	
troglitazone	
TZD 18	
Nonsteroidal anti-inflammatory drugs	[353, 360, 361]
indomethacin	
ibuprofen	
flufenamic acid	
fenoprofen	
L-tyrosine-based	[351, 352]
GW-7845	
GW-1929	
diindolylmethane analogs	[351, 362]
triterpenoid 2-cyano-3,12-dioxoleana-1,9-dien-28-oic acid (CDDO)	[46, 351]
CDDO C-28 methyl ester derivative (CDDO-Me)	[214, 363, 364]
CDDO C-28 imidazole (CDDO-Im)	[50]
1,1-bis[3'-(5-methoxyindolyl)]-1-(<i>p-t</i> -butylphenyl) methane (DIM #34),	[365]

of the ligand needs to be determined. However, it is well accepted that 15d-PGJ₂ is the most potent endogenous ligand for PPAR γ . The thiazolidinediones (TZDs) are a class of synthetic ligands with high affinity for PPAR γ that are used for their antidiabetic effects to sensitize cells to insulin [44]. Nonsteroidal anti-inflammatory drugs such as ibuprofen and indomethacin are low affinity PPAR γ ligands [45]. Furthermore, the synthetic triterpenoid, 2-cyano-3,12-dioxoleana-1,9-dien-28-oic acid (CDDO), and derivatives are high affinity ligands for PPAR γ [46] (Table 1).

Two overarching principles should be kept in mind when weighing the plethora of therapeutic benefits touted for PPAR γ agonists. First, PPAR γ agonists evoke both PPAR γ -dependent and PPAR γ -independent effects, thus therapeutic benefits ascribed to certain PPAR γ ligands do not necessarily require interaction with the PPAR γ ligand binding domain. Although PPAR γ -independent effects induced by 15d-PGJ₂ and CDDO are due in part to the electrophilic nature of these ligands [47–50], PPAR γ -independent effects induced

by TZDs are through a number of signaling pathways including inhibition of Bcl-2/Bcl-xL function, proteasomal degradation of cell cycle- and apoptosis-regulatory proteins, and transcriptional repression [51]. Second, PPAR γ agonists have been shown to have paradoxical physiological effects, likely due to tissue-specific and/or context-dependent regulatory signaling events.

Recently, we reviewed the role of PPAR γ and its ligands in the treatment of hematological malignancies, which is summarized in Tables 1 and 2 [3]. The purpose of this paper is twofold: first to highlight the potential uses for PPAR γ agonists in anticancer therapy with special emphasis on their role when used as adjuvant or combined therapy in the treatment of hematological malignancies, and second, to review the potential role PPAR γ and PPAR γ ligands may have in modulating cancer-associated angiogenesis and tumor-stromal microenvironment crosstalk in bone marrow—two pathophysiological events associated with most all types of cancer including hematological malignancies.

TABLE 2: PPAR γ and PPAR γ ligands as potential therapy for hematological malignancies.

Hematological malignancy/cell line	PPAR γ agonist	Comments	Ref
HL-60	troglitazone	Inhibited cell proliferation by G1 arrest; induced differentiation to monocytes	[366]
HL-60	15d-PGJ ₂ , troglitazone	Inhibited cell proliferation; induced caspase-dependent apoptosis	[367]
HL-60, K562	15d-PGJ ₂ , troglitazone	Induced apoptosis through Bax/Bcl-2 regulation	[368]
Mono Mac 6, U937	15d-PGJ ₂ , troglitazone	Induced apoptosis; downregulated cyclooxygenase-2	[369]
HL-60	15d-PGJ ₂	PPAR γ -independent TRAIL-induced apoptosis	[370]
Jurkat, PC3	15d-PGJ ₂	PPAR γ -independent TRAIL-induced apoptosis	[371]
EoL-1, U937, KPb-M15	troglitazone	Inhibited cell proliferation by G0/G1 arrest	[372]
HL-60, K562	15d-PGJ ₂ , troglitazone	Inhibited cell growth, adhesion, and invasion through Matrigel; inhibited MMP-2 and MMP-9 expression	[230]
AML	DIM #34	Inhibited cell growth; induced apoptosis through PPAR γ -dependent and independent mechanism	[365]
HL-60, U937, AML, CLL	rosiglitazone, 15d-PGJ ₂ , CDDO	Inhibited cell growth, induced differentiation, induced apoptosis when combined with RXR-selective ligands	[373]
HL-60	Thiazolidinedione	Inhibited cell proliferation by G0/G1 arrest; induced apoptosis; induced differentiation	[374]
U937	troglitazone	Inhibited cell proliferation by G1 arrest	[375]
NB4	15d-PGJ ₂ , pioglitazone	Inhibited cell proliferation; induced differentiation and lipogenesis when combined with specific RXR ligands	[376]
HL-60, AML	CDDO-Me	Induced cell differentiation; induced apoptosis	[214, 363, 364]
HL-60	CDDO	Induced apoptosis; induced differentiation and increased phagocytosis at sub-apoptotic doses	[377]
APL, NB4, MR2	CDDO	Enhanced all- <i>trans</i> -retinoic acid-induced differentiation and apoptosis	[378]
AML	CDDO	Induced apoptosis in a caspase-dependent and independent manner	[379]
U937	CDDO-Im	Inhibited cell proliferation; induced differentiation through PPAR γ -independent mechanism	[50]
U937	CDDO, CDDO-Me, CDDO-Im	Induced apoptosis by increasing reactive oxygen species and decreasing intracellular glutathione	[380]
THP-1	rosiglitazone	Inhibited 9- <i>cis</i> retinoic acid-induced cell growth	[381]
THP-1	troglitazone, rosiglitazone	Inhibited MCP-1-induced migration	[382]
K562, KU812, KCL22, BV173, SD1, SupB-15	TZD18	Inhibited cell growth through a PPAR γ -independent mechanism; inhibited proliferation; induced apoptosis	[359, 383]
K562	troglitazone, pioglitazone	Inhibited cell proliferation and erythroid phenotype; downregulated GATA-1	[384]
B-ALL	15d-PGJ ₂ , pioglitazone	Inhibited cell growth by G1 arrest; induced apoptosis partially dependent on caspase signaling	[385]
UTree-O2, Bay91, 380	troglitazone	Inhibited cell growth by G1 arrest; induced apoptosis; downregulates c-myc expression	[386]

TABLE 2: Continued.

Hematological malignancy/cell line	PPAR γ agonist	Comments	Ref
U266, RPMI 8226, BL-41, HS-Sultan	15d-PGJ ₂	Induced apoptosis; downregulation of NF- κ B-dependent antiapoptotic proteins	[387]
Jurkat, J-Jahn, T-ALL	15d-PGJ ₂ , PGD2	Induced apoptosis through PPAR γ -dependent mechanism	[388]
Karpas 299	15d-PGJ ₂ , GW7845, rosiglitazone	Induced cell death at high ligand concentration but promoted cell survival at low doses	[389]
CTCL and Sezary syndrome cell lines: MJ, Hut78, and HH	CDDO	Induced apoptosis through a PPAR γ -independent mechanism by decreasing antiapoptotic protein Bcl-xL and activating caspase 3	[390]
GRANTA-519, Hbl-2, JeKo-1	15d-PGJ ₂ , rosi-glitazone, pioglitazone	Induced apoptosis and downregulation of cyclin D1	[391]
CLL B cells	CDDO	Induced apoptosis in part by activation of caspase-8	[392]
CLL B cells, Jurkat	CDDO	Induced apoptosis through the intrinsic pathway	[393]
DLBCL	CDDO	Inhibited proliferation; induced apoptosis through a PPAR γ -independent mechanism	[47]
Primary B lymphocytes, Ramos, OCI-Ly19 DLBCL	CDDO, CDDO-Im, Di-CDDO	Induced apoptosis through a mitochondrial dependent pathway	[394]
ANBL6, RPMI 8226	15d-PGJ ₂ , ciglitazone	Induced apoptosis via caspase activation and mitochondrial depolarization	[208]
LP-1, U-266, RPMI 8226-S, OPM-2, IM-9	rosiglitazone, pioglitazone, 15d-PGJ ₂	Inhibited tumor cell growth	[395]
Waldenstrom's macroglobulinemia	rosiglitazone, ciglitazone	Inhibited cell growth; induced apoptosis	[396]
multiple myeloma (MM) drug sensitive MM.1S or drug resistant MM.1R cells, KAS6/1, ANBL-6	15d-PGJ ₂ , troglitazone	Inhibited cell adhesion to BMSCs and adhesion-triggered IL-6 production; overcame resistance to dexamethasone (MM.1R cells)	[212]
MM cells, U266, RPMI 8226, bone marrow mononuclear cells	CDDO, CDDO-Im	Induced apoptosis by disruption of mitochondrial membrane potential	[397]
Dexamethasone-resistant MM.R1, RPMI 8226/LR-5, RMPI 8226/Dox-40, U266	CDDO-Im	Induced apoptosis; decreased MM adhesion-triggered IL-6 production	[398]
RPMI 8226, JJN3	CDDO-Im	Inhibited Stat3 and Stat5 phosphorylation; induced Stat inhibitors SOCS-1 and SHP-1	[399]
Normal human B cells and B lymphoma cells (Daudi, Ramos, Raji)	rosiglitazone, pioglitazone, 15d-PGJ ₂	Inhibited cell proliferation; induced apoptosis	[209]
MM cell lines (RPMI 8226 and U266); BMSCs, HS-5	PPAR γ over-expression; ciglitazone	PPAR γ overexpression inhibited proliferation and induced apoptosis in MM cells; inhibited IL-6 production in BMSCs	[207]
B cell lymphoma (Raji, Ramos cell lines)	PPAR γ siRNA	Silencing of PPAR γ induced cell proliferation and cell differentiation; PPAR γ knockdown enhanced NF- κ B activity in Ramos cells	[206]

2. Tumor-Stromal Microenvironment Crosstalk and Tumor-Associated Angiogenesis

2.1. Cancer Stem Cell Theory and Tumor Dormancy. A key issue of debate in cancer biology is whether tumor growth is caused by a substantial proportion of the tumor cells or exclusively by an infrequent subpopulation of cells termed cancer stem cells (CSCs) [52]. Regardless of the cancer type, most patients who have experienced many years of disease-free survival after successful treatment of the primary tumor ultimately die from metastatic disease. Patients who relapse must harbor cancer cells for years or even decades until the cancer cells overcome the regulatory mechanisms that keep the tumor in check. Dormant cancer cells are defined by a prolonged absence of or a balance in either proliferation or apoptosis, resulting in essentially a perpetual state of quiescence that protects them from conventional cytotoxic drugs, which only target actively proliferating cells. It is unknown whether dormant cancer cells represent a specialized subpopulation of cells programmed to stay dormant, an unspecialized population of cells not able to grow in the new microenvironment, or a combination of both [53]. CSCs are usually slowly cycling cells and thus insensitive to cytotoxic drugs as well [54, 55]. Dormant cancer cells are inferred to be CSCs or tumor initiating cells, as some prefer to call them [56]. Nonetheless, the relative frequency of CSCs varies as a function of both the tumor type and the specific experimental system used [57]. To date, published data most strongly support the presence of CSCs in hematologic malignancies such as leukemia [58], and in three major solid tumor types, including aggressive brain, breast, and colon cancers [59, 60]. Moreover, the existence of treatment resistant tumor cells following disease relapse has bolstered the theory that CSCs exist [56]. Thus, new approaches to target CSCs are actively being sought.

Although little evidence is available to suggest whether PPAR γ agonists could be used to specifically target CSCs while sparing normal hematopoietic stem cells, a few studies have been reported. Chearwae and Bright [61] demonstrated that PPAR γ agonists inhibit the proliferation of brain CSCs by inducing cell cycle arrest and apoptosis, which was associated with upregulated expression of PPAR γ and inhibition of signal transducer and activator of transcription (Stat)-3 signaling. Saiki and colleagues [62] showed that pioglitazone inhibits the growth of human leukemia cell lines and primary leukemia cells while sparing normal stem cells. Preclinical testing has identified additional cancer therapeutics that selectively target leukemic stem cells but not normal stem cells, including idarubicin with the proteasome inhibitor, parthenolide (known as feverfew), and TDZD-8 [63]. These agents target the NF- κ B pathway, a critical link in the well-established association between inflammation and carcinogenesis. In that PPAR γ agonists inhibit both NF- κ B- and Stat3-mediated transactivation of target genes and both of these transcription factors play a prominent role in cancer progression (see Section 2.8 and references therein), it is a likely extension to consider a role for PPAR γ agonists to target CSCs.

2.2. Tumor-Associated Angiogenesis. Regardless of the type of cancer, once a primary tumor becomes established, it needs to develop its own blood supply for nutrient delivery and removal of toxic waste. The process of angiogenesis, that is the formation of new blood vessels from existing vasculature, involves complex interplay among cancer and stromal cell-secreted factors, extracellular matrix (ECM) constituents, and endothelial cells (ECs) (Figure 1). The adult vasculature is composed of quiescent ECs lining blood vessels and, with the exception of reproduction; the process of angiogenesis begins only in response to a broad array of tissue injury.

Several isoforms of VEGF-A/165 are produced by alternative mRNA processing of the primary transcript, and these isoforms differ primarily in their ability to adhere to heparin or heparan sulfate proteoglycans (HSPGs) found both in the ECM or on the surface of stromal and tumor cells [72]. The VEGF gene family encodes VEGF isoforms A-F and placenta growth factor (PLGF) with at least three cognate receptors, VEGFR1/Flt-1, VEGFR2/Flk-1/KDR, VEGFR3/Flt-4 and two coreceptors, neuropilin (NRP) and HSPGs. VEGF-A/165 (hereafter designated VEGF) signaling through VEGFR2 is the major isoform responsible for pathological angiogenesis and induction of vascular permeability in tumors [73, 74], which leads to enhanced transendothelial migration of cancer cells during intravasation and extravasation [75]. VEGF-C and VEGF-D bind to VEGFR2 as well as VEGFR3 and are important for lymphangiogenesis and cancer metastasis to lymph nodes and spread through the lymphatic system [76–78].

VEGF production and intracrine signaling through VEGFR2 by ECs is essential for vascular homeostasis but is dispensable for angiogenesis as shown in EC-specific VEGF knockout mice [79]. Intracrine VEGF signaling requires expression of both VEGF and VEGFRs by the same cell and resistance to VEGF inhibitors that fail to penetrate the intracellular compartment. Hematopoietic stem cell survival also involves a VEGF-dependent internal autocrine loop mechanism [80]. Although it was originally thought that VEGFR expression was restricted to ECs, it is now apparent that other cell types express functional VEGFRs. Furthermore, VEGF is an autocrine growth factor for VEGFR-positive human tumors, including Kaposi sarcoma, melanoma, breast, ovarian, pancreatic, thyroid and prostate carcinomas, and leukemia [81–87]. Thus, in VEGFR-expressing tumors, VEGF inhibition may directly inhibit tumor cell growth as well as tumor-associated angiogenesis [83]. A host of proangiogenic factors play a role in pathological angiogenesis [64]; however, since most anticancer therapeutic strategies target the VEGF signaling pathway [64, 88], this paper focuses thereon.

2.3. Tumor-Stromal Microenvironment. Paget's "seed and soil" hypothesis emphasizes the importance of the interaction between the tumor cell ("seed") and its environment ("soil") for metastasis to occur (reviewed in [89]). The stroma of the tumor microenvironment consists of several components including growth factors, chemokines, matrix glycoproteins and proteoglycans, proteases, and host cells

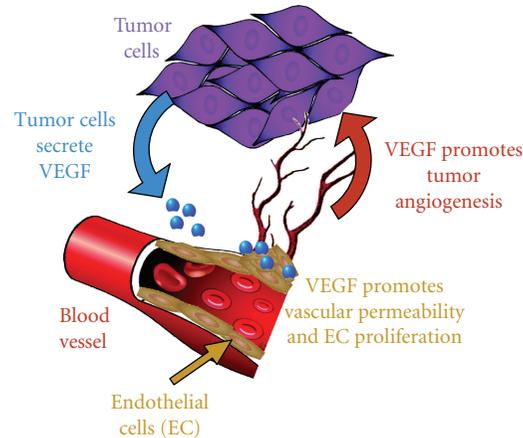


FIGURE 1: *Molecular mechanisms of tumor-associated angiogenesis.* Angiogenesis is essential for the persistence of solid tumor growth and, only recently, has it been appreciated that angiogenesis plays a role in progression of hematological malignancies as well. Cancer-associated angiogenesis in solid tumors begins once the tumor mass reaches a critical size such that the hypoxic environment inside the tumor leads to cancer cell-specific expression of proangiogenic factors including VEGF to shift the balance from endogenous antiangiogenic factors to tumor supplied proangiogenic factors—the angiogenic switch. Once proangiogenic factors overwhelm antiangiogenic factors, new blood vessels form in response to VEGF-induced endothelial permeability by EC sprouting, migration into the tumor mass, and proliferation from existing blood vessels—molecular mechanisms also induced by VEGF [64–67]. The tumor integrity of the vasculature is compromised in that it remains leaky with poor cell-to-cell adhesion, is abnormally branched and not well supported by pericytes (mural cells), the vascular smooth muscle cells that stabilize normal blood vessels [67, 68]. The chronic immaturity of tumor vessels has led Dvorak to characterize a tumor as a “wound that never heals” [69]. Notwithstanding, these features make tumor vessels viable targets for antitumor therapies. Benjamin et al. [70] demonstrated that removal of growth factors leads not only to the cessation of new vessel growth, but also to regression of the immature tumor vasculature [71].

that influence the behavior of cancer cells (reviewed in [90–102]). Host ECs, pericytes, macrophages, dendritic cells, lymphocytes, adipocytes, and fibroblasts/myofibroblasts present in the tumor microenvironment participate in the metastatic process (Figure 2). Initiation of new blood vessel formation requires activation of matrix metalloproteinases (MMPs) leading to degradation of the basement membrane, sprouting of ECs, and regulation of pericyte attachment for vessel stabilization. Activated fibroblasts, myofibroblasts, play an important role in synchronizing these events [94]. Furthermore, the topography of the ECM mediates vascular development and regulates the speed of cell migration during angiogenesis [103].

Chronic inflammation is associated with cancer initiation and progression [104–106]. Vascular ECs play a pivotal role in regulating leukocyte recruitment during inflammation [90]. Thus, in most cases, cancers exploit inflammation and recruited inflammatory cells for their own benefit [91]. Although activated inflammatory cells in the tumor microenvironment play important roles in cancer initiation, progression, angiogenesis, and metastasis [92], they are not the most numerous. Cancer-associated fibroblasts, which resemble myofibroblasts of healing wounds, are the most abundant cells of the tumor stroma [93], and contribute significantly to chronic inflammation, production of proangiogenic factors, and metastasis [94].

2.4. Inhibitors of Angiogenesis. As discussed above, angiogenesis is the hallmark pathology in tumor growth, progression,

and metastasis. Inhibiting tumor angiogenesis adds to the arsenal of treatment options for a number of solid tumor types [111, 112], and recently has been proposed for hematological malignancies as well [107, 113–119]. Endogenous inhibitors of angiogenesis are critical for tight regulation of pathological angiogenesis; however, in response to malignant transformation the putative “angiogenic switch” bypasses this tight regulation to promote tumor progression [120]. Whereas radiation and chemotherapy target killing of the tumor cells, antiangiogenic therapy is primarily directed against tumor blood vessels. Endostatin [121, 122], angiostatin [122], and TSP-1 [123] are among a host of well-known endogenous inhibitors of angiogenesis [98, 124]. TSP-1 is a large molecular weight glycoprotein that inhibits the proliferation and migration of ECs by interacting with CD36 expressed on the cell surface; CD36 is a PPAR γ target gene. Small molecules based on a CD36-binding peptide sequence from TSP-1 are being tested for cancer treatment. One analog, ABT510, exhibits potent proapoptotic activity in vitro, while clinically it is very well tolerated with therapeutic benefits against several malignancies reported in phase II clinical trials [125–129].

Targeting VEGF-induced angiogenesis is in current use as monotherapy or combination therapy to treat a wide variety of cancers [130–132]. Bevacizumab (Avastin) and ranibizumab (Lucentis) are FDA-approved humanized monoclonal antibodies that recognize and block VEGF signaling in cancer and age-related macular degeneration (AMD) [130–134]. Additional, but not all-inclusive VEGF inhibitors

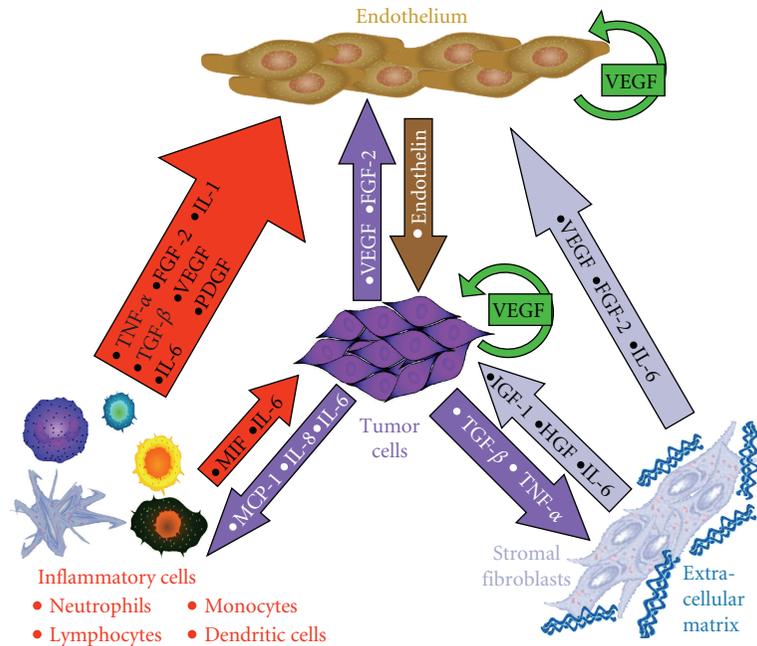


FIGURE 2: *Tumor-associated angiogenesis is sustained through stromal microenvironment crosstalk.* Most tumors are associated with the activation of tumor-promoting innate immune responses involving neutrophils, macrophages, and NK cells. Specific (adaptive) antitumor immune responses involving T- or B-lymphocytes are less efficient in suppressing tumor growth. Increased formation of blood and lymphatic vessels in bone marrow and lymph nodes provide oxygen and nutrients to malignant cells. Stromal cells, including ECs, inflammatory cells, and fibroblasts/myofibroblasts, produce cytokines and growth factors that act in a paracrine fashion to promote malignant cell proliferation or survival. In turn, malignant cells produce angiogenic factors and express their cognate receptors establishing functional autocrine loops to perpetuate their survival including signaling through the VEGF pathway [85–87, 107]. The secreted factors produced by and in response to those secreted by stromal and tumor cells include, but are not limited to VEGF, FGF-2, PDGF, IGF-1, HGF, TGF- α , TGF- β , TNF- α , IL-8, MCP-1/CCL2, MIF, IL-6, and IL-1 [95]. The potent vasoconstrictor peptide endothelin-1 has been implicated in the pathophysiology of atherosclerosis and its complications [108], as well as tumor angiogenesis and lymphangiogenesis [109, 110]. Proteases important for invasion through the basement membrane and remodeling of the ECM, such as plasminogen [96] and MMPs, including MMP-2 and MMP-9 [97], and their inhibitors, PAI-1/2 and TIMPs, respectively, are produced by stromal and tumor cells. Downregulation of endogenous inhibitors of angiogenesis such as thrombospondin (TSP)-1 occurs in the stromal compartment as well to favor angiogenesis, cancer cell growth, and metastasis [98]. In recent years, it has been recognized that a better understanding of the tumor-stromal microenvironment crosstalk may lead to elucidation of new therapeutic strategies for cancer therapy [99–102].

(direct or indirect) are the RNA aptamer, pegaptanib; VEGF receptor decoy, VEGF-Trap (Aflibercept); small interfering RNA-based therapies, bevasiranib, and AGN211745; rapamycin, sirolimus; tyrosine kinase inhibitors including vatalanib, pazopanib, imatinib (Gleevec), TG100801, TG101095, AG013958, and AL39324; soluble VEGFRs; proteasome inhibitors, bortezomib (Velcade); thalidomide and derivatives.

At present, established therapies have been very successful in reducing the vision loss associated with AMD [135, 136]; however, a number of reports on the clinical outcomes of antiangiogenic therapy with VEGF inhibitors have shown equivocal results [88, 137–141]. Unfortunately, no significant survival benefit has been demonstrated in anti-VEGF monotherapy trials. When anti-VEGF inhibitors are used in combination with standard chemotherapeutic approaches for solid tumors, such treatment does not prolong survival of cancer patients for more than a few months [137–141], except as shown in phase II and phase III clinical trials for metastatic colon cancer and metastatic breast cancer where median survival over chemotherapy alone was extended

~15–26 months (reviewed in [142]). Although different classes of VEGF-targeted therapies inhibit primary tumor growth, recent studies surprisingly report that treatment with VEGF inhibitors leads to more invasive and metastatic tumors [139, 143]. Most patients who initially respond to VEGF-targeted therapy will develop resistance, and the molecular and cellular mechanisms promoting resistance are poorly understood [137, 138]. Thus, resistance or refractoriness of tumor ECs to treatment with VEGF inhibitors limits the utility of long-term treatment [143]. These findings indicate that new studies and molecular approaches are needed to overcome the lack of sensitivity or resistance of tumor ECs to antiangiogenic therapies.

2.5. Targeting Transcription Factor Signaling Pathways Activated in Angiogenesis. Although VEGF is upregulated in response to many inducers activated in cancer, only two major transcription factors have been identified for its promoter, hypoxia inducible factor (HIF)-1 and Stat3 [144]. Both HIF-1 production and Stat3 activity are upregulated in many types of cancer. VEGF is strongly induced by the

hypoxic tumor microenvironment before the tumor becomes vascularized, and thus, is important in hypoxic regulation of angiogenesis [145, 146]. HIF-1 is composed of the constitutively expressed HIF-1 β subunit (aka the aryl hydrocarbon nuclear translocator/ARNT [146]) and an O₂- and growth factor-regulated HIF-1 α subunit. HIF-1 α is also constitutively expressed but rapidly degraded under normoxia due to hydroxylation at two proline residues within the central degradation domain. Hydroxylation increases the affinity of HIF-1 α for the tumor suppressor protein von Hippel-Lindau (pVHL) E3 ligase complex, which mediates ubiquitination and proteasomal degradation of HIF-1 α thereby preventing formation of an active HIF-1 heterodimer [147]. Because the HIF hydroxylases have an absolute requirement for oxygen, hydroxylation is suppressed under hypoxic conditions allowing the HIF-1 α subunit to accumulate, translocate to the nucleus, and heterodimerize with HIF-1 β to activate transcription of target genes [148].

Activation of the Jak/Stat3 pathway by IL-6 through its high affinity receptor, IL-6R α , and its binding partner, gp130, is a well-known inflammatory response evoked by the acute phase response of innate immunity [149, 150]. Stat3 is a latent transcription factor whose maximal activation requires both tyrosine (Y-705) and serine (S-727) phosphorylation. Inhibition of Stat3 activation blocks HIF-1 and VEGF expression in vitro and inhibits tumor growth and angiogenesis in vivo [151]. Activation of Stat3 signaling by various mitogens is prevalent in different types of cancers. Furthermore, when Stat3 is inhibited, tumor cells will no longer express proangiogenic mediators in response to IL-6R signaling. Because Stat3 is constitutively active in many types of cancers, it is considered oncogenic [152, 153]. Therefore, Stat3 is an apt upstream target for inhibiting tumor VEGF expression and angiogenesis [151].

NF- κ B transcription factor links inflammation and tumorigenesis, and its activation allows both premalignant and malignant cells to escape apoptosis [154]. NF- κ B signaling occurs in essentially all aspects of cancer progression from uncontrolled growth, evasion of apoptosis, tumor cell invasion through stromal compartments and into the blood stream, and sustained angiogenesis [104, 154]. Constitutive NF- κ B activation is found in lymphoid and myeloid malignancies, including preneoplastic conditions, emphasizing its role in malignant transformation [155, 156]. More than 200 genes involved in cell survival, apoptosis, cell growth, immune responses and inflammation are transactivated by NF- κ B [157]. NF- κ B is sequestered in the cytoplasm by inhibitor proteins such as I κ B α [104, 154–156]. Upon activation, proteasomal degradation of I κ B α releases NF- κ B, which then translocates to the nucleus to bind to the κ B response element in promoter regions of target genes. Thus, small inhibitory molecules that target these various steps are continually being sought for cancer treatment. PPAR γ agonists have anti-inflammatory properties that are conferred, in part, through their ability to inactivate transcription factors that regulate inflammation including Stat3, NF- κ B, and AP-1 [158–160]. The potential for PPAR γ agonists as inhibitors of Stat3 and NF- κ B survival signaling in hematological malignancies is discussed in Section 2.8.

2.6. Angiogenesis and Targeted Antiangiogenic Therapy in Hematological Malignancies. Since hematological malignancies originate in bone marrow and lymphatic organs and do not form solid tumor masses, it was generally believed that angiogenesis would not be as critical for cancer progression as in solid tumors. In the recent years, however, the importance of angiogenesis and lymphangiogenesis in hematological malignancies has been recognized and discussed in detail in a number of excellent reviews and references therein [113, 114, 116–119]. Because PPAR γ agonists are being tested as inhibitors of angiogenesis, it is important to understand the role of angiogenesis and associated signal transduction pathways in the progression of hematological malignancies. Increased bone marrow microvessel density (MVD), an in vivo measure of tumor-associated angiogenesis, is found in hematological malignancies [161], confirming the importance of angiogenesis for malignant progression.

In general, increased MVD correlates with increased disease burden and poor prognosis or treatment outcome [118]. A number of antiangiogenic agents have been used to treat hematological malignancies as discussed in the review articles cited above. For example, thalidomide, well known as a potent teratogen causing stunted limb growth, has gained favor as an inhibitor of angiogenesis in multiple myeloma (MM) [162–167]. Thalidomide and similar immunomodulatory drugs and proteasome inhibitors (e.g., bortezomib) exert their effects directly by induction of apoptosis of MM cells or indirectly by inhibiting production of cytokines and proangiogenic factors, including VEGF, by bone marrow stromal cells (BMSCs) [162, 168]. The angiogenic activity of MM ECs correlates with downregulated expression of the endogenous antiangiogenic factor, endostatin [169]. Increased MVD in bone marrow correlates with shorter overall disease-free survival in AML, and elevated VEGF mediates both autocrine and paracrine signaling in support of leukemia cell survival and induction of angiogenesis [86, 87, 113, 161].

Angiogenesis in chronic lymphocytic leukemia (CLL) occurs in both marrow and lymph nodes [170]. Increased vascularity leads to elevated production of hematopoietic growth factors by new vessel ECs, which stimulates expression of VEGF and VEGFRs by CLL cells for autocrine signaling to promote survival [113, 170]. Elevated levels of VEGF are found in the serum of patients with chronic myeloid leukemia (CML), which correlates with worse survival [171]. Non-Hodgkin lymphoma (NHL) cells secrete VEGF and express VEGFRs, which also contribute to autocrine and paracrine signaling [172]. A phase II clinical trial of bevacizumab (Avastin) therapy in patients with relapsed, aggressive NHL showed a median increase in disease-free survival by 5.2 months [115], suggesting that anti-VEGF therapy is a limited but viable target for treatment. Antiangiogenic therapy would likely be more efficacious if combined with active chemotherapy regimens [115, 173]. Increased MVD in lymph nodes and elevated VEGF are statistically correlated with a greater tumor burden in Hodgkin lymphoma in newly diagnosed patients [174, 175]. Survival after treatment of diffuse large-B-cell lymphoma is adversely affected in patients whose tumor

stroma show elevated MVD, indicating that differences in the tumor microenvironment play a critical role in treatment outcomes [176]. However, the role of angiogenesis varies in lymphoma subtypes due to heterogeneity in expression of proangiogenic factors [113, 177].

In addition to agents targeting VEGF-VEGFR signaling directly, a number of agents have been developed to target the tumor microenvironment (reviewed in [99–102]), including ECM modulators, tyrosine kinase inhibitors, and immunomodulators, many of which indirectly target cancer angiogenesis. Nonetheless, autocrine VEGF signaling to promote malignant cell survival appears to be a common theme in hematological malignancies [85–87, 107, 113, 170, 172, 178], suggesting that anti-VEGF/VEGFR targeted therapy would promote direct killing of tumor cells, as well as inhibit angiogenesis associated with several types of hematological malignancies. It should be noted that antiangiogenic therapy in combination with conventional therapy for metastatic colon cancer and metastatic breast cancer significantly increased survival [142]; these cancers represent two of the three solid tumors (the third being brain cancer) for which published data most strongly support the presence of CSCs [59, 60]. In that CSCs have been documented in hematologic malignancies such as leukemia [58], it is interesting to speculate that patients with hematological malignancies other than leukemias may benefit from adding antiangiogenic therapy to standard treatments if CSCs could be identified in the malignant population of cells.

2.7. Effects of PPAR γ and PPAR γ Ligands on EC Functions and Angiogenesis. The endothelium releases a balance of bioactive factors that regulate vasoconstriction and relaxation to facilitate vascular homeostasis [179]. During homeostasis, the endothelium also inhibits platelet and leukocyte adhesion to the vascular surface and maintains the balance between prothrombotic and profibrinolytic activities. Several common conditions with a predisposition to atherosclerosis, including hypercholesterolemia, hypertension, diabetes, and stroke, are associated with endothelial dysfunction, leading to a proinflammatory and prothrombotic endothelium [180]. For more than a decade investigators have studied the effects of PPAR γ ligands on EC functions with a particular interest in determining whether they could be used to inhibit cancer cell growth (reviewed in [25, 31, 181, 182]) and cancer-associated angiogenesis (reviewed in [23, 25, 31, 181–184]). The functions that PPAR γ ligands target during angiogenesis include induction of apoptosis, inhibition of EC proliferation, downregulation of proangiogenic factors, and as inhibitors of the inflammatory events that trigger and perpetuate pathological angiogenesis (Table 3). In addition to targeting tumor angiogenesis, PPAR γ ligands have direct effects on cancer cells due to their ability to promote apoptosis, inhibit cell proliferation or induce differentiation [3, 71, 185–188]. However, to date, disappointing results have been obtained in phase II clinical trials using the PPAR γ ligand troglitazone to inhibit progression of treatment-refractory metastatic breast cancer [189], chemotherapy-resistant metastatic colorectal cancer [190], and prostate cancer [191]. In recent years, the focus has shifted from treating

the tumor to targeting the signaling pathways that drive aberrant cell proliferation and survival and tumor-associated angiogenesis. Such targets have the potential for greater specificity together with reduced systemic toxicity [104].

2.8. Therapeutic Potential of PPAR γ and PPAR γ Ligands to Target Angiogenic Signaling Pathways in Treatment of Hematological Malignancies. It has been suggested that PPAR γ functions as a tumor suppressor gene [204]; therefore, it is important to understand the complexity of signal transduction pathways and molecular players affected by PPAR γ that promote tumor growth, cancer-associated angiogenesis, and metastasis. MM, a progressive hematological malignancy of plasma cells, remains largely incurable with survival averaging 3–5 years despite conventional and high-dose therapies; therefore, novel treatment approaches are desperately needed. MM is characterized by excessive numbers of abnormal plasma cells in the bone marrow and overproduction of intact monoclonal immunoglobulin (IgG, IgA, IgD, or IgE) or Bence Jones protein (free monoclonal κ and λ light chains). Common clinical manifestations of MM are hypercalcemia, anemia, renal damage, increased susceptibility to bacterial or viral infection, and impaired production of normal immunoglobulins (<http://www.themrf.org/living-with-multiple-myeloma/newly-diagnosed-patients/what-is-multiple-myeloma/definition.html>). Lytic lesions are often found in the bone including the pelvis, spine, ribs, and skull. Furthermore, neovascularization in bone marrow parallels disease progression of MM [205].

Our laboratory has shown that normal and malignant B cells, including MM, express PPAR γ [206–210], and that certain PPAR γ ligands can induce apoptosis in MM cells [207, 208]. Because PPAR γ ligands also have PPAR γ -independent effects, we examined the functional consequences of PPAR γ overexpression in human MM [207]. PPAR γ overexpression in myeloma cells decreased cell proliferation, induced spontaneous apoptosis even in the absence of exogenous ligand, and enhanced their sensitivity to PPAR γ ligand-induced apoptosis. Apoptosis was associated with the downregulation of anti-apoptotic proteins XIAP and Mcl-1 as well as induction of caspase-3 activity [207]. IL-6 mediates growth and survival of human myeloma cells through the MEK/MAPK and Jak/Stat signaling pathways, and IL-6 confers protection against dexamethasone-induced apoptosis via activation of the protein tyrosine phosphatase, SHP2 [211]. Binding of MM cells to BMSCs triggers expression of adhesive molecules and secretion of IL-6, promoting MM cell growth, survival, drug resistance, and migration. Furthermore, PPAR γ overexpression-induced cell death of myeloma cells is not abrogated by coculture with BMSCs [207]. Overexpression of PPAR γ in myeloma cells and BMSCs inhibited both basal and myeloma cell adhesion-induced IL-6 production by BMSCs. These results indicate that PPAR γ negatively controls MM growth and viability, in part, through inhibition of IL-6 production by BMSCs [207]. Wang et al. [211] showed that myeloma cells express PPAR γ and that the PPAR γ agonists, 15d-PG $_2$ and troglitazone, abolish IL-6-inducible myeloma cell proliferation and promote apoptosis

TABLE 3: Effects of PPAR γ agonists on endothelial cell function and angiogenesis.

Ref.	Goal of Study	Results	Pro- or antiangiogenic activity	Direct or Indirect Effects
[192]	To determine whether PPAR γ ligands induce EC proliferation or influence cytokine-induced proliferation in vitro.	PPAR γ ligands troglitazone and pioglitazone negligibly affected basal EC proliferation in vitro; troglitazone and pioglitazone significantly inhibited FGF-2-induced EC proliferation.	<ul style="list-style-type: none"> • Antiangiogenic activity as shown by inhibiting FGF-2-induced EC proliferation 	Not reported
[22]	To determine effects of PPAR γ ligands on in vitro and in vivo angiogenesis and EC proliferation.	15d-PGJ $_2$, BRL49653, or ciglitazone, dose-dependently suppresses HUVEC differentiation into tube-like structures and cell proliferation; 15d-PGJ $_2$ downregulated VEGFR1, VEGFR2 and uPA and increased PAI-1 mRNA expression in vitro; 15d-PGJ $_2$ inhibited angiogenesis in vivo.	<ul style="list-style-type: none"> • Antiangiogenic activity • Anti-cell proliferation and anti-cell differentiation activity 	Not reported
[193]	To determine whether human ECs express PPAR γ and if PPAR γ regulates PAI-1 expression in EC.	ECs expressed functionally active PPAR γ ; PPAR γ ligands (15d-PGJ $_2$) and oxidized linoleic acid regulated PAI-1 expression in ECs.	<ul style="list-style-type: none"> • Antiangiogenic activity by inhibiting fibrinolysis (fibrin induces angiogenesis) 	Not reported
[194]	To determine the antiangiogenic effects of PPAR γ agonists on CNV in vitro and on experimental laser photocoagulation-induced CNV in vivo.	PPAR γ ligands troglitazone and rosiglitazone inhibited VEGF-induced migration and proliferation of human RPE cells and bovine CECs and tube formation of CEC in a dose-response manner; troglitazone inhibited CNV in rat and monkey eyes.	<ul style="list-style-type: none"> • Antiangiogenic activity in the eye • Anti-cell proliferation activity 	Not reported
[195]	To determine whether PPAR γ ligands inhibit cancer cell growth and cancer-associated angiogenesis.	PPAR γ expressed in tumor EC; rosiglitazone suppressed primary tumor growth and metastasis; rosiglitazone inhibited bovine capillary EC but not tumor cell proliferation; rosiglitazone decreased VEGF production by tumor cells in vitro; rosiglitazone suppressed angiogenesis in vivo and in a variety of primary tumors.	<ul style="list-style-type: none"> • Antiangiogenic activity • Anti-EC but not tumor cell proliferation activity 	Direct and indirect
[196]	To determine whether PPAR γ ligands regulate PPAR γ and CD36 gene expression in microvascular and large vessel EC in vitro and modulate TSP-1 peptide ABT510 antiangiogenic activity in tumor-associated endothelium in vivo (mouse tumor models).	15d-PGJ $_2$, troglitazone, and rosiglitazone induced PPAR γ and CD36 gene expression in EC in vitro and inhibited angiogenic endothelial functions in vitro and neovascularization in vivo in an additive manner; ABT510 and PPAR γ ligands enhanced synergistically the antiangiogenic and antitumor effects of TSP-1 peptide ABT510.	<ul style="list-style-type: none"> • Antiangiogenic activity • Anti-proliferation activity in EC • Anti-invasion activity of EC • Cooperative inhibition of EC angiogenic functions • Synergistic inhibition of tumor angiogenesis 	Direct for in vitro activities

TABLE 3: Continued.

Ref.	Goal of Study	Results	Pro- or antiangiogenic activity	Direct or Indirect Effects
[197]	To determine whether PPAR γ agonists modulate bone marrow-derived bipotential APCs to promote endothelial lineage differentiation and re-endothelialization after vascular intervention.	Rosiglitazone promoted differentiation of bone marrow-derived APCs toward the endothelial lineage and attenuated restenosis after angioplasty in C57/BL6 mice; rosiglitazone inhibited APC differentiation toward smooth muscle cell lineage.	<ul style="list-style-type: none"> • Proangiogenic activity • Anti-inflammatory • Promoted lineage-specific differentiation 	Not reported
[198]	To determine the efficacy of pioglitazone to inhibit corneal neovascularization.	PPAR γ ligand pioglitazone decreased MVD in a VEGF-induced neovascularization in a rat cornea model.	<ul style="list-style-type: none"> • Antiangiogenic activity in the eye 	Not reported
[24]	To determine whether PPAR γ ligands can inhibit angiogenesis in A549 lung cancer cell xenograft in vivo and which signaling pathway is involved in vitro.	PPAR γ ligands troglitazone and pioglitazone significantly inhibited A549 primary tumor growth in SCID mice, likely due to inhibition of cancer-associated angiogenesis; in vitro studies on A549 cells suggested PPAR γ ligands inhibit chemokine expression and inhibit NF- κ B activity; the transcription factor necessary for chemokine expression.	<ul style="list-style-type: none"> • Antiangiogenic activity • Inhibited NF-κB transcription factor activity 	Direct and indirect
[199]	To determine effects of PPAR γ ligands on VEGF expression by human endometrial cells.	PPAR γ ligands rosiglitazone and 15d-PGJ ₂ repressed VEGF gene expression through a PPRE in the VEGF promoter.	<ul style="list-style-type: none"> • Antiangiogenic activity • Identified PPRE in VEGF promoter 	Not reported
[200]	Because endothelial precursor cell (EPC) function is impaired in type 2 diabetic patients and EC dysfunction can be ameliorated by treatment with TZDs, this study asked whether TZDs affect the number and function of EPCs.	Rosiglitazone improved number and migratory activity of EPCs from type 2 diabetic patients; rosiglitazone increased the CD133+ subpopulation of CD34+ cells (stem cells); rosiglitazone increased circulating levels of VEGF; effects may be due to increased bioavailability of NO by Akt-dependent phosphorylation of eNOS—a pathway that is activated by VEGF or the insulin signaling cascade.	<ul style="list-style-type: none"> • Proangiogenic activity • Akt survival pathway activated • Elevated CD133+/CD34+ stem cells towards EC lineage (VE-cadherin+ and CD31+) 	Not reported
[201]	To determine whether TZDs increase the number of bone marrow-derived EPCs in mice and the signaling pathways activated.	Treatment of mice with pioglitazone upregulated bone marrow and circulating EPCs; pioglitazone prevented apoptosis of human and mouse EPCs in a PI3K-dependent manner in vitro.	<ul style="list-style-type: none"> • Proangiogenic activity • PI3K activated • Anti-apoptotic 	Not reported; indirect activation of PI3K-Akt not activated by pioglitazone
[27]	To study the effect of PPAR γ agonists on VEGF- and FGF-2-induced angiogenesis and EC migration.	Pioglitazone and rosiglitazone inhibited the proangiogenic effects of FGF-2 and VEGF in the chick chorioallantoic membrane model angiogenesis; pioglitazone and rosiglitazone inhibited VEGF- and FGF-2-induced EC migration.	<ul style="list-style-type: none"> • Antiangiogenic in vivo • Inhibited EC migration 	not reported
[28]	To determine whether activation of PPAR α and PPAR γ stimulates angiogenesis.	PPAR α agonist WY14643 and PPAR γ agonist GW1929 induced EC tube formation in EC/interstitial cell cocultures by increasing VEGF production; WY14643 and GW1929 induced angiogenesis in murine corneal angiogenesis model and Akt activated in vitro.	<ul style="list-style-type: none"> • Proangiogenic activity • Induced VEGF production • Prosurvival 	Direct for both PPAR α and PPAR γ

TABLE 3: Continued.

Ref.	Goal of Study	Results	Pro- or antiangiogenic	Direct or Indirect Effects
[30]	To investigate the impact of diabetes on ischemia-induced collateral vessel growth, and tested the hypothesis that PPAR γ agonists augment collateral flow to ischemic tissue.	Pioglitazone ameliorated endothelial dysfunction and enhanced blood flow recovery after tissue ischemia in diabetic mice; pioglitazone restored VEGF levels that were reduced by ischemic injury; Activation of eNOS essential for pioglitazone to promote angiogenesis in ischemic tissue.	<ul style="list-style-type: none"> • Proangiogenic activity • Induced VEGF production 	Not reported
[202]	To determine effects of rosiglitazone on gastric cancer cell cycle, proliferation, migration, and invasion; endothelial capillary tube formation (an in vitro measure of angiogenesis).	Rosiglitazone inhibited gastric cancer cell growth, caused G1 cell cycle arrest and induced apoptosis in a dose-dependent and PPAR γ -dependent manner; rosiglitazone inhibited gastric cancer cell migration, invasion, and expression of MMP-2 in a dose-dependent manner in a PPAR γ -independent manner; rosiglitazone reduced VEGF-induced “angiogenesis” of HUVEC in a dose- and PPAR γ -dependent manner.	<ul style="list-style-type: none"> • Antiangiogenic activity • Antitumor cell proliferation activity • Anti-invasion • Proapoptotic 	Not reported
[32]	To determine the effects of PPAR γ ligands on pancreatic cancer-associated angiogenesis, VEGF expression, and tumor growth in vitro and in vivo.	Rosiglitazone inhibited pancreatic carcinoma growth both in vitro and in vivo; rosiglitazone suppressed xenograft tumor angiogenesis by downregulating VEGF expression; 15d-PGJ $_2$, 9-cis-RA, and their combination inhibited VEGF mRNA expression in PANC-1 cells in a dose- and time-dependent manner; MVD was decreased in rosiglitazone-treated mice.	<ul style="list-style-type: none"> • Antiangiogenic activity • Antitumor cell proliferation activity 	Not reported
[203]	To determine whether adipose tissue angiogenesis was stimulated by rosiglitazone using an assay to study angiogenic sprout formation ex vivo.	Obesity and TZD treatment in vivo induced angiogenic sprout formation from adipose tissue fragments, but not from aorta rings; rosiglitazone induced expression of VEGF-A, VEGF-B, and ANGPTL4; ANGPTL4 stimulated EC growth and capillary tube formation; ANGPTL4 alleviated the growth inhibitory actions of rosiglitazone on ECs in the presence or absence of VEGF likely causing a net expansion of the capillary network in adipose tissue in response to PPAR γ activators.	<ul style="list-style-type: none"> • Proangiogenic activity in adipose tissue • Induced VEGF production • Induced ANGPTL4 expression 	Indirect likely via a PPAR γ -stimulated adipocyte-specific factor ANGPTL4 capable of overcoming direct antiangiogenic effect of rosiglitazone on ECs

in a PPAR γ -dependent manner. These PPAR γ agonists also reduced cell-cell adhesion between BMSCs and MM cells and overcame resistance to dexamethasone-mediated apoptosis in the MM.1R cell line through a PPAR γ -dependent mechanism [212]. Taken together, the results of these studies demonstrate that PPAR γ agonists can be used to inhibit IL-6-dependent crosstalk between myeloma cells and BMSCs [207, 211, 212], validating novel therapeutic strategies that target the tumor-stromal microenvironment.

Dankbar and colleagues [205] demonstrated that biologically active VEGF is expressed and secreted by myeloma cell lines and plasma cells isolated from the marrow of patients with MM. However, the myeloma cells did not express or only weakly expressed VEGFR1 and VEGFR2, indicating that autocrine VEGF signaling in MM is unlikely. In contrast, they demonstrated that BMSCs abundantly express VEGFR2 and that such expression could be stimulated in response to IL-6. In addition, exposure of BMSCs and microvascular ECs to VEGF induced a time- and dose-dependent increase in IL-6 secretion. They showed that IL-6-stimulated VEGF expression in and secretion from myeloma cell lines and in plasma cells purified from the marrow of patients with MM as well. Thus, this study confirms that paracrine interactions between myeloma and marrow stromal cells triggered by VEGF and IL-6 represent feasible signal transduction pathways to target for treatment of MM [205].

PPAR γ ligands are known to inhibit or repress the activity of a number of transcription factors important in innate immunity, inflammation and cancer, including Stat3 and NF- κ B [158, 159]; therefore, targeted inhibition of Stat3 and NF- κ B activity with PPAR γ agonists is a relevant avenue of investigation for new cancer therapeutics [213]. Wang and colleagues [211] showed that 15d-PGJ₂ and troglitazone significantly inhibited Stat3 binding to its cognate response element and inhibited Stat3 binding to the promoters of c-MYC and MCL-1 thereby preventing transactivation of these Stat3 target genes. Whereas 15d-PGJ₂ promotes direct binding of PPAR γ to Stat3 forming a complex such that Stat3 is no longer capable of binding to the type II IL-6 response element on promoters of Stat3 target genes, troglitazone induces the redistribution of the corepressor NCoR/SMRT from PPAR γ to Stat3, which leads to repression of Stat3 transactivation of target genes [211] (Figure 3(a)). In contrast, 15d-PGJ₂ and troglitazone did not affect the expression of IL-6R or activation by phosphorylation of the downstream signaling molecules Jak/Stat3, MAPK, and PI3K/Akt in myeloma cells [211].

PPAR γ and its ligands effectively blocked IL-6 transcription and secretion from BMSCs that is induced in response to myeloma cell adhesion [212]. Such inhibition occurs through competition between PPAR γ and NF- κ B for the coactivator PGC-1, which is recruited from p65/p50 complexes by ligand-activated PPAR γ (Figure 3(b)). Direct complex formation between PPAR γ and C/EBP β also prevents transactivation of the IL-6 promoter. The natural PPAR γ ligand, 15d-PGJ₂, has a PPAR γ -independent effect on NF- κ B by decreasing phosphorylation of IKK and I κ B to prevent activation of NF- κ B [212]. Prolonged treatment with the PPAR γ ligand CDDO-Me inactivates

Erk signaling in AML cells effectively inhibiting cell growth [214]. In vitro studies show that CDDO-Me inactivates Stat3, Src, and Akt; reduces expression of the c-MYC gene; promotes accumulation of cells in the G2-M phase of the cell cycle; and, abrogates invasive growth and induction of apoptosis of mammary cells [215]. Furthermore, mammary cell growth and lung metastases were completely eliminated in mice treated with CDDO-Me starting one day after tumor implantation; tumor growth was significantly inhibited when started after 5 days. Thus, CDDO-Me may have therapeutic potential for hematological malignancies and solid tumors through inactivation of Stat3 [215].

Bortezomib (Velcade, formerly PS-341) is a proteasome inhibitor that is used for antiangiogenic therapy in various cancers including MM [216]. Bortezomib targets myeloma cells and also inhibits the binding of myeloma cells to BMSCs. Furthermore, intravenous bortezomib, with or without dexamethasone, is well tolerated and effective in treating patients with relapsed or refractory MM [216]. Because bone marrow angiogenesis plays an important role in the pathogenesis and progression of MM and bortezomib inhibits angiogenesis, Roccaro and colleagues [217] tested the effects of bortezomib on the angiogenic phenotype of MM patient-derived ECs (MMECs). At clinically relevant concentrations, bortezomib inhibited the proliferation of MMECs and human umbilical vein endothelial cells (HUVECs) in a dose-dependent and time-dependent manner. Bortezomib also inhibited angiogenesis as measured by capillary tube formation on Matrigel in vitro and in the chick embryo chorioallantoic membrane assay in vivo [217]. Furthermore, binding of drug sensitive MM cells (MM.1S) to MMECs triggered their proliferation, which was prevented by bortezomib. Bortezomib also triggered a dose-dependent inhibition of VEGF and IL-6 production by and secretion from MMECs and abrogated IL-6 triggered signaling cascades via caspase-dependent downregulation of gp130 in MM [218]; gp130 is the signaling component of the high affinity IL-6R complex that activates Stat3. These data provide mechanistic insight on the antiangiogenic effects of bortezomib on MMECs in the bone marrow microenvironment [217] and support the concept that adding antiangiogenic agents as adjuvant or combination therapy with standard therapy would be more efficacious in treating patients with relapsed or refractory MM [219], and perhaps other hematological malignancies as well.

Although inhibiting IL-6 signaling through its high affinity receptor promotes apoptosis of MM cells when cocultured with BMSCs, some myeloma cells survive suggesting that the marrow microenvironment stimulates IL-6-independent pathways that exert a prosurvival effect [220]. BMSCs stimulate MAPK signaling in myeloma cells through IL-6R-independent mechanisms thereby circumventing the need for Stat3-mediated signaling in response to IL-6 for myeloma cell survival. Chatterjee et al. [220] went on to show that disruption of both the IL-6R/Stat3 and MAPK signaling pathways led to significantly more apoptosis of MM cell lines and primary MM cells even in the presence of BMSCs than singly inhibiting each signaling pathway. These results suggest that combined targeting of different and independently

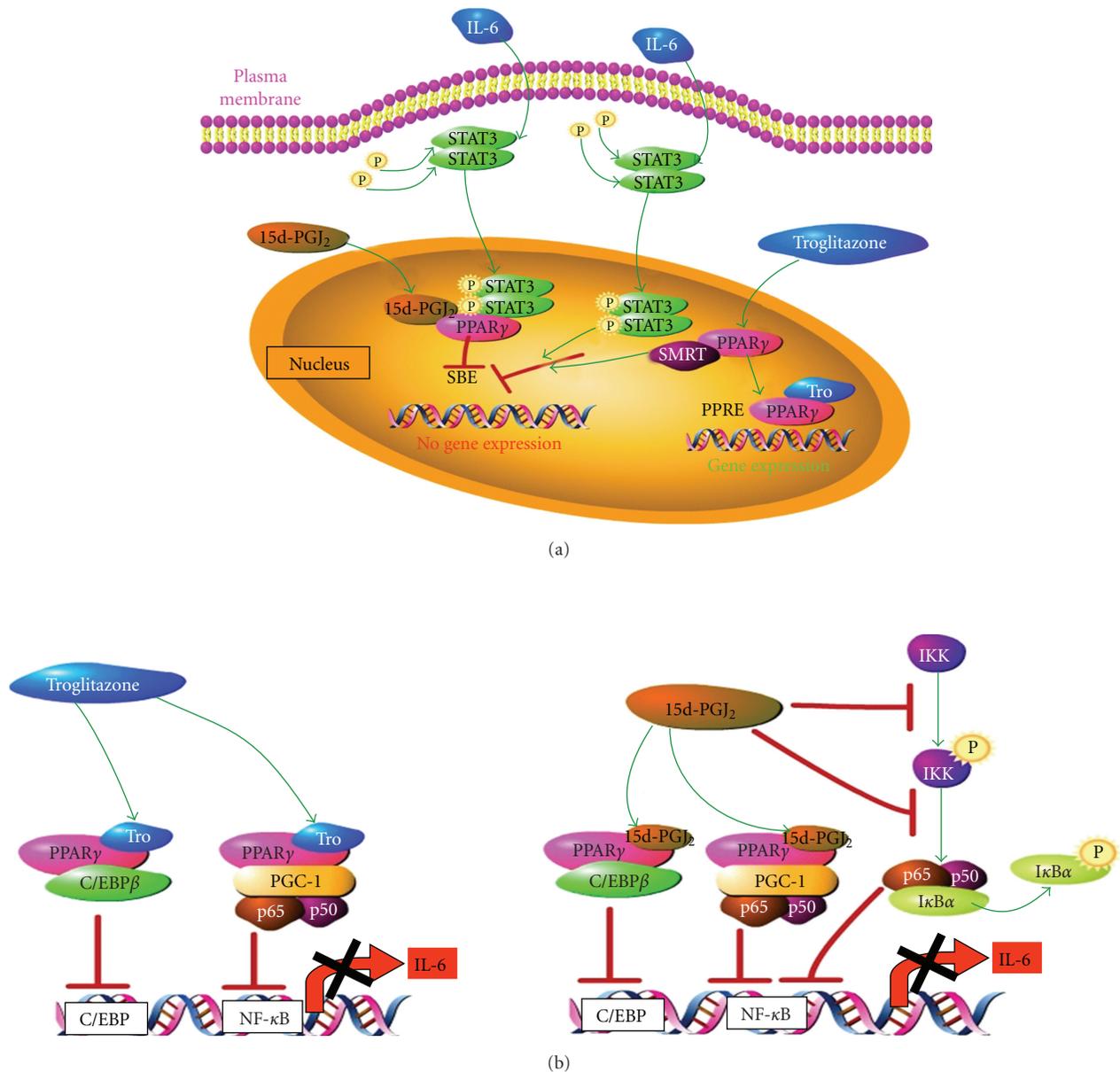


FIGURE 3: PPAR γ agonists inhibit Stat3-mediated IL-6 gene expression in myeloma cells. Inactivation of IL-6-activated Stat3 by PPAR γ agonists occurs in a PPAR γ -dependent manner; however, the molecular mechanisms by which two distinct PPAR γ agonists (15d-PGJ₂ and troglitazone) suppress IL-6-activated Stat3 in MM cells differ as shown in (a) [211]. Direct complex formation between phosphorylated Stat3 and PPAR γ activated by 15d-PGJ₂ prevents Stat3 binding to its cognate response element (SBE) on the promoters of target genes ((a), left). This mode of transcriptional inactivation does not require binding of the activated PPAR γ transcription factor to DNA in the promoter region and, thus, can occur in the absence of a PPRE. However troglitazone activated PPAR γ promotes redistribution of the corepressor SMRT from PPAR γ to phosphorylated Stat3 so that Stat3 can no longer recruit the transcriptional machinery necessary for gene expression ((a), right) [211]. High levels of IL-6 are found in MM and promote myeloma cell proliferation and survival and indirectly promote tumor-associated angiogenesis. The PPAR γ agonists troglitazone and 15d-PGJ₂ have been shown to inhibit transcription of the IL-6 promoter driven by C/EBP β and NF- κ B [212]. Troglitazone-activated PPAR γ binds to C/EBP β preventing binding to its cognate response element on the IL-6 promoter, which is the major mechanistic pathway of troglitazone-mediated downregulation of IL-6 expression. In addition activated PPAR γ competes with NF- κ B for the PGC-1 coactivator, which leads to decreased NF- κ B binding to the κ B response element on the IL-6 promoter contributing to inhibition of IL-6 gene expression, albeit to a lesser extent than inhibition of C/EBP β ((b), left). A slightly different mechanistic emphasis on PPAR γ -mediated inhibition of IL-6 gene expression occurs in response to 15d-PGJ₂. Although 15d-PGJ₂-activated PPAR γ inhibits C/EBP β -mediated transactivation of the IL-6 promoter similarly to troglitazone-activated PPAR γ , the predominant mode of inhibition is through 15d-PGJ₂-activated PPAR γ using the coactivator PGC-1 as a bridging protein to interact with NF- κ B to prevent transactivation of the IL-6 promoter. Furthermore, 15d-PGJ₂ inactivates NF- κ B by inhibiting phosphorylation of IKK and I κ B independently of PPAR γ activation ((b), right). The schematics in this figure were adapted from [211, 212].

activated pathways is required to efficiently induce apoptosis of MM cells in the marrow microenvironment [220].

It should be kept in mind that anti-VEGF/VEGFR-targeted therapy could occur through a number of mechanistic pathways, such as direct inhibition of VEGF-induced angiogenesis or indirectly through mechanisms that inhibit expression of additional proangiogenic factors, promote apoptosis, or induce tumor dormancy [88, 221]. Rather than target the VEGF-signaling pathway, it may be possible to alter the phenotype of the angiogenic endothelium. The angiogenic EC phenotype is characterized by marked downregulation of CD36/fatty acid translocase (FAT) [222]. CD36 is a glycoprotein associated with normal and pathologic processes including scavenger receptor functions, lipid metabolism and fatty acid transport, cell adhesion, angiogenesis, modulation of inflammation, activation of TGF- β , atherosclerosis, diabetes, and cardiomyopathy [223]. PPAR α regulates expression of CD36 in mouse liver and PPAR γ regulates its expression in mouse adipose tissues [224, 225]. Furthermore, statins and PPAR γ ligands together have an additive effect on upregulation of CD36 production by potentiating the transcription of the CD36 gene in monocytes [226]. CD36 is the cellular receptor for TSP-1 on microvascular endothelium and is necessary for its antiangiogenic, proapoptotic activity, making CD36 an attractive target for development of therapeutic agents [227].

Vascular endothelium expression of CD36 is sporadic however, with lower levels of expression in larger vessels [196, 228]. As discussed in Section 2.4, loss of endogenous inhibitors of angiogenesis in favor of proangiogenic factors produced by tumors leads to tumor-associated angiogenesis. A small peptide (ABT510) derived from TSP-1 type 1 repeats binds to CD36 and blocks tumorigenesis by reversing the “angiogenic switch” [229]. Huang et al. [196] demonstrated that 15d-PGJ₂, troglitazone, and rosiglitazone potentiate the antitumor activity of AB510 in a CD36-dependent manner. Furthermore, these ligands upregulated EC expression of PPAR γ and CD36 [43, 196], which likely leads to the synergistic inhibition of tumor-associated angiogenesis and induction of EC apoptosis in vivo [196]. Importantly, lower doses of PPAR γ agonists could be used in combination with AB510 to significantly reduce tumor-associated angiogenesis and promote EC apoptosis. This study provides compelling evidence that PPAR γ ligands could be useful as adjuvant or combination therapy in treatment of tumor angiogenesis.

Another important molecular mechanism to target for intervention of cancer progression in hematological malignancies is regulation of stromal matrix remodeling by proteases [193, 230]. PAI-1 production by ECs inhibits plasmin-mediated proteolytic degradation of the ECM. PPAR γ ligands upregulate expression and release of PAI-1 from ECs [193], which would inhibit degradation of tumor-associated fibrin leading to EC migration, proliferation, and angiogenesis [231]. PPAR γ ligands inhibit the adhesion of the myeloid leukemia HL-60 and K562 cells to the ECM as well as their invasion through Matrigel [230]. In addition, 15d-PGJ₂ and troglitazone in both the HL-60 and K562 cell lines significantly inhibited MMP-9 and MMP-2 expression and proteolytic activities. The results of this study suggest

that PPAR γ ligands may inhibit leukemic cell adhesion to and invasion through the ECM as well as regulate angiogenesis by inhibiting matrix remodeling that favors cancer cell invasion and EC migration [230].

2.9. MicroRNAs and PPAR γ Agonists in Hematological Malignancies. MicroRNAs (miRNAs) are short noncoding RNAs that function as negative regulators of the stability and/or translation of specific target mRNAs [232–234]. Typically, miRNAs target a cluster of genes instead of one specific gene, and a single miRNA can have more than 100 targets [233, 235]. Regulation of gene expression by miRNAs is increasingly being accepted as a pivotal point in cell function, either in normal development or disease states (recently reviewed in [234, 236–238]). Mature miRNAs derive from primary miRNA transcripts that are either transcribed from their own promoter regions [239] or processed introns spliced from pre-mRNAs [240]. Primary miRNAs are first processed in the nucleus by the RNase III endonuclease, Drosha, to form pre-miRNAs [241]. Pre-miRNAs are exported out of the nuclear compartment into the cytoplasm by exportin-5 [242]. Once in the cytoplasm, the pre-miRNA is further processed by another RNase III endonuclease, Dicer [243]. Finally, the mature miRNA is loaded onto the Argonaute (Ago) protein and incorporated into the ribonucleoprotein complex, RISC (RNA induced silencing complex) [244], which directs the miRNA to its target mRNA. Mature miRNAs primarily bind to transcripts through imperfect Watson-Crick base pairing to conserved miRNA binding sites in the 3′ untranslated region (UTR) of target mRNAs [234, 245]. The ability of miRNAs to regulate the expression of numerous genes at once often leads to pleiotropic effects and can modulate multiple cellular pathways.

There is growing evidence that dysfunctional expression of miRNAs is a common feature of malignancy in general and hematological malignancy in particular [233, 246]. Aberrant miRNAs have been documented in almost all hematological malignancies [247]. For example, Calin and colleagues [248] first implicated miRNAs in hematological malignancies when they demonstrated that miR-15 and miR-16 are frequently deleted or downregulated in CLL associated with deletions on chromosome 13q14. Deletion or downregulated expression of miR-15a and miR-16 on chromosome 13 is also found in MM cells [249]; deletion of chromosome 13 predicts significantly reduced survival in patients with MM [250]. In 2005, another group reported that the polycistronic precursor transcript of the miR-17~92 cluster, which encodes seven different miRNAs, is overexpressed in human B cell lymphomas and acts as an oncogene [251]. The miR-17~92 cluster is amplified and/or overexpressed in other hematological malignancies including AML [252, 253] and MM [246], as well as cancers of epithelial origin such as lung [254], thyroid [255], and hepatocellular [256] carcinomas. Overexpression of miR-21 occurs in MM [246, 257] and other cancers including glioblastoma [258] and breast cancer [259]. Thus, there is enormous hope that miRNA research will provide breakthroughs in the understanding of cancer pathogenesis and in the development of new prognostic markers [260].

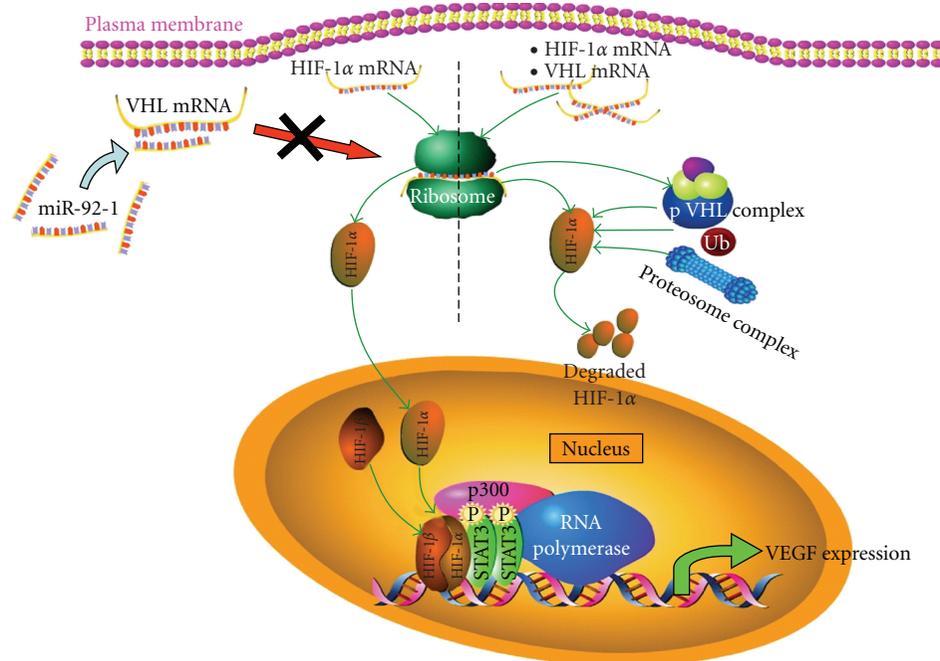


FIGURE 4: Autocrine production of VEGF in CLL B cells is regulated by miRNA-92-1 inhibition of pVHL production. Expression of high levels of VEGF by tumor cells is critical to promote and sustain the angiogenesis needed for cancer progression. Under normal oxygen tension, the HIF-1 α subunit of the transcription factor, HIF-1, is constitutively produced and rapidly degraded by pVHL-induced proteasomal degradation, which prevents transcription of the VEGF gene. In solid tumors, HIF-1-induced VEGF expression occurs when tumor growth exceeds the dimensions where existing blood vessels can feed the tumor and carry away waste products. The resulting hypoxia leads to stabilization of HIF-1 α and activation of the HIF-1 heterodimer resulting in high VEGF production by tumor cells. Although solid tumors do not develop in hematological malignancies, angiogenesis is an important process of disease progression. CLL B cells constitutively express high levels of VEGF and VEGFRs leading to autocrine signaling and increased resistance to apoptosis. Recently, Ghosh et al. [273] discovered that HIF-1 is stabilized in CLL B cells due to low levels of pVHL as a result of miR-92-1 overexpression and subsequent repression of translation of the VHL transcript. Therefore, HIF-1 accumulates and translocates to the nucleus where it forms an active complex with the transcriptional coactivator p300 and phosphorylated Stat3 and, together with the basal transcription machinery, transactivates the VEGF promoter. PPAR γ agonists could potentially inhibit overexpression of VEGF by inhibiting Stat3 signaling in CLL B cells. The schematic in this figure was adapted from [273].

Kuehbacher et al. [261] recently reviewed miRNAs that possess proangiogenic or antiangiogenic function. The miR-17~92 cluster, let-7f, and miR-27b possess proangiogenic functions, in part, by inhibiting expression of TSP-1 and CTGF. A role for miR-221 and miR-222 in blocking angiogenesis is suggested by their ability to inhibit EC migration, proliferation, and angiogenesis in vitro. In addition, miR-21 is implicated in the invasive and metastatic properties of colon and breast cancer cell lines by targeting multiple tumor suppressor genes, such as PTEN, TPM1, and MASPIN [259, 262, 263]. Moreover, miR-21 overexpression, which occurs in MM as discussed below, is associated with advanced clinical disease, lymph node metastasis and poor prognosis for overall survival in breast cancer [264]. The Sessa group demonstrated that a functional miRNA biogenesis pathway is required for angiogenesis [265, 266]. Inactivation of Dicer, the miRNA processing enzyme, impairs angiogenesis induced by multiple stimuli such as VEGF, and during tumorigenesis and wound healing [266]. VEGF also induces the expression of several proangiogenic miRNAs including the miR-17~92 cluster [266]. Furthermore, miR-130a

functions in angiogenesis by inhibiting expression of two antiangiogenic homeobox transcription factors, HOXA5 and GAX [267].

Although the mechanisms regulating expression of miRNAs are only beginning to be understood [234, 236–238, 268, 269], key regulators of the biosynthetic pathway are often abnormally expressed in hematological malignancies [270]. Recently, Löffler and colleagues [257] demonstrated that survival of IL-6-dependent MM cells involves Stat3-mediated induction of miR-21. Two bona fide IL-6 type II-response elements for Stat3 binding are located upstream of the miR-21 genes of various vertebrate species [257]. Stat3 regulates transactivation of several anti-apoptotic genes such as survivin, Bcl-2, and Mcl-1. Löffler et al. [257] suggest that Stat3 induction of miR-21 represents a “slow-acting yet long-lasting” survival stimulus to complement the immediate induction of anti-apoptotic proteins. The cancers in which miR-21 is overexpressed contain constitutively activated Stat3 for survival or growth [257]. These results suggest that miR-21 is important for the oncogenic potential of Stat3 in the pathogenesis of MM and other malignancies.

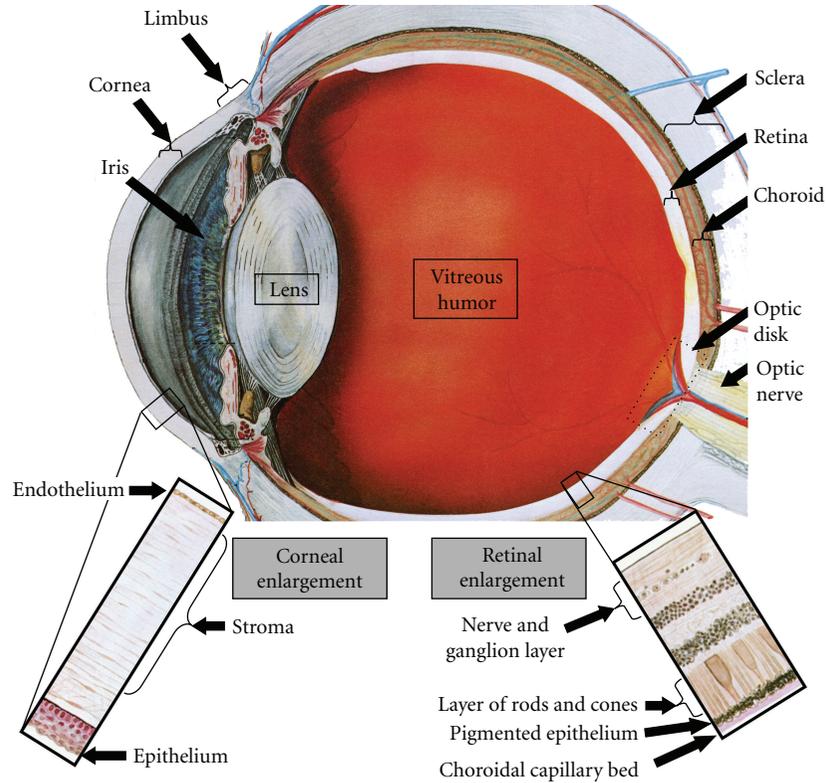


FIGURE 5: PPAR γ is broadly expressed in the eye providing a pharmacological target for treating ocular angiogenesis. PPAR γ expression is found in the retina including RPE cells, REC, pericytes [287], and ganglion cells. In the cornea, PPAR γ is most prominently localized in the epithelial and endothelial layers. Excessive angiogenesis is a pathological hallmark of a number of eye diseases, and anti-VEGF/VEGFR strategies are used therapeutically to treat ocular neovascularization. Manifestations of hematological malignancies in the eye have been documented for leukemia, lymphoma, and multiple myeloma. The potential benefits of PPAR γ agonist therapy to inhibit tumor-associated angiogenesis could also be applied to treatment of neovascular eye diseases.

IL-6-mediated activation of Stat3 is also important for transformation of nonmalignant breast epithelial cells to self-renewing mammospheres that contain CSCs [271]. Inflammation in cancer leads to elevated IL-6 production by two mechanisms: Src-mediated activation of NF- κ B leading to transactivation of the IL-6 gene, and rapid degradation of let-7 miRNA, which is a direct inhibitor of IL-6 expression [271]. Let-7 is downregulated in some cancers including Burkitt lymphoma [272] thereby leading to elevated IL-6 production, likely due to activation of the oncogenic NF- κ B-IL-6-Stat3 inflammatory pathway. In that the PPAR γ agonist CDDO-Me inactivates Src and Stat3 in cancer cells [215], further investigation of the efficacy of various PPAR γ ligands as anticancer agents is certainly warranted.

Recently, Roccaro and colleagues [249] identified a multiple myeloma-specific miRNA signature characterized by downexpression of miR-15a and miR-16 and overexpression of miR-222, miR-221, miR-382, miR-181a, and miR-181b in bone marrow-derived CD138+ MM cells. Both miR-15a and miR-16 regulate proliferation and growth of plasma cells by inhibiting Akt and MAPK cell survival signaling pathways. However, both miR-15a and miR-16 are deleted on chromosome 13 associated with MM [249] thereby preventing normal repression of cell proliferation during cancer

progression. Pichiorri et al. [246] also identified an miRNA signature associated with MM pathogenesis. Overexpression of miR-21, the miR-106b~25 cluster, and miR-181a and miR-181b was found in MM and monoclonal gammopathy of undetermined significance (MGUS) samples. On the other hand, selective upregulation of miR-32 and the miR-17~92 cluster was identified only in MM cells. Expression of suppressor of cytokine signaling (SOCS)-1, involved in negative feedback regulation of Jak/Stat signaling, is downregulated by miR-19a and miR-19b thereby leading to sustained IL-6-mediated MM cell proliferation [246]. Furthermore, miR-19a, miR-19b, miR-181a, and miR-181b antagonists suppress human MM tumor cell growth in nude mice, suggesting that miRNAs that modulate the expression of proteins critical to myeloma pathogenesis, including the IL-6-regulated Stat3 pathway, are potential targets for development of new therapeutic strategies for treatment [246].

The Stat3-regulated gene, HIF-1 α , is constitutively expressed under normoxia in CLL B cells, most likely as a result of low production of pVHL, which is responsible for HIF-1 α degradation. Ghosh and colleagues [273] demonstrated that overexpression of miR-92 in CLL B cells targets the VHL transcript to repress its translation (Figure 4). Furthermore, stabilized HIF-1 α forms an active complex

with the transcriptional coactivator p300 and activated Stat3 on the VEGF promoter, which likely explains the anomalous autocrine VEGF secretion from CLL B cells [273]. In that PPAR γ agonists inhibit the IL-6-regulated Stat3 signaling cascade, a role for PPAR γ agonists in regulating expression of miRNAs critical to the pathogenesis of hematological malignancies may be an important avenue of future scientific investigations.

Recently, miRNAs have emerged as epigenetic regulators of metabolism and energy homeostasis [274]. It is clear that there is an obesity epidemic in the United States [275]. Increased body weight is associated with increased mortality for most all types of cancers including hematological malignancies [276]. Additional studies have confirmed that obesity puts patients at a moderate increased risk of developing MM [276–279], and that this risk may be higher in women than men [279]. An important link between obesity and MM is elevated expression of IL-6 in adipose tissue [280] and bone marrow [207], which also leads to elevations in circulating IL-6. Lin et al. [274] demonstrated that the miR-27 gene family is downregulated during adipogenic differentiation. Furthermore, overexpression of miR-27 specifically inhibits adipocyte formation and expression of PPAR γ and C/EBP α , the two master transcriptional regulators of adipogenesis. Although PPAR γ and C/EBP α mRNA and protein levels were markedly reduced by miR-27a or miR-27b, it was not a direct miRNA effect [274]. Expression of miR-27 is increased in fat tissue of obese mice and is regulated by hypoxia, an important extracellular stress associated with both obesity and cancer. During adipogenesis the expression of miR-27b, an important regulator of angiogenesis, is downregulated in human adipogenic stem cells, and PPAR γ mRNA expression increases concomitantly with decreasing miR-27b expression [281]. Both miR-27a and miR-27b directly bind RXR α mRNA and regulate RXR α translation in rat hepatic stellate cells [282]. It is well known that RXR α heterodimerizes with PPAR γ to activate numerous genes required for adipogenesis and energy metabolism. These data suggest that miR-27 represents a new class of adipogenic inhibitors and their downregulation may play a role in the pathological development of obesity [274]. Furthermore, in that PPAR γ is a master regulator of adipogenesis and target of insulin sensitizing drugs, it is reasonable to consider that the beneficial effects of PPAR γ agonists in cancer treatment may be exerted through regulation of energy homeostasis, at least in part, by modulation of miRNA expression. Indeed, the anticarcinogenic activity of one of the triterpenoids is due to repression of oncogenic miR-27a [283].

All known forms of the human PPAR γ mRNA contain numerous miRNA binding sites in the 3'UTR as predicted through different bioinformatic algorithm databases (TargetScan [284], miRanda [285], PicTar [286]). The miRNA binding sites for miR-27a/b, miR-130a/b, miR-301, miR-34a/b in the PPAR γ 3'UTR are conserved in human, chimp, mouse, and rat. Notably, two conserved binding sites for miRNAs in the PPAR γ 3'UTR are for miR-27b and miR-130a that have angiogenic or proliferative functions. It would be interesting to determine whether these miRNAs suppress PPAR γ function during angiogenesis and/or tumor growth.

This could lead to identification of novel targets that may induce PPAR γ expression leading to the anticancer functions of cell differentiation and loss of proliferation. However, a role for PPAR γ agonists in miRNA-based therapeutic strategies to treat cancer awaits further clarification by new research endeavors.

3. Anticancer Role of PPAR γ Agonists as Adjuvant or Combination Therapy in Hematological Malignancies of the Eyes

3.1. Ocular Hematological Malignancy. Ocular lymphoma is relatively uncommon, accounting for 5–10% of all extranodal lymphomas [288]. However, it is one of the most common orbital malignancies and it is increasing in incidence because of its association with the acquired immunodeficiency syndrome (AIDS) [289]. Ocular lymphoma can be divided into intraocular and adnexal disorders, the former, including malignant lymphoid cells, invade the retina, vitreous body, or optic nerve head; the latter include conditions affecting the eyelid, the conjunctiva, the lacrimal gland, and the orbit [290]. Primary intraocular lymphoma (PIOL) is a subset of primary central nervous system lymphoma. It is usually a large B-cell NHL [291]. PIOL typically presents as a vitritis that is unresponsive to corticosteroid therapy. Diagnosis of PIOL requires pathologic confirmation of malignant cells in specimens of the cerebrospinal fluid, vitreous, or chorioretinal biopsies. The extranodal marginal zone lymphoma (mucosaassociated lymphoid tissue lymphoma) is the dominant lymphoma subtype in the orbit and ocular adnexa. Extranodal marginal zone lymphoma is considered to be the neoplastic counterpart of the marginal zone cells in reactive follicles [292]. Although optimal therapy has yet to be determined [293], it is believed that PIOL should be treated with a combination of chemotherapy and radiation.

Ocular involvement is common in patients with acute leukemia and has been described in up to half of patients at the time of diagnosis [294]. Eye involvement may be due to leukemic infiltration of various ocular tissues or as a result of one of the secondary complications of the disease [295]. These complications include anemia, thrombocytopenia, and leukostasis, which can lead to retinal hemorrhaging and ischemia [294]. Hemorrhaging in the retina is the most striking feature of ocular leukemia. Furthermore, retinal microaneurysms, capillary closure, and neovascularization have been documented in individuals with chronic leukemia [296, 297]. The treatments include chemotherapy, radiation, or bone marrow transplantation. Ocular findings may be the first manifestation of MM [298]. It may also occur as one of the extramedullary manifestations of the disease or as the first sign of insufficient chemotherapy. MM causes ocular pathology by direct infiltration or as extramedullary plasmacytomas resulting in the displacement or compression of tissues causing hyperviscosity syndrome and immunoglobulin light chain deposition in ocular tissues. Virtually any ocular structure can be affected, including the conjunctiva, cornea, sclera, lens, retina, optic nerve, lacrimal glands, and orbit [298] (Figure 5).

3.2. Ocular Neovascularization. Ocular angiogenesis or ocular neovascularization, the abnormal growth of blood vessels in the eye, is the hallmark of the vast majority of eye diseases that cause a catastrophic loss of vision including diabetic retinopathy, AMD, retinopathy of prematurity, and vein occlusion retinopathy [299, 300]. The new vessels may grow into nearly all mature ocular tissue and affect the cornea, iris, retina, and optic disk [301]. They are structurally weak, both leaking fluid and lacking structural integrity. Moreover, the resultant hemorrhage, exudate, and accompanying fibrosis often cause blindness [302].

The cornea is a highly organized transparent tissue located in the anterior part of the eye and it is normally avascular. However, under certain conditions, such as corneal trauma, chemical burns, infection, and inflammation, the development of new blood vessels starts from the vessel of the limbal area (Figure 5). Newly formed blood vessels cover the corneal surface [303], which can lead to severe or permanent visual impairment [302]. The choroid is the layer of blood vessels and connective tissue between the sclera and retina and supplies nutrients to the inner parts of the eye [304]. Choroidal neovascularization (CNV) is associated with many other conditions, such as AMD, inflammatory, infectious, degenerative, hereditary, congenital disorders, tumors, trauma, and a few miscellaneous ocular disorders [302]. In CNV, neovascular channels grow from the choroidal vasculature and extend into the subretinal space leading to local tissue damage. Activation and migration of choroidal ECs (CECs) and retinal pigment epithelial (RPE) cells into the CNV membranes play an important role in the development of the lesion [305]. The mammalian retina is a light sensitive tissue lining the inner surface of the eye, which is composed of multiple cell-types organized within defined layers. It has a dual blood supply from the central retinal artery and the choroidal blood vascular system [304]. Neovascularization of the retina is a critical part of the disease process associated with retinopathy in diabetes, prematurity, and sickle cell disease [302].

3.3. Expression of PPAR γ in the Eye and Effects on Ocular Neovascularization. PPAR γ expression in the mammalian eye has been reported prominently in retina [306, 307] including RPE cells [194, 308, 309], retinal capillary ECs (REC) [310, 311], retinal pericytes [287], and retinal ganglion cells [312]. PPAR γ is most prominently localized in the epithelial and endothelial layers of the cornea [198]. PPAR γ is also found in CECs [194] and in orbital fibroblasts [313, 314]. The broad expression of PPAR γ in the eye provides a pharmacological target for treating ocular angiogenesis.

In vivo alkali-burned mouse cornea experiments showed that neovascularization and scar formation are suppressed by introduction of PPAR γ gene expression. PPAR γ overexpression suppressed monocyte/macrophage invasion and suppressed the generation of myofibroblasts, as well as upregulation of inflammation/scarring-related growth factors (TGF- β , CTGF, and VEGF) and MMPs in a healing cornea. In vitro experiments showed that overexpression of PPAR γ suppressed epithelial cell expression of MMP-2/-9 and TGF- β 1,

inhibited cell migration, and suppressed myofibroblast generation upon exposure to TGF- β 1. Thus, adenoviral-driven expression of the PPAR γ gene led to inhibition of the anti-inflammatory and antifibrogenic responses induced in an alkali-burned mouse cornea, and also inhibited activation of ocular fibroblasts and macrophages in vitro [12]. In a VEGF-induced neovascular rat cornea model, intrastromal implantation of the PPAR γ ligands pioglitazone [198] or 15d-PGJ₂ [22] resulted in decreasing MVD, indicating inhibition of ocular angiogenesis. Furthermore, systemic oral administration of rosiglitazone and troglitazone significantly inhibits vessel growth in a dose-dependent fashion in a model of FGF-2-induced mouse corneal neovascularization [195].

PPAR γ ligands troglitazone and rosiglitazone inhibit VEGF-induced cell proliferation and migration in bovine CECs and human RPE cells in vitro. Troglitazone also inhibits VEGF-induced tube formation (neovascularization) of CECs [194]. Troglitazone pretreatment can significantly prevent TGF- β -induced epithelial-mesenchymal transition of human RPE cells, and retard cell migration [315]. In vivo, laser photocoagulation induced CNV was markedly inhibited by intravitreal injection of troglitazone in rat and monkey eyes. The lesions showed significantly less fluorescein leakage and were histologically thinner in the troglitazone-treated animals without apparent adverse effects in the adjacent retina or in control eyes [194], indicating that the PPAR γ ligands are logical for therapy to suppress vascular permeability in the eye.

PPAR γ agonists, troglitazone, rosiglitazone, Pioglitazone, RWJ241947, and 15d-PGJ₂, inhibit proliferation of human REC and pericytes in vitro through a PPAR γ -independent pathway [316]. TZDs downregulate cyclin E (S-phase cyclin) and cyclin A (G2/M-phase cyclin) resulting in cell cycle arrest [316]. Troglitazone and rosiglitazone inhibit VEGF-induced proliferation and tube formation by bovine REC in collagen gels, and inhibit VEGF-induced REC migration in a dose-dependent manner [311]. Retinal angiogenesis is induced in newborn mice by oxygen-induced ischemic injury; however, intravitreal injection of troglitazone or rosiglitazone markedly reduced development of retinal neovascular tissue [311]. In the chick chorioallantoic membrane model of angiogenesis, pioglitazone and rosiglitazone significantly inhibit EC migration as well as the proangiogenic effects of FGF-2 and VEGF [27]. Rosiglitazone may delay the onset of proliferative diabetic retinopathy, possibly because of its antiangiogenic activity [317].

Taken together, these studies demonstrate that PPAR γ ligands are potent inhibitors of angiogenesis in vivo and in vitro, and suggest that PPAR γ may be an important molecular target for inhibiting angiogenesis. The use of PPAR γ ligands to prevent pathological angiogenesis holds great potential as a novel therapeutic for neovascularized eye diseases. It may also apply to other neovascularization-related diseases, including hematological malignancies of the eye. However, future clinical investigations should consider analysis of the potential benefits of PPAR γ agonist treatment along with ongoing evaluation of potential cardiac risk in studies where the risk-benefit profiles are deemed appropriate [317].

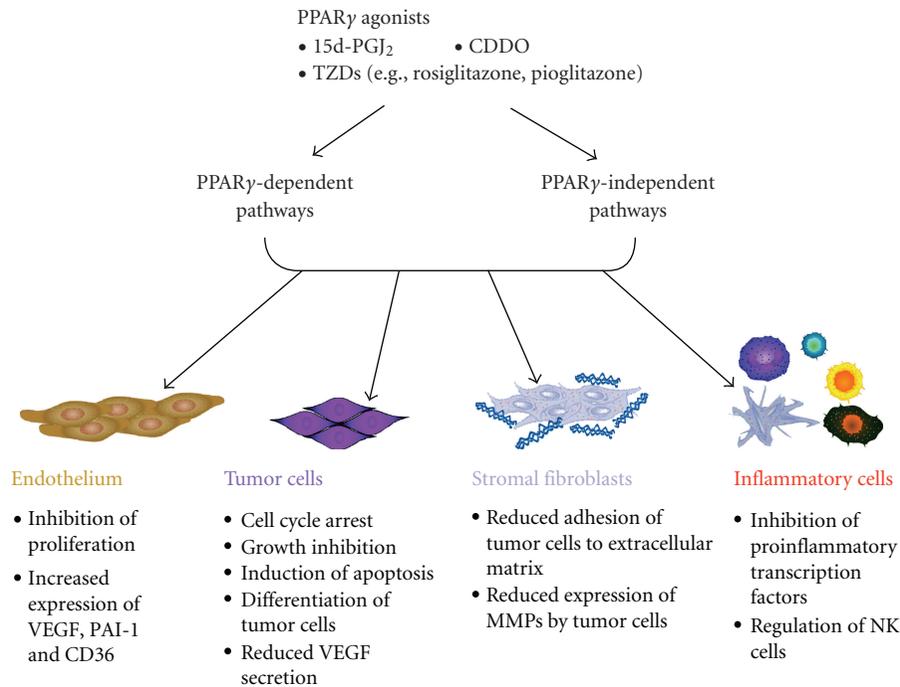


FIGURE 6: Direct and indirect effects of PPAR γ agonists on tumor and stromal cells. “Off-target” (PPAR γ -independent) effects of PPAR γ agonists frequently occur when the agonists are used at high concentrations (much higher than needed to activate PPAR γ by ligand binding) and in response to electrophilic PPAR γ agonists such as 15d-PGJ₂ and CDDO, which can promote covalent bond formation with cellular proteins in a redox-sensitive manner to modulate signal transduction pathways. PPAR γ agonists have been shown to affect almost every stage of tumor progression from inhibition of uncontrolled tumor growth, induction of apoptosis, inhibition of tumor cell adhesion and invasion through stromal compartments into or out of the blood stream, and inhibition of tumor-associated angiogenesis. PPAR γ agonists induce expression of tumor-inhibiting molecules such as CD36, the EC receptor for TSP-1, as well as promote the differentiation of tumor cells, which tends to reduce their invasive and metastatic capabilities. The schematic in this figure was adapted from [181].

4. The Paradox of PPAR γ as a Molecular Target in Anticancer Therapy

The aforementioned studies examining the role of PPAR γ ligands for treatment of hematological, ocular, and solid malignancies is by no means a complete review of the available literature. The list of off-target effects of PPAR γ agonists continues to grow [51]. Furthermore, many of the published studies suggesting that PPAR γ ligands exert antitumor properties did not determine whether the effects required ligand activation of the PPAR γ transcription factor per se (Table 3). Many human cancer cell lines express high levels of PPAR γ , which when treated with high concentrations of TZDs, undergo cell cycle arrest, apoptosis, or differentiation, suggesting a link between PPAR γ signaling and their antitumor activities. In contrast, mounting evidence refutes the dependence of the antitumor effects of TZDs on PPAR γ activation [25, 51, 318]. Of note, the off-target effects of PPAR γ ligands usually occur at much higher concentrations than those required for ligand-dependent PPAR γ effects, and there is no correlation between the expression levels of PPAR γ in cancer cells and their sensitivity to TZDs [25, 51, 318]. Indeed, PPAR γ agonists exert pleiotropic effects on signal transduction pathways involved in cell proliferation, survival and differentiation [25, 51, 71, 188, 318–322] (Table 3 and Figure 6).

Currently, two PPAR γ agonists belonging to the TZDs remain on the market, rosiglitazone (Avandia) and pioglitazone (Actos). In 2000, troglitazone (Resulin) was removed from the market due to severe hepatotoxicity. Moreover, the incidence of delayed drug-induced liver injury that progresses after discontinuation of drug therapy, and whether such injury is specific to just troglitazone or TZDs as a class of drugs, remains unknown [323]. Additional adverse effects associated with TZDs used for insulin sensitizing therapy include edema, weight gain, macular edema, and heart failure [323, 324]. TZDs may cause hypoglycemia when combined with other antidiabetic drugs as well as decrease hematocrit and hemoglobin levels. Furthermore, an increased risk of bone fracture is linked to TZD therapy [324, 325]. When considering the use of PPAR γ agonists as adjuvant or combination therapy in hematological malignancies, it will be important to design appropriate preclinical studies that assess the severity of these side effects in the context of each type of cancer. For example, increased edema is associated with increased vascular permeability. The loss of endothelial barrier integrity leads to increased vascular permeability, enhanced transendothelial migration, and metastatic spread of cancer cells [75]. Thus, the potential for TZDs to promote rather than prevent the metastatic spread of cancer should be considered. The malignant proliferation of plasma cells in MM produces skeletal lesions

leading to bone pain and pathologic fractures such as vertebral compressions [326]. In that TZDs are associated with increased risk of bone fractures; the use of TZDs for treatment of MM must be evaluated as well.

Evidence suggesting that the effects of TZDs on improving endothelial-dependent vascular function and decreasing inflammatory biomarkers independently of insulin-sensitizing effects came from studies reporting the effects of TZDs in diabetic and nondiabetic individuals with atherosclerosis [327–329]. In general, PPAR γ agonists inhibit tumor-associated angiogenesis by inhibiting FGF-2- and VEGF-induced EC growth, invasion and migration in vitro and in vivo [27, 192], downregulate expression of VEGF by tumor cells [195, 199] and VEGFRs by EC [32], and decrease tumor-associated MVD [24, 32, 198] and EC tube formation [202], measures of angiogenesis in vivo and in vitro, respectively. TZDs inhibit pathological angiogenesis associated with diabetic retinopathy [287, 317], as well as choroidal and retinal neovascularization [194, 198, 311], and suppress primary tumor growth and metastasis by inhibiting angiogenesis [35] (Table 3). Interestingly, in contrast to these reports, TZDs increase VEGF expression in human vascular smooth muscle cells [330] and promote angiogenesis after ischemia [331]. Additional reports suggest that PPAR γ ligands are capable of promoting angiogenesis by inducing VEGF expression [28, 30, 203].

Huang and colleagues [30] have suggested that pioglitazone has different effects on pathological angiogenesis compared to ischemia-induced collateral vessel growth [332]. TZDs promote differentiation of EPCs/APCs towards the endothelial lineage [197, 200, 201], consistent with the idea that PPAR γ ligands have differential effects on angiogenesis needed for restoration of homeostasis in cardiovascular disease or diabetes compared to pathological angiogenesis associated with cancer progression. The role of PPAR γ and its ligands in inhibiting or promoting angiogenesis is likely context dependent (Section 2.7 and Table 3) [30, 332]; thus, the use of PPAR γ ligands alone or in addition to antiangiogenic agents for treatment of hematological malignancies will require a better understanding of the effects of PPAR γ agonists on EC function during pathological angiogenesis.

Many studies have demonstrated beneficial effects of PPAR γ agonists on atherosclerosis and ischemia reperfusion injury by reducing inflammation, preventing restenosis after percutaneous coronary intervention, and in some instances, preventing myocardial infarction and cardiovascular death. Recently, however, a number of review articles have discussed the “rosiglitazone debate” about whether taking rosiglitazone puts patients at a higher overall risk of cardiovascular death. The higher risk is based on findings derived from meta-analyses of existing clinical trial data, the release of FDA safety warnings that rosiglitazone increases cardiac ischemic risk, manufacturer updates on TZD labels with a black-box warning for heart failure, as well as warnings and precautions about coadministration of rosiglitazone with nitrate or insulin [333–336]. TZDs are known to induce salt and water retention, which exacerbate the risk of congestive heart failure in patients with type 2 diabetes. Rosiglitazone is a more potent agonist of PPAR γ than pioglitazone, thus

increased fluid retention and salt imbalance may explain the higher risk of heart failure with this TZD [336]. However, even though treatment with rosiglitazone may, in general, be associated with a higher incidence of cardiovascular events, some studies suggest that there is no increase in all-cause or cardiovascular mortality observed with rosiglitazone treatment [333, 335]. Clearly, prospective randomized trials need to include outcomes measures to determine whether the TZDs and other such compounds under development put patients at a higher overall risk of cardiovascular death.

As cancer treatments improve, the number of patients who reach the 5-year benchmark of disease-free survival continues to grow. However, adverse effects of anticancer therapy may confound long-term survival. For example, as methods for detecting and treating breast cancer improve, survival of breast cancer patients is increasing but the side effects of adjuvant therapy, including cardiotoxicity, remain clinically important [337]. Agents commonly used for the treatment of breast cancer, including anthracyclines and trastuzumab, have been associated with cardiotoxicity [338], which ranges from subclinical to life-threatening pathology and even fatal results [339]. Imatinib (Gleevec) inhibits the continuously active tyrosine kinase, Bcr-Abl, which results from the translocation of chromosomes 9 and 22 and is effective for the treatment of CML as well as ALL; however, cardiotoxicity is a potentially serious side effect of this drug as well [340]. In that the TZD class of PPAR γ agonists is associated with adverse cardiovascular events, additional studies on the efficacy of PPAR γ agonists and other lead compounds as adjuvant or combination therapy to treat cancer should be designed to look at the cardiovascular risks and benefits in addition to their efficacy in treating the primary disease.

5. Conclusions

The goal to find a cure for all types of cancer is a major initiative of both public and private grant funding institutions and foundations. Thus, forwarding thinking researchers are exploring strategies to identify molecular expression profiles of cancer subtypes and CSCs, to optimize tumor imaging methods to identify cancer micrometastases, as well as to develop more-specific, less toxic drugs through medicinal chemistry to provide tailored therapy to treat and cure cancer in individual patients. However, metastatic disease remains the major cause of morbidity and mortality in both solid tumors and hematological malignancies. Because tumor-associated angiogenesis is critical for cancer progression and metastatic disease, the initiative to identify molecular targets and new or improved chemotherapeutic or biologic agents to inhibit angiogenesis is a high priority area of research in cancer medicine.

Specific areas of research where PPAR γ agonists may be further examined for efficacy in treatment of angiogenesis in hematological malignancies as well as comorbidities that affect quality of life for long-term cancer survivors include signal transduction pathways (e.g., Jak/Stat, PI3K/Akt, PTEN, mTOR) [181, 341, 342], aberrant/oncogenic miRNAs [246, 257, 261, 283, 343–345], targeting CSCs while

sparing normal hematopoietic stem cells, and correcting dysregulated metabolic pathways due to drug side effects such as hyperglycemia, hypertension, gastrointestinal toxicity, coagulation disorders, and depression associated with the neurotoxicity of chemotherapeutic drugs [341, 346–348]. Moreover, limitations in the experimental design of published studies should be carefully evaluated. A significant number of studies continue to use troglitazone as a PPAR γ agonist despite its having been pulled from the marketplace due to hepatotoxicity. In vitro experiments examining the efficacies of candidate drugs as inhibitors of angiogenesis need to reflect the complexity of the tumor microenvironment in keeping with the in vivo context. For example, large vessel ECs isolated from the veins of human umbilical cords (HUVECs) are frequently used to study angiogenesis by capillary tube formation in 2D-matrix configurations in vitro; however, in vivo tumor-associated angiogenesis occurs in a complex environment composed of multiple cell types including microvessel ECs and matrix constituents in a 3D-configuration. It will also be important to determine whether the therapeutic effects of PPAR γ agonists are due to off-target interactions. In conclusion, we hope that this paper has provided a conceptual framework upon which future studies will be designed to unravel the pleiotropic effects of PPAR γ in the context of the stromal microenvironment during tumor angiogenesis, growth and metastasis in hematological malignancies.

Abbreviations

15d- PGJ ₂ :	15-deoxy- Δ -12-14-prostaglandin J ₂	CTGF:	Connective tissue growth factor
Ago:	Argonaute	DIM #34:	1,1-bis[3'-(5-methoxyindolyl)]-1-(p-t-butylphenyl) methane
AIDS:	Acquired immunodeficiency syndrome	DLBCL:	Diffuse large B cell lymphoma
Akt/PKB:	v-akt murine thymoma viral oncogene homolog/protein kinase B	EC:	Endothelial cell
AMD:	Age-related macular degeneration	ECM:	Extracellular matrix
AML:	Acute myeloid leukemia	EPC:	Endothelial precursor cell
ANGPTL4:	Angiopoietin-like factor-4	FAT:	Fatty acid translocase
AP-1:	Activator protein 1	FGF-2:	Fibroblast growth factor-2
APC:	Angiogenic precursor cell	gp130:	Glycoprotein 130
APL:	Acute promyelocytic leukemia	HIF:	Hypoxia inducible factor
ARNT:	Aryl hydrocarbon nuclear translocator	HSF:	Hepatocyte stimulatory factor
B-ALL:	B type acute lymphoblastic leukemia	HSPG:	Heparan sulfate proteoglycan
Bcr-Abl:	Breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1/Philadelphia chromosome	HUVEC:	Human umbilical vein endothelial cell
BMSC:	Bone marrow stromal cell	IGF-1:	Insulin-like growth factor
C/EBP:	CAAT enhancer binding protein	I κ B:	Inhibitor of κ B
CAM:	Chorioallantoic membrane	LDL:	Low density lipoprotein
CDDO-Im:	CDDO C-28 imidazole	MAPK:	Mitogen-activated protein kinase
CDDO-Me:	CDDO C-28 methyl ester derivative	MASPIN:	Mammary serine protease inhibitor (tumor suppressor gene)
CDDO:	2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid	MCP-1/CCL2:	Macrophage chemotactic protein
CEC:	Choroidal endothelial cell	MIF:	Macrophage inhibitory factor
CLL:	Chronic lymphocytic leukemia	miRNA:	MicroRNA
CML:	Chronic myeloid leukemia	MM:	Multiple myeloma
CNV:	Choroidal neovascularization	MMEC:	Multiple myeloma derived endothelial cell
CSC:	Cancer stem cell	MMP:	Matrix metalloproteinase
CTCL:	Cutaneous T cell lymphoma	mTOR:	Mammalian target of the rapamycin
		MVD:	Microvessel density
		NF- κ B:	Nuclear factor κ B
		NHL:	Non-Hodgkin lymphoma
		NOD/SCID:	Nonobese diabetic/severe combined immune deficiency
		NRP:	Neuropilin
		p300/CBP:	Transcriptional coactivator protein/cAMP-response element-binding protein (CREB) binding protein
		PAI:	Plasminogen activator inhibitor
		PDGF:	Platelet derived growth factor
		PGC-1:	PPAR γ coactivator-1
		PI3K:	Phosphatidylinositol 3-kinase
		PIOL:	Primary intraocular lymphoma
		PLGF:	Placenta growth factor
		PPAR:	Peroxisome proliferator-activated receptor
		PPRE:	PPAR γ response element
		PTEN:	Phosphatase and tensin homolog (tumor suppressor gene)
		pVHL:	Protein von Hippel-Lindau
		REC:	Retinal capillary endothelial cell
		RISC:	RNA induced silencing complex
		RPE:	Retinal pigmented epithelial
		SBE:	Stat3 Binding Element
		SMRT/NCoR:	Silencing mediator for retinoid and thyroid hormone receptors/nuclear receptor corepressor
		SOCS:	Suppressor of cytokine signaling

Src: v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian); aka, p60-Src
 STAT: Signal transducer and activator of transcription
 TGF- α/β : Transforming growth factor
 TIMP: Tissue inhibitor of metalloproteases
 TNF- α : Tumor necrosis factor
 TPM1: Tropomyosin 1 (tumor suppressor gene)
 Tro: Troglitazone
 TSP: Thrombospondin
 TZDs: Thiazolidinediones
 UTR: Untranslated region
 VEGF: Vascular endothelial growth factor
 VEGFR: VEGF receptor
 VPF: Vascular permeability factor.

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References

- [1] D. J. Mangelsdorf, C. Thummel, M. Beato, et al., "The nuclear receptor super-family: the second decade," *Cell*, vol. 83, no. 6, pp. 835–839, 1995.
- [2] M. A. Lazar, "PPAR γ , 10 years later," *Biochimie*, vol. 87, no. 1, pp. 9–13, 2005.
- [3] T. M. Garcia-Bates, G. M. Lehmann, P. J. Simpson-Haidaris, S. H. Bernstein, P. J. Sime, and R. P. Phipps, "Role of peroxisome proliferator-activated receptor gamma and its ligands in the treatment of hematological malignancies," *PPAR Research*, vol. 2008, Article ID 834612, 18 pages, 2008.
- [4] I. Goldenberg, M. Benderly, and U. Goldbourt, "Update on the use of fibrates: focus on bezafibrate," *Vascular Health and Risk Management*, vol. 4, no. 1, pp. 131–141, 2008.
- [5] A. M. Sharma and B. Staels, "Review: peroxisome proliferator-activated receptor γ and adipose tissue—understanding obesity-related changes in regulation of lipid and glucose metabolism," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 2, pp. 386–395, 2007.
- [6] J. L. Evans, J. J. Lin, and I. D. Goldfine, "Novel approach to treat insulin resistance, type 2 diabetes, and the metabolic syndrome: simultaneous activation of PPAR α , PPAR γ , and PPAR δ ," *Current Diabetes Reviews*, vol. 1, no. 3, pp. 299–307, 2005.
- [7] P. Meerarani, J. J. Badimon, E. Zias, V. Fuster, and P. R. Moreno, "Metabolic syndrome and diabetic atherothrombosis: implications in vascular complications," *Current Molecular Medicine*, vol. 6, no. 5, pp. 501–514, 2006.
- [8] I. Palomo, M. Alarcon, R. Moore-Carrasco, and J. M. Argiles, "Hemostasis alterations in metabolic syndrome (review)," *International Journal of Molecular Medicine*, vol. 18, no. 5, pp. 969–974, 2006.
- [9] B. Staels, "PPAR agonists and the metabolic syndrome," *Therapie*, vol. 62, no. 4, pp. 319–326, 2007.
- [10] M. A. Jay and J. Ren, "Peroxisome proliferator-activated receptor (PPAR) in metabolic syndrome and type 2 diabetes mellitus," *Current Diabetes Reviews*, vol. 3, no. 1, pp. 33–39, 2007.
- [11] R. S. Rosenson, "Fenofibrate: treatment of hyperlipidemia and beyond," *Expert Review of Cardiovascular Therapy*, vol. 6, no. 10, pp. 1319–1330, 2008.
- [12] S. Saika, O. Yamanaka, Y. Okada, et al., "Effect of overexpression of PPAR γ on the healing process of corneal alkali burn in mice," *American Journal of Physiology*, vol. 293, no. 1, pp. C75–C86, 2007.
- [13] L. Michalik, B. Desvergne, N. S. Tan, et al., "Impaired skin wound healing in peroxisome proliferator-activated receptor (PPAR) α and PPAR β mutant mice," *Journal of Cell Biology*, vol. 154, no. 4, pp. 799–814, 2001.
- [14] R. Zhang and F. Zheng, "PPAR- γ and aging: one link through klotho?" *Kidney International*, vol. 74, no. 6, pp. 702–704, 2008.
- [15] M. S. Sulistio, A. Zion, N. Thukral, and R. Chilton, "PPAR γ agonists and coronary atherosclerosis," *Current Atherosclerosis Reports*, vol. 10, no. 2, pp. 134–141, 2008.
- [16] L. Villacorta, F. J. Schopfer, J. Zhang, B. A. Freeman, and Y. E. Chen, "PPAR γ and its ligands: therapeutic implications in cardiovascular disease," *Clinical Science*, vol. 116, no. 3, pp. 205–218, 2009.
- [17] H. Duez, J.-C. Fruchart, and B. Staels, "PPARs in inflammation, atherosclerosis and thrombosis," *Journal of Cardiovascular Risk*, vol. 8, no. 4, pp. 187–194, 2001.
- [18] D. M. Ray, S. L. Spinelli, J. J. O'Brien, N. Blumberg, and R. P. Phipps, "Platelets as a novel target for PPAR γ ligands: implications for inflammation, diabetes, and cardiovascular disease," *BioDrugs*, vol. 20, no. 4, pp. 231–241, 2006.
- [19] S. L. Spinelli, J. J. O'Brien, S. Bancos, et al., "The PPAR-platelet connection: modulators of inflammation and potential cardiovascular effects," *PPAR Research*, vol. 2008, Article ID 328172, 16 pages, 2008.
- [20] F. Akbiyik, D. M. Ray, K. F. Gettings, N. Blumberg, C. W. Francis, and R. P. Phipps, "Human bone marrow megakaryocytes and platelets express PPAR γ , and PPAR γ agonists blunt platelet release of CD40 ligand and thromboxanes," *Blood*, vol. 104, no. 5, pp. 1361–1368, 2004.
- [21] Z. Cao and Y. Zhou, "Thiazolidinediones may be effective in the prevention of stent thrombosis with DES," *Medical Hypotheses*, vol. 70, no. 2, pp. 329–332, 2008.
- [22] X. Xin, S. Yang, J. Kowalski, and M. E. Gerritsen, "Peroxisome proliferator-activated receptor γ ligands are potent inhibitors of angiogenesis in vitro and in vivo," *Journal of Biological Chemistry*, vol. 274, no. 13, pp. 9116–9121, 1999.
- [23] A. Margeli, G. Kouraklis, and S. Theocharis, "Peroxisome proliferator activated receptor- γ (PPAR- γ) ligands and angiogenesis," *Angiogenesis*, vol. 6, no. 3, pp. 165–169, 2003.
- [24] V. G. Keshamouni, D. A. Arenberg, R. C. Reddy, M. J. Newstead, S. Anthwal, and T. J. Standiford, "PPAR- γ activation inhibits angiogenesis by blocking ELR+CXC chemokine production in non-small cell lung cancer," *Neoplasia*, vol. 7, no. 3, pp. 294–301, 2005.
- [25] D. Panigrahy, S. Huang, M. W. Kieran, and A. Kaipainen, "PPAR γ as a therapeutic target for tumor angiogenesis and metastasis," *Cancer Biology and Therapy*, vol. 4, no. 7, pp. 687–693, 2005.

- [26] L. Piqueras, A. R. Reynolds, K. M. Hodivala-Dilke, et al., "Activation of PPAR β/δ induces endothelial cell proliferation and angiogenesis," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 27, no. 1, pp. 63–69, 2007.
- [27] A. Aljada, L. O'Connor, Y.-Y. Fu, and S. A. Mousa, "PPAR γ ligands, rosiglitazone and pioglitazone, inhibit bFGF- and VEGF-mediated angiogenesis," *Angiogenesis*, vol. 11, no. 4, pp. 361–367, 2008.
- [28] F. Biscetti, E. Gaetani, A. Flex, et al., "Selective activation of peroxisome proliferator-activated receptor (PPAR) α and PPAR γ induces neovascularization through a vascular endothelial growth factor-dependent mechanism," *Diabetes*, vol. 57, no. 5, pp. 1394–1404, 2008.
- [29] P. Fraisl, M. Baes, and P. Carmeliet, "Hungry for blood vessels: linking metabolism and angiogenesis," *Developmental Cell*, vol. 14, no. 3, pp. 313–314, 2008.
- [30] P.-H. Huang, M. Sata, H. Nishimatsu, M. Sumi, Y. Hirata, and R. Nagai, "Pioglitazone ameliorates endothelial dysfunction and restores ischemia-induced angiogenesis in diabetic mice," *Biomedicine and Pharmacotherapy*, vol. 62, no. 1, pp. 46–52, 2008.
- [31] E.-H. Kim and Y.-J. Surh, "The role of 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂, an endogenous ligand of peroxisome proliferator-activated receptor γ , in tumor angiogenesis," *Biochemical Pharmacology*, vol. 76, no. 11, pp. 1544–1553, 2008.
- [32] Y.-W. Dong, X.-P. Wang, and K. Wu, "Suppression of pancreatic carcinoma growth by activating peroxisome proliferator-activated receptor γ involves angiogenesis inhibition," *World Journal of Gastroenterology*, vol. 15, no. 4, pp. 441–448, 2009.
- [33] D. Panigrahy, A. Kaipainen, S. Huang, et al., "PPAR α agonist fenofibrate suppresses tumor growth through direct and indirect angiogenesis inhibition," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 3, pp. 985–990, 2008.
- [34] S. Han and J. Roman, "Peroxisome proliferator-activated receptor γ : a novel target for cancer therapeutics?" *Anti-Cancer Drugs*, vol. 18, no. 3, pp. 237–244, 2007.
- [35] C. Giaginis, A. Tsantili-Kakoulidou, and S. Theocharis, "Peroxisome proliferator-activated receptor- γ ligands: potential pharmacological agents for targeting the angiogenesis signaling cascade in cancer," *PPAR Research*, vol. 2008, Article ID 431763, 12 pages, 2008.
- [36] J. Roman, "Peroxisome proliferator-activated receptor gamma and lung cancer biology: implications for therapy," *Journal of Investigative Medicine*, vol. 56, no. 2, pp. 528–533, 2008.
- [37] D. Wang and R. N. DuBois, "Peroxisome proliferator-activated receptors and progression of colorectal cancer," *PPAR Research*, vol. 2008, Article ID 931074, 7 pages, 2008.
- [38] Y.-M. Zhou, Y.-H. Wen, X.-Y. Kang, H.-H. Qian, J.-M. Yang, and Z.-F. Yin, "Troglitazone, a peroxisome proliferator-activated receptor γ ligand, induces growth inhibition and apoptosis of HepG2 human liver cancer cells," *World Journal of Gastroenterology*, vol. 14, no. 14, pp. 2168–2173, 2008.
- [39] J. D. Burton, D. M. Goldenberg, and R. D. Blumenthal, "Potential of peroxisome proliferator-activated receptor gamma antagonist compounds as therapeutic agents for a wide range of cancer types," *PPAR Research*, vol. 2008, Article ID 494161, 7 pages, 2008.
- [40] D. Bonfiglio, S. Gabriele, S. Aquila, et al., "Peroxisome proliferator-activated receptor gamma activates fas ligand gene promoter inducing apoptosis in human breast cancer cells," *Breast Cancer Research and Treatment*, vol. 113, no. 3, pp. 423–434, 2009.
- [41] T. Inamoto, J. B. Shah, and A. M. Kamat, "Friend or foe? Role of peroxisome proliferator-activated receptor- γ in human bladder cancer," *Urologic Oncology*, vol. 27, no. 6, pp. 585–591, 2009.
- [42] S. A. Kliewer, S. S. Sundseth, S. A. Jones, et al., "Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors α and γ ," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 9, pp. 4318–4323, 1997.
- [43] T. Westendorf, J. Graessler, and S. Kopprasch, "Hypochlorite-oxidized low-density lipoprotein upregulates CD36 and PPAR γ mRNA expression and modulates SR-BI gene expression in murine macrophages," *Molecular and Cellular Biochemistry*, vol. 277, no. 1–2, pp. 143–152, 2005.
- [44] J. M. Lehmann, L. B. Moore, T. A. Smith-Oliver, W. O. Wilkison, T. M. Willson, and S. A. Kliewer, "An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPAR γ)," *Journal of Biological Chemistry*, vol. 270, no. 22, pp. 12953–12956, 1995.
- [45] J. M. Lehmann, J. M. Lenhard, B. B. Oliver, G. M. Ringold, and S. A. Kliewer, "Peroxisome proliferator-activated receptors α and γ are activated by indomethacin and other non-steroidal anti-inflammatory drugs," *Journal of Biological Chemistry*, vol. 272, no. 6, pp. 3406–3410, 1997.
- [46] Y. Wang, W. W. Porter, N. Suh, et al., "A synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), is a ligand for the peroxisome proliferator-activated receptor γ ," *Molecular Endocrinology*, vol. 14, no. 10, pp. 1550–1556, 2000.
- [47] D. M. Ray, K. M. Morse, S. P. Hilchey, et al., "The novel triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) induces apoptosis of human diffuse large B-cell lymphoma cells through a peroxisome proliferator-activated receptor gamma-independent pathway," *Experimental Hematology*, vol. 34, no. 9, pp. 1202–1211, 2006.
- [48] D. M. Ray, F. Akbiyik, and R. P. Phipps, "The peroxisome proliferator-activated receptor γ (PPAR γ) ligands 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ and ciglitazone induce human B lymphocyte and B cell lymphoma apoptosis by PPAR γ -independent mechanisms," *Journal of Immunology*, vol. 177, no. 8, pp. 5068–5076, 2006.
- [49] H. E. Ferguson, A. Kulkarni, G. M. Lehmann, et al., "Electrophilic peroxisome proliferator-activated receptor- γ ligands have potent antifibrotic effects in human lung fibroblasts," *American Journal of Respiratory Cell and Molecular Biology*, vol. 41, no. 6, pp. 722–730, 2009.
- [50] A. E. Place, N. Suh, C. R. Williams, et al., "The novel synthetic triterpenoid, CDDO-imidazolidide, inhibits inflammatory response and tumor growth in vivo," *Clinical Cancer Research*, vol. 9, no. 7, pp. 2798–2806, 2003.
- [51] S. Wei, J. Yang, S.-L. Lee, S. K. Kulp, and C.-S. Chen, "PPAR γ -independent antitumor effects of thiazolidinediones," *Cancer Letters*, vol. 276, no. 2, pp. 119–124, 2009.
- [52] J. M. Adams and A. Strasser, "Is tumor growth sustained by rare cancer stem cells or dominant clones?" *Cancer Research*, vol. 68, no. 11, pp. 4018–4021, 2008.
- [53] A. L. Allan, S. A. Vantghem, A. B. Tuck, and A. F. Chambers, "Tumor dormancy and cancer stem cells: implications for the biology and treatment of breast cancer metastasis," *Breast Disease*, vol. 26, no. 1, pp. 87–98, 2006.
- [54] J. Rak, C. Milsom, and J. Yu, "Vascular determinants of cancer stem cell dormancy—do age and coagulation system

- play a role?" *Acta Pathologica, Microbiologica et Immunologica Scandinavica*, vol. 116, no. 7-8, pp. 660–676, 2008.
- [55] L. Li and W. B. Neaves, "Normal stem cells and cancer stem cells: the niche matters," *Cancer Research*, vol. 66, pp. 4553–4557, 2006.
- [56] M. H. Tomasson, "Cancer stem cells: a guide for skeptics," *Journal of Cellular Biochemistry*, vol. 106, no. 5, pp. 745–749, 2009.
- [57] J. M. Rosen and C. T. Jordan, "The increasing complexity of the cancer stem cell paradigm," *Science*, vol. 324, no. 5935, pp. 1670–1673, 2009.
- [58] M. L. Guzman and C. T. Jordan, "Lessons learned from the study of JunB: new insights for normal and leukemia stem cell biology," *Cancer Cell*, vol. 15, no. 4, pp. 252–254, 2009.
- [59] W. A. Woodward, R. G. Bristow, M. F. Clarke, et al., "Radiation therapy oncology group translational research program stem cell symposium: incorporating stem cell hypotheses into clinical trials," *International Journal of Radiation Oncology Biology Physics*, vol. 74, no. 5, pp. 1580–1591, 2009.
- [60] W. A. Woodward and E. P. Sulman, "Cancer stem cells: markers or biomarkers?" *Cancer and Metastasis Reviews*, vol. 27, no. 3, pp. 459–470, 2008.
- [61] W. Chearwae and J. J. Bright, "PPAR γ agonists inhibit growth and expansion of CD133+ brain tumour stem cells," *British Journal of Cancer*, vol. 99, no. 12, pp. 2044–2053, 2008.
- [62] M. Saiki, Y. Hatta, T. Yamazaki, et al., "Pioglitazone inhibits the growth of human leukemia cell lines and primary leukemia cells while sparing normal hematopoietic stem cells," *International Journal of Oncology*, vol. 29, no. 2, pp. 437–443, 2006.
- [63] C. T. Jordan, "The leukemic stem cell," *Best Practice and Research in Clinical Haematology*, vol. 20, no. 1, pp. 13–18, 2007.
- [64] J. Folkman, "Angiogenesis: an organizing principle for drug discovery?" *Nature Reviews Drug Discovery*, vol. 6, no. 4, pp. 273–286, 2007.
- [65] G. P. van Nieuw Amerongen, P. Koolwijk, A. Versteilen, and V. W. M. Van Hinsbergh, "Involvement of RhoA/Rho kinase signaling in VEGF-induced endothelial cell migration and angiogenesis in vitro," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 23, no. 2, pp. 211–217, 2003.
- [66] V. W. M. van Hinsbergh and P. Koolwijk, "Endothelial sprouting and angiogenesis: matrix metalloproteinases in the lead," *Cardiovascular Research*, vol. 78, no. 2, pp. 203–212, 2008.
- [67] J. A. Nagy and D. R. Senger, "VEGF-A, cytoskeletal dynamics, and the pathological vascular phenotype," *Experimental Cell Research*, vol. 312, no. 5, pp. 538–548, 2006.
- [68] D. C. Darland and P. A. D'Amore, "Blood vessel maturation: vascular development comes of age," *Journal of Clinical Investigation*, vol. 103, no. 2, pp. 157–158, 1999.
- [69] H. F. Dvorak, L. F. Brown, M. Detmar, and A. M. Dvorak, "Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis," *American Journal of Pathology*, vol. 146, no. 5, pp. 1029–1039, 1995.
- [70] L. E. Benjamin, D. Golijanin, A. Itin, D. Pode, and E. Keshet, "Selective ablation of immature blood vessels in established human tumors follows vascular endothelial growth factor withdrawal," *Journal of Clinical Investigation*, vol. 103, no. 2, pp. 159–165, 1999.
- [71] J. L. Hatton and L. D. Yee, "Clinical use of PPAR γ ligands in cancer," *PPAR Research*, vol. 2008, Article ID 159415, 13 pages, 2008.
- [72] C. J. Robinson and S. E. Stringer, "The splice variants of vascular endothelial growth factor (VEGF) and their receptors," *Journal of Cell Science*, vol. 114, no. 5, pp. 853–865, 2001.
- [73] H. Gille, J. Kowalski, B. Li, et al., "Analysis of biological effects and signaling properties of Flt-1 (VEGFR-1) and KDR (VEGFR-2): a reassessment using novel receptor-specific vascular endothelial growth factor mutants," *Journal of Biological Chemistry*, vol. 276, no. 5, pp. 3222–3230, 2001.
- [74] P. Koolwijk, E. Peters, B. van Der Vecht, et al., "Involvement of VEGFR-2 (kdr/flk-1) but not VEGFR-1 (flt-1) in VEGF-A and VEGF-C-induced tube formation by human microvascular endothelial cells in fibrin matrices in vitro," *Angiogenesis*, vol. 4, no. 1, pp. 53–60, 2001.
- [75] A. Sahni, M. T. Arevalo, S. K. Sahni, and P. J. Simpson-Haidaris, "The VE-cadherin binding domain of fibrinogen induces endothelial barrier permeability and enhances transendothelial migration of malignant breast epithelial cells," *International Journal of Cancer*, vol. 125, no. 3, pp. 577–584, 2009.
- [76] V. Joukov, K. Pajusola, A. Kaipainen, et al., "A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases," *EMBO Journal*, vol. 15, no. 2, pp. 290–298, 1996.
- [77] B. K. McColl, M. E. Baldwin, S. Roufail, et al., "Plasmin activates the lymphangiogenic growth factors VEGF-C and VEGF-D," *Journal of Experimental Medicine*, vol. 198, no. 6, pp. 863–868, 2003.
- [78] S. Hirakawa, L. F. Brown, S. Kodama, K. Paavonen, K. Alitalo, and M. Detmar, "VEGF-C-induced lymphangiogenesis in sentinel lymph nodes promotes tumor metastasis to distant sites," *Blood*, vol. 109, no. 3, pp. 1010–1017, 2007.
- [79] S. Lee, T. T. Chen, C. L. Barber, et al., "Autocrine VEGF signaling is required for vascular homeostasis," *Cell*, vol. 130, no. 4, pp. 691–703, 2007.
- [80] H.-P. Gerber, A. K. Malik, G. P. Solar, et al., "VEGF regulates haematopoietic stem cell survival by an internal autocrine loop mechanism," *Nature*, vol. 417, no. 6892, pp. 954–958, 2002.
- [81] T.-H. Lee, S. Seng, M. Sekine, et al., "Vascular endothelial growth factor mediates intracrine survival in human breast carcinoma cells through internally expressed VEGFR1/FLT1," *PLoS Medicine*, vol. 4, no. 6, article e186, pp. 1101–1116, 2007.
- [82] R. Masood, J. Cai, T. Zheng, D. L. Smith, Y. Naidu, and P. S. Gill, "Vascular endothelial growth factor/vascular permeability factor is an autocrine growth factor for AIDS-Kaposi sarcoma," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 3, pp. 979–984, 1997.
- [83] R. Masood, J. Cai, T. Zheng, D. Lynne Smith, D. R. Hinton, and P. S. Gill, "Vascular endothelial growth factor (VEGF) is an autocrine growth factor for VEGF receptor-positive human tumors," *Blood*, vol. 98, no. 6, pp. 1904–1913, 2001.
- [84] J. M. Vieira, S. C. Rosa Santos, C. Espadinha, et al., "Expression of vascular endothelial growth factor (VEGF) and its receptors in thyroid carcinomas of follicular origin: a potential autocrine loop," *European Journal of Endocrinology*, vol. 153, no. 5, pp. 701–709, 2005.

- [85] S. Dias, K. Hattori, Z. Zhu, et al., "Autocrine stimulation of VEGFR-2 activates human leukemic cell growth and migration," *Journal of Clinical Investigation*, vol. 106, no. 4, pp. 511–521, 2000.
- [86] H. Zhang, Y. Li, H. Li, et al., "Inhibition of both the autocrine and the paracrine growth of human leukemia with a fully human antibody directed against vascular endothelial growth factor receptor 2," *Leukemia and Lymphoma*, vol. 45, no. 9, pp. 1887–1897, 2004.
- [87] S. C. R. Santos and S. Dias, "Internal and external autocrine VEGF/KDR loops regulate survival of subsets of acute leukemia through distinct signaling pathways," *Blood*, vol. 103, no. 10, pp. 3883–3889, 2004.
- [88] L. M. Ellis and D. J. Hicklin, "VEGF-targeted therapy: mechanisms of anti-tumour activity," *Nature Reviews Cancer*, vol. 8, no. 8, pp. 579–591, 2008.
- [89] M. Mendoza and C. Khanna, "Revisiting the seed and soil in cancer metastasis," *International Journal of Biochemistry and Cell Biology*, vol. 41, no. 7, pp. 1452–1462, 2009.
- [90] H. M. McGettrick, A. Filer, G. E. Rainger, C. D. Buckley, and G. B. Nash, "Modulation of endothelial responses by the stromal microenvironment: effects on leucocyte recruitment," *Biochemical Society Transactions*, vol. 35, no. 5, pp. 1161–1162, 2007.
- [91] G. Lorusso and C. Rugg, "The tumor microenvironment and its contribution to tumor evolution toward metastasis," *Histochemistry and Cell Biology*, vol. 130, no. 6, pp. 1091–1103, 2008.
- [92] D. G. DeNardo, M. Johansson, and L. M. Coussens, "Immune cells as mediators of solid tumor metastasis," *Cancer and Metastasis Reviews*, vol. 27, no. 1, pp. 11–18, 2008.
- [93] T. D. Tlsty and L. M. Coussens, "Tumor stroma and regulation of cancer development," *Annual Review of Pathology*, vol. 1, pp. 119–150, 2006.
- [94] O. De Wever, P. Demetter, M. Mareel, and M. Bracke, "Stromal myofibroblasts are drivers of invasive cancer growth," *International Journal of Cancer*, vol. 123, no. 10, pp. 2229–2238, 2008.
- [95] W.-W. Lin and M. Karin, "A cytokine-mediated link between innate immunity, inflammation, and cancer," *Journal of Clinical Investigation*, vol. 117, no. 5, pp. 1175–1183, 2007.
- [96] S. Ulisse, E. Baldini, S. Sorrenti, and M. D'Armiento, "The urokinase plasminogen activator system: a target for anti-cancer therapy," *Current Cancer Drug Targets*, vol. 9, no. 1, pp. 32–71, 2009.
- [97] E. I. Deryugina and J. P. Quigley, "Matrix metalloproteinases and tumor metastasis," *Cancer and Metastasis Reviews*, vol. 25, no. 1, pp. 9–34, 2006.
- [98] D. Ribatti, "Endogenous inhibitors of angiogenesis. A historical review," *Leukemia Research*, vol. 33, no. 5, pp. 638–644, 2009.
- [99] F. Mbeunkui and D. J. Johann Jr., "Cancer and the tumor microenvironment: a review of an essential relationship," *Cancer Chemotherapy and Pharmacology*, vol. 63, no. 4, pp. 571–582, 2009.
- [100] E. Hanna, J. Quick, and S. K. Libutti, "The tumour microenvironment: a novel target for cancer therapy," *Oral Diseases*, vol. 15, no. 1, pp. 8–17, 2009.
- [101] G. Chometon and V. Jendrossek, "Targeting the tumour stroma to increase efficacy of chemo- and radiotherapy," *Clinical and Translational Oncology*, vol. 11, no. 2, pp. 75–81, 2009.
- [102] K. Anton and J. Glod, "Targeting the tumor stroma in cancer therapy," *Current Pharmaceutical Biotechnology*, vol. 10, no. 2, pp. 185–191, 2009.
- [103] A. L. Bauer, T. L. Jackson, and Y. Jiang, "Topography of extracellular matrix mediates vascular morphogenesis and migration speeds in angiogenesis," *PLoS Computational Biology*, vol. 5, no. 7, article e1000445, 2009.
- [104] V. Baud and M. Karin, "Is NF- κ B a good target for cancer therapy? Hopes and pitfalls," *Nature Reviews Drug Discovery*, vol. 8, no. 1, pp. 33–40, 2009.
- [105] W. E. Naugler and M. Karin, "The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer," *Trends in Molecular Medicine*, vol. 14, no. 3, pp. 109–119, 2008.
- [106] M. Karin, "The I κ B kinase—a bridge between inflammation and cancer," *Cell Research*, vol. 18, no. 3, pp. 334–342, 2008.
- [107] S. Aboudola and A. R. Kini, "Angiogenesis in lymphoproliferative disorders: a therapeutic target?" *Current Opinion in Hematology*, vol. 12, no. 4, pp. 279–283, 2005.
- [108] Y. Bao, R. Li, J. Jiang, et al., "Activation of peroxisome proliferator-activated receptor gamma inhibits endothelin-1-induced cardiac hypertrophy via the calcineurin/NFAT signaling pathway," *Molecular and Cellular Biochemistry*, vol. 317, no. 1–2, pp. 189–196, 2008.
- [109] F. Spinella, E. Garrafa, V. D. Castro, et al., "Endothelin-1 stimulates lymphatic endothelial cells and lymphatic vessels to grow and invade," *Cancer Research*, vol. 69, no. 6, pp. 2669–2676, 2009.
- [110] J. Knowles, M. Loizidou, and I. Taylor, "Endothelin-1 and angiogenesis in cancer," *Current Vascular Pharmacology*, vol. 3, no. 4, pp. 309–314, 2005.
- [111] A. Grothey and L. M. Ellis, "Targeting angiogenesis driven by vascular endothelial growth factors using antibody-based therapies," *Cancer Journal*, vol. 14, no. 3, pp. 170–177, 2008.
- [112] T. Shih and C. Lindley, "Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies," *Clinical Therapeutics*, vol. 28, no. 11, pp. 1779–1802, 2006.
- [113] X. Dong, Z. C. Han, and R. Yang, "Angiogenesis and antiangiogenic therapy in hematologic malignancies," *Critical Reviews in Oncology/Hematology*, vol. 62, no. 2, pp. 105–118, 2007.
- [114] W. W. Li, M. Hutnik, and G. Gehr, "Antiangiogenesis in haematological malignancies," *British Journal of Haematology*, vol. 143, no. 5, pp. 622–631, 2008.
- [115] A. T. Stopeck, J. M. Unger, L. M. Rimsza, et al., "A phase II trial of single agent bevacizumab in patients with relapsed, aggressive non-Hodgkin lymphoma: southwest oncology group study S0108," *Leukemia and Lymphoma*, vol. 50, no. 5, pp. 728–735, 2009.
- [116] D. Ribatti, "Lymphangiogenesis in haematological malignancies," *Leukemia Research*, vol. 33, no. 6, pp. 753–755, 2009.
- [117] D. Ribatti, "Is angiogenesis essential for the progression of hematological malignancies or is it an epiphenomenon?" *Leukemia*, vol. 23, no. 3, pp. 433–434, 2009.
- [118] S. V. Rajkumar, R. A. Mesa, and A. Tefferi, "A review of angiogenesis and anti-angiogenic therapy in hematologic malignancies," *Journal of Hematology and Stem Cell Research*, vol. 11, no. 1, pp. 33–47, 2002.
- [119] T. Kessler, F. Fehrmann, R. Bieker, W. E. Berdel, and R. M. Mesters, "Vascular endothelial growth factor and its receptor as drug targets in hematological malignancies," *Current Drug Targets*, vol. 8, no. 2, pp. 257–268, 2007.

- [120] D. Ribatti, B. Nico, E. Crivellato, A. M. Roccaro, and A. Vacca, "The history of the angiogenic switch concept," *Leukemia*, vol. 21, no. 1, pp. 44–52, 2007.
- [121] M. S. O'Reilly, T. Boehm, Y. Shing, et al., "Endostatin: an endogenous inhibitor of angiogenesis and tumor growth," *Cell*, vol. 88, no. 2, pp. 277–285, 1997.
- [122] M. S. O'Reilly, L. Holmgren, Y. Shing, et al., "Angiostatin: a circulating endothelial cell inhibitor that suppresses angiogenesis and tumor growth," *Cold Spring Harbor Symposia on Quantitative Biology*, vol. 59, pp. 471–482, 1994.
- [123] K. Gupta, P. Gupta, R. Wild, S. Ramakrishnan, and R. P. Hebbel, "Binding and displacement of vascular endothelial growth factor (VEGF) by thrombospondin: effect on human microvascular endothelial cell proliferation and angiogenesis," *Angiogenesis*, vol. 3, no. 2, pp. 147–158, 1999.
- [124] P. Nyberg, L. Xie, and R. Kalluri, "Endogenous inhibitors of angiogenesis," *Cancer Research*, vol. 65, no. 10, pp. 3967–3979, 2005.
- [125] F. Haviv, M. E. Bradley, D. M. Kalvin, et al., "Thrombospondin-1 mimetic peptide inhibitors of angiogenesis and tumor growth: design, synthesis, and optimization of pharmacokinetics and biological activities," *Journal of Medicinal Chemistry*, vol. 48, no. 8, pp. 2838–2846, 2005.
- [126] R. Hoekstra, F. Y. F. L. De Vos, F. A. L. M. Eskens, et al., "Phase I safety, pharmacokinetic, and pharmacodynamic study of the thrombospondin-1-mimetic angiogenesis inhibitor ABT-510 in patients with advanced cancer," *Journal of Clinical Oncology*, vol. 23, no. 22, pp. 5188–5197, 2005.
- [127] A. Tomillero and M. A. Moral, "Gateways to clinical trials," *Methods and Findings in Experimental and Clinical Pharmacology*, vol. 30, no. 5, pp. 383–408, 2008.
- [128] S. N. Markovic, V. J. Suman, R. A. Rao, et al., "A phase II study of ABT-510 (thrombospondin-1 analog) for the treatment of metastatic melanoma," *American Journal of Clinical Oncology*, vol. 30, no. 3, pp. 303–309, 2007.
- [129] S. Ebbinghaus, M. Hussain, N. Tannir, et al., "Phase 2 study of ABT-510 in patients with previously untreated advanced renal cell carcinoma," *Clinical Cancer Research*, vol. 13, no. 22, pp. 6689–6695, 2007.
- [130] R. A. Brekken, J. P. Overholser, V. A. Stastny, J. Waltenberger, J. D. Minna, and P. E. Thorpe, "Selective inhibition of vascular endothelial growth factor (VEGF) receptor 2 (KDR/Flk-1) activity by a monoclonal anti-VEGF antibody blocks tumor growth in mice," *Cancer Research*, vol. 60, no. 18, pp. 5117–5124, 2000.
- [131] L. Witte, D. J. Hicklin, Z. Zhu, et al., "Monoclonal antibodies targeting the VEGF receptor-2 (Flk1/KDR) as an anti-angiogenic therapeutic strategy," *Cancer and Metastasis Reviews*, vol. 17, no. 2, pp. 155–161, 1998.
- [132] S. Shinkaruk, M. Bayle, G. Lain, and G. Deleris, "Vascular endothelial cell growth factor (VEGF), an emerging target for cancer chemotherapy," *Current Medicinal Chemistry*, vol. 3, no. 2, pp. 95–117, 2003.
- [133] G. Ranieri, R. Patruno, E. Ruggieri, S. Montemurro, P. Valerio, and D. Ribatti, "Vascular endothelial growth factor (VEGF) as a target of bevacizumab in cancer: from the biology to the clinic," *Current Medicinal Chemistry*, vol. 13, no. 16, pp. 1845–1857, 2006.
- [134] S. Lien and H. B. Lowman, "Therapeutic anti-VEGF antibodies," *Handbook of Experimental Pharmacology*, no. 181, pp. 131–150, 2008.
- [135] M. R. Barakat and P. K. Kaiser, "VEGF inhibitors for the treatment of neovascular age-related macular degeneration," *Expert Opinion on Investigational Drugs*, vol. 18, no. 5, pp. 637–646, 2009.
- [136] T. A. Ciulla and P. J. Rosenfeld, "Anti-vascular endothelial growth factor therapy for neovascular ocular diseases other than age-related macular degeneration," *Current Opinion in Ophthalmology*, vol. 20, no. 3, pp. 166–174, 2009.
- [137] A. R. Quesada, M. A. Medina, and E. Alba, "Playing only one instrument may be not enough: limitations and future of the antiangiogenic treatment of cancer," *BioEssays*, vol. 29, no. 11, pp. 1159–1168, 2007.
- [138] L. Ellis and D. J. Hicklin, "Pathways mediating resistance to vascular endothelial growth factor-targeted therapy," *Clinical Cancer Research*, vol. 14, no. 20, pp. 6371–6375, 2008.
- [139] S. Loges, M. Mazzone, P. Hohensinner, and P. Carmeliet, "Silencing or fueling metastasis with VEGF inhibitors: antiangiogenesis revisited," *Cancer Cell*, vol. 15, no. 3, pp. 167–170, 2009.
- [140] M. Paez-Ribes, E. Allen, J. Hudock, et al., "Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis," *Cancer Cell*, vol. 15, no. 3, pp. 220–231, 2009.
- [141] J. M. L. Ebos, C. R. Lee, W. Cruz-Munoz, G. A. Bjarnason, J. G. Christensen, and R. S. Kerbel, "Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis," *Cancer Cell*, vol. 15, no. 3, pp. 232–239, 2009.
- [142] J. Ma and D. J. Waxman, "Combination of antiangiogenesis with chemotherapy for more effective cancer treatment," *Molecular Cancer Therapeutics*, vol. 7, no. 12, pp. 3670–3684, 2008.
- [143] A. C. Dudley and M. Klagsbrun, "Tumor endothelial cells join the resistance," *Clinical Cancer Research*, vol. 15, no. 15, pp. 4787–4789, 2009.
- [144] D. Wei, X. Le, L. Zheng, et al., "Stat3 activation regulates the expression of vascular endothelial growth factor and human pancreatic cancer angiogenesis and metastasis," *Oncogene*, vol. 22, no. 3, pp. 319–329, 2003.
- [145] G. L. Semenza, "HIF-1 and tumor progression: pathophysiology and therapeutics," *Trends in Molecular Medicine*, vol. 8, no. 4, pp. S62–S67, 2002.
- [146] Q. Ke and M. Costa, "Hypoxia-inducible factor-1 (HIF-1)," *Molecular Pharmacology*, vol. 70, no. 5, pp. 1469–1480, 2006.
- [147] G. L. Semenza, "HIF-1 and mechanisms of hypoxia sensing," *Current Opinion in Cell Biology*, vol. 13, no. 2, pp. 167–171, 2001.
- [148] I. P. Stolze, D. R. Mole, and P. J. Ratcliffe, "Regulation of HIF: prolyl hydroxylases," *Novartis Foundation Symposium*, vol. 272, pp. 15–25, 2006.
- [149] H. Baumann and J. Gauldie, "The acute phase response," *Immunology Today*, vol. 15, no. 2, pp. 74–80, 1994.
- [150] N. Ohbayashi, O. Ikeda, N. Taira, et al., "LIF- and IL-6-induced acetylation of STAT3 at Lys-685 through PI3K/Akt activation," *Biological and Pharmaceutical Bulletin*, vol. 30, no. 10, pp. 1860–1864, 2007.
- [151] Q. Xu, J. Briggs, S. Park, et al., "Targeting Stat3 blocks both HIF-1 and VEGF expression induced by multiple oncogenic growth signaling pathways," *Oncogene*, vol. 24, no. 36, pp. 5552–5560, 2005.
- [152] P. Yue and J. Turkson, "Targeting STAT3 in cancer: how successful are we?" *Expert Opinion on Investigational Drugs*, vol. 18, no. 1, pp. 45–56, 2009.

- [153] D. R. Hodge, E. M. Hurt, and W. L. Farrar, "The role of IL-6 and STAT3 in inflammation and cancer," *European Journal of Cancer*, vol. 41, no. 16, pp. 2502–2512, 2005.
- [154] W. E. Naugler and M. Karin, "NF- κ B and cancer—identifying targets and mechanisms," *Current Opinion in Genetics and Development*, vol. 18, no. 1, pp. 19–26, 2008.
- [155] A. Keutgens, I. Robert, P. Viatour, and A. Chariot, "Deregulated NF- κ B activity in haematological malignancies," *Biochemical Pharmacology*, vol. 72, no. 9, pp. 1069–1080, 2006.
- [156] T. Braun, G. Carvalho, C. Fabre, J. Grosjean, P. Fenaux, and G. Kroemer, "Targeting NF- κ B in hematologic malignancies," *Cell Death and Differentiation*, vol. 13, no. 5, pp. 748–758, 2006.
- [157] B. B. Aggarwal, "Nuclear factor- κ B: the enemy within," *Cancer Cell*, vol. 6, no. 3, pp. 203–208, 2004.
- [158] S. Ghisletti, W. Huang, S. Ogawa, et al., "Parallel SUMOylation-dependent pathways mediate gene- and signal-specific transrepression by LXRs and PPAR γ ," *Molecular Cell*, vol. 25, no. 1, pp. 57–70, 2007.
- [159] J.-H. Yi, S.-W. Park, R. Kapadia, and R. Vemuganti, "Role of transcription factors in mediating post-ischemic cerebral inflammation and brain damage," *Neurochemistry International*, vol. 50, no. 7-8, pp. 1014–1027, 2007.
- [160] K. Subbaramaiah, D. T. Lin, J. C. Hart, and A. J. Dannenberg, "Peroxisome proliferator-activated receptor γ ligands suppress the transcriptional activation of cyclooxygenase-2. Evidence for involvement of activator protein-1 and CREB-binding protein/p300," *Journal of Biological Chemistry*, vol. 276, no. 15, pp. 12440–12448, 2001.
- [161] I. Kuzu, M. Beksac, M. Arat, H. Celebi, A. H. Elhan, and S. Erekul, "Bone marrow microvessel density (MVD) in adult acute myeloid leukemia (AML): therapy induced changes and effects on survival," *Leukemia and Lymphoma*, vol. 45, no. 6, pp. 1185–1190, 2004.
- [162] K. Anargyrou, M.-A. Dimopoulos, O. Sezer, and E. Terpos, "Novel anti-myeloma agents and angiogenesis," *Leukemia and Lymphoma*, vol. 49, no. 4, pp. 677–689, 2008.
- [163] K. C. Anderson, "Multiple Myeloma. Advances in disease biology: therapeutic implications," *Seminars in Hematology*, vol. 38, no. 2, supplement 3, pp. 6–10, 2001.
- [164] K. C. Anderson, "Targeted therapy of multiple myeloma based upon tumor-microenvironmental interactions," *Experimental Hematology*, vol. 35, no. 4, supplement 1, pp. 155–162, 2007.
- [165] M. T. Cibeira, M. Rozman, M. Segarra, et al., "Bone marrow angiogenesis and angiogenic factors in multiple myeloma treated with novel agents," *Cytokine*, vol. 41, no. 3, pp. 244–253, 2008.
- [166] M. A. Dimopoulos and E. Kastiris, "Thalidomide plus dexamethasone as primary therapy for newly diagnosed patients with multiple myeloma," *Nature Clinical Practice Oncology*, vol. 5, no. 12, pp. 690–691, 2008.
- [167] J. Folkman and M. S. Rogers, "Thalidomide for multiple myeloma," *The New England Journal of Medicine*, vol. 354, no. 22, pp. 2389–2390, 2006.
- [168] A. Vacca, C. Scavelli, V. Montefusco, et al., "Thalidomide downregulates angiogenic genes in bone marrow endothelial cells of patients with active multiple myeloma," *Journal of Clinical Oncology*, vol. 23, no. 23, pp. 5334–5346, 2005.
- [169] D. Mangieri, B. Nico, V. Benaglio, M. De Giorgis, A. Vacca, and D. Ribatti, "Angiogenic activity of multiple myeloma endothelial cells in vivo in the chick embryo chorioallantoic membrane assay is associated to a down-regulation in the expression of endogenous endostatin," *Journal of Cellular and Molecular Medicine*, vol. 12, no. 3, pp. 1023–1028, 2008.
- [170] T. Letilovic, R. Vrhovac, S. Verstovsek, B. Jaksic, and A. Ferrajoli, "Role of angiogenesis in chronic lymphocytic leukemia," *Cancer*, vol. 107, no. 5, pp. 925–934, 2006.
- [171] P. Liu, J. Li, Z. C. Han, et al., "Elevated plasma levels of vascular endothelial growth factor is associated with marked splenomegaly in chronic myeloid leukemia," *Leukemia and Lymphoma*, vol. 46, no. 12, pp. 1761–1764, 2005.
- [172] E. S. Wang, J. Teruya-Feldstein, Y. Wu, Z. Zhu, D. J. Hicklin, and M. A. S. Moore, "Targeting autocrine and paracrine VEGF receptor pathways inhibits human lymphoma xenografts in vivo," *Blood*, vol. 104, no. 9, pp. 2893–2902, 2004.
- [173] J. Ruan and J. P. Leonard, "Targeting angiogenesis: a novel, rational therapeutic approach for non-Hodgkin lymphoma," *Leukemia and Lymphoma*, vol. 50, no. 5, pp. 679–681, 2009.
- [174] T. Mainou-Fowler, B. Angus, S. Miller, S. J. Proctor, P. R. A. Taylor, and K. M. Wood, "Micro-vessel density and the expression of vascular endothelial growth factor (VEGF) and platelet-derived endothelial cell growth factor (PdEGF) in classical Hodgkin lymphoma (HL)," *Leukemia and Lymphoma*, vol. 47, no. 2, pp. 223–230, 2006.
- [175] A. Rueda, D. Olmos, V. Villareal, E. Torres, B. I. Pajares, and E. Alba, "Elevated vascular endothelial growth factor pretreatment levels are correlated with the tumor burden in Hodgkin lymphoma and continue to be elevated in prolonged complete remission," *Clinical Lymphoma and Myeloma*, vol. 7, no. 6, pp. 400–405, 2007.
- [176] G. Lenz, G. Wright, S. S. Dave, et al., "Stromal gene signatures in large-B-cell lymphomas," *The New England Journal of Medicine*, vol. 359, no. 22, pp. 2313–2323, 2008.
- [177] A. Tzankov, S. Heiss, S. Ebner, et al., "Angiogenesis in nodal B cell lymphomas: a high throughput study," *Journal of Clinical Pathology*, vol. 60, no. 5, pp. 476–482, 2007.
- [178] K. J. Till, D. G. Spiller, R. J. Harris, H. Chen, M. Zuzel, and J. C. Cawley, "CLL, but not normal, B cells are dependent on autocrine VEGF and $\alpha 4\beta 1$ integrin for chemokine-induced motility on and through endothelium," *Blood*, vol. 105, no. 12, pp. 4813–4819, 2005.
- [179] T. Matsumoto, T. Kobayashi, and K. Kamata, "Relationships among ET-1, PPAR γ , oxidative stress and endothelial dysfunction in diabetic animals," *Journal of Smooth Muscle Research*, vol. 44, no. 2, pp. 41–55, 2008.
- [180] U. Landmesser, B. Hornig, and H. Drexler, "Endothelial function: a critical determinant in atherosclerosis?" *Circulation*, vol. 109, no. 21, supplement 1, pp. II27–II33, 2004.
- [181] C. Hafner, A. Reichle, and T. Vogt, "New indications for established drugs: combined tumor-stroma-targeted cancer therapy with PPAR γ agonists, COX-2 inhibitors, mTOR antagonists and metronomic chemotherapy," *Current Cancer Drug Targets*, vol. 5, no. 6, pp. 393–419, 2005.
- [182] L. Michalik and W. Wahli, "PPARs mediate lipid signaling in inflammation and cancer," *PPAR Research*, vol. 2008, Article ID 134059, 15 pages, 2008.
- [183] L. Gelman, J.-C. Fruchart, and J. Auwerx, "An update on the mechanisms of action of the peroxisome proliferator-activated receptors (PPARs) and their roles in inflammation and cancer," *Cellular and Molecular Life Sciences*, vol. 55, no. 6-7, pp. 932–943, 1999.
- [184] F. Biscetti, G. Straface, D. Pitocco, F. Zaccardi, G. Ghirlanda, and A. Flex, "Peroxisome proliferator-activated receptors

- and angiogenesis," *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 19, no. 11, pp. 751–759, 2009.
- [185] A. Papi, P. Rochhi, A. M. Ferreri, F. Guerra, and M. Orlandi, "Enhanced effects of PPAR γ ligands and RXR selective retinoids in combination to inhibit migration and invasiveness in cancer cells," *Oncology Reports*, vol. 21, no. 4, pp. 1083–1089, 2009.
- [186] X. Y. Yang, L. H. Wang, and W. L. Farrar, "A role for PPAR γ in the regulation of cytokines in immune cells and cancer," *PPAR Research*, vol. 2008, Article ID 961753, 12 pages, 2008.
- [187] K. Tachibana, D. Yamasaki, K. Ishimoto, and T. Doi, "The role of PPARs in cancer," *PPAR Research*, vol. 2008, Article ID 102737, 15 pages, 2008.
- [188] I. Sainis, K. Vareli, V. Karavasilis, and E. Briasoulis, "PPAR γ : the portrait of a target ally to cancer chemopreventive agents," *PPAR Research*, vol. 2008, Article ID 436489, 10 pages, 2008.
- [189] H. J. Burstein, G. D. Demetri, E. Mueller, P. Sarraf, B. M. Spiegelman, and E. P. Winer, "Use of the peroxisome proliferator-activated receptor (PPAR) γ ligand troglitazone as treatment for refractory breast cancer: a phase II study," *Breast Cancer Research and Treatment*, vol. 79, no. 3, pp. 391–397, 2003.
- [190] M. H. Kulke, G. D. Demetri, N. E. Sharpless, et al., "A phase II study of troglitazone, an activator of the PPAR γ receptor, in patients with chemotherapy-resistant metastatic colorectal cancer," *Cancer Journal*, vol. 8, no. 5, pp. 395–399, 2002.
- [191] M. R. Smith, J. Manola, D. S. Kaufman, et al., "Rosiglitazone versus placebo for men with prostate carcinoma and a rising serum prostate-specific antigen level after radical prostatectomy and/or radiation therapy," *Cancer*, vol. 101, no. 7, pp. 1569–1574, 2004.
- [192] M. R. Gralinski, P. E. Rowse, and M. A. Breider, "Effects of troglitazone and pioglitazone on cytokine-mediated endothelial cell proliferation in vitro," *Journal of Cardiovascular Pharmacology*, vol. 31, no. 6, pp. 909–913, 1998.
- [193] N. Marx, T. Bourcier, G. K. Sukhova, P. Libby, and J. Plutzky, "PPAR γ activation in human endothelial cells increases plasminogen activator inhibitor type-1 expression: PPAR γ as a potential mediator in vascular disease," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 19, no. 3, pp. 546–551, 1999.
- [194] T. Murata, S. He, M. Hangai, et al., "Peroxisome proliferator-activated receptor- γ ligands inhibit choroidal neovascularization," *Investigative Ophthalmology and Visual Science*, vol. 41, no. 8, pp. 2309–2317, 2000.
- [195] D. Panigrahy, S. Singer, L. Q. Shen, et al., "PPAR γ ligands inhibit primary tumor growth and metastasis by inhibiting angiogenesis," *Journal of Clinical Investigation*, vol. 110, no. 7, pp. 923–932, 2002.
- [196] H. Huang, S. C. Campbell, D. F. Bedford, et al., "Peroxisome proliferator-activated receptor γ ligands improve the antitumor efficacy of thrombospondin peptide ABT510," *Molecular Cancer Research*, vol. 2, no. 10, pp. 541–550, 2004.
- [197] C.-H. Wang, N. Ciliberti, S.-H. Li, et al., "Rosiglitazone facilitates angiogenic progenitor cell differentiation toward endothelial lineage: a new paradigm in glitazone pleiotropy," *Circulation*, vol. 109, no. 11, pp. 1392–1400, 2004.
- [198] M. A. Sarayba, L. Li, T. Tungsiripat, et al., "Inhibition of corneal neovascularization by a peroxisome proliferator-activated receptor- γ ligand," *Experimental Eye Research*, vol. 80, no. 3, pp. 435–442, 2005.
- [199] L. L. H. Peeters, J.-L. Vigne, K. T. Meng, D. Zhao, L. L. Waite, and R. N. Taylor, "PPAR γ represses VEGF expression in human endometrial cells: implications for uterine angiogenesis," *Angiogenesis*, vol. 8, no. 4, pp. 373–379, 2006.
- [200] F. Pistrosch, K. Herbrig, U. Oelschlaegel, et al., "PPAR γ -agonist rosiglitazone increases number and migratory activity of cultured endothelial progenitor cells," *Atherosclerosis*, vol. 183, no. 1, pp. 163–167, 2005.
- [201] C. Gensch, Y. P. Clever, C. Werner, M. Hanhoun, M. Bohm, and U. Laufs, "The PPAR- γ agonist pioglitazone increases neoangiogenesis and prevents apoptosis of endothelial progenitor cells," *Atherosclerosis*, vol. 192, no. 1, pp. 67–74, 2007.
- [202] Q. He, R. Pang, X. Song, et al., "Rosiglitazone suppresses the growth and invasiveness of SGC-7901 gastric cancer cells and angiogenesis in vitro via PPAR γ dependent and independent mechanisms," *PPAR Research*, vol. 2008, Article ID 649808, 9 pages, 2008.
- [203] O. Gealekman, A. Burkart, M. Chouinard, S. M. Nicoloso, J. Straubhaar, and S. Corvera, "Enhanced angiogenesis in obesity and in response to PPAR γ activators through adipocyte VEGF and ANGPTL4 production," *American Journal of Physiology*, vol. 295, no. 5, pp. E1056–E1064, 2008.
- [204] L. Patel, I. Pass, P. Coxon, C. P. Downes, S. A. Smith, and C. H. Macphee, "Tumor suppressor and anti-inflammatory actions of PPAR γ agonists are mediated via upregulation of PTEN," *Current Biology*, vol. 11, no. 10, pp. 764–768, 2001.
- [205] B. Dankbar, T. Padró, R. Leo, et al., "Vascular endothelial growth factor and interleukin-6 in paracrine tumor-stromal cell interactions in multiple myeloma," *Blood*, vol. 95, no. 8, pp. 2630–2636, 2000.
- [206] T. M. Garcia-Bates, S. A. Peslak, C. J. Baglolle, S. B. Maggirwar, S. H. Bernstein, and R. P. Phipps, "Peroxisome proliferator-activated receptor gamma overexpression and knockdown: impact on human B cell lymphoma proliferation and survival," *Cancer Immunology, Immunotherapy*, vol. 58, no. 7, pp. 1071–1083, 2009.
- [207] T. M. Garcia-Bates, S. H. Bernstein, and R. P. Phipps, "Peroxisome proliferator-activated receptor γ overexpression suppresses growth and induces apoptosis in human multiple myeloma cells," *Clinical Cancer Research*, vol. 14, no. 20, pp. 6414–6425, 2008.
- [208] D. M. Ray, S. H. Bernstein, and R. P. Phipps, "Human multiple myeloma cells express peroxisome proliferator-activated receptor γ and undergo apoptosis upon exposure to PPAR γ ligands," *Clinical Immunology*, vol. 113, no. 2, pp. 203–213, 2004.
- [209] J. Padilla, E. Leung, and R. P. Phipps, "Human B lymphocytes and B lymphomas express PPAR- γ and are killed by PPAR- γ agonists," *Clinical Immunology*, vol. 103, no. 1, pp. 22–33, 2002.
- [210] J. Padilla, K. Kaur, H. J. Cao, T. J. Smith, and R. P. Phipps, "Peroxisome proliferator activator receptor- γ agonists and 15-deoxy- $\Delta^{12,14}$ -PGJ $_2$ induce apoptosis in normal and malignant B-lineage cells," *Journal of Immunology*, vol. 165, no. 12, pp. 6941–6948, 2000.
- [211] L. H. Wang, X. Y. Yang, X. Zhang, et al., "Transcriptional inactivation of STAT3 by PPAR γ suppresses IL-6-responsive multiple myeloma cells," *Immunity*, vol. 20, no. 2, pp. 205–218, 2004.
- [212] H. W. Li, Y. Y. Xiao, X. Zhang, and W. L. Farrar, "Inhibition of adhesive interaction between multiple myeloma and bone marrow stromal cells by PPAR γ cross talk with NF- κ B and C/EBP β ," *Blood*, vol. 110, no. 13, pp. 4373–4384, 2007.

- [213] H. W. Li, Y. Y. Xiao, X. Zhang, and W. L. Farrar, "Nuclear receptors as negative modulators of STAT3 in multiple myeloma," *Cell Cycle*, vol. 4, no. 2, pp. 242–245, 2005.
- [214] M. Konopleva, T. Tsao, P. Ruvalo, et al., "Novel triterpenoid CDDO-Me is a potent inducer of apoptosis and differentiation in acute myelogenous leukemia," *Blood*, vol. 99, no. 1, pp. 326–335, 2002.
- [215] X. Ling, M. Konopleva, Z. Zeng, et al., "The novel triterpenoid C-28 methyl ester of 2-cyano-3, 12-dioxoolen-1, 9-dien-28-oic acid inhibits metastatic murine breast tumor growth through inactivation of STAT3 signaling," *Cancer Research*, vol. 67, no. 9, pp. 4210–4218, 2007.
- [216] M. P. Curran and K. McKeage, "Bortezomib: a review of its use in patients with multiple myeloma," *Drugs*, vol. 69, no. 7, pp. 859–888, 2009.
- [217] A. M. Roccaro, T. Hideshima, N. Raje, et al., "Bortezomib mediates antiangiogenesis in multiple myeloma via direct and indirect effects on endothelial cells," *Cancer Research*, vol. 66, no. 1, pp. 184–191, 2006.
- [218] T. Hideshima, D. Chauhan, T. Hayashi, et al., "Proteasome inhibitor PS-341 abrogates IL-6 triggered signaling cascades via caspase-dependent downregulation of gp130 in multiple myeloma," *Oncogene*, vol. 22, no. 52, pp. 8386–8393, 2003.
- [219] S. Giralt, E. A. Stadtmauer, J. L. Harousseau, et al., "International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100)," *Leukemia*, vol. 23, no. 10, pp. 1904–1912, 2009.
- [220] M. Chatterjee, T. Stühmer, P. Herrmann, K. Bommert, B. Dörken, and R. C. Bargou, "Combined disruption of both the MEK/ERK and the IL-6R/STAT3 pathways is required to induce apoptosis of multiple myeloma cells in the presence of bone marrow stromal cells," *Blood*, vol. 104, no. 12, pp. 3712–3721, 2004.
- [221] R. J. Epstein, "VEGF signaling inhibitors: more pro-apoptotic than anti-angiogenic," *Cancer and Metastasis Reviews*, vol. 26, no. 3-4, pp. 443–452, 2007.
- [222] C. R. Anderson, N. E. Hastings, B. R. Blackman, and R. J. Price, "Capillary sprout endothelial cells exhibit a CD36^{low} phenotype: regulation by shear stress and vascular endothelial growth factor-induced mechanism for attenuating anti-proliferative thrombospondin-1 signaling," *American Journal of Pathology*, vol. 173, no. 4, pp. 1220–1228, 2008.
- [223] M. L. Febbraio, E. Guy, C. Coburn, et al., "The impact of overexpression and deficiency of fatty acid translocase (FAT)/CD36," *Molecular and Cellular Biochemistry*, vol. 239, no. 1-2, pp. 193–197, 2002.
- [224] O. Sato, C. Kuriki, Y. Fukui, and K. Motojima, "Dual promoter structure of mouse and human fatty acid translocase/CD36 genes and unique transcriptional activation by peroxisome proliferator-activated receptor α and γ ligands," *Journal of Biological Chemistry*, vol. 277, no. 18, pp. 15703–15711, 2002.
- [225] K. Motojima, P. Passilly, J. M. Peters, F. J. Gonzalez, and N. Latruffe, "Expression of putative fatty acid transporter genes are regulated by peroxisome proliferator-activated receptor α and γ activators in a tissue- and inducer-specific manner," *Journal of Biological Chemistry*, vol. 273, no. 27, pp. 16710–16714, 1998.
- [226] N. Ruiz-Velasco, A. Domínguez, and M. A. Vega, "Statins upregulate CD36 expression in human monocytes, an effect strengthened when combined with PPAR- γ ligands putative contribution of Rho GTPases in statin-induced CD36 expression," *Biochemical Pharmacology*, vol. 67, no. 2, pp. 303–313, 2004.
- [227] R. Simantov and R. L. Silverstein, "CD36: a critical anti-angiogenic receptor," *Frontiers in Bioscience*, vol. 8, pp. s874–s882, 2003.
- [228] R. A. Swerlick, K. H. Lee, T. M. Wick, and T. J. Lawley, "Human dermal microvascular endothelial but not human umbilical vein endothelial cells express CD36 in vivo and in vitro," *Journal of Immunology*, vol. 148, no. 1, pp. 78–83, 1992.
- [229] F. K. Reiher, O. V. Volpert, B. Jimenez, et al., "Inhibition of tumor growth by systemic treatment with thrombospondin-1 peptide mimetics," *International Journal of Cancer*, vol. 98, no. 5, pp. 682–689, 2002.
- [230] J. Liu, H. Lu, R. Huang, et al., "Peroxisome proliferator activated receptor- γ ligands induced cell growth inhibition and its influence on matrix metalloproteinase activity in human myeloid leukemia cells," *Cancer Chemotherapy and Pharmacology*, vol. 56, no. 4, pp. 400–408, 2005.
- [231] P. J. Simpson-Haidaris and B. Rybarczyk, "Tumors and fibrinogen: the role of fibrinogen as an extracellular matrix protein," *Annals of the New York Academy of Sciences*, vol. 936, pp. 406–425, 2001.
- [232] P. S. Meltzer, "Cancer genomics: small RNAs with big impacts," *Nature*, vol. 435, no. 7043, pp. 745–746, 2005.
- [233] C. H. Lawrie, "MicroRNAs and haematology: small molecules, big function," *British Journal of Haematology*, vol. 137, no. 6, pp. 503–512, 2007.
- [234] D. P. Bartel, "MicroRNAs: target recognition and regulatory functions," *Cell*, vol. 136, no. 2, pp. 215–233, 2009.
- [235] J. Brennecke, A. Stark, R. B. Russell, and S. M. Cohen, "Principles of microRNA-target recognition," *PLoS Biology*, vol. 3, no. 3, article e85, 2005.
- [236] V. N. Kim, J. Han, and M. C. Siomi, "Biogenesis of small RNAs in animals," *Nature Reviews Molecular Cell Biology*, vol. 10, no. 2, pp. 126–139, 2009.
- [237] C. Urbich, A. Kuehnbacher, and S. Dimmeler, "Role of microRNAs in vascular diseases, inflammation, and angiogenesis," *Cardiovascular Research*, vol. 79, no. 4, pp. 581–588, 2008.
- [238] P. K. Mishra, N. Tyagi, M. Kumar, and S. C. Tyagi, "MicroRNAs as a therapeutic target for cardiovascular diseases," *Journal of Cellular and Molecular Medicine*, vol. 13, no. 4, pp. 778–789, 2009.
- [239] A. Marson, S. S. Levine, M. F. Cole, et al., "Connecting microRNA genes to the core transcriptional regulatory circuitry of embryonic stem cells," *Cell*, vol. 134, no. 3, pp. 521–533, 2008.
- [240] J. G. Ruby, C. H. Jan, and D. P. Bartel, "Intronic microRNA precursors that bypass Drosha processing," *Nature*, vol. 448, no. 7149, pp. 83–86, 2007.
- [241] Y. Lee, C. Ahn, J. Han, et al., "The nuclear RNase III Drosha initiates microRNA processing," *Nature*, vol. 425, no. 6956, pp. 415–419, 2003.
- [242] E. Lund, S. Güttinger, A. Calado, J. E. Dahlberg, and U. Kutay, "Nuclear export of microRNA precursors," *Science*, vol. 303, no. 5654, pp. 95–98, 2004.
- [243] G. Hutvagner and P. D. Zamore, "A microRNA in a multiple-turnover RNAi enzyme complex," *Science*, vol. 297, no. 5589, pp. 2056–2060, 2002.
- [244] G. Meister, M. Landthaler, A. Patkaniowska, Y. Dorsett, G. Teng, and T. Tuschl, "Human Argonaute2 mediates RNA

- cleavage targeted by miRNAs and siRNAs," *Molecular Cell*, vol. 15, no. 2, pp. 185–197, 2004.
- [245] W. Filipowicz, S. N. Bhattacharyya, and N. Sonenberg, "Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight?" *Nature Reviews Genetics*, vol. 9, no. 2, pp. 102–114, 2008.
- [246] F. Pichiorri, S.-S. Suh, M. Ladetto, et al., "MicroRNAs regulate critical genes associated with multiple myeloma pathogenesis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 35, pp. 12885–12890, 2008.
- [247] M. Fabbri, C. Croce, and G. Calin, "MicroRNAs in the ontogeny of leukemias and lymphomas," *Leukemia and Lymphoma*, vol. 50, no. 2, pp. 160–170, 2009.
- [248] G. A. Calin, C. D. Dumitru, M. Shimizu, et al., "Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 24, pp. 15524–15529, 2002.
- [249] A. M. Roccaro, A. Sacco, B. Thompson, et al., "MicroRNAs 15a and 16 regulate tumor proliferation in multiple myeloma," *Blood*, vol. 113, no. 26, pp. 6669–6680, 2009.
- [250] R. Fonseca, E. Blood, M. Rue, et al., "Clinical and biologic implications of recurrent genomic aberrations in myeloma," *Blood*, vol. 101, no. 11, pp. 4569–4575, 2003.
- [251] L. He, J. M. Thomson, M. T. Hemann, et al., "A microRNA polycistron as a potential human oncogene," *Nature*, vol. 435, no. 7043, pp. 828–833, 2005.
- [252] Z. Li, J. Lu, M. Sun, et al., "Distinct microRNA expression profiles in acute myeloid leukemia with common translocations," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 40, pp. 15535–15540, 2008.
- [253] Z. Li, R. T. Luo, S. Mi, et al., "Consistent deregulation of gene expression between human and murine MLL rearrangement leukemias," *Cancer Research*, vol. 69, no. 3, pp. 1109–1116, 2009.
- [254] Y. Hayashita, H. Osada, Y. Tatematsu, et al., "A polycistronic microRNA cluster, miR-17-92, is overexpressed in human lung cancers and enhances cell proliferation," *Cancer Research*, vol. 65, no. 21, pp. 9628–9632, 2005.
- [255] S. Takakura, N. Mitsutake, M. Nakashima, et al., "Oncogenic role of miR-17-92 cluster in anaplastic thyroid cancer cells," *Cancer Science*, vol. 99, no. 6, pp. 1147–1154, 2008.
- [256] E. Connolly, M. Melegari, P. Landgraf, et al., "Elevated expression of the miR-17-92 polycistron and miR-21 in hepatitis virus-associated hepatocellular carcinoma contributes to the malignant phenotype," *American Journal of Pathology*, vol. 173, no. 3, pp. 856–864, 2008.
- [257] D. Löffler, K. Brocke-Heidrich, G. Pfeifer, et al., "Interleukin-6-dependent survival of multiple myeloma cells involves the Stat3-mediated induction of microRNA-21 through a highly conserved enhancer," *Blood*, vol. 110, no. 4, pp. 1330–1333, 2007.
- [258] T. Papagiannakopoulos, A. Shapiro, and K. S. Kosik, "MicroRNA-21 targets a network of key tumor-suppressive pathways in glioblastoma cells," *Cancer Research*, vol. 68, no. 19, pp. 8164–8172, 2008.
- [259] S. Zhu, H. Wu, F. Wu, D. Nie, S. Sheng, and Y.-Y. Mo, "MicroRNA-21 targets tumor suppressor genes in invasion and metastasis," *Cell Research*, vol. 18, no. 3, pp. 350–359, 2008.
- [260] W. Zhang, J. E. Dahlberg, and W. Tam, "MicroRNAs in tumorigenesis: a primer," *American Journal of Pathology*, vol. 171, no. 3, pp. 728–738, 2007.
- [261] A. Kuehnbacher, C. Urbich, and S. Dimmeler, "Targeting microRNA expression to regulate angiogenesis," *Trends in Pharmacological Sciences*, vol. 29, no. 1, pp. 12–15, 2008.
- [262] I. A. Asangani, S. A. K. Rasheed, D. A. Nikolova, et al., "MicroRNA-21 (miR-21) post-transcriptionally downregulates tumor suppressor Pcd4 and stimulates invasion, intravasation and metastasis in colorectal cancer," *Oncogene*, vol. 27, no. 15, pp. 2128–2136, 2008.
- [263] R. Baffa, M. Fassan, S. Volinia, et al., "MicroRNA expression profiling of human metastatic cancers identifies cancer gene targets," *Journal of Pathology*, vol. 219, no. 2, pp. 214–221, 2009.
- [264] L.-X. Yan, X.-F. Huang, Q. Shao, et al., "MicroRNA miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient poor prognosis," *RNA*, vol. 14, no. 11, pp. 2348–2360, 2008.
- [265] Y. Suárez, C. Fernández-Hernando, J. S. Pober, and W. C. Sessa, "Dicer dependent microRNAs regulate gene expression and functions in human endothelial cells," *Circulation Research*, vol. 100, no. 8, pp. 1164–1173, 2007.
- [266] Y. Suárez, C. Fernández-Hernando, J. Yu, et al., "Dicer-dependent endothelial microRNAs are necessary for post-natal angiogenesis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 37, pp. 14082–14087, 2008.
- [267] Y. Chen and D. H. Gorski, "Regulation of angiogenesis through a microRNA (miR-130a) that down-regulates antiangiogenic homeobox genes GAX and HOXA5," *Blood*, vol. 111, no. 3, pp. 1217–1226, 2008.
- [268] H. K. Saini, S. Griffiths-Jones, and A. J. Enright, "Genomic analysis of human microRNA transcripts," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 45, pp. 17719–17724, 2007.
- [269] T. Avnit-Sagi, L. Kantorovich, S. Kredon-Russo, E. Hornstein, and M. D. Walker, "The promoter of the pri-miR-375 gene directs expression selectively to the endocrine pancreas," *PLoS ONE*, vol. 4, no. 4, article e5033, 2009.
- [270] C. H. Lawrie, C. D. O. Cooper, E. Ballabio, J. Chi, D. Tramonti, and C. S. R. Hutton, "Aberrant expression of microRNA biosynthetic pathway components is a common feature of haematological malignancy," *British Journal of Haematology*, vol. 145, no. 4, pp. 545–548, 2009.
- [271] D. Iliopoulos, H. A. Hirsch, and K. Struhl, "An epigenetic switch involving NF- κ B, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation," *Cell*, vol. 139, no. 4, pp. 693–706, 2009.
- [272] V. B. Sampson, N. H. Rong, J. Han, et al., "MicroRNA let-7a down-regulates MYC and reverts MYC-induced growth in Burkitt lymphoma cells," *Cancer Research*, vol. 67, no. 20, pp. 9762–9770, 2007.
- [273] A. K. Ghosh, T. D. Shanafelt, A. Cimmino, et al., "Aberrant regulation of pVHL levels by microRNA promotes the HIF/VEGF axis in CLL B cells," *Blood*, vol. 113, no. 22, pp. 5568–5574, 2009.
- [274] Q. Lin, Z. Gao, R. M. Alarcon, J. Ye, and Z. Yun, "A role of miR-27 in the regulation of adipogenesis," *FEBS Journal*, vol. 276, no. 8, pp. 2348–2358, 2009.
- [275] A. C. Morrill and C. D. Chinn, "The obesity epidemic in the United States," *Journal of Public Health Policy*, vol. 25, no. 3–4, pp. 353–366, 2004.

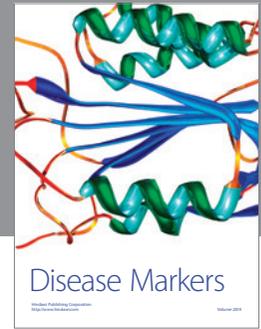
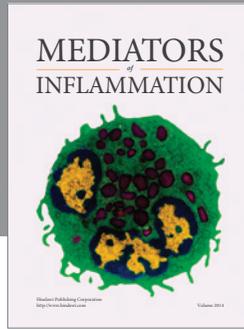
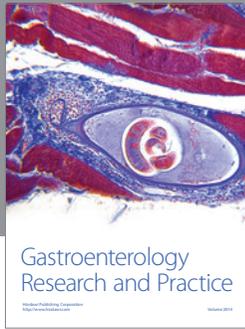
- [276] E. E. Calle, C. Rodriguez, K. Walker-Thurmond, and M. J. Thun, "Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults," *The New England Journal of Medicine*, vol. 348, no. 17, pp. 1625–1638, 2003.
- [277] S. C. Larsson and A. Wolk, "Body mass index and risk of multiple myeloma: a meta-analysis," *International Journal of Cancer*, vol. 121, no. 11, pp. 2512–2516, 2007.
- [278] C. K. Blair, J. R. Cerhan, A. R. Folsom, and J. A. Ross, "Anthropometric characteristics and risk of multiple myeloma," *Epidemiology*, vol. 16, no. 5, pp. 691–694, 2005.
- [279] C. Bosetti, E. Negri, S. Gallus, L. Dal Maso, S. Franceschi, and C. La Vecchia, "Anthropometry and multiple myeloma," *Epidemiology*, vol. 17, no. 3, pp. 340–341, 2006.
- [280] K. Eder, N. Baffy, A. Falus, and A. K. Fulop, "The major inflammatory mediator interleukin-6 and obesity," *Inflammation Research*, vol. 58, no. 11, pp. 727–736, 2009.
- [281] M. Karbiener, C. Fischer, S. Nowitsch, et al., "MicroRNA miR-27b impairs human adipocyte differentiation and targets PPAR γ ," *Biochemical and Biophysical Research Communications*, vol. 390, no. 2, pp. 247–251, 2009.
- [282] J. Ji, J. Zhang, G. Huang, J. Qian, X. Wang, and S. Mei, "Over-expressed microRNA-27a and 27b influence fat accumulation and cell proliferation during rat hepatic stellate cell activation," *FEBS Letters*, vol. 583, no. 4, pp. 759–766, 2009.
- [283] S. Chintharlapalli, S. Papineni, M. Abdelrahim, et al., "Oncogenic microRNA-27a is a target for anticancer agent methyl 2-cyano-3,11-dioxo-18 β -olean-1,12-dien-30-oate in colon cancer cells," *International Journal of Cancer*, vol. 125, no. 8, pp. 1965–1974, 2009.
- [284] B. P. Lewis, I.-H. Shih, M. W. Jones-Rhoades, D. P. Bartel, and C. B. Burge, "Prediction of mammalian microRNA target," *Cell*, vol. 115, no. 7, pp. 787–798, 2003.
- [285] B. John, A. J. Enright, A. Aravin, T. Tuschl, C. Sander, and D. S. Marks, "Human microRNA targets," *PLoS Biology*, vol. 2, no. 11, article e363, 2004.
- [286] A. Krek, D. Grun, M. N. Poy, et al., "Combinatorial microRNA target predictions," *Nature Genetics*, vol. 37, no. 5, pp. 495–500, 2005.
- [287] J. Kim, Y.-S. Oh, and S.-H. Shinn, "Troglitazone reverses the inhibition of nitric oxide production by high glucose in cultured bovine retinal pericytes," *Experimental Eye Research*, vol. 81, no. 1, pp. 65–70, 2005.
- [288] C. Freeman, J. W. Berg, and S. J. Cutler, "Occurrence and prognosis of extranodal lymphomas," *Cancer*, vol. 29, no. 1, pp. 252–260, 1972.
- [289] L. D. Ormerod and J. E. Puklin, "AIDS-associated intraocular lymphoma causing primary retinal vasculitis," *Ocular Immunology and Inflammation*, vol. 5, no. 4, pp. 271–278, 1997.
- [290] R. H. Sagerman, W. Alberti, and D. H. Abramson, *Radiotherapy of Intraocular and Orbital Tumors*, Springer, New York, NY, USA, 2003.
- [291] C.-C. Chan, "Molecular pathology of primary intraocular lymphoma," *Transactions of the American Ophthalmological Society*, vol. 101, pp. 275–292, 2003.
- [292] L. D. Sjö, "Ophthalmic lymphoma: epidemiology and pathogenesis," *Acta Ophthalmologica*, vol. 87, thesis1, pp. 1–20, 2009.
- [293] S. K. Kim, C.-C. Chan, and D. J. Wallace, "Management of primary intraocular lymphoma," *Current Oncology Reports*, vol. 7, no. 1, pp. 74–79, 2005.
- [294] K. B. Gordon, H. S. Rugo, J. L. Duncan, et al., "Ocular manifestations of leukemia: leukemic infiltration versus infectious process," *Ophthalmology*, vol. 108, no. 12, pp. 2293–2300, 2001.
- [295] S. C. Reddy, N. Jackson, and B. S. Menon, "Ocular involvement in leukemia—a study of 288 cases," *Ophthalmologica*, vol. 217, no. 6, pp. 441–445, 2003.
- [296] A. R. Rosenthal, "Ocular manifestations of leukemia. A review," *Ophthalmology*, vol. 90, no. 8, pp. 899–905, 1983.
- [297] T. Sharma, J. Grewal, S. Gupta, and P. I. Murray, "Ophthalmic manifestations of acute leukaemias: the ophthalmologist's role," *Eye*, vol. 18, no. 7, pp. 663–672, 2004.
- [298] A. E. Omoti and C. E. Omoti, "Ophthalmic manifestations of multiple myeloma," *West African Journal of Medicine*, vol. 26, no. 4, pp. 265–268, 2007.
- [299] J. S. Penn, G. W. McCollum, J. M. Barnett, X. Q. Werdich, K. A. Koepke, and V. S. Rajaratnam, "Angiostatic effect of penetrating ocular injury: role of pigment epithelium-derived factor," *Investigative Ophthalmology and Visual Science*, vol. 47, no. 1, pp. 405–414, 2006.
- [300] E. Aguilar, M. I. Dorrell, D. Friedlander, et al., "Chapter 6. Ocular models of angiogenesis," *Methods in Enzymology*, vol. 444, pp. 115–158, 2008.
- [301] P. Henkind, "Ocular neovascularization. The Krill memorial lecture," *American Journal of Ophthalmology*, vol. 85, no. 3, pp. 287–301, 1978.
- [302] P. Lee, C. C. Wang, and A. P. Adamis, "Ocular neovascularization: an epidemiologic review," *Survey of Ophthalmology*, vol. 43, no. 3, pp. 245–269, 1998.
- [303] B. Kim, Q. Tang, P. S. Biswas, et al., "Inhibition of ocular angiogenesis by siRNA targeting vascular endothelial growth factor pathway genes: therapeutic strategy for herpetic stromal keratitis," *American Journal of Pathology*, vol. 165, no. 6, pp. 2177–2185, 2004.
- [304] S. X. Zhang and J. X. Ma, "Ocular neovascularization: implication of endogenous angiogenic inhibitors and potential therapy," *Progress in Retinal and Eye Research*, vol. 26, no. 1, pp. 1–37, 2007.
- [305] P. A. Campochiaro, "Retinal and choroidal neovascularization," *Journal of Cellular Physiology*, vol. 184, no. 3, pp. 301–310, 2000.
- [306] H. A. Pershadsingh and D. M. Moore, "PPAR γ agonists: potential as therapeutics for neovascular retinopathies," *PPAR Research*, vol. 2008, Article ID 164273, 13 pages, 2008.
- [307] A. Tawfik, T. Sanders, K. Kahook, S. Akeel, A. Elmarakby, and M. Al-Shabraway, "Suppression of retinal peroxisome proliferator-activated receptor gamma in experimental diabetes and oxygen-induced retinopathy: role of NADPH oxidase," *Investigative Ophthalmology and Visual Science*, vol. 50, no. 2, pp. 878–884, 2009.
- [308] S. Qin, A. P. McLaughlin, and G. W. De Vries, "Protection of RPE cells from oxidative injury by 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ by augmenting GSH and activating MAPK," *Investigative Ophthalmology and Visual Science*, vol. 47, no. 11, pp. 5098–5105, 2006.
- [309] F. Willermain, S. Dulku, N. S. Gonzalez, et al., "15-Deoxy-12,14-prostaglandin J₂ inhibits interferon gamma induced MHC class II but not class I expression on ARPE cells through a PPAR gamma independent mechanism," *Prostaglandins and Other Lipid Mediators*, vol. 80, no. 3-4, pp. 136–143, 2006.
- [310] Y. Sassa, Y. Hata, L. P. Aiello, Y. Taniguchi, K. Kohno, and T. Ishibashi, "Bifunctional properties of peroxisome proliferator-activated receptor γ 1 in KDR gene regulation mediated via interaction with both Sp1 and Sp3," *Diabetes*, vol. 53, no. 5, pp. 1222–1229, 2004.

- [311] T. Murata, Y. Hata, T. Ishibashi, et al., "Response of experimental retinal neovascularization to thiazolidinediones," *Archives of Ophthalmology*, vol. 119, no. 5, pp. 709–717, 2001.
- [312] P. Aoun, J. W. Simpkins, and N. Agarwal, "Role of PPAR- γ ligands in neuroprotection against glutamate-induced cytotoxicity in retinal ganglion cells," *Investigative Ophthalmology and Visual Science*, vol. 44, no. 7, pp. 2999–3004, 2003.
- [313] S. E. Feldon, C. W. O'Loughlin, D. M. Ray, S. Landskroner-Eiger, K. E. Seweryniak, and R. P. Phipps, "Activated human T lymphocytes express cyclooxygenase-2 and produce proadipogenic prostaglandins that drive human orbital fibroblast differentiation to adipocytes," *American Journal of Pathology*, vol. 169, no. 4, pp. 1183–1193, 2006.
- [314] D. Pasquali, G. M. Pierantoni, A. Fusco, et al., "Fenofibrate increases the expression of high mobility group AT-hook 2 (HMGA2) gene and induces adipocyte differentiation of orbital fibroblasts from Graves' ophthalmopathy," *Journal of Molecular Endocrinology*, vol. 33, no. 1, pp. 133–143, 2004.
- [315] H.-C. Cheng, T.-C. Ho, S.-L. Chen, H.-Y. Lai, K.-F. Hong, and Y.-P. Tsao, "Troglitazone suppresses transforming growth factor beta-mediated fibrogenesis in retinal pigment epithelial cells," *Molecular Vision*, vol. 14, pp. 95–104, 2008.
- [316] M. Artwohl, C. Furnsinn, W. Waldhausl, et al., "Thiazolidinediones inhibit proliferation of microvascular and macrovascular cells by a PPAR γ -independent mechanism," *Diabetologia*, vol. 48, no. 3, pp. 586–594, 2005.
- [317] L. Q. Shen, A. Child, G. M. Weber, J. Folkman, and L. P. Aiello, "Rosiglitazone and delayed onset of proliferative diabetic retinopathy," *Archives of Ophthalmology*, vol. 126, no. 6, pp. 793–799, 2008.
- [318] M. A. K. Rumi, S. Ishihara, H. Kazumori, Y. Kadowaki, and Y. Kinoshita, "Can PPAR γ ligands be used in cancer therapy?" *Current Medicinal Chemistry*, vol. 4, no. 6, pp. 465–477, 2004.
- [319] E. Papageorgiou, N. Pitulis, P. Msaouel, P. Lembessis, and M. Koutsilieris, "The non-genomic crosstalk between PPAR γ ligands and ERK1/2 in cancer cell lines," *Expert Opinion on Therapeutic Targets*, vol. 11, no. 8, pp. 1071–1085, 2007.
- [320] D. P. Kelly, "The pleiotropic nature of the vascular PPAR gene regulatory pathway," *Circulation Research*, vol. 89, no. 11, pp. 935–937, 2001.
- [321] A. R. Collins, "Pleiotropic vascular effects of PPAR γ ligands," *Drug News and Perspectives*, vol. 16, no. 4, pp. 197–204, 2003.
- [322] H. Takano, H. Hasegawa, Y. Zou, and I. Komuro, "Pleiotropic actions of PPAR γ activators thiazolidinediones in cardiovascular diseases," *Current Pharmaceutical Design*, vol. 10, no. 22, pp. 2779–2786, 2004.
- [323] N. L. Julie, I. M. Julie, A. I. Kende, and G. L. Wilson, "Mitochondrial dysfunction and delayed hepatotoxicity: another lesson from troglitazone," *Diabetologia*, vol. 51, no. 11, pp. 2108–2116, 2008.
- [324] C. V. Rizos, M. S. Elisaf, D. P. Mikhailidis, and E. N. Liberopoulos, "How safe is the use of thiazolidinediones in clinical practice?" *Expert Opinion on Drug Safety*, vol. 8, no. 1, pp. 15–32, 2009.
- [325] D. H. Solomon, S. M. Cadarette, N. K. Choudhry, C. Canning, R. Levin, and T. Sturmer, "A cohort study of thiazolidinediones and fractures in older adults with diabetes," *Journal of Clinical Endocrinology and Metabolism*, vol. 94, no. 8, pp. 2792–2798, 2009.
- [326] R. A. Kyle and S. V. Rajkumar, "Treatment of multiple myeloma: a comprehensive review," *Clinical Lymphoma, Myeloma & Leukemia*, vol. 9, no. 4, pp. 278–288, 2009.
- [327] M. Wang and S. Tafuri, "Modulation of PPAR γ activity with pharmaceutical agents: treatment of insulin resistance and atherosclerosis," *Journal of Cellular Biochemistry*, vol. 89, no. 1, pp. 38–47, 2003.
- [328] U. Campia, L. A. Matuskey, and J. A. Panza, "Peroxisome proliferator-activated receptor- γ activation with pioglitazone improves endothelium-dependent dilation in nondiabetic patients with major cardiovascular risk factors," *Circulation*, vol. 113, no. 6, pp. 867–875, 2006.
- [329] A. Pflutzner, C. Hohberg, G. Lubben, et al., "Pioneer study: PPAR γ activation results in overall improvement of clinical and metabolic markers associated with insulin resistance independent of long-term glucose control," *Hormone and Metabolic Research*, vol. 37, no. 8, pp. 510–515, 2005.
- [330] K. Yamakawa, M. Hosoi, H. Koyama, et al., "Peroxisome proliferator-activated receptor- γ agonists increase vascular endothelial growth factor expression in human vascular smooth muscle cells," *Biochemical and Biophysical Research Communications*, vol. 271, no. 3, pp. 571–574, 2000.
- [331] K. Chu, S.-T. Lee, J.-S. Koo, et al., "Peroxisome proliferator-activated receptor- γ -agonist, rosiglitazone, promotes angiogenesis after focal cerebral ischemia," *Brain Research*, vol. 1093, no. 1, pp. 208–218, 2006.
- [332] S. Z. Duan, M. G. Usher, and R. M. Mortensen, "Peroxisome proliferator-activated receptor- γ -mediated effects in the vasculature," *Circulation Research*, vol. 102, no. 3, pp. 283–294, 2008.
- [333] S. Singh, Y. K. Loke, and C. D. Furberg, "Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis," *Journal of the American Medical Association*, vol. 298, no. 10, pp. 1189–1195, 2007.
- [334] A. Zinn, S. Felson, E. Fisher, and A. Schwartzbard, "Reassessing the cardiovascular risks and benefits of thiazolidinediones," *Clinical Cardiology*, vol. 31, no. 9, pp. 397–403, 2008.
- [335] E. Mannucci, M. Monami, M. Di Bari, et al., "Cardiac safety profile of rosiglitazone. A comprehensive meta-analysis of randomized clinical trials," to appear in *International Journal of Cardiology*.
- [336] D. N. Juurlink, T. Gomes, L. L. Lipscombe, P. C. Austin, J. E. Hux, and M. M. Mamdani, "Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study," *British Medical Journal*, vol. 339, article b2942, 2009.
- [337] B. R. Bird and S. M. Swain, "Cardiac toxicity in breast cancer survivors: review of potential cardiac problems," *Clinical Cancer Research*, vol. 14, no. 1, pp. 14–24, 2008.
- [338] K. Towns, P. L. Bedard, and S. Verma, "Matters of the heart: cardiac toxicity of adjuvant systemic therapy for early-stage breast cancer," *Current Oncology*, vol. 15, pp. S16–S29, 2008.
- [339] M. Sereno, A. Brunello, A. Chiappori, et al., "Cardiac toxicity: old and new issues in anti-cancer drugs," *Clinical and Translational Oncology*, vol. 10, no. 1, pp. 35–46, 2008.
- [340] D. E. Gerber, "Targeted therapies: a new generation of cancer treatments," *American Family Physician*, vol. 77, no. 3, pp. 311–319, 2008.
- [341] N. T. Ihle, R. Lemos, D. Schwartz, et al., "Peroxisome proliferator-activated receptor γ agonist pioglitazone prevents the hyperglycemia caused by phosphatidylinositol 3-kinase pathway inhibition by PX-866 without affecting antitumor activity," *Molecular Cancer Therapeutics*, vol. 8, no. 1, pp. 94–100, 2009.
- [342] D. Veliceasa, F. T. Schulze-Hoepfner, and O. V. Volpert, "PPAR γ and agonists against cancer: rational design of complementation treatments," *PPAR Research*, vol. 2008, Article ID 945275, 13 pages, 2008.

- [343] M. L. G. Janssen-Heijnen, H. A. A. M. Maas, S. Houterman, V. E. P. P. Lemmens, H. J. T. Rutten, and J. W. W. Coebergh, "Comorbidity in older surgical cancer patients: influence on patient care and outcome," *European Journal of Cancer*, vol. 43, no. 15, pp. 2179–2193, 2007.
- [344] J. Shen, X. Yang, B. Xie, et al., "MicroRNAs regulate ocular neovascularization," *Molecular Therapy*, vol. 16, no. 7, pp. 1208–1216, 2008.
- [345] Y. M. Shah, K. Morimura, Q. Yang, T. Tanabe, M. Takagi, and F. J. Gonzalez, "Peroxisome proliferator-activated receptor α regulates a microRNA-mediated signaling cascade responsible for hepatocellular proliferation," *Molecular and Cellular Biology*, vol. 27, no. 12, pp. 4238–4247, 2007.
- [346] R. S. McIntyre, J. K. Soczynska, H. O. Woldeyohannes, et al., "Thiazolidinediones: novel treatments for cognitive deficits in mood disorders?" *Expert Opinion on Pharmacotherapy*, vol. 8, no. 11, pp. 1615–1628, 2007.
- [347] J. M. Roodhart, M. H. Langenberg, E. Witteveen, and E. E. Voest, "The molecular basis of class side effects due to treatment with inhibitors of the VEGF/VEGFR pathway," *Current Clinical Pharmacology*, vol. 3, no. 2, pp. 132–143, 2008.
- [348] C. A. Krone and J. T. A. Ely, "Controlling hyperglycemia as an adjunct to cancer therapy," *Integrative Cancer Therapies*, vol. 4, no. 1, pp. 25–31, 2005.
- [349] T. M. McIntyre, A. V. Pontsler, A. R. Silva, et al., "Identification of an intracellular receptor for lysophosphatidic acid (LPA): LPA is a transcellular PPAR γ agonist," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 1, pp. 131–136, 2003.
- [350] F. J. Schopfer, Y. Lin, P. R. S. Baker, et al., "Nitrolinoleic acid: an endogenous peroxisome proliferator-activated receptor γ ligand," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 7, pp. 2340–2345, 2005.
- [351] C. Ulivieri and C. T. Baldari, "The potential of peroxisome proliferator-activated receptor γ (PPAR γ) ligands in the treatment of hematological malignancies," *Mini-Reviews in Medicinal Chemistry*, vol. 7, no. 9, pp. 877–887, 2007.
- [352] T. M. Willson, P. J. Brown, D. D. Sternbach, and B. R. Henke, "The PPARs: from orphan receptors to drug discovery," *Journal of Medicinal Chemistry*, vol. 43, no. 4, pp. 527–550, 2000.
- [353] T. Wang, J. Xu, X. Yu, R. Yang, and Z. C. Han, "Peroxisome proliferator-activated receptor γ in malignant diseases," *Critical Reviews in Oncology/Hematology*, vol. 58, no. 1, pp. 1–14, 2006.
- [354] L. Gelman, J. N. Feige, and B. Desvergne, "Molecular basis of selective PPAR γ modulation for the treatment of Type 2 diabetes," *Biochimica et Biophysica Acta*, vol. 1771, no. 8, pp. 1094–1107, 2007.
- [355] B. M. Forman, P. Tontonoz, J. Chen, R. P. Brun, B. M. Spiegelman, and R. M. Evans, "15-deoxy- $\Delta^{12,14}$ -prostaglandin J_2 is a ligand for the adipocyte determination factor PPAR γ ," *Cell*, vol. 83, no. 5, pp. 803–812, 1995.
- [356] S. A. Kliewer, J. M. Lenhard, T. M. Willson, I. Patel, D. C. Morris, and J. M. Lehmann, "A prostaglandin J_2 metabolite binds peroxisome proliferator-activated receptor γ and promotes adipocyte differentiation," *Cell*, vol. 83, no. 5, pp. 813–819, 1995.
- [357] J. Wigren, S. Surapureddi, A. G. Olsson, C. K. Glass, S. Hammarstrom, and M. Soderstrom, "Differential recruitment of the coactivator proteins CREB-binding protein and steroid receptor coactivator-1 to peroxisome proliferator-activated receptor gamma/9-cis-retinoic acid receptor heterodimers by ligands present in oxidized low-density lipoprotein," *Journal of Endocrinology*, vol. 177, no. 2, pp. 207–214, 2003.
- [358] B. Staels and J.-C. Fruchart, "Therapeutic roles of peroxisome proliferator-activated receptor agonists," *Diabetes*, vol. 54, no. 8, pp. 2460–2470, 2005.
- [359] C. Zang, H. Liu, M. Waechter, et al., "Dual PPAR α/γ ligand TZD18 either alone or in combination with imatinib inhibits proliferation and induces apoptosis of human CML cell lines," *Cell Cycle*, vol. 5, no. 19, pp. 2237–2243, 2006.
- [360] M.-B. Debril, J.-P. Renaud, L. Fajas, and J. Auwerx, "The pleiotropic functions of peroxisome proliferator-activated receptor γ ," *Journal of Molecular Medicine*, vol. 79, no. 1, pp. 30–47, 2001.
- [361] K. L. Houseknecht, B. M. Cole, and P. J. Steele, "Peroxisome proliferator-activated receptor gamma (PPAR γ) and its ligands: a review," *Domestic Animal Endocrinology*, vol. 22, no. 1, pp. 1–23, 2002.
- [362] C. Qin, D. Morrow, J. Stewart, et al., "A new class of peroxisome proliferator-activated receptor γ (PPAR γ) agonists that inhibit growth of breast cancer cells: 1,1-Bis(3'-indolyl)-1-(p-substituted phenyl) methanes," *Molecular Cancer Therapeutics*, vol. 3, no. 3, pp. 247–259, 2004.
- [363] Y. Ito, P. Pandey, A. Place, et al., "The novel triterpenoid 2-cyano-3,12-dioxolean-1,9-dien-28-oic acid induces apoptosis of human myeloid leukemia cells by a caspase-8-dependent mechanism," *Cell Growth and Differentiation*, vol. 11, no. 5, pp. 261–267, 2000.
- [364] N. Suh, Y. Wang, T. Honda, et al., "A novel synthetic oleanane triterpenoid, 2-cyano-3,12-dioxolean-1,9-dien-28-oic acid, with potent differentiating, antiproliferative, and anti-inflammatory activity," *Cancer Research*, vol. 59, no. 2, pp. 336–341, 1999.
- [365] R. Contractor, I. J. Samudio, Z. Estrov, et al., "A novel ring-substituted diindolylmethane, 1,1-bis(3'-(5-methoxyindolyl))-1-(p-t-butylphenyl) methane, inhibits extracellular signal-regulated kinase activation and induces apoptosis in acute myelogenous leukemia," *Cancer Research*, vol. 65, no. 7, pp. 2890–2898, 2005.
- [366] S. Fujimura, J. Suzumiya, K. Nakamura, and J. Ono, "Effects of troglitazone on the growth and differentiation of hematopoietic cell lines," *International Journal of Oncology*, vol. 13, no. 6, pp. 1263–1267, 1998.
- [367] N. Yamakawa-Karakida, K. Sugita, T. Inukai, et al., "Ligand activation of peroxisome proliferator-activated receptor γ induces apoptosis of leukemia cells by down-regulating the c-myc gene expression via blockade of the Tcf-4 activity," *Cell Death and Differentiation*, vol. 9, no. 5, pp. 513–526, 2002.
- [368] J. J. Liu, R. W. Huang, D. J. Lin, et al., "Expression of survivin and bax/bcl-2 in peroxisome proliferator activated receptor- γ ligands induces apoptosis on human myeloid leukemia cells in vitro," *Annals of Oncology*, vol. 16, no. 3, pp. 455–459, 2005.
- [369] J.-J. Liu, P.-Q. Liu, D.-J. Lin, et al., "Downregulation of cyclooxygenase-2 expression and activation of caspase-3 are involved in peroxisome proliferator-activated receptor- γ agonists induced apoptosis in human monocyte leukemia cells in vitro," *Annals of Hematology*, vol. 86, no. 3, pp. 173–183, 2007.
- [370] H. Han, S.-W. Shin, C.-Y. Seo, et al., "15-Deoxy- $\Delta^{12,14}$ -prostaglandin J_2 (15d-PG J_2) sensitizes human leukemic HL-60 cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through Akt

- downregulation," *Apoptosis*, vol. 12, no. 11, pp. 2101–2114, 2007.
- [371] S. Nakata, T. Yoshida, T. Shiraishi, et al., "15-Deoxy- $\Delta^{12,14}$ -prostaglandin J_2 induces death receptor 5 expression through mRNA stabilization independently of PPAR γ and potentiates TRAIL-induced apoptosis," *Molecular Cancer Therapeutics*, vol. 5, no. 7, pp. 1827–1835, 2006.
- [372] A. Sugimura, Y. Kiriya, H. Nochi, et al., "Troglitazone suppresses cell growth of myeloid leukemia cell lines by induction of p21WAF1/CIP1 cyclin-dependent kinase inhibitor," *Biochemical and Biophysical Research Communications*, vol. 261, no. 3, pp. 833–837, 1999.
- [373] M. Konopleva, E. Elstner, T. J. McQueen, et al., "Peroxisome proliferator-activated receptor and retinoid X receptor ligands are potent inducers of differentiation and apoptosis in leukemias," *Molecular Cancer Therapeutics*, vol. 3, no. 10, pp. 1249–1262, 2004.
- [374] N. Hirase, T. Yanase, Y.-M. Mu, et al., "Thiazolidinedione induces apoptosis and monocytic differentiation in the promyelocytic leukemia cell line HL60," *Oncology*, vol. 57, supplement 2, pp. 17–25, 1999.
- [375] H. Asou, W. Verbeek, E. Williamson, et al., "Growth inhibition of myeloid leukemia cells by troglitazone, a ligand for peroxisome proliferator activated receptor gamma, and retinoids," *International Journal of Oncology*, vol. 15, no. 5, pp. 1027–1031, 1999.
- [376] E. Yasugi, A. Horiuchi, I. Uemura, et al., "Peroxisome proliferator-activated receptor γ ligands stimulate myeloid differentiation and lipogenesis in human leukemia NB4 cells," *Development Growth and Differentiation*, vol. 48, no. 3, pp. 177–188, 2006.
- [377] S. Koschmieder, F. D'Alo, H. Radomska, et al., "CDDO induces granulocytic differentiation of myeloid leukemic blasts through translational up-regulation of p42 CCAAT enhancer-binding protein alpha," *Blood*, vol. 110, no. 10, pp. 3695–3705, 2007.
- [378] Y. Tabe, M. Konopleva, Y. Kondo, et al., "PPAR γ -active triterpenoid CDDO enhances ATRA-induced differentiation in APL," *Cancer Biology and Therapy*, vol. 6, no. 12, pp. 1967–1977, 2007.
- [379] M. Konopleva, T. Tsao, Z. Estrov, et al., "The synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid induces caspase-dependent and -independent apoptosis in acute myelogenous leukemia," *Cancer Research*, vol. 64, no. 21, pp. 7927–7935, 2004.
- [380] T. Ikeda, M. Sporn, T. Honda, G. W. Gribble, and D. Kufe, "The novel triterpenoid CDDO and its derivatives induce apoptosis by disruption of intracellular redox balance," *Cancer Research*, vol. 63, no. 17, pp. 5551–5558, 2003.
- [381] L. Zhu, B. Gong, C. L. Bisgaier, M. Aviram, and R. S. Newton, "Induction of PPAR γ 1 expression in human THP-1 monocytic leukemia cells by 9-cis-retinoic acid is associated with cellular growth suppression," *Biochemical and Biophysical Research Communications*, vol. 251, no. 3, pp. 842–848, 1998.
- [382] U. Kintscher, S. Goetze, S. Wakino, et al., "Peroxisome proliferator-activated receptor and retinoid X receptor ligands inhibit monocyte chemotactic protein-1-directed migration of monocytes," *European Journal of Pharmacology*, vol. 401, no. 3, pp. 259–270, 2000.
- [383] H. Liu, C. Zang, M. H. Fenner, et al., "Growth inhibition and apoptosis in human Philadelphia chromosome-positive lymphoblastic leukemia cell lines by treatment with the dual PPAR α/γ ligand TZD18," *Blood*, vol. 107, no. 9, pp. 3683–3692, 2006.
- [384] N. Hirase, T. Yanase, Y.-M. Mu, et al., "Thiazolidinedione suppresses the expression of erythroid phenotype in erythroleukemia cell line K562," *Leukemia Research*, vol. 24, no. 5, pp. 393–400, 2000.
- [385] C. Zang, H. Liu, M. G. Posch, et al., "Peroxisome proliferator-activated receptor γ ligands induce growth inhibition and apoptosis of human B lymphocytic leukemia," *Leukemia Research*, vol. 28, no. 4, pp. 387–397, 2004.
- [386] M. Takenokuchi, K. Saigo, Y. Nakamachi, et al., "Troglitazone inhibits cell growth and induces apoptosis of B-cell acute lymphoblastic leukemia cells with t(14;18)," *Acta Haematologica*, vol. 116, no. 1, pp. 30–40, 2006.
- [387] R. Piva, P. Gianferretti, A. Ciucci, R. Taulli, G. Belardo, and M. G. Santoro, "15-Deoxy- $\Delta^{12,14}$ -prostaglandin J_2 induces apoptosis in human malignant B cells: an effect associated with inhibition of NF- κ B activity and down-regulation of antiapoptotic proteins," *Blood*, vol. 105, no. 4, pp. 1750–1758, 2005.
- [388] S. G. Harris and R. P. Phipps, "Prostaglandin D_2 , its metabolite 15-d-PG J_2 , and peroxisome proliferator activated receptor- γ agonists induce apoptosis in transformed, but not normal, human T lineage cells," *Immunology*, vol. 105, no. 1, pp. 23–34, 2002.
- [389] C. Yang, S.-H. Jo, B. Csernus, et al., "Activation of peroxisome proliferator-activated receptor γ contributes to the survival of T lymphoma cells by affecting cellular metabolism," *American Journal of Pathology*, vol. 170, no. 2, pp. 722–732, 2007.
- [390] C. Zhang, X. Ni, M. Konopleva, M. Andreeff, and M. Duvic, "The novel synthetic oleanane triterpenoid CDDO (2-cyano-3, 12-dioxoolean-1, 9-dien-28-oic acid) induces apoptosis in Mycosis fungoides/Sezary syndrome cells," *Journal of Investigative Dermatology*, vol. 123, no. 2, pp. 380–387, 2004.
- [391] J. Eucker, J. Sterz, H. Krebbel, et al., "Peroxisome proliferator-activated receptor-gamma ligands inhibit proliferation and induce apoptosis in mantle cell lymphoma," *Anti-Cancer Drugs*, vol. 17, no. 7, pp. 763–769, 2006.
- [392] I. M. Pedersen, S. Kitada, A. Schimmer, et al., "The triterpenoid CDDO induces apoptosis in refractory CLL B cells," *Blood*, vol. 100, no. 8, pp. 2965–2972, 2002.
- [393] S. Inoue, R. T. Snowden, M. J. S. Dyer, and G. M. Cohen, "CDDO induces apoptosis via the intrinsic pathway in lymphoid cells," *Leukemia*, vol. 18, no. 5, pp. 948–952, 2004.
- [394] P. S. Brookes, K. Morse, D. Ray, et al., "The triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid and its derivatives elicit human lymphoid cell apoptosis through a novel pathway involving the unregulated mitochondrial permeability transition pore," *Cancer Research*, vol. 67, no. 4, pp. 1793–1802, 2007.
- [395] J. Eucker, K. Bangeroth, I. Zavrski, et al., "Ligands of peroxisome proliferator-activated receptor γ induce apoptosis in multiple myeloma," *Anti-Cancer Drugs*, vol. 15, no. 10, pp. 955–960, 2004.
- [396] C. S. Mitsiades, N. Mitsiades, P. G. Richardson, S. P. Treon, and K. C. Anderson, "Novel biologically based therapies for Waldenstrom's macroglobulinemia," *Seminars in Oncology*, vol. 30, no. 2, pp. 309–312, 2003.
- [397] T. Ikeda, Y. Nakata, F. Kimura, et al., "Induction of redox imbalance and apoptosis in multiple myeloma cells by the novel triterpenoid 2-cyano-3, 12-dioxoolean-1,9-dien-28-oic

- acid," *Molecular Cancer Therapeutics*, vol. 3, no. 1, pp. 39–45, 2004.
- [398] D. Chauhan, G. Li, K. Podar, et al., "The bortezomib/proteasome inhibitor PS-341 and triterpenoid CDDO-Im induce synergistic anti-multiple myeloma (MM) activity and overcome bortezomib resistance," *Blood*, vol. 103, no. 8, pp. 3158–3166, 2004.
- [399] K. Liby, N. Voong, C. R. Williams, et al., "The synthetic triterpenoid CDDO-Imidazolide suppresses STAT phosphorylation and induces apoptosis in myeloma and lung cancer cells," *Clinical Cancer Research*, vol. 12, no. 14, part 1, pp. 4288–4293, 2006.



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