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Mini-review

Anti-leukemic effects of PPARγ ligands

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ABSTRACT

The peroxisome proliferator-activated receptor (PPAR) γ, a subtype of PPARs, is a member of the nuclear receptor family. PPARγ and its ligands contribute to various types of diseases including cancer. Given that currently developed therapies against leukemia are not very effective or safe, PPARγ ligands have been shown to be a new class of compounds with the potential to treat hematologic malignancies, particularly leukemia. The capability of PPARγ ligands to induce apoptosis, inhibit proliferation, and promote differentiation of leukemia cells suggests it has significant potential as a drug against leukemia. However, the specific mechanisms and molecules involved are not well-understood, although a number of PPARγ ligands with anti-leukemic effects have been identified. This may explain why PPARγ ligands have not been widely evaluated in clinical trials. To fill the gaps in the lack of understanding of specific anti-leukemic processes of PPARγ ligands and further adapt these molecules as anti-leukemic agents, this review describes previous studies of the anti-leukemic effects of PPARγ ligands.

1. Introduction

Despite the development of modern chemotherapeutic medicines against cancer cells, leukemia, a type of hematologic malignancy, remains mostly incurable [1,2]. Moreover, cutting-edge therapies with new modes of action tend to cause considerable side effects, mainly drug-induced damage to healthy cells and tissues [2,3]. However, worldwide research over the last two decades has revealed some details regarding the underlying mechanisms that lead to the development of leukemia; leukemia is the consequence of multiple collaborative molecular mechanisms that lead to genetic or epigenetic alterations that eventually bring about this condition [4,5]. This understanding has enabled the development of cancer therapies based on specific molecular pathways involved in tumorigenesis [6,7]. Particularly, numerous transcription factors are known to affect leukemia cells by regulating gene expression in a stage- and lineage-specific manner [8–10].

Peroxisome proliferator-activated receptor (PPAR), a member of the nuclear hormone receptor superfamily, is a well-known transcription factor affecting the oncogenic process upon its activation by various ligands or proteins [11–15]. The three major isoforms of PPARs identified to date are PPARα, PPARβ/δ, and PPARγ (also known as NR1C1, NR1C2, and NR1C3, respectively) [16–18]. Among the three subtypes, PPARγ and its ligands have been shown to be promising sources of anti-cancer therapeutics [19–23]. However, the results of *in vivo* studies examining how PPARγ affects cancer cells are not as consistent as those of *in vitro* studies. Some *in vivo* studies suggested that PPARγ exacerbates tumor development [24–26], while most other studies confirmed the anti-cancer effects of PPARγ in animal models [27,28]. Some researchers suggested that *in vivo* studies show different results because the anti-neoplastic effects of PPARγ may not be induced by PPARγ signaling, but rather by an unknown action of the ligands [24]. Thus, the anti-tumor mechanisms of these ligands remain unknown. In addition, relatively fewer studies have examined the effects of PPARγ ligands in leukemia as compared to solid tumors. In fact, 21 clinical trials

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examining the role of PPAR ligands on cancer are registered at clinicaltrials.gov, and only 2 trials have targeted leukemia. To improve the understanding of the specific anti-tumorigenic processes of various types of PPARγ ligands and further adapt them as anti-leukemic agents based on their specific mechanisms, this review discusses previous findings related to the anti-tumorigenic function of PPARγ ligands in hematologic cancers, particularly leukemia.

2. PPARγ and its ligands

2.1. PPARγ and its actions

PPARγ is an isoform of PPAR, a subfamily of the larger nuclear hormone receptor superfamily of transcription factors [16–18]. The *PPARγ* gene contains three promoters that yield three different isoforms, PPARγ1, PPARγ2, and PPARγ3, and the primary transcript of each isoform exhibits alternative splicing and/or polyadenylation [29,30]. PPARγ1 is highly expressed in various tissues, however, PPARγ2 is only found in adipose tissue, while PPARγ3 is rich in macrophages, the large intestine, and white adipose tissue [30–32]. Although these receptors act as master regulators of many biological pathways, they are particularly highly expressed in tissues related to energy homeostasis [33,34]. Indeed, PPARs play a major role in both lipid and glucose homeostasis, but are also critically involved in cell cycle regulation, inflammation, and apoptosis [35–37].

PPARγ stimulates gene transcription by forming heterodimers with retinoid X receptor (RXR) and binding to specific DNA sequences known as peroxisome proliferator response elements (PPREs) located in the promoter region of target genes to further regulate these biological pathways (Fig. 1) [38–43]. Specifically, PPARγ is well-known for its role in lipid homeostasis, as it is involved in cell growth and cell cycle arrest-related pathways [44,45]. These pathways lead to the differentiation of adipocytes and the stimulation of adipogenesis [44–46]. Additionally, PPARγ improves insulin and glucose parameters or increases whole body insulin sensitivity. This increased insulin sensitization has resulted in the widespread use of PPARγ to treat diabetes [47,48]. Apart from its role in lipid and glucose metabolism as a transcription factor, PPARγ also acts as a *trans*-repressor of inflammatory genes [49]. Given that they can reduce the inflammatory responses in many cell types, PPARγ ligands have been used to treat arthritis, inflammatory bowel syndrome, and atherosclerosis [50,51]. More importantly, PPARγ ligands exhibit anti-cancer properties in solid tumors such as colon cancer, pancreatic cancer, breast cancer, bladder cancer, prostate cancer, and gastric cancer, and in hematologic malignancies such as leukemia [52–59]. Acute myeloid leukemia (AML), PPARγ ligands alone and in combination with retinoic acid receptor α ligands in particular have been shown to control cell proliferation, differentiation, and apoptosis [58]. The capability of PPARγ and its ligands to induce apoptosis, inhibit proliferation, and promote differentiation of leukemia cells indicates its potential as a drug against this disease.

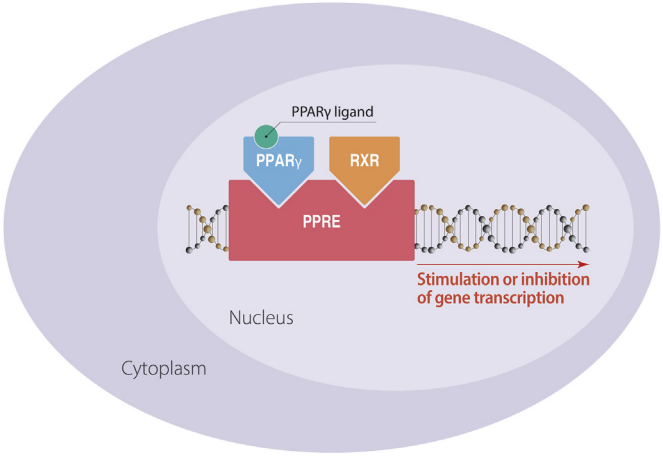

Fig. 1. Schematic diagram of gene transcription mediated by PPARγ. PPARγ stimulates gene transcription by forming heterodimers with RXR and binding to specific DNA sequences known as PPREs in the promoter region of target genes. RXR, retinoid X receptor; PPPE, peroxisome proliferator response element.

2.2. PPARγ ligands including agonists and antagonists

For the transcriptional activity of PPARγ, a broad range of natural or synthetic ligands are required to bind to the large binding pocket of PPARγ [60,61]. The types of natural and synthetic ligands are listed and classified as agonists and antagonists in Table 1. First, naturally occurring ligands mainly include fatty acids or their derivatives such as linoleic acid [62], 9-, 13-, and 15-hydroxyoctadecadienoic acids [60,63], and arachidonic acids including prostaglandin D_2 (PGD_2) and 15-deoxy-Δ12,14-prostaglandin J_2 (15d-PGJ_2), [64,65]. 15d-PGJ_2 is known as the most potent endogenous ligand of PPARγ [66]. Flavonoids are a group of plant metabolites such as hesperidin and oroxylin A that also stimulate PPARγ transcriptional activities [67,68].

There are two types of synthetic PPARγ ligands, agonists and antagonists. For instance, some of the synthetic compounds that act as PPARγ agonists include the novel synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) and thiazolidinediones (TZD) such as ciglitazone, rosiglitazone, pioglitazone, and troglitazone [69,70]. Both CDDO and TZD have pro-apoptotic and anti-proliferative activities and thus show potential as chemotherapeutic agents [71,72]. Other types of synthetic agonists are newly synthesized ring-substituted diindolylmethane derivatives, 1,1-bis[3′-(5-methoxyindolyl)]-1-(p-*t*-butylphenyl) methane (DIM #34) [73], isoxazolidinedione JTT-501 [74], L-tyrosine-based GW-7845, and GW-1929 [60,75], and some nonsteroidal anti-inflammatory drugs including indomethacin and ibuprofen [76]. Conversely, several synthetic ligands act as PPARγ antagonists

Table 1
Types of PPARγ ligands: agonists and antagonists.

Natural ligand	Synthetic ligand	
Agonist	Agonist	Antagonist
Linoleic acid	CDDO	GW-9662
9-HODE	CDDO derivatives	Diclofenac
13-HODE	CDDO-Me	BADGE
15-HODE	CDDO-Im	SR 202
Arachidonic acid	Thiazolidinedione (TZD)	T0070907
PGD_2	Ciglitazone	
15d-PGJ_2	Rosiglitazone	
Flavonoid	Pioglitazone	
Hesperidin	Troglitazone	
Oroxylin A	DIM#34 (diindolylmethane derivatives)	
	JTT-501 (isoxazolidinedione)	
	GW-7845	
	GW-1929	
	Nonsteroidal anti-inflammatory drugs	
	Indomethacin	
	Ibuprofen	

HODE, hydroxyoctadecadienoic acid; PGD_2, prostaglandin D_2; 15d-PGJ_2,15-deoxy-Δ12,14-prostaglandin J_2; CDDO, triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid; CDDO-Me, CDDO-methyl ester; CDDO-Im, CDDO-imidazolide; BADGE, biphenol-A-diglicydyl ether.