

Review Article

Effects of PPAR γ Ligands on Leukemia

Yoko Tabe,¹ Marina Konopleva,² Michael Andreeff,² and Akimichi Ohsaka³

¹Department of Clinical Laboratory Medicine, Juntendo University School of Medicine, Hongo 2-1-1, Bunkyo-ku, Tokyo 113-8421, Japan

²Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

³Department of Transfusion Medicine and Stem Cell Regulation, Juntendo University School of Medicine, Hongo 2-1-1, Bunkyo-ku, Tokyo 113-8421, Japan

Correspondence should be addressed to Yoko Tabe, tabe@juntendo.ac.jp

Received 1 January 2012; Accepted 21 March 2012

Academic Editor: Stefan Alexson

Copyright © 2012 Yoko Tabe et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peroxisome proliferator-activated receptors (PPARs) and retinoic acid receptors (RARs), members of the nuclear receptor superfamily, are transcription factors that regulate a variety of important cellular functions. PPARs form heterodimers with retinoid X receptor (RXR), an obligate heterodimeric partner for other nuclear receptors. Several novel links between retinoid metabolism and PPAR responses have been identified, and activation of PPAR/RXR expression has been shown to increase response to retinoids. PPAR γ has emerged as a key regulator of cell growth and survival, whose activity is modulated by a number of synthetic and natural ligands. While clinical trials in cancer patients with thiazolidinediones (TZD) have been disappointing, novel structurally different PPAR γ ligands, including triterpenoids, have entered clinical arena as therapeutic agents for epithelial and hematopoietic malignancies. Here we shall review the antitumor advances of PPAR γ , alone and in combination with RAR α ligands in control of cell proliferation, differentiation, and apoptosis and their potential therapeutic applications in hematological malignancies.

1. Introduction

Acute myelogenous leukemia (AML) remains incurable in most patients because of the likelihood of relapse and the development of resistant disease [1]. Many novel agents do not improve survival of patients once relapse occurs, which enforces the need for more effective treatment strategies for AML exploiting apoptosis and/or differentiation induction.

Ligands of nuclear hormone receptors (NHRs) have been shown to induce apoptosis and/or inhibiting proliferation in a variety of preclinical models. The most striking improvement in AML therapy was achieved by the treatment of acute promyelocytic leukemia (APL) using the retinoic acid (RA) receptor- (RAR-) specific ligand, all-trans RA (ATRA) [2, 3]. ATRA, combined with chemotherapy, results in complete remission (CR) rates ranging from 72% to 90% in APL patients with the oncogenic transcriptional repressor PML-RAR α [4–8]. However, approximately 10% to 30% of patients relapse [8] and frequently develop resistance to

ATRA [9, 10]. Acquisition of specific mutations in the ligand binding site, which leads to altered interactions with transcriptional coregulators, is a well-documented mechanism of acquired ATRA resistance [11, 12]. In addition, several alternative mechanisms such as DNA methylation [13] or impaired telomerase regulation [14] have been proposed to cause ATRA-resistant disease.

Considering the potential of using PPAR γ ligands in APL “transcriptional” therapy, this paper summarizes the effects of endogenous and synthetic PPAR γ ligands in AML and focuses on elucidating the mechanisms underlying the anti-tumor effects of novel synthetic PPAR γ ligand 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) in APL.

2. PPAR γ and PPAR γ Ligands

PPARs belong to the NHR superfamily of ligand-dependent transcription factors, which includes RAR and RXR among others. Three PPAR isotypes have been identified: PPAR α ,

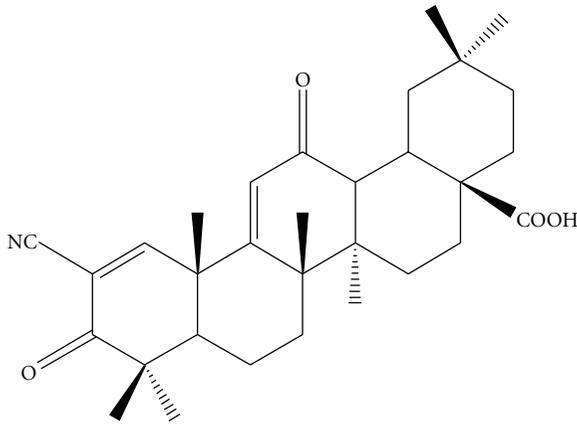


FIGURE 1: Molecular structure of CDDO 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO).

PPAR α , and PPAR β/δ . PPAR γ exists as a heterodimer with RXR, and upon activation by endogenous or synthetic ligands, PPAR γ /RXR binds to the specific response elements PPRE in the promoter regions of target genes, respectively, which in turn functions as a transcription factor [15–17].

PPAR γ modulates gene networks involved in controlling growth, cellular differentiation, and apoptosis [18]. PPAR γ receptor can be activated by endogenous ligands (e.g., prostaglandin D2 (PGD2), 15-deoxy prostaglandin J2 (15dPGJ2), or 15-hydroxyeicosatetraenoic acid (15-HETE)) [19, 20], and synthetic ligands that include insulin sensitizing antidiabetic thiazolidinediones (TZD); troglitazone (TGZ), rosiglitazone (RGZ), ciglitazone (CGZ), or pioglitazone (PGZ) [21–23]; nonsteroidal anti-inflammatory compounds indomethacin, ibuprofen, flufenamic acid, or fenoprofen [24]; triterpenoids 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) [25] are a semisynthetic triterpenoid derived from oleanolic acid, whose structure contains two α , β -unsaturated carbonyl moieties. CDDO was shown to release nuclear receptor corepressor (NCoR) and recruit CCAAT/enhancer-binding protein (CBP/p300) to PPAR γ [25] (Figure 1).

PPAR γ ligands induce differentiation and inhibit proliferation in several tumor models [26–34]. The regulation of gene transcription by ligand-bound PPAR γ involves cofactor proteins, which bridge transcription factors to the basal transcriptional machinery or modify chromatin structure. These include release of small accessory molecules known as corepressors (e.g., NCoR or silencing mediator for retinoid receptor and thyroid hormone receptors (SMRT)) and recruitment of coactivators (e.g., CBP/p300, cyclic adenosine monophosphate response-element binding protein (CREB), steroid receptor coactivator-1 (SRC-1), receptor interacting protein 140(RIP140), or PPAR γ interacting protein (PRIP/RAP250) [35–40]. The multiprotein complex induces transcription by chromatin remodeling and interaction with the basal transcriptional machinery [41, 42], and the relative levels of cofactor expression (e.g., availability of cofactors CBP/p300 versus SRC-1) also control the specificity of the physiological response to target gene transcription [43].

3. Antitumor Effects of PPAR γ in AML

High PPAR γ expression was observed in normal bone marrow and peripheral blood CD34⁺ progenitor cells [44]. Furthermore, significantly higher PPAR γ mRNA expression was observed in primary AML cases compared to normal peripheral blood or bone marrow mononuclear cells [45, 46].

The mechanisms of cell differentiation and cell cycle arrest by activated PPAR γ depend heavily on the specificity of PPAR γ ligands. The induction of differentiation by activation of PPAR γ may represent a promising novel therapeutic approach for cancer as already demonstrated for liposarcoma [27] and in xenograft models of prostate [47] and colon cancer [30]. Differentiation therapy may well play a role in acute myeloid leukemias, analogous to ATRA-induced differentiation in APL. PPAR γ is known to be induced and/or expressed in cells of the myeloid/monocytic lineage [48, 49].

In PPAR γ expressing AML cell lines, PPAR γ ligand TGZ suppressed their clonal growth with G1 cell cycle phase arrest, induced differentiation into monocytes, and increased apoptosis at higher concentrations [50, 51]. Troglitazone-induced G0/G1 cell cycle arrest with upregulation of p21 mRNA in myeloid leukemia cell lines [52]. In concert with these findings, PPAR γ ligand PGZ and 15dPGJ2 suppressed proliferation, and the combined treatment with ATRA synergistically induced myeloid differentiation in promyelocytic leukemia NB4 cells [53]. Furthermore, simultaneous treatment with TGZ and RXR or RAR ligands resulted in additive suppression of growth indicating that PPAR γ ligand combined with a retinoid is a potent inhibitor of clonogenic growth of AML [50]. CDDO has been reported to induce monocytic differentiation of human myeloid leukemia cells and adipogenic differentiation of mouse fibroblasts [54].

CDDO-Me also induced granulo-monocytic differentiation in primary AML cells and cell lines. Combinations with ATRA or the RXR-specific ligand LG100268 enhanced the effects of CDDO-Me on cell viability and/or terminal differentiation of myeloid leukemic cell lines [54]. CDDO-Me-induced enhanced apoptosis when combined with ara-C and retinoids indicating potential activity in the future therapy for AML [55].

With respect to the mechanisms of PPAR γ -ligand-induced differentiation, CCAAT enhancer-binding protein alpha (CEBPA) translational upregulation has been reported to be required for CDDO-induced granulocytic differentiation of AML patients samples and cell lines [56]. CDDO increases the ratio of transcriptionally active p42 and the inactive p30 CEBPA isoform, which in turn leads to transcriptional activation of CEBPA-regulated genes and associates with dephosphorylation of eIF2alpha and phosphorylation of eIF4E [56].

PPAR γ ligands are additionally known to induce apoptosis. The mechanisms of apoptosis induction by activated PPAR γ depend heavily on the specificity of PPAR γ ligands. PPAR γ activation by natural ligand 15dPGJ2 and synthetic ligand TGZ induce apoptosis accompanied by caspase-3 activation and downregulated c-myc gene expression in myeloid leukemic cells [57]. 15dPGJ2 and TGZ have been also

reported to induce upregulation of bax and downregulation of antiapoptotic proteins survivin and bcl-2 in AML and CML [58]. Furthermore, downregulation of cyclooxygenase-2 expression, disruption of mitochondrial membrane potential, activation of caspase-3, downregulation of Bcl-2, Bcl-XL, and Mcl-1, and upregulation of Bax by these PPAR γ agonists 15dPGJ2 and TGZ has been reported in human monocytic leukemia cells [59]. Semisynthetic oleanane triterpenoid CDDO has potent differentiating, antiproliferative, anti-inflammatory, and apoptosis-inducing properties [54]. CDDO has been reported to activate caspase-8 and -3 and to induce mitochondrial cytochrome *c* release in leukemic cells and in osteosarcoma cells [60–62]. CDDO has been further shown to activate the intrinsic pathway of apoptosis that involves the release of cytochrome *c* and AIF and initiates caspase-dependent and independent cell death in AML [63]. The C-28 methyl ester of CDDO, CDDO-Me [55], and C-28 imidazolide imide of CDDO (CDDO-Im) [64] has been shown to be more potent than CDDO in inducing apoptosis and differentiation of acute myeloid leukemia (AML) cells. CDDO-Me is 3- to 5-fold more active than CDDO in inhibiting the viability of AML cells in an MDR-1- and p53-independent manner, inducing apoptosis through a loss of mitochondrial membrane potential, and increasing caspase-3 cleavage and proapoptotic Bax protein. It has significantly less cytotoxicity against normal CD34⁺ progenitor cells, assuring therapeutic window [55].

In addition, CDDO was shown to inhibit NF- κ B-mediated gene expression in leukemic cells [62]. CDDO/tumor-necrosis-factor- (TNF-) induced apoptosis occurs through selective inhibition of NF- κ B-dependent antiapoptotic proteins, bypassing potential mitochondrial resistance mechanisms [62]. CDDO-Me also inhibits both constitutive and inducible NF- κ B through inhibition of I κ B α kinase, leading to the suppression of expression of NF- κ B-regulated gene products and enhancement of apoptosis induced by TNF α [65].

Notably, certain PPAR γ ligands execute anti-tumor activities without requiring interaction with the PPAR ligand binding domain [66]. For example, CDDO, CDDO-Me, and CDDO-Im activate PPAR γ -dependent and -independent pathways that inhibit cancer-cell growth [67]. They activate PPAR γ in transactivation assays, and CDDO-induced apoptosis was diminished by dominant-negative PPAR γ in myeloid HL-60 cells and by T007 in myeloid U937 cells [68], but CDDO-Im-induced differentiation in leukemia cells was not inhibited by the PPAR γ antagonist GW9662 [61], and T007 did not affect inhibition of SKOV3 ovarian cancer cell growth by CDDO [69]. In these scenarios, interaction with the PPAR γ receptor is irrelevant to the anti-cancer effects, which may depend on cell type, presence/activity of the receptor(s), and cellular abundance of coactivators/corepressors. PPAR-independent effects of PPAR γ ligands are due in part to their electrophilic nature, proteasomal degradation of cell cycle-, and apoptosis-regulatory proteins, transcriptional repression, and other mechanisms [70–72]. Both, PPAR γ -dependent and -independent pathways that contribute to inhibition of cancer cell growth may be beneficial for cancer chemotherapy [67].

4. Antitumor Effects of PPAR γ -Active Triterpenoid CDDO on APL

RARs bind with high affinity to the RA-responsive element (RARE) as a heterodimer with RXR, which also heterodimerizes with other nuclear receptors, such as PPAR γ .

In APL cells, the oncogenic transcription factor PML-RAR α , a dominant negative transcriptional repressor, targets consist of two copies of an AGGTCA, a highly conserved consensus for RAR α . PML-induced dimerization allows the two RAR α moieties of PML-RAR α to bind very distant monomeric DNA sites. The spectrum of response elements for PML-RAR α and PML-RAR α -RXR (DR1-DR16 response elements) is much broader than one for the wild-type RAR-RXR (DR1, DR2, and DR5), and PML-RAR α -RXR oligomers silence a wide range of nuclear receptor target genes [73].

X-RAR α fusion proteins in APL have been demonstrated to negatively affect transactivation of PPAR γ [74], indicating that inhibition of PPAR γ activity may contribute to the pathophysiology of the differentiation block in APL, and that PPAR γ ligands could sensitize APL cells to the differentiating effects of ATRA including ATRA-resistant cells [45].

PML-RAR α recruits the nuclear corepressors and histone deacetylase (HDAC), which leads to histone condensation and transcriptional repression [75–77]. ATRA acts by causing the PML-RAR α /HDAC complex to dissociate, thereby converting PML-RAR α into a transcriptional activator [76]. Reactivation of ATRA target genes by inducing an appropriate level of histone acetylation in their promoters is a potential strategy for restoring anticancer effects of ATRA in refractory APL [77]. Differentiating agents including ATRA, arsenic, cAMP, HDAC inhibitors, and rexinoids relieve this repression through various molecular mechanisms, allowing spontaneous differentiation of leukemic blasts [73].

In fact, it has been demonstrated that HDAC inhibitors (HDACI) such as trichostatin A (TSA), sodium phenylbutyrate (PB), and suberoylanilide hydroxamic acid (SAHA) can augment the cell growth inhibition induced by ATRA, and that ATRA combined with SAHA increased survival and induced remissions in APL transgenic mice harboring the PLZF-RAR α translocation [78]. In addition, the PML-RAR α fusion protein was observed to induce hypermethylation on RAR promoter, and the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine (5-Aza-dC) enhanced ATRA-induced RAR promoter transactivation in APL cells [13].

Induction of APL cell differentiation by ATRA is associated with modulation of several critical genes, including RAR β 2 [78], C/EBP β [79], p21 [80], PU.1 [81], or a dominant repressor of RAR signaling PRAME [82]. Notably, PML-RAR α has a significant affinity for DR1 [83], a binding site for RXR/PPAR γ heterodimers, and negatively contributes to transactivation by ligand-activated PPARE.

The RA-target gene RAR β plays a crucial role in mediating the growth-inhibitory and tumor suppressive effects of retinoids in various cancer cells [84–87], and RAR β is silenced in many tumors [84, 87, 88] and myeloid leukemias [89, 90] including APL [13]. Its upregulation has been proposed as a general mechanism of retinoid-induced growth inhibition and differentiation induction

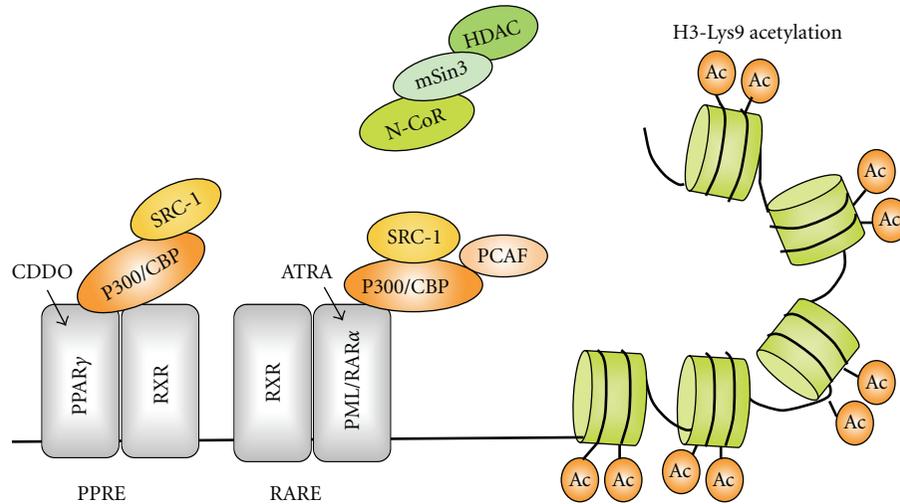


FIGURE 2: CDDO augments ATRA-induced reactivation of *RARβ2* in APL via histone acetylation. Combination of all-trans RA (ATRA) and 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) increases H3-Lys9 acetylation in *RARβ* P2 and *RARβ2* transcription. CDDO-bound PPAR γ may recruit coactivator proteins, including CBP-p300 and SRC-1 to PPAR γ /RXR, which in turn induce histone acetylation and reactivation of ATRA target genes. Ac: acetylated histone H3-Lys9, HDAC: histone deacetylase, mSin3: mammalian homolog of the *S. cerevisiae* corepressor, Sin 3, NCoR: nuclear receptor corepressor, SRC-1: steroid receptor coactivator-1, CBP/p300: CCAAT/enhancer-binding protein, PCAF: P300/CBP-associated factor.

[72]. *RARβ2* induction has been implicated in several tumor cell models in which retinoids inhibit growth and induce differentiation [91]. In HeLa cells, the transfected *RARβ2* transgene inhibits proliferation, while exogenous RA further increases the ability of the transgene to inhibit proliferation [92]. Disruption of *RARβ2* expression in *RARβ2* positive cancer cells abolishes RA effects of growth arrest [72], and the presence of *RARβ2* antisense predisposed the murine lung tissue to tumor formation [91].

Semisynthetic PPAR γ ligand triterpenoid CDDO augmented the ATRA-induced reactivation of *RARβ2* in APL via histone acetylation [93]. In combination with ATRA, CDDO may activate the transcription of PPAR γ target genes, which in turn increase the affinity of *RARβ* for β RARE. CDDO caused a prominent increase in *RARβ2* binding to the response element in the gel shift assay, and ATRA/CDDO combination increased H3-Lys9 acetylation in *RARβ* P2 and *RARβ2* transcription [93]. These findings support the concept that ligation of the PPAR γ and RAR nuclear receptors is capable of inducing cell maturation and enhances proapoptotic effects of ATRA in APL cells. PPAR γ and RXR form a complex with β RARE in the *RARβ* promoter, and the combination of ligands of PPAR γ and RXR was reported to induce *RARβ* in ATRA-resistant breast cancer cells in the presence of histone deacetylase inhibitor [94]. Based on these findings, CDDO may induce recruitment of PPAR γ /RXR to the RARE, which promotes affinity of *RARβ* for β RARE.

Ligand-bound RAR/RXR heterodimer has been shown to recruit the histone acetylase PCAF and the coactivator CBP/p300, which accumulates the HAT activity on the heterodimer/DNA complex and finally leads to enhanced retinoid-responsive transcription [95]. Likewise, the regulation of gene transcription by ligand-bound PPAR γ involves

the recruitment of coactivator proteins, including CBP/p300 and SRC-1 [17, 25, 39, 40]. CDDO has been shown to induce transactivation and PPAR γ interaction with multiple coactivators including SRC-1, SRC-2, SRC-3, TRAP 220, CARM-1, and PGC-1 in colon cancer cells [67]. While CDDO alone did not recruit CBP to the *RARβ2* promoter, the CDDO/ATRA combination increased ATRA-induced CBP recruitment. Altogether, the ability of ATRA/CDDO to restore RAR signaling and to cause cell maturation might be in part dependent on the PPAR γ -mediated induction of histone acetylation and reactivation of ATRA target genes (Figure 2).

ATRA is a nonselective retinoid capable of transactivating both, *RARα* and RXR receptors [96, 97]. Although PPAR γ /RXR heterodimers promote transcriptional activity of PPAR γ [16], RXR-selective ligand LG100268 and CDDO combination was not sufficient for *RARβ2* induction, suggesting that *RARβ2* gene induction is not due to ligand-induced RXR activation in APL cells [93].

Whereas CDDO alone failed to induce maturation of APL cells, the combination of CDDO with ATRA induced ATRA sensitive- and resistant-APL cells to differentiate into mature granulocytes with striking increase in Nitro Blue Tetrazolium (NBT) reduction positive and CD11b-positive cells above effects elicited by single agent ATRA [93]. Furthermore, the combined use of CDDO derivative CDDO-Me and ATRA in the murine model of APL resulted in the significant increase of mature granulocytic cells in peripheral blood and prolongation of survival compared to the single compound treatment of ATRA or CDDO. Ikeda et al. [64] also demonstrated that CDDO-Im selectively downregulated expression of PML-RAR α fusion protein with an activation of caspase 8, which might contribute to enhanced ATRA-induced differentiation in APL cells, and arsenic-trioxide-

(ATO-) induced apoptosis in both ATRA-sensitive NB4 and resistant R2 cell lines and primary APL cells.

RA signaling is a common mechanism in AML other than APL, and HDAC inhibitors have been shown to restore RA-dependent transcriptional activation and trigger terminal differentiation of primary blasts from AML patients [89]. Recent reports of *in vivo* differentiation of the leukemic clone following HDAC inhibitor valproic acid/ATRA treatment in AML patients [98] further suggest the possibility that the ATRA/CDDO or its more potent derivatives combination may be useful transcriptional/differentiation therapy in non-APL AML. Randomized trial AML HD98B showed that administration of ATRA in addition to intensive chemotherapy improved the outcomes of the patients with genotype of “mutant (mt-) *NPM1* without *FLT3-ITD*” [99]. *NPM1* has been reported to be a possible transcriptional corepressor [100]. Inhibition of *NPM1* oligomerization or knockdown of *NPM1*-induced apoptosis and sensitized to ATRA in mt-*NPM1*-bearing AML cells [101]. These findings suggest new avenues of exploration for ATRA and CDDO derivatives combination therapy targeting “mt-*NPM1* wt-*FLT3*” genotype AML.

Acknowledgment

The authors thank an anonymous for the paper review. There is no conflict of interests between the paper's authors and the companies involved in the paper.

References

- [1] E. H. Estey, “Treatment of relapsed and refractory acute myelogenous leukemia,” *Leukemia*, vol. 14, no. 3, pp. 476–479, 2000.
- [2] L. Degos, C. Chomienne, M. T. Daniel et al., “Treatment of first relapse in acute promyelocytic leukaemia with all-trans retinoic acid,” *The Lancet*, vol. 336, no. 8728, pp. 1440–1441, 1990.
- [3] Z. X. Chen, Y. Q. Xue, R. Zhang et al., “A clinical and experimental study on all-trans retinoic acid-treated acute promyelocytic leukemia patients,” *Blood*, vol. 78, no. 6, pp. 1413–1419, 1991.
- [4] H. Meng-er, Y. Yu-chen, C. Shu-rong et al., “Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia,” *Blood*, vol. 72, no. 2, pp. 567–572, 1988.
- [5] R. P. Warrell, S. R. Frankel, W. H. Miller et al., “Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid),” *New England Journal of Medicine*, vol. 324, no. 20, pp. 1385–1393, 1991.
- [6] F. Mandelli, D. Diverio, G. Avvisati et al., “Molecular remission in PML/RAR α -positive acute promyelocytic leukemia by combined all-trans retinoic acid and Idarubicin (AIDA) therapy,” *Blood*, vol. 90, no. 3, pp. 1014–1021, 1997.
- [7] S. Castaigne, C. Chomienne, M. T. Daniel et al., “All-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia. I. Clinical results,” *Blood*, vol. 76, no. 9, pp. 1704–1709, 1990.
- [8] M. S. Tallman, “Therapy of acute promyelocytic leukemia: all-trans retinoic acid and beyond,” *Leukemia*, vol. 12, no. 1, pp. S37–S40, 1998.
- [9] R. P. Warrell, “Retinoid resistance in acute promyelocytic leukemia: new mechanisms, strategies, and implications,” *Blood*, vol. 82, no. 7, pp. 1949–1953, 1993.
- [10] M. Cornic and C. Chomienne, “Induction of retinoid resistance by all-trans retinoic acid in acute promyelocytic leukemia after remission,” *Leukemia and Lymphoma*, vol. 18, no. 3-4, pp. 249–257, 1995.
- [11] W. Shao, L. Benedetti, W. W. Lamph, C. Nervi, and W. H. Miller, “A retinoid-resistant acute promyelocytic leukemia subclone expresses a dominant negative PML-RAR α mutation,” *Blood*, vol. 89, no. 12, pp. 4282–4289, 1997.
- [12] S. Cote, D. Zhou, A. Bianchini, C. Nervi, R. E. Gallagher, and W. H. Miller, “Altered ligand binding and transcriptional regulation by mutations in the PML/RAR α ligand-binding domain arising in retinoic acid-resistant patients with acute promyelocytic leukemia,” *Blood*, vol. 96, no. 9, pp. 3200–3208, 2000.
- [13] L. Di Croce, V. A. Raker, M. Corsaro et al., “Methyltransferase recruitment and DNA hypermethylation of target promoters by an oncogenic transcription factor,” *Science*, vol. 295, no. 5557, pp. 1079–1082, 2002.
- [14] F. Pendino, T. Sahraoui, M. Lanotte, and E. Ségal-Bendirdjian, “A novel mechanism of retinoic acid resistance in acute promyelocytic leukemia cells through a defective pathway in telomerase regulation,” *Leukemia*, vol. 16, no. 5, pp. 826–832, 2002.
- [15] 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.
- [16] I. G. Schulman, G. Shao, and R. A. Heyman, “Transactivation by retinoid X receptor-peroxisome proliferator-activated receptor γ (PPAR γ) heterodimers: intermolecular synergy requires only the PPAR γ hormone-dependent activation function,” *Molecular and Cellular Biology*, vol. 18, no. 6, pp. 3483–3494, 1998.
- [17] E. D. Rosen and B. M. Spiegelman, “PPAR γ : a nuclear regulator of metabolism, differentiation, and cell growth,” *Journal of Biological Chemistry*, vol. 276, no. 41, pp. 37731–37734, 2001.
- [18] M. Pfahl, R. Apfel, I. Bendik et al., “Nuclear retinoid receptors and their mechanism of action,” *Vitamins and Hormones*, vol. 49, no. C, pp. 327–382, 1994.
- [19] J. T. Huang, J. S. Welch, M. Ricote et al., “Interleukin-4-dependent production of PPAR- γ ligands in macrophages by 12/15-lipoxygenase,” *Nature*, vol. 400, no. 6742, pp. 378–382, 1999.
- [20] L. Nagy, P. Tontonoz, J. G. A. Alvarez, H. Chen, and R. M. Evans, “Oxidized LDL regulates macrophage gene expression through ligand activation of PPAR γ ,” *Cell*, vol. 93, no. 2, pp. 229–240, 1998.
- [21] J. Berger, P. Bailey, C. Biswas et al., “Thiazolidinediones produce a conformational change in peroxisomal proliferator-activated receptor- γ : binding and activation correlate with antidiabetic actions in db/db mice,” *Endocrinology*, vol. 137, no. 10, pp. 4189–4195, 1996.
- [22] 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.
- [23] K. G. Lambe and J. D. Tugwood, “A human peroxisome-proliferator-activated receptor- γ is activated by inducers of adipogenesis, including thiazolidinedione drugs,” *European Journal of Biochemistry*, vol. 239, no. 1, pp. 1–7, 1996.

- [24] 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.
- [25] 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.
- [26] P. Tontonoz, S. Singer, B. M. Forman et al., "Terminal differentiation of human liposarcoma cells induced by ligands for peroxisome proliferator-activated receptor γ and the retinoid X receptor," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 1, pp. 237–241, 1997.
- [27] G. D. Demetri, C. D. M. Fletcher, E. Mueller et al., "Induction of solid tumor differentiation by the peroxisome proliferator-activated receptor- γ ligand troglitazone in patients with liposarcoma," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 7, pp. 3951–3956, 1999.
- [28] E. Elstner, C. Müller, K. Koshizuka et al., "Ligands for peroxisome proliferator-activated receptor and retinoic acid receptor inhibit growth and induce apoptosis of human breast cancer cells in vitro and in BNX mice," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 15, pp. 8806–8811, 1998.
- [29] E. Mueller, P. Sarraf, P. Tontonoz et al., "Terminal differentiation of human breast cancer through PPAR γ ," *Molecular Cell*, vol. 1, no. 3, pp. 465–470, 1998.
- [30] P. Sarraf, E. Mueller, D. Jones et al., "Differentiation and reversal of malignant changes in colon cancer through PPAR γ ," *Nature Medicine*, vol. 4, no. 9, pp. 1046–1052, 1998.
- [31] P. Sarraf, E. Mueller, W. M. Smith et al., "Loss-of-function mutations in PPAR γ associated with human colon cancer," *Molecular Cell*, vol. 3, no. 6, pp. 799–804, 1999.
- [32] E. Mueller, M. Smith, P. Sarraf et al., "Effects of ligand activation of peroxisome proliferator-activated receptor γ in human prostate cancer," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 20, pp. 10990–10995, 2000.
- [33] T. H. Chang and E. Szabo, "Induction of differentiation and apoptosis by ligands of peroxisome proliferator-activated receptor γ in non-small cell lung cancer," *Cancer Research*, vol. 60, no. 4, pp. 1129–1138, 2000.
- [34] F. Marra, E. Efsen, R. G. Romanelli et al., "Ligands of peroxisome proliferator-activated receptor γ modulate profibrogenic and proinflammatory actions in hepatic stellate cells," *Gastroenterology*, vol. 119, no. 2, pp. 466–478, 2000.
- [35] S. Westin, R. Kurokawa, R. T. Nolte et al., "Interactions controlling the assembly of nuclear-receptor heterodimers and co-activators," *Nature*, vol. 395, no. 6698, pp. 199–202, 1998.
- [36] P. Puigserver, G. Adelmant, Z. Wu et al., "Activation of PPAR γ coactivator-1 through transcription factor docking," *Science*, vol. 286, no. 5443, pp. 1368–1371, 1999.
- [37] P. Tontonoz, E. Hu, and B. M. Spiegelman, "Stimulation of adipogenesis in fibroblasts by PPAR γ 2, a lipid-activated transcription factor," *Cell*, vol. 79, no. 7, pp. 1147–1156, 1994.
- [38] R. T. Nolte, G. B. Wisely, S. Westin et al., "Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor- γ ," *Nature*, vol. 395, no. 6698, pp. 137–143, 1998.
- [39] W. Yang, C. Rachez, and L. P. Freedman, "Discrete roles for peroxisome proliferator-activated receptor γ and retinoid X receptor in recruiting nuclear receptor coactivators," *Molecular and Cellular Biology*, vol. 20, no. 21, pp. 8008–8017, 2000.
- [40] Y. Kodera, K. I. Takeyama, A. Murayama, M. Suzawa, Y. Masuhiro, and S. Kato, "Ligand type-specific interactions of peroxisome proliferator-activated receptor γ with transcriptional coactivators," *Journal of Biological Chemistry*, vol. 275, no. 43, pp. 33201–33204, 2000.
- [41] J. Chen, H. K. Kinyamu, and T. K. Archer, "Changes in attitude, changes in latitude: nuclear receptors remodeling chromatin to regulate transcription," *Molecular Endocrinology*, vol. 20, no. 1, pp. 1–13, 2006.
- [42] M. G. Rosenfeld, V. V. Lunyak, and C. K. Glass, "Sensors and signals: a coactivator/corepressor/epigenetic code for integrating signal-dependent programs of transcriptional response," *Genes and Development*, vol. 20, no. 11, pp. 1405–1428, 2006.
- [43] J. N. Feige, L. Gelman, L. Michalik, B. Desvergne, and W. Wahli, "From molecular action to physiological outputs: peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions," *Progress in Lipid Research*, vol. 45, no. 2, pp. 120–159, 2006.
- [44] T. Ikezoe, C. W. Miller, S. Kawano et al., "Mutational analysis of the peroxisome proliferator-activated receptor γ in human malignancies," *Cancer Research*, vol. 61, no. 13, pp. 5307–5310, 2001.
- [45] M. Konopleva and M. Andreeff, "Role of peroxisome proliferator-activated receptor- γ in hematologic malignancies," *Current Opinion in Hematology*, vol. 9, no. 4, pp. 294–302, 2002.
- [46] T. Tsao, S. Kornblau, S. Safe et al., "Role of peroxisome proliferator-activated receptor- γ and its coactivator DRIP205 in cellular responses to CDDO (RTA-401) in acute myelogenous leukemia," *Cancer Research*, vol. 70, no. 12, pp. 4949–4960, 2010.
- [47] T. Kubota, K. Koshizuka, E. A. Williamson et al., "Ligand for peroxisome proliferator-activated receptor γ (Troglitazone) has potent antitumor effect against human prostate cancer both in vitro and in vivo," *Cancer Research*, vol. 58, no. 15, pp. 3344–3352, 1998.
- [48] P. Tontonoz, L. Nagy, J. G. A. Alvarez, V. A. Thomazy, and R. M. Evans, "PPAR γ promotes monocyte/macrophage differentiation and uptake of oxidized LDL," *Cell*, vol. 93, no. 2, pp. 241–252, 1998.
- [49] K. J. Moore, E. D. Rosen, M. L. Fitzgerald et al., "The role of PPAR- γ in macrophage differentiation and cholesterol uptake," *Nature Medicine*, vol. 7, no. 1, pp. 41–47, 2001.
- [50] 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.
- [51] 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.
- [52] 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.

- [53] 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.
- [54] N. Suh, Y. Wang, T. Honda et al., "A novel synthetic oleanane triterpenoid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, with potent differentiating, antiproliferative, and anti-inflammatory activity," *Cancer Research*, vol. 59, no. 2, pp. 336–341, 1999.
- [55] M. Konopleva, T. Tsao, P. Ruvolo 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.
- [56] S. Koschmieder, F. D'Alò, 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.
- [57] 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.
- [58] 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.
- [59] 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.
- [60] Y. Ito, P. Pandey, A. Place et al., "The novel triterpenoid 2-cyano-3,12-dioxoolean-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.
- [61] Y. Ito, P. Pandey, M. B. Sporn, R. Datta, S. Kharbanda, and D. Kufe, "The novel triterpenoid CDDO induces apoptosis and differentiation of human osteosarcoma cells by a caspase-8 dependent mechanism," *Molecular Pharmacology*, vol. 59, no. 5, pp. 1094–1099, 2001.
- [62] T. A. Stadheim, N. Suh, N. Ganju, M. B. Sporn, and A. Eastman, "The novel triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) potently enhances apoptosis induced by tumor necrosis factor in human leukemia cells," *Journal of Biological Chemistry*, vol. 277, no. 19, pp. 16448–16455, 2002.
- [63] 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.
- [64] T. Ikeda, F. Kimura, Y. Nakata et al., "Triterpenoid CDDO-Im downregulates PML/RAR α expression in acute promyelocytic leukemia cells," *Cell Death and Differentiation*, vol. 12, no. 5, pp. 523–531, 2005.
- [65] S. Shishodia, G. Sethi, M. Konopleva, M. Andreeff, and B. B. Aggarwal, "A synthetic triterpenoid, CDDO-Me, inhibits I κ B α kinase and enhances apoptosis induced by TNF and chemotherapeutic agents through down-regulation of expression of nuclear factor κ B-regulated gene products in human leukemic cells," *Clinical Cancer Research*, vol. 12, no. 6, pp. 1828–1838, 2006.
- [66] P. J. Simpson-Haidaris, S. J. Pollock, S. Ramon et al., "Anticancer role of PPAR γ agonists in hematological malignancies found in the vasculature, marrow, and eyes," *PPAR Research*, vol. 2010, article 814609, 2010.
- [67] S. Chintharlapalli, S. Papineni, M. Konopleva, M. Andreeff, I. Samudio, and S. Safe, "2-Cyano-3,12-dioxoolean-1,9-dien-28-oic acid and related compounds inhibit growth of colon cancer cells through peroxisome proliferator-activated receptor γ -dependent and -independent pathways," *Molecular Pharmacology*, vol. 68, no. 1, pp. 119–128, 2005.
- [68] 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.
- [69] B. Melichar, M. Konopleva, W. Hu, K. Melicharova, M. Andreeff, and R. S. Freedman, "Growth-inhibitory effect of a novel synthetic triterpenoid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, on ovarian carcinoma cell lines not dependent on peroxisome proliferator-activated receptor- γ expression," *Gynecologic Oncology*, vol. 93, no. 1, pp. 149–154, 2004.
- [70] 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.
- [71] D. M. Ray, F. Akbiyik, and R. P. Phipps, "The peroxisome proliferator-activated receptor γ (PPAR γ) ligands 15-deoxy- Δ 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.
- [72] 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.
- [73] D. Kamashev, D. Vitoux, and H. De Thé, "PML-RARA-RXR oligomers mediate retinoid and rexinoid/cAMP cross-talk in acute promyelocytic leukemia cell differentiation," *Journal of Experimental Medicine*, vol. 199, no. 8, pp. 1163–1174, 2004.
- [74] S. A. Hamadani, T. Zhang, C. Dorrell et al., "X-retinoic acid receptor fusion genes in acute promyelocytic leukemia interfere with retinoid and peroxisome-proliferator signaling pathways," *Blood*, vol. 98, p. 88a, 2001.
- [75] L. Z. He, F. Guidez, C. Tribioli et al., "Distinct interactions of PML-RAR α and PLZF-RAR α with co-repressors determine differential responses to RA in APL," *Nature Genetics*, vol. 18, no. 2, pp. 126–135, 1998.
- [76] F. Grignani, S. De Matteis, C. Nervi et al., "Fusion proteins of the retinoic acid receptor- α recruit histone deacetylase in promyelocytic leukaemia," *Nature*, vol. 391, no. 6669, pp. 815–818, 1998.
- [77] L. Z. He, T. Tolentino, P. Grayson et al., "Histone deacetylase inhibitors induce remission in transgenic models of therapy-resistant acute promyelocytic leukemia," *Journal of Clinical Investigation*, vol. 108, no. 9, pp. 1321–1330, 2001.
- [78] T. N. Faria, C. Mendelsohn, P. Chambon, and L. J. Gudas, "The targeted disruption of both alleles of RAR β 2 in F9 cells

- results in the loss of retinoic acid-associated growth arrest," *Journal of Biological Chemistry*, vol. 274, no. 38, pp. 26783–26788, 1999.
- [79] E. Duprez, K. Wagner, H. Koch, and D. G. Tenen, "C/EBP β : a major PML-RARA-responsive gene in retinoic acid-induced differentiation of APL cells," *EMBO Journal*, vol. 22, no. 21, pp. 5806–5816, 2003.
- [80] M. Liu, A. Iavarone, and L. P. Freedman, "Transcriptional activation of the human p21(WAF1/CIP1) gene by retinoic acid receptor. Correlation with retinoid induction of U937 cell differentiation," *Journal of Biological Chemistry*, vol. 271, no. 49, pp. 31723–31728, 1996.
- [81] B. U. Mueller, T. Pabst, J. Fos et al., "ATRA resolves the differentiation block in t(15;17) acute myeloid leukemia by restoring PU.1 expression," *Blood*, vol. 107, no. 8, pp. 3330–3338, 2006.
- [82] M. T. Epping, L. Wang, M. J. Edel, L. Carlée, M. Hernandez, and R. Bernards, "The human tumor antigen PRAME is a dominant repressor of retinoic acid receptor signaling," *Cell*, vol. 122, no. 6, pp. 835–847, 2005.
- [83] A. Perez, P. Kastner, S. Sethi, Y. Lutz, C. Reibel, and P. Chambon, "PMLRAR homodimers: distinct DNA binding properties and heteromeric interactions with RXR," *EMBO Journal*, vol. 12, no. 8, pp. 3171–3182, 1993.
- [84] Y. Li, M. I. Dawson, A. Agadir et al., "Regulation of RAR β expression by RAR- and RXR-selective retinoids in human lung cancer cell lines: effect on growth inhibition and apoptosis induction," *International Journal of Cancer*, vol. 75, pp. 88–95, 1998.
- [85] B. Houle, C. Rochette-Egly, and W. E. C. Bradley, "Tumor-suppressive effect of the retinoic acid receptor β in human epidermoid lung cancer cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 3, pp. 985–989, 1993.
- [86] Y. Liu, M. O. Lee, H. G. Wang et al., "Retinoic acid receptor β mediates the growth-inhibitory effect of retinoic acid by promoting apoptosis in human breast cancer cells," *Molecular and Cellular Biology*, vol. 16, no. 3, pp. 1138–1149, 1996.
- [87] C. Li and Y. J. Y. Wan, "Differentiation and antiproliferation effects of retinoic acid receptor β in hepatoma cells," *Cancer Letters*, vol. 124, no. 2, pp. 205–211, 1998.
- [88] B. R. Haugen, L. L. Larson, U. Pugazhenthii et al., "Retinoic acid and retinoid X receptors are differentially expressed in thyroid cancer and thyroid carcinoma cell lines and predict response to treatment with retinoids," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 1, pp. 272–280, 2004.
- [89] F. F. Ferrara, F. Fazi, A. Bianchini et al., "Histone deacetylase-targeted treatment restores retinoic acid signaling and differentiation in acute myeloid leukemia," *Cancer Research*, vol. 61, no. 1, pp. 2–7, 2001.
- [90] S. Lehmann, C. Paul, and H. Törmä, "The expression of cellular retinoid binding proteins in non-APL leukemic cells and its association with retinoid sensitivity," *Leukemia and Lymphoma*, vol. 43, no. 4, pp. 851–858, 2002.
- [91] P. Chambon, "A decade of molecular biology of retinoic acid receptors," *FASEB Journal*, vol. 10, no. 9, pp. 940–954, 1996.
- [92] S. P. Si, X. Lee, H. C. Tsou et al., "ARy2-mediated growth inhibition in HeLa cells," *Experimental Cell Research*, vol. 223, pp. 102–111, 1996.
- [93] 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.
- [94] S. Y. James, F. Lin, S. K. Kolluri, M. I. Dawson, and X. K. Zhang, "Regulation of retinoic acid receptor β expression by peroxisome proliferator-activated receptor γ ligands in cancer cells," *Cancer Research*, vol. 63, no. 13, pp. 3531–3538, 2003.
- [95] J. C. G. Blanco, S. Minucci, J. Lu et al., "The histone acetylase PCAF is a nuclear receptor coactivator," *Genes and Development*, vol. 12, no. 11, pp. 1638–1651, 1998.
- [96] D. J. Mangelsdorf, E. S. Ong, J. A. Dyck, and R. M. Evans, "Nuclear receptor that identifies a novel retinoic acid response pathway," *Nature*, vol. 345, no. 6272, pp. 224–229, 1990.
- [97] R. A. Heyman, D. J. Mangelsdorf, J. A. Dyck et al., "9-Cis retinoic acid is a high affinity ligand for the retinoid X receptor," *Cell*, vol. 68, no. 2, pp. 397–406, 1992.
- [98] G. Cimino, F. Lo-Coco, S. Fenu et al., "Sequential valproic acid/all-trans retinoic acid treatment reprograms differentiation in refractory and high-risk acute myeloid leukemia," *Cancer Research*, vol. 66, no. 17, pp. 8903–8911, 2006.
- [99] R. F. Schlenk, K. Döhner, M. Kneba et al., "German-Austrian AML Study Group (AMLSG). Gene mutations and response to treatment with all-trans retinoic acid in elderly patients with acute myeloid leukemia: results from the AMLSG Trial AML HD98B," *Haematologica*, vol. 94, pp. 54–60, 2009.
- [100] H. Liu, B. C. M. Tan, K. H. Tseng et al., "Nucleophosmin acts as a novel AP2 α -binding transcriptional corepressor during cell differentiation," *EMBO Reports*, vol. 8, no. 4, pp. 394–400, 2007.
- [101] R. Balusu, W. Fiskus, R. Rao et al., "Targeting levels or oligomerization of nucleophosmin 1 induces differentiation and loss of survival of human AML cells with mutant NPM1," *Blood*, vol. 118, pp. 3096–3106, 2011.



Hindawi
Submit your manuscripts at
<http://www.hindawi.com>

