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Retinoid Pharmacology, an Old Hot Topic: Discussion on Retinoic Acid Action in APL

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Retinoic acid (RA), a derivative of vitamin A (retinol), exerts a wide range of biological effects on cell proliferation and differentiation, and embryonic development. The pleiotropic effects of RA are mediated by its binding to specific nuclear RA receptors (RARs) which function as transcription factor after ligand-dependent activation. To date, three species of human RARs (α, β and γ) have been described. In several hundreds of publications as to retinoic acid (RA) action, Dr. Zhu in earlier years (1990-91) postulate molecular model of RA action, which reported in Voice of America, 1992 [1]; presented at 2nd and 3rd biomedical world congress, Dubai, UAE, 2013, 2014 [2,3] and published early in JCCM (EBSCO cited), 2007, 2010 [4,5], in *Curr Pharm Biotechnol*, vol 14 issue 9, 2013 [6], later updated in *Univ J Pharm Res*, vol 4 issue 6, 2018 [7], in *Am J Biomed Sci & Res*, vol 3 issue 2, 2019 [8] and recent updated in *Med J Clin Trials Case Stud*, and in *EC Endocrinol and Metab Res*, 2020 [9-11]. It is well demonstrated that oncogenic pml/RARa act as constitutive transcriptional repressor (also designated as a dominant negative inhibitor, Raelson., *et al*.) of RARa and retinoic acid signalling in differentiation block at promyelocytes stage in APL pathogenesis. As to this point of review, at least 50 research articles consistently demonstrated the conclusion [12-29]. In Rousselot's earlier experiments [12], HL-60 cells transfected with 15 - 30 ug of PML-RARa fusion in cell culture show no features of granulocytic differentiation after 7 days of incubation with 10^{-7}, 10^{-6} uM RA (only 5.5 - 9.5% of differentiated cells by the NBT test). At 5 ug of PML-RARa plasmid concentration, the blockage of RA-dependent myeloid differentiation could be overcome with high doses (10^{-6} uM) of RA (99% of differentiated cells by NBT test). The results clearly indicate that PML-RARa mediated transcriptional repression, as well as PML-RARa oncoprotein blocks RA-mediated promyelocytic differentiation. *In vitro*, the construct of human RAR alpha (hRARa) into murine bone marrow cells, most cells infected with overexpressed hRARa exhibited promyelocytic morphology and were thought to be blocked at the promyelocytic stage in their myeloid differentiation. In the presence of RA (10^{-6} uM), these immature cells differentiated terminally into mature granulocytes [30,31]. More data, Villa., *et al*. [19] also observed that PML-RARa at high concentration repress RARβ2 promoter activity (PML-RARa: + vs ++), and U93-PR9 cells harboring PML-RARa merely become refractory to VD/TGFβ differentiation by the percentage of CD14 of positive cells [19].

The most intriguing at least 15 original researches [32-42], *in vivo*, transgenic mice expressing PML-RARa fusion can disrupt normal hematopoiesis, given sufficient time, develop acute leukemia with a differentiation block at the promyelocytic stage that closely mimics human APL (APL-like syndrome). This also represent a steroid receptor in tumorigenesis, in addition to oncogenic ESR1-CCDC170 [43-45], a novel FAS/ER-alpha fusion [46] and oncogenic androgenic receptor (AR) signaling [47-50].

Using Xenopus Oocyte system to uniquely the comparison of the transcriptional properties of wild-type RARa and oncogenic receptor pml-RARa, Segalla., *et al.* [17] demonstrated that, indeed, pml-RARa is a stronger transcriptional repressor that does not require the cofactor RXR, and is able to impose its silencing effect on chromatin state. Only pharmacological concentration of RA, pml/RARa become transcriptional activator function. Schrader., *et al*. [51] also found that in Drosophila SL-3 cells that are devoid of endogenous RARs and RXRs the presence of RAR is sufficient to confer a response to all-trans retinoic acid, which implicated RXR-dependent and RXR- independent transactivation by retinoic acid receptor. The same conclusion was reported in over 15 laboratories work [12-29]. The pml/RARa transcriptional repressor was well evidenced by others in RARE-tu-luc assay and AP-1 element. In βRARE-luc expression system, pml-RARa acts as transcriptional repressor in human myeloid cells even in the presence of RA (10^{-6}~10^{-8}M) [12] while delta pml/RARa cleavage product is less potent activator of RARE-tk-luc assay than wild-type RARa in the presence of RA (0.01 uM, 1 uM) in NB4 cells [18]. Moreover, in absence of RA, PML- RARa is transcriptional repressor of AP-1 activity [52] and PU1/DAPK2 expression [27,53], which are associated with differentiation of leukemic cells in several contexts. Whether pml/RARa targeting AP-1 and PU1/DAPK2 expression or other enzyme are key regulators for promyelocytic differentiation, which is under investigation.

As the isolation of RARs, the physiological function of retinoids are primarily exerted through the regulation of specific target genes by RARs. RARs modulate transcription through interaction with cofactors, and transcriptional regulation by RARs involve modification of chromatin by histone deacetylases. The N-terminal domain of RARa is a ligand-independent context-dependent manner. The C-terminal E domain of RARs contains the ligand-dependent activation as well as a dimerization interface for RXR. RARa function as a heterodimers with RXR. In the absence of RA ligand, the wild-type RAR (or RAR/RXR) bind to RARE in the promoter region of target genes and repress transcription by recruiting nuclear corepressors, such as the silencing mediator of retinoid and thyroid hormone receptor (SMRT), the nuclear receptor corepressor (N-CoR) and histone de-acetylases (HDACs). Once RA binds to RAR and triggers conformational changes that release corepressor complex (N-CoR/SMRT/HDACs) and recruitment of co-activators. Subsequently, transcription of target gene is initiated, alteration of chromatin and unwinding of DNA [6-8,19,21,54].

In contrast, in APL patients, RXR may effort its stronger transcriptional repressor than wild-type RARa (e.g. pml/RARa-RXR vs RARa/RXR). In actual, pml/RARa/RXR fusion has still not been detected in APL samples. Moreover, retinoid X receptor (RXR) is the obligatory heterodimerization partner for a large number of non-classical nuclear receptors. The RXR is nuclear receptor that binds and is activated by 9-cis retinoic acid (9-cis RA) [55]. The transfection of both RAR and RXR and stimulation with their respective all-trans and 9-cis RA leads to a synergistic enhanced response presumably mediated by RAR/RXR heterodimers [51]. In spite of this, heterodimerization with RXR is not a prerequisite for RARa-mediated transcriptional response, and RARa alone is sufficient to confer response to all-trans retinoic acid [51]. In the absence of exogenous 9-cis RA, all-trans RA seems to be mediated by RXR- independent pathway, despite the presence of RXRs in cells [51]. Therefore, it should avoid confounding that, more evidence supporting this concept, oncogenic pml/RARa (other than pml/RARa/RXR) is by far the most frequent in 98% of newly diagnosed APL, which was directly linked to the master driver of APL pathogenesis. Retinoic acid ligand (cis-RA and ATRA) which normally derepresses the PML-RARa fusion protein, subsequently, transcriptional derepression and activation was induced, degradation of PML-RARa (PML-RARa loss) allow terminal maturation of APL cells (see figure, George Zhu, 1990-January, 1991; Vitaliano-prunier A, Halftermeyer J, de The H., *et al*. 2014) [1-15,17-27,56-59]. This is irrefutable.

Intriguing, the dramatic response of APL cells to RA appears confined to this particular subtype of human leukemia, and most other forms of human myelogenous leukemia exhibit little response to retinoids. To defining RARs in controlling the differentiation of specific cell lineages involves the use of RARs constructs exhibiting dominant- negative activity. Truncating of an artificial mutant RARa harboring a 59-amino acids at the C terminus (RARa430) [60] results in an altered RAR while retaining the DNA- binding domain as well as the ability to heterodimerize with RXR. A mutant RARa430 was introduced into GM-CSF-dependent MPRO promyelocytic cells and the multipotent (having erythroid, lymphoid and myeloid) SCF-dependent EML cell, which lead to the expression of relatively high levels of the RARa403 mRNA and are predominates in complexes with RAR-RXR response element in both EML and MPRO cells. Surprising, all-trans RA (1~10 uM), 9-cis RA (10 uM) and RXR agonist (AGN 194204) induces terminal granulocytic differentiation of the MPRO promyelocytes by triggering the activation of RXR-RARa403 heterodimers. However, the RAR-specific pan agonist (AGN193695 10 uM) had virtually no activity. In the pluripotent, SCF-dependent EML cells, RA potentiates the interleukin-3 (IL-3)-mediated commitment of these cells to the granulocyte/monocyte lineage. The same RXR agonist had little effect in the multipotent EML cells, despite the presence of RXR/RAR heterodimers. Why did the RXR-RARa403 complex readily activate in presence of RA in MPRO promyelocytes but not in another multipotent EML cells harboring the same RAR- RARa403 complex? This might represent the differential activation of the RXR-RARa 403 heterodimers at these different stages of myeloid development [60]. In a certain content, this can also explain the favorable clinical outcome of 9-cis RA in APL treatment [61]. If the promyelocytes in APL contain mutant RARa403 truncation, which is unknown.

Whether the corepressor N-CoR and HDACs are certain to be required in the specific APL cells? In this regard, there is the most possible or not, or PML/RARa and corepressor synergistically in blocking differentiation, which depend on distinct hematopoietic cell types.

In the absence of RA, transcriptional repression by RA receptor involves the interaction of nuclear RA receptor with multicomponent complexes including specific corepressors such as N-CoR, SMRT, Sin 3A and HDACs. In literature, there were limit data to determine whether HDAC activity inhibitors were benefit to patients with this disease. With HDAC inhibitors such as trichostatin A (TSA) has been shown to potentiate ATRA-induced differentiation of the PML-RARa-positive NB4 cell line [62]. Clinical response was documented in two relapsed ATRA- resistant patients following addition of sodium phenylbutyrate or sodium valproate [63,64]. It is commonly accepted that, compared with RA merely, HDAC inhibitors had negligible effects. When combination with RA, HDAC inhibitors reverse the transcriptional repression by PML-RARa, also overcome the transcriptional repressor activity of PML-RARa, stimulated from 2 to 23 fold RA-dependent transactivation by PML-RARa and RARa, induced accumulation of acetylated histones in target organ [62]. Villa., *et al*. [19] observed that HDAC3- MBD1 and PML-RARa are both required for complete silencing of PML-RARa target genes, subsequent to promoter hypermethylation. However, only MBD1 had no repression of RARβ promoter activity. Moreover, the ability of MBD1 to repress RARβ2 activity synergistically with PML-RARa was strictly dependent on the binding of PML-RARa to an intact RARE within the target promoter. Combination of 5-Aza-dC (1 uM) and TSA (100 nM) almost completely prevented promoter methylation. Moreover, MBD1 mutant [MBD1-dm (R22A/1527R)] drastically inhibited the ability of PML-RARa to block hematopoietic differentiation, thus restore cell differentiation.

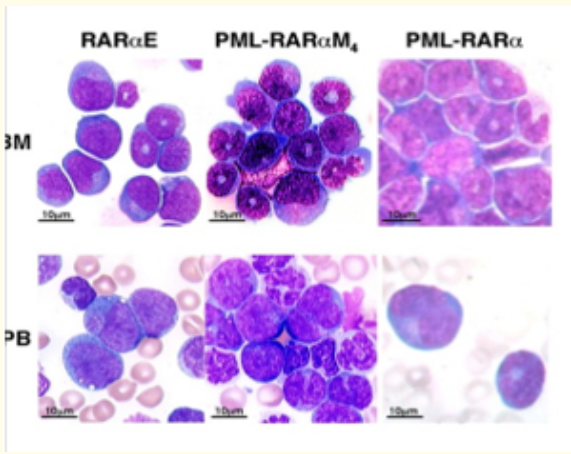
Curiously, Johnson [60] has been uncovered that HDAC inhibitor TSA could readily activate (derepresses) the RXR-RARa403 heterodimer reporter in more primitive EML cells but not in MPRO promyelocytic cells. The murine MPRO cells closely resemble human promyelocytic leukemia (APL) cells in their block to differentiation at promyelocytic stage and the terminal granulocytic differentiation display in response to RA. These results suggest that the functionally significant differences in HDAC- containing repressor complexes might exist among leukemias of different hematopoietic cell types, and/or HDAC-containing repressor is likely not critical in determining the terminal granulocytic differentiation of this MPRO promyelocytic cells.

To further test *in vivo* role of N-CoR and HDAC linked to RARa in APL, Tomita., *et al*. [65] has been showed clearly that unliganded RAR/RXR and PML/RARa repressed the RA-dependent promoter in chromatin *in vivo* and associated with N-CoR-TBLR1 (transducin beta-like protein 1-related protein) in the frog oocyte, whereas RA treatment reversed this repression. In quantitative analyses of the ChIP assay, N-CoR-TBLR1-HDAC corepressors are recruited respectively by unliganded PML-RARa. Of note, the relative intensity of N-CoR and TBLR1 were displayed stronger repression than that of F-PML-RARa/RXR merely in the presence of RA (See figure B line 3) [65]. Considering that the PML coiled-coil region and the DNA binding property of PML/RARa are indispensable for differentiation block [14], as transgenic HDAC1-RARa [20], transgenic models of N-CoR responsible for its blocking differentiation in APL cells, which remains further testable.

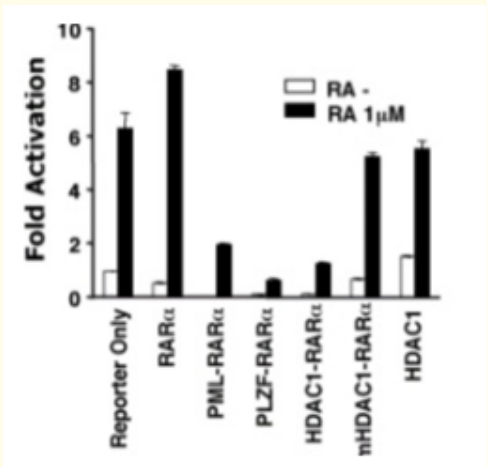
In Matsushita's group important experiments [20], HDAC1 and HDAC1-RARa both inhibited histone H3 and H4. Luciferase assay demonstrated that HDAC1-RARa, rather than HDAC1, act as a potent transcriptional corepressor. HDAC1-RARa and PML-RARa repressed transcription equally in the presence of RA. However, transgenic mice harboring an artificial HDAC1-RARa fusion protein did not cause a block in myeloid differentiation *in vivo* and were not leukemogenic at long latency (19 - 23 months median follow up), whereas only PML-RARaM4 (RARa L398P) and RARaE (G303E) developed leukemia with promyelocytic features as evidenced by PML-RARa in transgenic mice (Figure 1) [20], indicating that the RARa and PML-RARa blockade is necessary, but not sufficient, for leukemogenesis. The results also suggest that additional events such as MYC proto-oncogene [29] and MYB proto-oncogene [28] are likely necessary to complete the transforming process. MYC alone was able to drive APL development in the presence of PML/RARA [29]. Whereas HDAC- dependent dominant-negative blockade of RARa function is neither sufficient to cause leukemia nor to block myeloid differentiation *in vivo*. In clinical actual, sodium phenylbutyrate or sodium valproate, two HDAC inhibitors, proved its uncertain limit efficacy in APL treatment. In this respect, like oncogenic receptor derivative pml/RARa fusion, It is likely that the convincing growing evidence is transgenic models of transcriptional corepressors N-CoR and HDAC and their antagonist, and definiting clinical trials to clarify the linkage of specific corepressors and aberrant RARa in APL pathogenesis.

Transgene	Line	No. of followed mice	Median follow up (Months)	Leukemia	Phenotype	Latency (months)
ΔRARα	#501	6	12	No	-	-
	#504	9	12	No	-	-
	#512	7	12	No	-	-
	#513	8	12	No	-	-
	#519	11	12	No	-	-
	#528	8	13	No	-	-
RARαE	#3201	31	26	No	-	-
	#3211	7	25	No	-	-
	#3212	8	19	No	-	-
	#3213	11	27	No	-	-
	#3125	11	24	No	-	-
	#3216	17	24	Yes	APL like	18-19
RARαM$_4$	#5902	18	12	No	-	-
	#5906	17	14	No	-	-
	#5916	13	12	No	-	-
	#5931	5	11	No	-	-
PML-RARαM$_4$	#1017	12	12	Yes	APL like	9
	#1031	8	12	Yes	APL like	8
	#1034	13	14	No	-	
	#1039	3	12	Yes	APL like	8.5
	#1048	13	9	No	-	-
HDAC1-RARα	#18	38	23	No	-	-
	#49	27	19	No	-	-
	#56	30	20	No	-	-
mHDAC1-RARα	#4	30	20	No	-	-
	#29	37	21	No	-	-
	#37	20	21	No	-	-

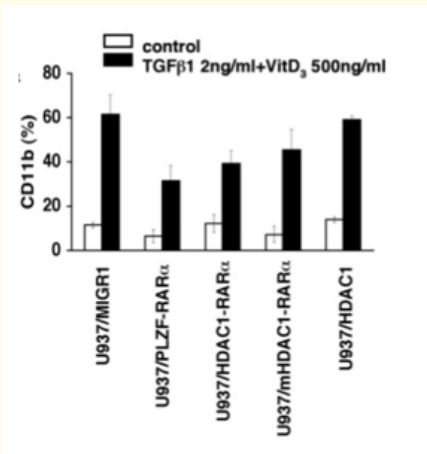
A



B



C



D

Figure 1: *Characteristics of leukemias induced by RARaE, PML-RARaM4 and PML-RARa. (A). Schematic representation of transgenic lines and respective leukemia incidence. (B). Peripheral blood (PB) and bone marrow cells (BM) from representative leukemic RARaE, PML-RARaM4 and PML-RARa transgenic mice stained with the wright-Giemsa stain (x1, 000). (C). Luciferase assay in transfected 293 cells, compared with HDAC1 alone, HDAC1-RARa is a transcriptional corepressor. (D). Compared with U937/HDAC1 cells and U937/PLZF-RARa cells, HDAC1-RARa moderately inhibits the differentiation of U937 cells in vitro, implicating the role of X-RARa (From Matsushita., et al. JEM, 2006, 203:821-828) [20].*

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