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REVIEW ARTICLE

VITAMIN A, RETINOIC ACID AND TAMIBAROTENE, A FRONT TOWARD ITS ADVANCES: A REVIEW

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Abstract

Vitamin A and its derivative retinoic acid (13-cis RA, 9-cis RA, all-trans RA) and recent tamibarotene have been shown a broad variety of biological actives in human, such as vision, embryonic development, cell growth and cellular differentiation and immune function. These precise functions of RA are mediated by their retinoic acid receptors (RARs). In the past five decades, retinoic acid (RA) proved therapeutic benefits in cancer prevention, in skin diseases and in acute promyelocytic leukemia (APL).The elucidation of the molecular basis of vitamin A acid and its retinoid pharmacology in APL has been illustrated in several publications, the detail molecular model of gene regulation had also been proposed by Zhu in earlier 90s. A molecular model is further revised. As an approach to APL treatment, one possible the action of retinoic acid (RA), A consensus sequence (TCAGGTCA motif) has been postulated for thyroid hormone (TRE) and retinoic acid responsive element (RARE)-containing in the promoter region of target genes. High dose of RA-RARE-PML/RARa complexes in intracellular localization appears to relieve repressors from DNA-bound receptor, including the dissociation of co-repressor complexes N-CoR, SMRT and HDACs from PML-RARa or PML-RARa/RXR. Also release PML/RARa -mediated transcription repression. This transcriptional derepression occurs at RARa target gene promoter. Consequentially, PML-RARa chimera converted receptor from a repressor to a RA-dependent activator of transcription. Here, oncogenic pml/RARa as constitutive transcriptional repressor that blocks myeloid differentiation at promyelocytic phenotype. RA can overcome the transcriptional repressor activity of pml/RARa. The oncogenic pml/RARa uncovers a pathogenic role in leukemogenesis of APL through blocking promyelocytic differentiation. This oncogenic receptor derivative pml/ RARa chimera is locked in their "off" regular mode thereby constitutively repressing transcription of target genes or key enzymes (such as AP-1, PTEN, DAPK2, UP.1, p21WAF/CCKN1A) that are critical for differentiation of hematopoietic cells. This is first described in eukaryotes.

Keywords: Gene transcription; molecular model of RA, retinoic acid and retinoid pharmacology, Vitamin A.

INTRODUCTION

The biologic potency of vitamin A has been known for near one century. In 1912, Frederick Gowl and Hopkins demonstrated that a unknown accessory factors found in milk, other than carbohydrates, proteins, and fats were necessary for growth in rats. Hopkins received a Nobel Prize for this discovery in 1929[1-2]. By 1913, one of these substances was independently discovered by Elmer McCollum and Merguerite Davis at the University of Wisconsin Madison, and Lafayette Mendel[3] and Thomas Burr Osborne at Yale University who studied the role of fats in the diet[4]. The "accessory factors" were termed "fat soluble" in 1918[5] and later "Vitamin A" in 1920[6]. In 1931, Swiss chemist Paul Karrer described the chemical structure of vitamin A. Vitamin A was first synthesized in 1947 by two Dutch chemists, David Adriaan Van Dorp and Jozef Ferdinand Arens. In the early 1960s, retinoids were introduced in dermatology for treatment of ichthyosis[7] and later for psoriasis and acne[8]. In 1975, Vitamin A acid, and the development of the synthetic retinoids are the pioneering work of Bollag W and Ott F in Sweden[9]. *In vivo*, the fat soluble vitamin A (retinol) can be reversibly metabolised to the aldehyde (retinal) which can in turn, be further

oxidised in a non-reversible manner to retinoic acid (RA). Enzymes that oxidize retinol to retinaldehyde belong to two classes: the cytosolic alcohol dehydrogenases (ADHs) belonging to the medium-chain dehydrogenases/reductase family; and micro-somal short-chain dehydrogenases/reductases (retinol dehydrogenases, RDHs[10]. The next step in RA synthesis is the oxidation of retinaldehyde to RA, which is carried out by three retinaldehyde dehydro-genases (RALDHs):RALDH1, RALDH2 and RALD H3[10,11].The orange pigment of carrots (beta-carotene) can be represented as two connected retinyl groups, which are used in the body to contribute to vitamin A levels[12].The physiological and biological actions of this class of substances centre on vision, embryonic development and production, cellular growth and differentiation, skin health, and maintenance of immune function. Initial studies had focused on vitamin A deficiency and its major consequences: night blindness and Xerophthalmia. Fridericia and Holm[13] investigated the influence of dietary A in the rhodopsin of the retina. Clearly, the rats lacking the fat-soluble vitamin A had a defect in the function of visual purple.

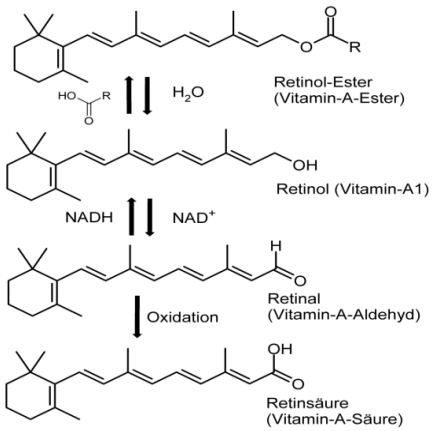

Figure 1: Chemical structure of retinol, one of the major forms of Vitamin A.

Yudkin[14] achieved one of the earliest identifications of vitamin A as a component of the retina. Subsequently, Wald[15] determined the amount of vitamin A present in pig retinas. Wald G[16,17] was well established the visual cycle: light decomposed rhodopsin to retinal and opsin. Retinal could either recombine with opsin to reform rhodopsin or it converted to free retinol. Retinol could reform rhodopsin, but only in the presence of the RPE (Kuhne). The further structure and metabolism of retinoids implicated that retinaldehyde was the visual pigment. More recently, vitamin A and its metabolites play a key importance in embryo morphogenesis, cell differentiation and clinical practice. Figure 1, chemical structure of retinol, one of the major forms of vitamin A (Vitamin A-Wikipedia).

Vision cycle

Vitamin A is needed by the eye retina, 11-cis-retinal (a derivative of vitamin A) is bound to the protein "opsin" to form rhodopsin (visual purple) in rods cells[17], the molecule necessary for both low light (scotopic vision). As light enters the eye, the 11-cis-retinal is isomerized to all-trans retinal in photoreceptor cells of the retina. This isomerization induces a nervous signal (a type of G regulatory protein) along the optic nerve to the visual center of the brain. After separating from opsin, the all-trans-retinal is recycled and converted back to the 11-cis-retinal form via a series of enzymatic reactions. The all-trans- retinal dissociates from opsin in a series of steps called photo-bleaching. The final stage is conversion of 11-cis-retinal rebind to opsin to reform rhodopsin in the retina[15-17]. Kuhne showed that rhodopsin in the retina is only regenerated when the retina is attached to retinal pigmented epithelium (RPE)[17]. As the retinal component of rhodopsin is derived from vitamin A, a deficiency of Vitamin A inhibits the reformation of rhodopsin and lead to night blindness. Within this cycle, all-trans retinal is reduced to all-trans retinol in photoreceptors via RDH8 and possible RDH12 in rods, and transported to RPE. In the RPE, all-trans retinol is converted to 11-cis retinol, then 11-cis retinol is oxidized to 11-cis-retinal via RDH5 with possible RDH11 and RDH11[10]. This represents each RDH for the roles in the visual cycle.

Embryonic development, cell growth and differentiation

The inclusion of retinoic acid in super family of steroid and thyroid hormones underlines its importance in the development and differentiation in normal tissues. Retinoic acid (RA) is lipophilic molecule that act as ligand for nuclear RA receptors (RARs), converting them from transcriptional repressor to activators[11,18] in RA signaling pathway. It has been demonstrated that retinoic acid was identified as a morphogen (teratogen) responsible for the determination of the orientation of the limb outgrowth in chicken[19], and its retinoic acid receptors (RARs) appear at early stage of human embryonic development in certain types of tissues[19,20]. Vitamin A plays a role in the differentiation of this cerebral nerve system in *Xenopus laev*i. The other molecules that interact with RA are FGF-8, Cdx and Hox genes, all participating in the development of various structures within fetus. For instance, this molecule plays an important role in hindbrain development. Both too little or too much vitamin A results in the embryo: defect in the central nervous system, various abnormalities in head and neck,the heart, the limb, and the urogenital system[20]. With an accumulation of these malformations, an individual can be diagnosed with DeGeorge syndrome[11]. *In vitro*, all-trans retinoic acid (ATRA) stimulates at least two-fold the clonal growth of normal human CFU-GM and early erythroid precursor BFU-E[21]. Cis-RA stimulates clonal growth of some myeloid leukemia cells. In suspension culture, there was an increase in cell number at day 5 in the presence of RA in half of 31 samples, which suggest that RA may play a role in the proliferation and survival of certain leukemia clones *in vitro*[22]. In contrast to the enhancement of normal hematopoietic proliferation, RA (10-6-10-9 mol/l) is capable of inducing differentiation of the F9 mouse teratocarcinoma, HL-60 cells[23,24] and some blasts from patients with promyelocytic leukemia[23]. Maximum HL-60 differentiation (90% of cells) occurs after a 6 day exposure to 10-6 mol/l retinoic acid. Further *in vitro* studies found that retinoic acid induced differentiation

of leukemic blast cells in only 2 of 21 patients with AML, both of these patients had promyelocytic variant[24]. These data suggest that retinoids may induce maturation of promyelocytes. Retinoic acid also inhibits the proliferation of other dermatological malignant cells.

Maintenance of Immune homeostasis

There is a link between retinoid and immune homeostasis. In the presence of retinoic acid,dendritic cells located in the gut are able to mediate the differentiation of T cells into regulatory T cells[25,26],which implicate that vitamin A exerts its areas of immune response via its against "self" and the prevention of host damage. Vitamin A metabolite retinoic acid act as a key regulator of TGF-beta-dependent immune responses. Vitamin A is capable of inducing the IL-6-driven induction of proinflammatory T(H) 17 cells, promoting anti- inflammatory T reg cells differentiation, thus regulating the balance between pro- and anti-inflammatory immunity[26].

Retinoic acids in APL treatment

Acute promyelocytic leukemia (APL, M3 in the FAB subtype) represent 5% to 15% of cases of acute promyelocytic leukemia[27], with characteristic t (15; 17) translocation. APL treatment was initial for 13-cis RA[28-30], later currently all-trans RA[31], and recent tamibarotene[32]. In retrospective analysis, 3 of 5 (60%) these initial reported cases with 13-cis RA obtained complete remission (CR). Two of five obtained a CR for 11 months[29] and 1 year[30] respectively, the similar to 20 months in isolated CR APL for all-trans RA then observation[33,34]. Another one patient with 13-cis RA early died from disseminated *candidiasis*, while the peripheral blood count rose from 0.3x109/l to 6.7x109/l with 2.3x109/l mature cells[28]. Moreover, Castaigne S and Chomienne C[31] reported that treatment with all-trans RA alone (45 mg/m^2/day) produced CR in 14 of 22(63.6%) cases of APL. The results confirmed Chinese investigation. This also confirmed previous isolated case reports of remission induction with 13-cis RA. In literature, an isolated APL obtained CR after treatment with 13-cis retinoic acid first and repeated CR with ATRA in relapse[35]. Accordingly, ATRA plus chemotherapy or ATRA plus ATO regimen is the standard of care[36]. And more, 80% (4/5) CR in newly APL and 33% (4/12) CR in relapsed APL were achieved after treatment with 9-cis retinoic acid (L-GD1057) alone[37].The data suggest that 9-cis RA is also effective agent for remission induction. Long-term follow up data, the rates of CR were found from 72%[38]-94.3%[39] following ATRA treatment. Unlike other leukemia, APL has a very good prognosis, with long-term survival rates up to near 70%-90%[40]. Based on the total of 2080 APL with ATRA combination protocol from seven larger cohort of study[36,38,39,41-44], the 3-year (range 1-115 months) disease-free survival (DFS) and overall survival (OS) were 87.7% and 90.6% respectively[41]; 6-year overall survival and disease-free survival in CR patients 83.9% and 68.5% respectively[44]; 10-12 year survival about 68.9-77% (66.4- 71.4%)[36,42]. But inclusion of early death[45], a total of another 1400 APL between 1992 and 2007, and the overall early death rate was 17.3%. The 3-year OS improved from 54.6% to 70.1% and a significantly lower in patients aged over 55 years (only 46.4%)[46]; 5-year overall and disease-free survival rates of 51.6% and 50.1% respectively (73 APL unpublished data in 501 army hospital,Tehran,1995-2015);6 year OS 62% rates[47]. Thus, the 10-year cumulative incidence of deaths in CR was 5.7%, 15.4% and 21.7% in younger than 55, 55 to 65, and older than 65 years, respectively[42]. Nowadays, a lot of cohort trials on using tamibarotene, 61.5% (24/39) achieved CR including 5 newly APL and 13 relapse APL twice or more[32]. Among 269 APL with CR underwent maintenance random, 4-year relapse-free survival rate was 84% (ATRA) and 91% (Tamibarotene). In 52 high risk patients, this becomes significant: 50% for ATRA, 87% for tamibarotene[48]. In comparative analysis among those relapsed APL[49], 80% (28/35) achieved CR and 22.86% CRm in tamibarotene - ATO versus 54.2% (19/35) CR with only 2.86-3.7% CRm in ATRA - ATO regimen. From another 20 patients with relapsed APL, ATRA did not seem to significantly improve the response to ATO in patients relapsing from APL[50]. In particular, appreciable benefits of tamibarotene-ATO regimen might occur at significantly lower frequency of leukocytosis with development of retinoic acid syndrome, an important adverse reaction during treatment of APL. Therefore, Tamibarotene demonstrated more efficacy in both untreated APL patients and relapsed who have been treated with ATRA and chemotherapy, especially as novel strategy in relapsed APL in Japan and others[49,51,52]. This is encouraging perspective.

RARs Structure

The retinoic acid receptors (RAR) belong to the large family of ligand responsive gene regulatory proteins that includes receptors for steroid and thyroid hormones[53]. There are three retinoic acid receptors (RAR), RARα, RARβ and RARγ which are conserved throughout vetebrates encoded by their different RAR (chr 17q21, chr 3p24 and chr12q13) gene, respectively. The RARA contains 462 amino acids (aa)[54,55], RARB consists of 455aa[56] and RARG contains 454aa[57], respectively. The RAR is a type of nuclear receptor which acts as a transcription factor that is activated by both all-trans RA and 9-cis RA. The RARs have different functions and may activate distinct target genes. The RARa is expressed in a wide variety of different hematopoietic cells[54,55]; the RARβ in a variety of epithelial cells; and the RARr in differentiation of squamous epithelia and human skin tissue[56,57]. All RARs contain a variable N-terminal region (A/B), a highly conserved cysteine-rich central domain(C) responsible for the DNA binding activity, and a relatively well-conserved C-terminal half (E) functionally its role in ligand binding and nuclear translocation. These three main domain are separated by a hinge region (D)[18,53,58]. The central DNA binding domain (88-153aa) exhibits an array of cysteine residues compatible with the formation of two so-called zinc finger. Each of them a zinc atom tetrahedrically coordinated to four cysteine, and each of the hypothetical zinc finger is encoded by a separate exon of the receptor gene [Zinc finger 1, 88-108aa,

Zinc finger 2, 124-148aa][53-58]. The N-terminal zinc finger of the DNA binding domain confers hormone responsiveness to HREs, determining target gene specificity, and responsible for functional discrimination between HREs whereas the C-terminal finger contains the sugar-phosphamide backbone of the flanking sequences[58].

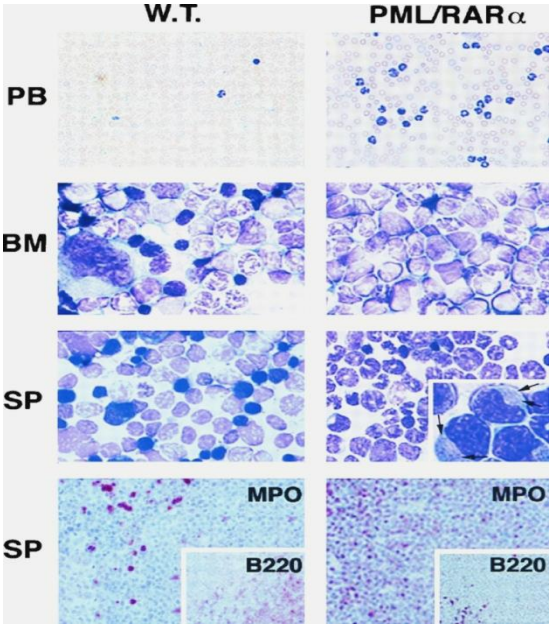

Figure 2: pml/RARa fusion in differentiation block at promyelocytic stage in transgenic mice

(Figure from He LZ, *et al.*, Proc Natl Acad Sci USA, 1997, 94:5302-07)[74]

Oncogenic pml/RARa act as constitutive transcriptional repressor that blocks neutrophil differentiation at the promyelocyte stage

Acute promyelocytic leukemia (APL) is a clonal expansion of hematopoietic precursors blocked at the promyelocytic stage. Approximately 98% of APL, RARa translocates and fuses with the PML gene on chromosome[15]. The resulting RAR chimeric genes encode pml/RARa fusion protein, which is specifically expressed in the promyelocytic lineage[59,60]. In addition to oncogenic receptor derivative pml/RARa[18,61-63], the translocation involves oncogenic TBL1XR1-RARB[64] and NUP98/RARG[65], and oncogenic PML-RARG[66] which share high homolog (90%) of three RAR family that were also detected in APL rare cases. Most studies have shown that PML-RARA is an oncogenic transcription factor forming in APL. Without its ligand, retinoic acid (RA), PML-RARA functions as a constitutive transcriptional repressor, abnormally associating NcoR/HDACs complex and blocking hematopoietic differentiation. In the presence of pharmacological concentration of RA, RA induce the corepressors NcoR/HDACs dissociation from PML-RARA, thereby PML-RARa activates transcription and stimulate differentiation[18,61,67]. *In vitro* by using a dominant negative RAR construct transfected with interleukin 3(IL-3)-dependent multipotent hematopoietic cell line(FDCP mix A4) and normal mouse bone marrow cells, GM-CSF induced neutrophil differentiation was blocked at the promyelocyte stage. The blocked promyelocytes could be induced to terminally differentiate into neutrophils with supraphysiological concentration of ATRA[68].

Similarly, over expression of normal RARa transduced cells displayed promyelocyte like morphology in semisolid culture, and immature RARa transduced cells differentiate into mature granulocytes under high dose of RA(10-6M)[69]. Moreover, mutation of the N-CoR binding site abolishes the ability of PML-RARa to block differentiation[70,71]. Therefore, ectopic expression of RAR fusion protein in hematopoietic precursor cells blocks their ability to undergo terminal differentiation via recruiting nuclear core pressor N-CoR/histone deactylase complex and histone methyltransferase SUV39H1[72]. *In vivo*, transgenic mice expressing PML-RARA fusion can disrupt normal hematopoiesis, give sufficient time, and develop acute leukemia with a differentiation block at the promyelocytic stage that closely mimics human APL (APL-like syndrome, see Figure 2) even in its response to RA in many studies. These results are conclusive *in vivo* evidence that PML/RARa is etiology of APL pathogenesis[73-79]. Structure and function analysis of pml/RARA uncovered that RAR component of the fusion protein is indispensable for its ability to impair terminal differentiation, and resolved the pml/RARa as constitutive repressor in differentiation block[18,61,80-92]. PML-RARa retains both DNA binding domains and ligand binding domains of RARa. RARa is a member of nuclear receptors that bind to specific-RARE as heterodimers with RXR. By using RARa promoter-drived receptor plasmid containing RARE, the chimeric pml/RARa fusion reduces the induction of transcription by RA from a RARE by 50-90% in Hepa G cells[59]. Many other two groups have further shown that PML-RARa act as strong transcriptional repressor in inhibiting transcription from RAREs to a great content than RARa, which may be critical for differentiation block in APL. In Rousselot's group experiments, HL-60 cells transfected with 15-30 µg of PML-RARa fusion in culture show no features of granulocytic differentiation after 7 days of incubation with 10-7, 10-6 M RA (5.5-9.5% of differentiated cells by the NBT test). At 5 µg of PML-RARa plasmid concentration, the blockage of RA-dependent myeloid differentiation could be overcomes with high doses (10-6M) of RA (99% of differentiated cells by NBT test) [Figure 3]. The results clearly indicate that PML-RARa mediated transcriptional repression, as well as PML-RARa oncoprotein blocks RA-mediate promyelocyte differentiation. By using *Xenopus oocyte system* to uniquely the comparison of the transcriptional properties of RAR and PML-RAR is due to the lack of endogenous nuclear receptors and the opportunity to evaluate the role of chromatin in transcriptional regulation. The experimental results demonstrated that, indeed, PML-RARA is a stronger transcriptional repressor that is able to impose its silencing effect on chromatin state even in the absence of RXR. Only pharmacological concentration of RA, pml/RARA become transcriptional activator function[67]. Moreover, ATRA treatment overcomes the differentiation block through dissociation of corepressor

complexes from pml/RARa and transcription activation, thereby induces pml-RARA degradation, and subsequently promotes promyelocytic differentiation. *In vitro* experiments, ATRA induce pml-RARA itself cleavage into a 85-97kd delta PML-RARA product (a truncated pml/RARA form) in RA sensitive NB4[93-96] [Figure 4].

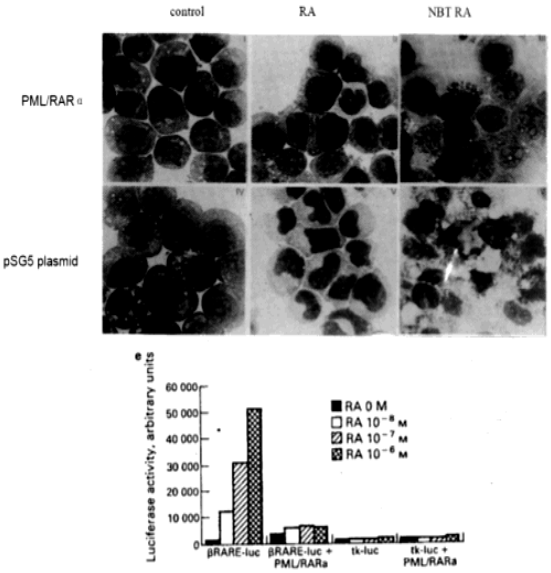

Figure 3: Expression of pml-RARa in HL-60 cells: blocks ATRA-induced promyelocytic differentiation (in the presence of 10-7 M RA,top), and transcriptional repressive properties of pml-RARa in human myeloid cells as βRARE-luc assay(bottom)(Figure from Rousselot P, Oncogene, 1994, 9:545-551)[80]

Delta PML-RARa is not formed in ATRA differentiation resistant NB4 subclones[93,96], which indicate that the loss of PML/RARa may be directly linked to ATRA-induced differentiation[93,96]. This induction of PML-RARa cleavage and degradation by RA(ATRA,9-cis RA,Am80) involve the proteasome-dependent[93-95] and caspase mediated pathway[97], or independent of proteasome and caspase cleavage[96], and possibly ubiquitin-activating enzyme EI-like(UBEIL) induction in NB4 cells. This is reason that proteasome inhibitor MG-132 and caspase inhibitor ZVAD do not block ATRA-induced pml/RARa cleavage and differentiation whereas this delta pml-RARA is blocked by RARA itself antagonist Ro-41-5253[96]. The proteasome-dependent pml/RARA degradation, by using proteasome inhibitor lactacystin test, allows APL cells to differentiation by relieving the differentiation block[94]. These data suggest a set of multiple molecular mechanisms for restoration by RA induced myeloid differentiation in APL cells. Next we further examine the pml/RARa three region functions; *in vitro* deletion of the RARa DNA binding domain decreased the ability of pml/RARa to inhibit Vit D3 and TGF-induced the myeloid precursor U937and TF-1 cell differentiation[70]. This is also supported by functional analysis of DNA binding domain artificial mutation *in vitro*. The RARa zinc finger is a sequence-specific DNA binding through which RARa contacts the RA target genes. Moreover, deletion of PML coiled-coil region also blocked the differentiation capacity of TF-1 cells[70]. The coiled-coil region directs the formation of pml/RARa homodimers tightly interact with the N-CoR/HDACs complex, so that transcriptional de-repression cannot occur at RARA target gene promoter even if the presence of ATRA [RA resistant[18,90]].

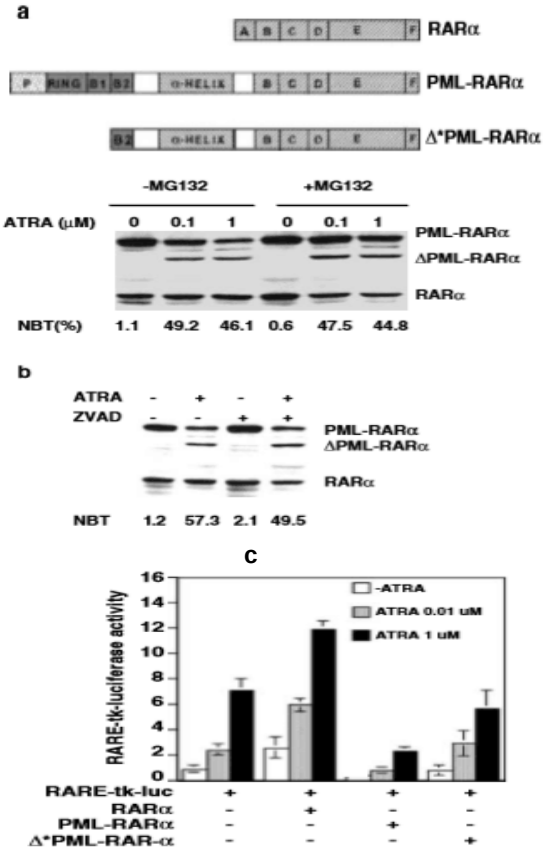

Figure 4: Delta pml/RARa cleavage products:

independent of proteasome and caspase in the presence of ATRA (a, b), and pml/RARa act as transcriptional repressor even in the presence of ATRA (0.01uM,1uM) in RARE-tu-luc assay while delta pml/ RARa is less potent activator of RARE-tk-leu activation than wild-type RARa (c) in NB4 cells (Figure from Jing Y, Oncogene, 2003, 22:4083-91)[96]. *In vitro*, using established subclones of NB4 resistant to both ATRA and 9-cis RA, they were significantly less able to stimulate transcription of a RARE driven CAT-reporter gene induction by ATRA and showed altered DNA binding activaty on a RARE[98]. In the resistant cases, mut PML stabilizes PML-RARa[99]. PML-RARA with ligand-binding domain (LBD) mutation, ligand RA binding with LBD is impaired. Trichostatin A (TSA), known as HDAC inhibitor, antagonize HDAC activity and thereby enhance histone acetylation resulting in open chromatin state[86].

TSA proved useful in therapeutic targeting of transcription in two APL patients[100,101]. In accordance, the pml/RARa/RXR target genes are thought to block differentiation by constitutively silencing a set of RA-responsive genes in the control of hematopoietic precursor cells.

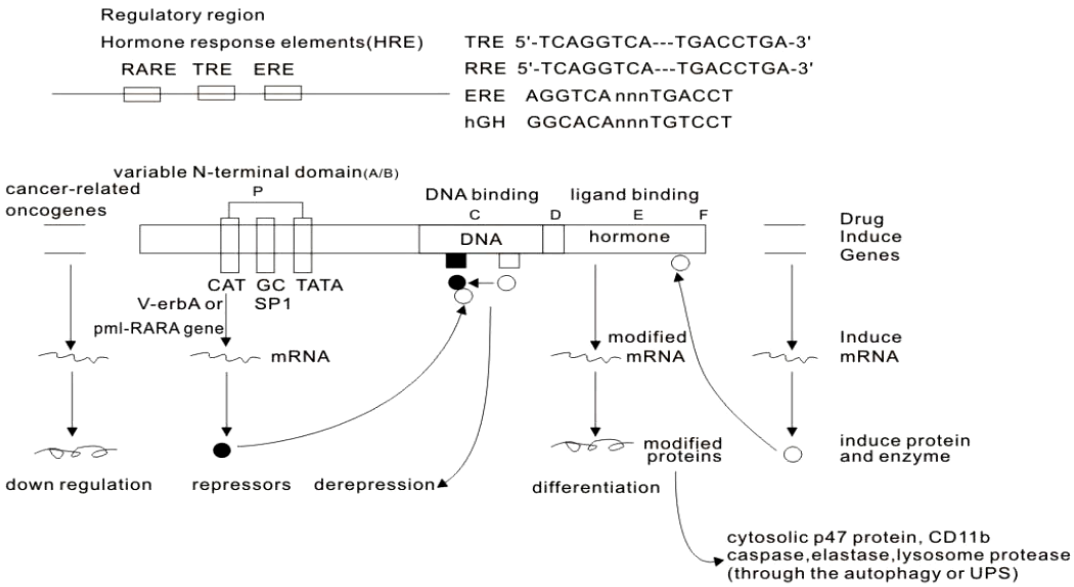

Figure 5: Molecular model of the gene regulation of retinoic acid (RA) action.

(George Zhu, January 1991, revised in 2012). Schematic alignment of the receptor protein. The two highly conserved regions, identified as the putative DNA-binding (C) and hormone- binding (E), a hinge region (D) and the non-conserved variable NH2-terminus (A/B) as described above. CAT: CAAT box,CCAAT-enhancer binding proteins(or C/EBPs); GC:GC box; TATA:TATA box. Note: In APL cells, PML-RARa fusion point is located in the first 60 amino acids from the N-terminus(A/B) of RARa.(Figure from Zhu G, Curr Pharm Biotechnol 2013; 41(9):849-858).

These include Jun/Fos/Ap-1, C/EBPa, C/EBPepsilon, DAPK2/PU.1, HOXA7, HOXA9, HOXA10, MEIST, SAP30, p21WAF/CCKN1A[81,102-106]. Five major transcription factors, Ap-1[81], C/EBPepsilon[102,103], Pu.1/DAPK2[104], PTEN[105], and p21WAF/CCKN1A[106], directly regulate genes important in myeloid differentiation, such as G-CSFR, CD11b, Myeloper-oxidase, Gr-1 or Mac-1. PML/RARA fusion is oncogenic transcriptional repressor of five genes. Inhibited expression or functions of these five transcription factors lead to a block in myeloid differentiation, which is a hallmark of APL. Importantly, restoring DAPK2 expression in PU.1 knockdown APL cells partially rescued neutrophil differentiation[107]. DAP-Kinase is a calcium/ Calmodulin (CaM)- dependent, cytoskeletal-associated protein kinase (ser/thr). In addition, DAPK2 interacts with other cyclin- dependent kinase inhibitors such as p15INK4b and p21WAF1/CIP, which is needed for the cell-cycle arrest in terminal differentiation of neutrophils. Moreover, DAPK2 can bind and activate the key autophagy gene beclin-1[107]. PU.1, an ETS transcription factor known to regulate myeloid differentiation. Silencing of PU.1 in the adult hematopoietic tissue produces dysfunctional stem cells and impaires granulopoiesis by inducing a maturation block. Overexpression of PU.1 overcomes the differentiation block in SCa 1+/Lin- HSC with transduction of PML/RARa fusion, as measured by the Gr-1 and Mac-1 expression[108]. Thus, pml/RARa represses PAPK2/PU.1 - mediated transcription of myeloid genes in APL, linking a novel autophagy mechanism of pml/RARA degradation[109].

Molecular model of the gene regulation of retinoic acid action in APL

The molecular mechanism of retinoic acid action in APL has been proposed in several publications[86,89,110]. Based on review more researches publications[27-52,53-109], the detail mechanism has also been described by Zhu[18,111,113]. In the absence of RA, RARa functions as a nuclear receptor that binds to specific DNA sequence called RA responsive element (RARE: AGGTCA motif) in target gene promoter, normally as heterodimer with RXR. RAR-RXR heterodimer induce transcriptional repression throughout chromatin remodeling by recruiting corepressor N-CoR/SMRT, and histone deacetylases (HDACs) and histone methyltransferases. Physiological levels of RA induce the dissociation of corepressor complexes and allow for the recruitment of co-activators, including histone acetylases. Consequentially, RA treatment leads to transcriptional activation, thereby trigger expression of genes involved in myeloid differentiation[11,18,67,84,90]. In special APL, oncogenic pml/RARa binds to consensus sequence of target gene promoter primarily as homodimer, also as a heterodimer with RXR. PML-RARa behave as a constitutive transcriptional repressor of RARE-containing genes[18,61,67,80-92,102-106] through tightly binding with the corepressor complexes, and promiscuously interfering with RARa and retinoid acid signaling, thereby inducing a differentiation block at promyelocytic stage which can be overcome with supraphysiological doses of 9-cis or/and ATRA ligand.

As an approach to APL treatment, one possible the action of retinoic acid (RA), A consensus sequence (TCAGGTCA motif) has been postulated for thyroid hormone (TRE) and retinoic acid responsive element(RARE)-containing in the promoter region of target genes[114]. High dose of RA-RARE-PML/RARa complexes in intracellular localization appears to relieve repressors from DNA-bound receptor[18,70,82,115-117], including the dissociation of corepressor complexes N-CoR, SMRT and HDACs from PML-RARa or PML-RARa/RXR[18,71,82,84,90]. Also release PML/RARa - mediated transcription repression[87]. This transcriptional derepression occurs at RARa target gene

promoter[18,84,90]. Consequentially, PML-RARa chimera converted receptor from a repressor to a RA-dependent activator of transcription[81,85,87,90,92]. The resulting pml-RARA oncoprotein proteolytic degradation occurs through the autophagy-lysosome pathway[109] and the ubiquitin SUMO-proteasome system(UPS)[93-96] as well as caspase 3[97], or lysosomal protease (cathepsin D) enzyme or/and EI-like ubiquitin-activating enzyme (UBEIL) induction[83]. An effect is to relieve the blockade of pml/RARa-mediated RA dependent promyelocytic differentiation, and retinoic acid (9-cis RA, ATRA, Am80) in APL therapy (Figure 5, Zhu, March 1990- January 1991, revised in 2012). Here, RA can overcome the transcriptional repressor activity of pml/RARa[18,61,67,80-92,102-106]. The oncogenic pml/RARa uncover a pathogenic role in leukemogenesis of APL through blocking promyelocytic differentiation. This oncogenic receptor derivative pml/RARa chimera is locked in their "off" regular mode thereby constitutively repressing transcription of target genes or key enzymes (such as AP-1, PTEN, DAPK2, UP.1, p21WAF/CCKN1A)[81,102-106] that are critical for differentiation of hematopoietic cells. This is first described in eukaryotes.

CONCLUSIONS

To date, the discovery of the fat soluble vitamin A has been known for over 100 years, more scientists have made their contribution in this field. Vitamin A and its derivative retinoic acids (RA) have been shown a broad variety of biological actives in human, such as vision, embryonic development, cellular growth and differentiation, and immune function. These precise functions of RA are mediated by their RA receptors (RAR). Retinoic acids have therapeutic benefits in the past five decades the advances in treatment of skin diseases and acute promyelocytic leukemia (APL). More than ten to twenty laboratories are trying to uncovering the molecular model of RA action in APL, the detail mechanism had also been proposed by Zhu in January 1991. This earlier hypothesis have now been demonstrated by structure and functional analysis of oncogenic pml/RARa chimera protein *in vitro* and *in vivo* in numerous studies, and partially mentioned above in this paper. This appears to be its centre and its main aim in this researching review. This is key important useful paradigm and perspective in our highlight on ‘genetic dissection of gene regulation in clinical cancer biology’; Professor LP Wu says 5 years ago. Whether silencing of these RARE-responsive target genes such as myeloid transcription factors C/EBPa,PU.1 or other unknown key enzymes that are really crucial for neutrophil differentiation needs to further identification and under investigation.

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AUTHOR’S CONTRIBUTION

Zhu G: writing original draft, methodology, investigation, formal analysis, data curation, conceptualization. **Al-kaf AGA:** writing, review and editing, methodology, formal analysis, data curation, conceptualization. All authors read and approved the final manuscript for publication.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICTS OF INTEREST

None to declare.

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