Original Research Article

Vitamin A,retinoic acid and retinoid pharmacology,From front move center

Abstract

Retinol (Vitamin A) and its derivative retinoic acid(RA) are essential in the control of epithelial cell growth and cellular differentiation. Retinoid is indispensable in vision and RA inhibits the growth of some malignant cells. RA also has striking effect on pattern formation in developing and regenerating limbs,and also a potent morphogen in chick limb bud. 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 and its retinoid pharmacology emerged as paradigm for the connection between RA and its structure of RA receptors(RAR),oncogenic pml/RARa as constitutive transcriptional repressor that block myeloid differentiation at promyelocytic phenotype,and the molecular model of retinoic acid action in a special APL. 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 corepressor 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. Consquentially,PML-RARa chimera converted receptor from a repressor to a RA-dependent activator of transcription.The resulting pml-RARA oncoprotein proteolytic degradation through the autophagy-lysosome pathway and the ubiquitin SUMO-proteasome system(UPS) as well as caspase 3, or lysosomal protease (cathepsin D) enzyme or/and EI-like ubiquitin-activating enzyme(UBEIL) induction. An effect to relieve the blockade of pml/RARa-mediated RA dependent promyelocytic differentiation,and retinoic acid(9-cid RA,ATRA,Am80) in APL therapy(See figure,George Zhu ,September1990- January 1991,revised in 2012). Here,RA can overcome the transcrptional repressor activity of pml/RARa.The oncogenic pml/RARa uncover a pathogenic role in leukemogenesis of APL through blocking promyelocytic differentiation; and this oncogenic receptor derivative pml/RARa chimera is locked in their "off" regular mode thereby constitutively repressing transcription of target genes(such as AP-1,PTEN, DAPK2,UP.1,p21WAF/CCKN1A) or key enzymes(such as myeloblastin /proteinase-3, Aurora A kinase) that are critical for differentiation of hematopoietic cells. This is first described in eukaryotes.

Keywords: Vitamin A; retinoic acid and retinoid pharmacology; gene transcription; molecular model of RA

The physiology and biochemistry of retinoic acid

The biologic potency of vitamin A has been known for near one century. In 1912,Frederick Gowland 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 descibed 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 [8,9]. In 1975,Vitamin A acid,and the development of the synthetic retinoids are the pioneering work of Bollag W and Ott F in Sweden [10].

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 microsomal short-chain dehydrogenases/reductases (retinol dehydrogenases,RDHs [11].The next step in RA synthesis is the oxidation of retinaldehyde to RA,which is carried out by three retinaldehyde dehydrogenases (RALDHs):RALDH1,RALDH2 and RALDH3 [11,12].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 [13].The physiological and biological actions of this class of substances centre on vision,embryonic development and production,cellular growth and differention,skin health,and maintenance of immune function. Initial studies had focused on vitamin A deficiency and its major consequences: night blindness and Xerophtalmia. Fridericia and Holm [14] 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. Yudkin [15] achieved one of the earliest identifications of vitamin A as a component of the retina. Subsequently,Wald [16] determined the amount of vitamin A present in pig retinas.Wald G [17,18] 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 [19]

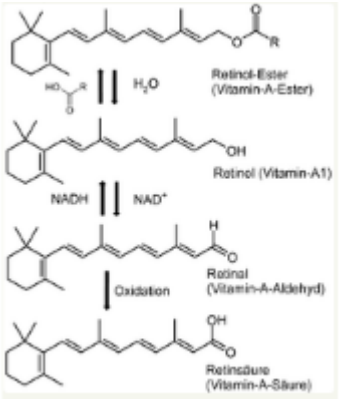

Figure 1. Chemical structure of retinol,one of the major forms of Vitamin A (Figure from Vitamin A - Wikipedia)

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 [18], 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 [16-19,figure 2: vision cycle]. Kuhne showed that rhodopsin in the retina is only regenerated when the retina is attached to retinal pimented epithelium(RPE) [18]. As the retinal component of rhodopsin is derived from vitamin A,a deficiency of vitamin A inhibit 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 [11]. This represent each RDH for the roles in the visual cycle.

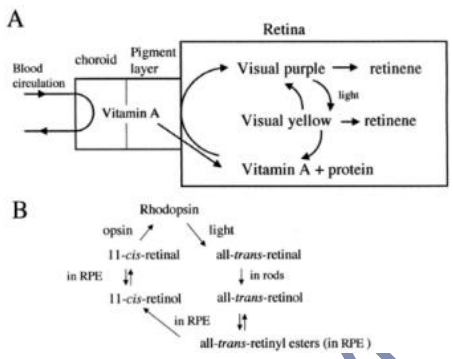

Figure 2. Vision cycle (Figure data adapted from Wald G,1935;Wolf G,2001)

Embryonic development,cell growth and differentiation

The inclusion of retinoic acid in superfamily 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 [12,20] 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 [21,22],and its retinoic acid receptors(RARs) appear at early stage of human embryonic development in certain types of tissues[23]. Vitamin A play a role in the differentiation of this cerebral nerve system in Xenopus laevi. 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 [24]. With an accumulation of these malformations,an individual can be diagnosed with DeGeorge syndrome [12].

Vitamin A,in the retinoic acid form,plays an important role in maintaining normal skin health through differentiating keratinocytes(immature skin cells) into immature epidermal cells. In earlier studies,Frazier and Hu(1931) [25] made the observation that both hypovitaminosis A and hypervitaminosis A provokes epithelial alterations together with decreased keratinization and hair loss. At present,13-cis retinoic acid(Isotretinoin) in clinical used to acne treatment,which was shown to reducing secretion of the sebaceous glands,triggering NGAL(neutrophil gelatinase-associated lipocalin) and other gene expression,and selectively inducing apoptosis [26]. But precise action of retinoid therapeutic agents in dermatological diseases are being researched. In addition to T cells,vitamin A is important for the regulation of hematopoietic stem cell dormancy [27]. Mice maintained on a vitamin A-free diet loss HSCs(hematopoietic stem cells),showing a disrupted re-entry into dormancy after exposure to inflammatory stress stimuli,which highlight the impact of dietary vitamin A on the regulation of cell-cycle mediated stem cell plasticity [28]. 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 [29]. 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,and suggest that RA may play a role in the proliferation and survival of certain leukemia clones in vitro [30,31].

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 [32,33] and some blasts from patients with promyelocytic leukemia [32]. Maximum HL-60 differentiation(90% of cells) occurs after a 6 day exposure to 10-6mol/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 [33].These data suggest that retinoids may induce maturation of promyelocytes. Retinoic acid also inhibits the proliferation of other dermatological malignant cells(Myger,1975; Peck,1975).

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 [34,35],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 as a key regulator of TGF-beta-dependent immune responses,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 [35].

There is now a well developed medicinal chemistry of RA(see figure 3, From Shroot B,1990) [36]. In view of this broad spectrum of pharmacological activity,spanning retinoic acid signaling in development,cell growth and differentiation,and immune modification, these substances provide useful to treat multifactorial dermatological disorders and other hematological disorders such as acute promyelocytic leukemias (APL)

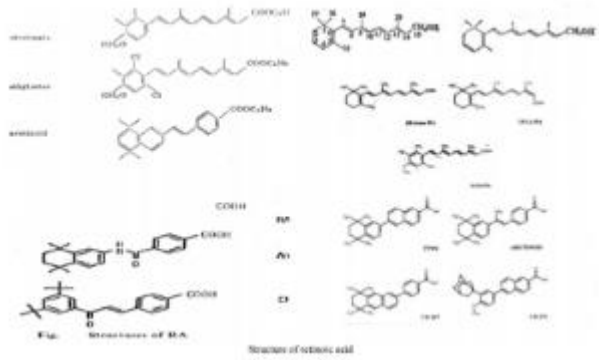

Figure 3. Is now a well developed medical chemistry of retinoic acid(RA).The all-trans and 13-cis forms of retinoic acid, two isomers of RA,are equally effective inhibiting proliferation. Retinyl acetate,and retinal(Vitamin A) are less potent inhibitor. Am80(Tamibarotene) is more potent inhibitor.The chemical structures of more potent analogues involved from the labile flexible polyene structures to aromatic stable mioieties are shown(Figure from Shroot B:Round table conference:Retinoic acid,1990;Hashimoto Y,1988)[36,37].

Retinoic acids in APL treatment

Acute promyelocytic leukemia(APL,M3 in the FAB subtype) represent 5% to 15% of cases of acute promyelocytic leukemia [38],with characteristic t(15;17) translocation. APL treatment was initial for 13-cis RA [39-43],later currently all-trans RA [44],and recent tamibarotene [45]. In retrospective analysis,3 of 5 (60%) these initial reported cases with 13-cis RA obtained complete remission(CR),2 of them a CR obtained for 11 months [40] and 1 year [43] respectively,the similar to 20 months in isolated CR APL for all-trans RA then observation [46,47]. 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 [39]. Moreover, Castaigne S and Chomienne C [44] reported that treatment with all-trans RA alone(45mg/m2/day) produced CR in 14 of 22(63.6%) cases of APL. The results confirmed chinese investigatigation. 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 [48]. Accordingly,ATRA plus chemotherapy or ATRA plus ATO regimen is the standard of care [49]. 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 [50].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% [51,52] - 94.3% [53] following ATRA treatment. Unlike other leukemiad,APL has a very good prognosis,with long-term survival rates up to near 70%-90% [54,55]. Based on the total of 2080 APL with ATRA combination protocol from seven larger cohort of study [47,52,53,56-60],the 3-year(range 1-115 months) disease-free survival(DFS) and overall survival(OS) were 87.7% and 90.6% respectively [56,57];6-year overall survival and disease-free survival in CR patients 83.9% and 68.5% respectively [60];10-year survival about 77% [58];and 12-years survival 68.9%(66.4-71.4%) [53]. But inclusion of early death [61],a total of another 1400 APL between 1992 and 2007,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%) [62];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 [63]. 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 [58].

Nowdays,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 [45]. 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 become significant:50% for ATRA, 87% for tamibarotene [64]. In comparative analysis among those relapsed APL [65], 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 20 patients with relapsed APL, ATRA did not seem to significantly improve the response to ATO in patients relapsing from APL [66]. 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 [65,67-68]. This is encouraging perspective.

Retinoid acids in MDS treatment

The geometric isomer of the naturally occurring retinoic acid is 13-cis retinoic acid (13-CRA).Based on in vitro and in vivo antineoplastic activity,this agent has entered clinical trials for a variety of neoplasms including MDS. Retinoic acid is one of the biological inducers of differentiation that has been preliminarily tested in patients with preleukaemia. Myelodysplastic syndrome(MDS) are a group of hematopoietic disorders characterized by ui- or multilineage maturation defects of the bone marrow [69]. Differentiation induction therapy is used in MDS to improve this maturation defects and induce a multilineage clinical response in a subgroup of MDS patients.13-CRA may have moderate effect on 20-30% of patients with MDS [70]. A various of combination therapy with 13-cis RA and growth factors G-CSF or erythropoietin(EPO) improve impaired cytokine secretion (IL-1beta,IL-6,IL-8) from monocytes [71]. In a prospective multicenter study,EPO-beta-ATRA [72] or EPO-13-cis RA [73] combination appears to erythroid response reaching about 36%-60% of therapeutic efficacy in anemia of low/intermediate risk MDS(LDMDS) (marrow blasts < 10% or excluding RARBt). More data analysis, erythroid response maintained an independent positive impact on survival, partcularly in non-RARE patients in the first 3 years from diagnosis (90% survival in EPO responders compared to 50% of non-responders) [74]. Zhu [75] successfully conducted a CR patient with refractory anemia with multilineage megaloblastic dysplasia following traditional medicine and erythropoiesis-stimulating agent vitamin B12 and folate growth factor. His peripheral parameters presented pancytopenia (hemoglobin 59g/l,red blood cell count 1.9x1012/l,leukocyte count 2.6x109/l,platelet value 11.8x109/l). He remained well over 10 years. While another MDS had its unequivocal evidence of disease progression in response to phytohemagglutinin(PHA),inducing the generation of interleukin-2, accelerating the number recovery of CFU-S and initiating DNA synthesis of cells. She had 2.5% blast plus promyelocytes in ~70% cellular marrow before beginning PHA,and 20.7% blast plus promyelocytes in a 90% cellular marrow after ten days(total dosage 250mg) of PHA. Venditt etal [76] conduct that 23 patients with high-risk myelodysplastic

syndrome (HRMDS) were treated with a 10 days course of oral ATRA(45mg/m2) and subcutaneous low-dose cytosine arabinoside(LDARAc) given at the dose of 20mg twice a day. In all cases (RAEB9,RAEBt9 and CMML4) [77],bone marrow blasts infiltration was greater than 10%(12-30%). Overall, 5(23%) of 22 patients achieved complete responder and 2(9%) as partial responders.The overall median survival was 8 months(range 1-27months),whereas the median survival of responders was 16months(8-27months),the median duration of response was 11months(2-21months). It seems that the combination of ATRA and LDARA-c may be effective in approximately 30% of HRMDS patients [76].

Valproic acid (VPA) has been used as an anticovulsant for decades. VPA is a potent inhibitor of histone deacetylases(HDAc). It can modify the structure of chromatin allowing recruitment of transcription factors to restore epigenetically suppressed genes. VPA has been shown to posses antiproliferative activity and to overcome the differentiation block in leukemia blast cells [78]. Some clinical trials with VPA monotherapy or in combination with ATRA have been reported in MDS. In a piloty study of Kuendgen and colleagues [79- 81],patients with MDS or AML secondary to MDS were treated with VPA monotherapy or with ATRA later resulting in a 44% of response rate. In the follow-up study of 43 patients, an even higher response rate of 52% was observed in those low-risk MDS patients,while for the patients with excess blasts(RAEB) and CMML response rates were 6% and 0% respectively,which implicate the difference of MDS subtypes.In another trials, Siitonen etal [82] reported that according to IWG criteria,3 patients(16%) of 19 MDS responded to treatment following VPA,13-cis RA and 1,25(OH)2D3 combination. All the responses were hematological improvement. One patient responded to the treatment with an increase in platelet value from 67x109/l to 105x109/l. His peripheral blood and bone marrow blast cells decreased from 4% to 0% and from 19% to 7%,respectively. Furthermore, the disease remained stable in 11 patients but progressed in 5 during treatment. This is encouraging results.

A series of these studies are summaried in table 1. While some patients experienced improvement in peripheral blood counts,complete responses were reported in only a small proportion of these studies [83-85]. The sole exception was a patient who presented with 29% marrow blasts and 90% abnormal metaphases with 13-cis RA.He obtained a complete clinical and cytogenetic remission therapy.This clinical response to 13-cis RA drug was due to in vivo growth inhibition of malignant monocytoid clone [93]. Continued follow-up of this study in this field will be of interest.

Table 1. Results of retinoic acid therapy in MDS

Number of patients	Drug protocol	Dose Schedule	Response	Median Survival	Authors
15	13-cis retinoic acid (13-CRA)	20-125mg/m2 day	5PR		Gold etal(1983)[86]
18	13-CRA	1-2mg/kg twice a day	2PR		Greenberg etal(1985)[87]
15	13-CRA	2.5-4mg/kg	5PR		Picozzi etal(1986)[88]
24	13-CRA	100mg/m2/day	2CR/5PR		Besa etal(1985)[89]
66	21:13-CRA alone		1CR,3PR(20%)		Besa etal(1990)[90
	45:13-CRA+α-tocopherol		1CR,10PR(26%)		
24	13-CRA+α-tocopherol	100mg/m2/day	1CR/6PR(34.8%)	34months	Besa etal(1998)[91]
1	13-CRA		1CR		Abrahm etal(1986) [93]
14	13-CRA,LDARAc	13-CRA:60mg/m2/day	1PR,1MR		Ho etal(1987)[94]
15	ATRA alone	30-90mg/m2/day	3MR		Aul etal(1993)[95]
18	ATRA,G-CSF		8responses		Maurer etal(1995)[71]
22(HRMDS)	ATRA+LDARAc	ATRA:45mg/m2/day LDARAc:20mg,twice/day	5CR(23%),2PR(9%)	16monthsh (8-27months)	Venditt(2000) [76]
30	9-CRA alone	6mg/m2-140mg/m2/day	1CR,4MR(20%)		Hofmann etal(2000)[96]
18	VPA monotherapy		1CR,8responders(44%)	4months	Kuendgen(2004)[79]
	VPA+ATRA from start	ATRA:80mg/m2/day	only 1 response with sAML/MDS		
	VPA,ATRA added later		2/5 response after VPA replapsing		
60	VPA+ATRA		1CR,1PR,22SD (RA36%,RARS39%,RAEB5%,RAEBt11%, CMML0%,Overall IWG response:22%)		Kuendgen(2006)[82]
19	VPA,13-CRA,1,25(OH)2D3		3 response(16%)		Siitonen etal(2007)[82]
59(LDMDS)	ATRA+EPO		erythroid response 49%(IWG2000),36%(IWG2006)		Itzykson(2009)[72]
63	13-CRA,EPO,1,25(OH)2D3		erythroid response 60%(IWG2006 criteria)		
(excluding RAEB2)			55months for non-RAEB	14months for RAEB1	Ferrero(2009)[73]
34	13-CRA	10-60mg/m2/day	4PR(11.7%)	1-5years	Bouranta(2010)[97]

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Retinoic acids in skin disease

Vitamin A is necessary for normal epithelial cell differentiation and maturation [10,98-101]. Retinoids influence on skin keratocyte proliferation,epidermal differentiation and kerintinisation. Those retinoids including natural and chemically synthesized vitamin A derivatives are common used as systemic and topical treatment of various skin disorders. At present there have well developed three generations:the naturally occurring retinoids (all-trans retinol,Aretinoin,Isotretinoin,Alitretinoin),the monoaromatic retinoid derivatives (Acitretin,etretinate) and the polyaromatic retinoid derivatives (Bexarotene, topical tazarotene)[102].

Isotretinoin is an orally active retinoic acid derivative for the treatment of acne (papulo-pustular,nodulo-cystic,conglobata) [103],since it shows an excellent efficacy against severe refractory nodulocystic acne. Peck's [104,105] original observation in 1978-79 of the effectives of 13-cis RA in cystic acne has been well supported. In double-blind studies using small doses of 13-cis RA regimen, Farrell [106] in 15 patients,Jones [107] in 76 patients,Plewig [108,109] in 79 patients and Rapini [110] 150 patients reporting have confirmed this results. A summary study of limited review on 365 affected persons are presented in table 3. The drug action involves an inhibition of sebum excretion rate(SER) in sebaceous glands and production rate of free fatty acids[105,106,109,111- 116] through trigerring NGAL(neutrophil gelatinase-associated lipocalin) expression [26],normalise follicular keratinisation [117] and the decrease in colonisation of propionibacterium acnes and associated inflammation in skin surface microflora [118,119].This response,mediated by toll-like-receptor 2(TLR2),is increased in acne patients due to high expression of TLR2 [120].

Encouraging results have also been used 13-cis RA in small numbers of patients with rosacea,Gram-negative folliculitis,Darier's disease,ichthyosis and pityriasis rubra pilaris [104,121-123]. In the treatment of rosacea, isotretinoins led to a significant reduction of erythemia,papules,and pustules in several studies [122,124]. During treatment of rosacea,13-cis RA act as a potent anti-inflammatory and sebum-suppressive agent. Long-lasting remission can be reported for first patient over 12 months [121].The use of low dose isotretinoin(0.15-0.3mg/kg bw daily) showef high efficacy and was well tolerated. Isotretinoin is only partially effective in psoriasis,in contrast etretinate which is effective in psoriasis but ineffective in severe acne. Promising,some trials have reported with isotretinoin in patients with squamous and basal cell carcinomas [125,126],cutaneous T-cell lymphoma[99],recurrent malignant glioma [127],malignant eccrine poroma [128],and keratoacanthomas [129,130],and xeroderma pigmentosum with squamous cell carcinoma [130]. In literature,there were at least 10 CR patients with squamous cell carcinoma(SCC). Skroza etal [125] reported a CR patient with well-differentialed SCC following the daily dosage of 0.5mg/kg/day for 5 months. Dring 1-year follow up,he remained all in normal range. Using combination chemotherapy and isotretinoin for 4 months,Zaman [131] reported a complete clinical remission of tumors in a case of 15 year old female of xeroderma pigmentosum with SCC. Another collection of four SCC of skin obtained CR through isotretinoin at daily dose of 1mg/kg/day twice a day for 4 months(see figure 4) [100]. The mechanism may involve the modification of epidermal growth factor receptor(EGFR) and certain protein kinase. At present, It has clearly known the results that amplified(50-fold EGF receptor in SCC relative to normal skin keratinocytes) or mutant EGFR is oncogenic in origin of some SCC [132,133]. This oncogenic receptor EGFRvIII has also been found in malignant glioma and invasive breast carcinoma [132-137]. Zhu [136,137] conduct a short CR using chemotherapy and topical 5% Fu of retinoic acid ointment in a 75-year old patient with SCC. She had a 8x5cm rodent ulcer in her left ear and facial area. A shrinkage of irregular and harden marginal valgus converted to flat,and superficial red and scar noted after one month treatment. These findings suggest that retinoids may be effective and well-tolerated therapy for advanced epidermoid SCCs in some studies.

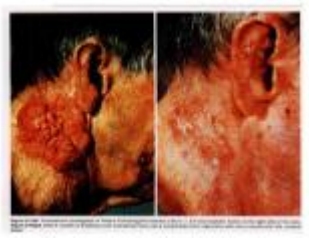


Figure 4. An advanced squamous cell carcinoma of skin before(left) and after(right) isotretinoin(Figure from Lippman etal,Ann Intern Med,1987,107:499-502)[100]

Table 2. Results of 13-cis RA in severe acne treatment

Number of patients	Dose of 13-cis RA	A Dose-Response	Authors
14	2.0mg/kg/day	13/14 CR,complete clearing 1/14 with 75% improvement	Peck etal(1979)[105]
14	0.1-1.0mg/kg/day	100%	Farrell etal(1980)[106]
76	0.5mg/kg bw	90%,66% long remission during follow up	Jones etal(1983)
40	40mg/day	77.5% CR,9 cases with improvement	Gansdola etal(1984)[138]
56	1mg/kg/day	facial lesion marked improvement	Goldstein etal(1982)[111]
10		70%	Leyden etal(1982)[139]
48		all improvement	Prendiville etal(1988)[112]
87	1.0mg/kgx3days,later 0.2mg/kg/day	96%	Hennes etal(1984)[140]
5	0.9mg/kgx6wk,then 0.3-0.6mg/kgx9months	100%	Pigatto etal(1983)[141]
15	40mg/day	100%	Ott etal(1982)[142]

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 [143]. 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) [144,145],RARB consists of 455aa [146] and RARG contains 454aa [147],respectively. The RAR is a type of nuclear receptor which act 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 [144,145];the RARβ in a variety of epithelial cells [146];and the RARr in differentiation of squamous epithelia and human skin tissue [147,148].

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) [20,143,149].The central DNA binding domain(88-153aa) exhibits an array of cysteine residues compatible with the formation of two so-called zinc finger(Miller,1985),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 [see figure 5,Zinc finger 1, 88-108aa,Zinc finger 2,124-148aa,143-149].The N-terminal zinc finger of the DNA binding domain confers hormone responsiveness to HREs,determing target gene specificity,and responsible for functional discrimination between HREs whereas the C-terminal finger contains the sugar-phosphamide backbone of the flanking sequences [149,150]

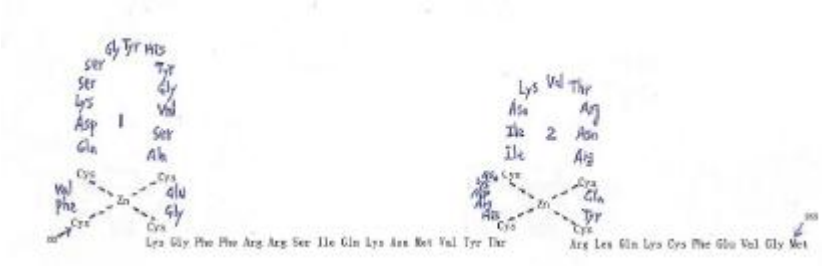


Figure 5. Amino acid sequence of the DNA binding domain of the hRARa into two putative zinc–binding finger (Figure from George Zhu a feeling for scientific drawing based on Evans RM,Science,1988,240:899-895; Beato M,Cell,1989, 56: 335-344; Giguere V,Nature,1987;330:624-29; Petkovich M, Nature, 1987,330: 444-450)

The molecular basis of retinoic acid action and the RAR gene transcription

Retinoic acid(RA) is a lipophilic signal molecule which is able to induce acute and direct activation of the expression of specific genes supports its molecular model of action that resembles that of steroid hormones [151,152]. The cellular retinoic acid-binding protein (CRABP) may be involved in this transfer [36,37]. In the nucleus,RA receptors (RAR) function as a heterodimer with retinoid X receptors(RXRs) [153-157]. RAR/RXR can bind to DNA motif at RA-response elements (RAREs,also HRE) in the regulatory sequences of target genes in the absence of ligand, thereby interacting with multiple protein complexes that include co-repressors N-CoR [158],SMRT [159] and histone deacetylases (HDACs), and maintaining gene repression. Here,RAREs consist of a direct repeat of a core hexameric sequence 5' (A/G)G(G/T)TCA-3' [160] or of the more relaxed 5'-(A/G)G(G/T) (G/T)(G/C)A-3' motif,separated by 1,2,5 bp [161]. A corepressor represses expression of genes by binding to and activating a repressor transcription factor,the repressor in turn bind to target gene's operator including RARE sequence,then blocking transcription of that gene(see corepressor-wikipedia).Transcriptional regulation thus drives from the binding of hormone-receptor complexes to RARE sites on target DNA [20,143,149]. In the presence of RA(all-trans RA,9-cis RA),binding of the RA ligand to RAR alter the conformation of the RAR,a conformational change in the DNA-bound receptor leads to the release of co-repressor complexes associated with the RAR/RXR dimer and the recruitment of co-acitivator complexes. These induce chromatin remodeling and facilitate assembly of the transcription pre-initiation complex including RNA polymerase II(Pol II) [162],TATA-binding protein(TBP) and TBP-associated factors(TAFs) [12,20,143,149,153, 163,164,See figure 6]. Subsequently,transcription of target genes is initiated. This also represent ligand-dependent transcriptional activation which mediated by nuclear receptors. Like thyroid hormone receptor(THR) [165,167], retinoic acid act as ligand for RARs,converting RARa from transcriptional repressor to activators [12,20,168-173]. Numerous RAR target genes after RA induction have been identified including genes within retinoid pathway,such as RARB,Crbp1/2 (Rbp1/2),Crabp1/2 and CYP26a1.And also,several members of HOX gene family, including HOXa1,HOXb1,HOXb4 and HOXd4,and other genes Tshz1 and Cdx1 [174-175],the function of which has been demonstrated in vivo in the normal roles of retinoids in patterning vertebrate embryogenesis,early neurogenesis,cell growth and differentiation.

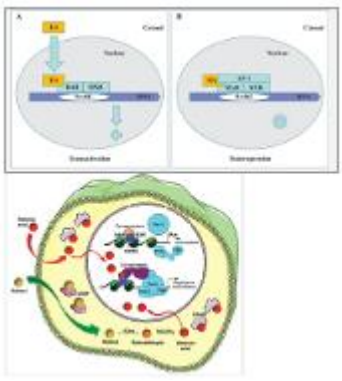
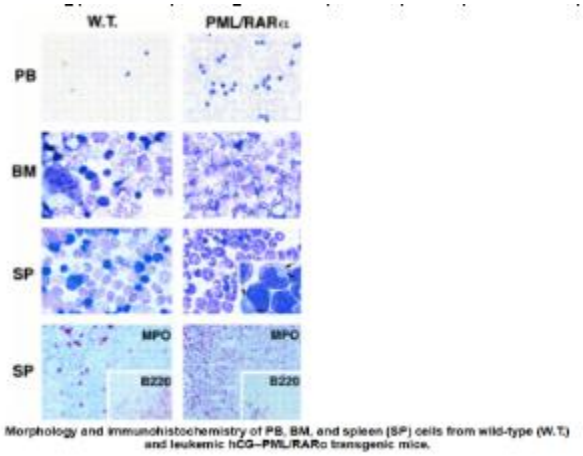


Figure 6. At top figure: Retinoid receptor-dependent gene regulation (Figure from Bechenbach L etal,Eur J Dermatol,2015,25(5):384-91)[165]; At bottom figure:Gene regulation by retinoic acid signaling (Figure from Rhinn & Dolle,Development,2012, 139(5):843-58)[164]

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 [176]. 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 [20,177-180]. In addition to oncogenic receptor derivative pml/RARa [20,156, 181-184],the translocation involves oncogenic TBL1XR1-RARB [185],and NUP98/RARG [186,187],and oncogenic PML-RARG [188] which share high homolog(90%) of three RAR family were also detected in APL rare cases.

Most studies have shown that PML-RARA is an oncogenic transcription factor forming in APL [185]. 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 [20,156,189]. 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 [190]. Similarly,overexpression 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) [191]. Moreover,mutation of the N-CoR binding site abolishes the ability of PML-RARa to block differentiation [192,193]. Therefore,ectopic expression of RAR fusion protein in hematopoietic precursor cells blocks their ability to undergo terminal differentiation via recruiting nuclear corepressor N-CoR/histone deactylase complex and histone methyltransferase SUV39H1 [194]. In vivo,transgenic mice expressing PML-RARA fusion can disrupt normal hematopoiesis,give sufficient time,develop acute leukemia with a differentiation block at the promyelocytic stage that closely mimics human APL(APL-like syndrome,see figure 7) even in its response to RA in many studies.These results are conclusive in vivo evidence that PML/RARa is etiology of APL pathogenesis [195-202].



Morphology and immunohistochemistry of PB, BM, and spleen (SP) cells from wild-type (W.T.) and leukemic hCG–PML/RARα transgenic mice.

Figure 7 shows pml/RARa fusion in differentiation block at promyelocytic stage in transgenic mice(Figure from He LZ,etal,Proc Natl Acad Sci USA,1997,94:5302-07)[196]

Structure and function analysis of pml/RARA uncovered that RAR compent of the fusion protein is indispensable for its ability to impair terminal differentiation,and resolved the pml/RARa as constitutive repressor in differentiation block [20,156,194,203-217]. 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 [178]. Many other two groups have 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 15-30ug of PML-RARa fusion in culture show no features of granulocytic diffetentiation after 7 days of incubation with 10-7,10-6 M RA(5.5-9.5% of differentiated cells by the NBT test). At 5ug 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) [See figure 8 ,Rousselot,1994,203].The results clearly indicate that PML-RARa mediated transcriptional repression, as well as PML-RARa oncoprotein blocks RA-mediate promyelocyte differentiation.

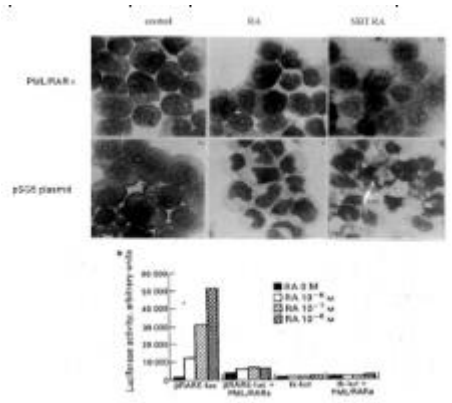


Figure 8. Expression of pml-RARa in HL-60 cells blocks ATRA-induced promyelocytic differentiation(in the presence of 10-7 M RA,top),and transcriptional repressive properties of pml-RARa in human myeloid cells as βRARE-luc assay(bottom)(Figure from Rousselot P,Oncogene,1994,9:545-551)[203]

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 results shown in Figure 9 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 [189].

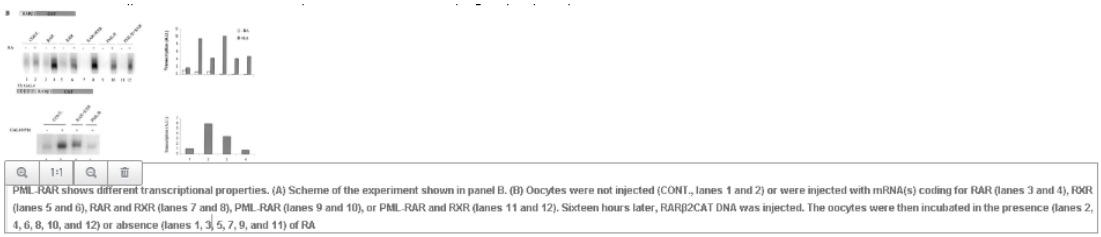
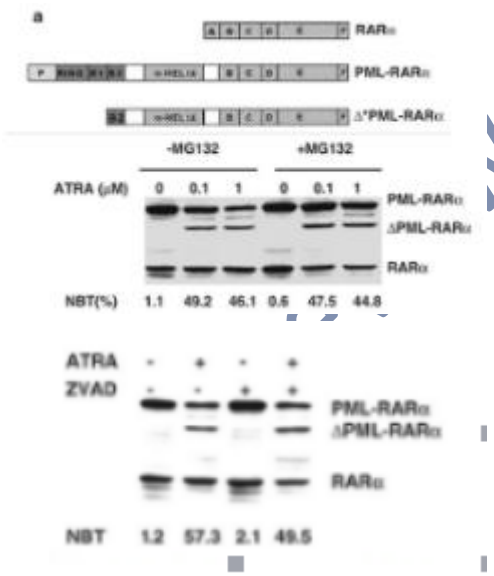


Figure 9 shows pml/RARa as a constitutive transcriptional repressor in *xenopus oocyte system*,as measured by RARE3 CAT and GAL4 assay(Figure from Segalla,Mol Cell Biol,2003,23:8795-808)[189]

Moreover,ATRA treatment overcomes the differentiation block through dissociation of corepressor complexes from pml/RARa and transcription activation,thereby induces pml-RARA degradation. 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 [218-221,see figure 10]. Delta PML-RARa is not formed in ATRA differentiation resistant NB4 subclones [218,221],which indicate the loss of PML/RARa may be directly linked to ATRA-induced differentiation [218,221].This induction of of PML-RARa cleavage and degradation by RA(ATRA,9-cis RA,Am80) involve the proteasome-dependent [218-220] and caspase mediated pathway [222],or independent of proteasome and caspase cleavage[221],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 diffetentiation whereas this delta pml-RARA is blocked by RARA itself antagonist Ro-41-5253 [221].The proteasome-dependent pml/RARA degradation,by using proteasome inhibitor lactacystin test,allows APL cells to differentiation by relieving the differentiation block [219]. These data suggest a set of multiple molecular mechanisms for restoration by RA induced myeloid differentiation in APL cells.



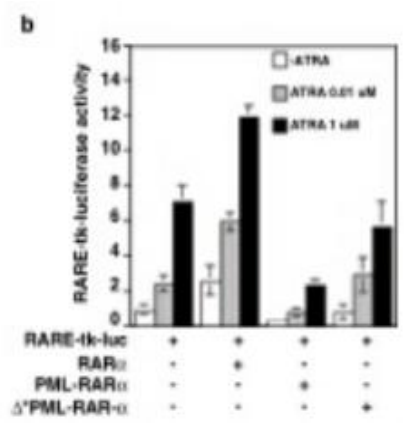


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Figure 10 shows delta pml/RARa cleavage products independent of proteasome and caspase in the presence of ATRA(a,b),and pml/RARa act as transcriptional repressor even in the presence of ATRA(0.01uM,0.1uM) in RARE-tu-luc assay while delta pml/ RARa 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)[221]

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 vitD3 and TGF-induced the myeloid precursor U937and TF-1 cell differentiation [192]. This is also supported by functional analysis of DNA binding domain 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 [192]. The coiled-coil region directs the formation of pml/RARa homodimers tightly interact with the N-CoR/HDACs complex,so that transcriptional de-regulation can not occur at RARA target gene promoter even if the presence of ATRA [RA resistant,20,215]. In the resistant cases,mut PML stabilizes PML-RARa [223]. 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 open chromatin state [211]. TSA proved useful in therapeutic targeting of transcription in two APL patients [224,225].These results have clearly shown that PML protein dimerization and RARa DNA binding domain is indispensible for the myeloid precursors differentiation block by PML/RARA,and eventually leukemic transformation.

In accordance,the pml/RARa/RXR target genes is though to block differentiation by consitutively silencing a set of RA-responsive genes in the control of hematopoietic precursor cells. These include Jun/Fos/Ap-1,C/EBPa,C/EBPepsilon, DAPK2/PU.1, myeloblastin,HOXA7,HOXA9,HOXA10,MEIST,XIST,HCK,SAP30,p21WAF/CCKN1A[176,204,226-229). Five major transcription factors,Ap-1 [204],C/EBPepsilon[226,227], Pu.1/DAPK2 [228],PTEN [229],and p21WAF/CCKN1A [230],directly regulate genes important in myeloid differentiation,such as G-CSFR,CD11b,Myeloperoxidase, 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.

In vitro cotransfection of pml/RARA with plasmid expressing AP-1 of c-Jun and c-fos proteins in MCF-7 cells,by using CAT assay,PML-RARa is a repressor of AP-1 transcriptional activity in the absence of RA while RA treatment converted the chimera into a strong activator [204]. Since high AP-1 activity is associated with differentiation of leukemic cells in several context [204],the stimulatory effects in the presence of RA could be relevance to its reversal by provoking differentiation. Another,in pml/RARa-containing cell lines,a close link exists between induction of differentiation and induction of C/EBP epsilon expression[226]. C/EBPepsilon knockout mice had a block in myeloid differentiation[227]. In absence of retinoic acid(RA),induction of pml/RARa expression in U937PR9 cells stably transfected with zinc-inducible pml/RARa suppressed the expression of C/EBPepsilon, whereas,in the presence of a pharmacologic concentration of

RA,pml/RARa significantly increased the level of C/EBPepsilon expression in a time and dose-dependent manner [226].The findings implicate that C/EBPepsilon is critical downstream target gene in RA-dependent granulocytic differentiation in the treatment of APL.

Phosphotase and Tensin homolog (PTEN) is a protein and lipid phosphatase,which plays a pivotal dual role in tumor suppression and self-renewal of hematopoietic stem cells as its promoting exhaustion of normal hematopoietic stem cells(HSCs),and generation of leukemia-initiating cells(LICs) [231-233]. PTEN expression is downregulated in APL,while ATRA treatment increases PTEN leves by inducing PU.1 transcriptional activity via pml/RARa degradation,allowing the binding of PU.1 in PTEN promoter, in turn promotes PTEN nuclear re-location and decreases expression of the PTEN target Aurora A kinases. Therefore, PTEN is one of the primary target gene of pml/RARa in APL [229].

Importantly,restoring DAPK2 expression in PU.1 knockdown APL cells partially rescued neutrophil differentiation [226,234]. 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 [235]. DAPK phosphorylates beclin 1 on Thr 119 located at a crucial position within its BH3 domain,and thus promotes the dissociation of beclin 1 from BCL-XL inhibitor and induction of autophagy [235]. Here,beclin 1 was initially identified as a BCL-2-binding protein,which is part of a class III PI3K(phosphatidylinositol -3-kinase) multiprotein complex that participate in autophagosome nucleation.Death- associated protein kinase(DAPK1) is a calcium/calmodulin(CaM) serine/threonine kinase for mediator of cell death [236]. 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 [237]. Thus,pml/RARa represses PAPK2/PU.1 - mediated transcription of myeloid genes in APL,linking a novel autophagy mechanism of pml/RARA degradation [238].

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(237,214). Based on review more researches publications [38-68,144-239], the detail mechanism has also been described by Zhu [20,240,241].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 coactivators, including histone acetylases. Consequentially,RA treatment leads to transcriptional activation,thereby trigger expression of genes involved in myeloid differentiation[12,20, 167,209,215,233]. 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[20,156,194,203-217,226,228-230] through tightly binding with the corepressor complexes,and 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[160]. High dose of RA-RARE-PML/RARa complexes in intracellular localization appears to relieve repressors from DNA-bound receptor[20,166,192,206],including the dissociation of corepressor complexes N-CoR,SMRT and HDACs from PML-RARa or PML-RARa/RXR[20,192-194,206,215,228], also release PML/RARa -mediated transcription repression[212].This transcriptional derepression occurs at RARa target gene promoter[20,209,215]. Consquentially,PML-RARa chimera converted receptor from a repressor to a RA-dependent activator of transcription[189,204,210,215,221].The resulting pml-RARA oncoprotein proteolytic degradation through the autophagy-lysosome pathway[238] and the ubiquitin SUMO-proteasome system(UPS)[218-221] as well as caspase 3[222],or lysosomal protease(cathepsin D) enzyme or/and E1-like ubiquitin-activating enzyme(UBEIL) induction[207]. An effect to relieve the blockade of pml/RARa-mediated RA dependent promyelocytic differentiation,and retinoic acid(9-cid RA,ATRA,Am80) in APL therapy[20,203,209-214,216,217](See figure 11, Zhu,September 1990- January 1991,revised in 2012). Here,RA can overcome the transcrptional repressor activity of pml/RARa[20,156,194,203-217,228-230].The oncogenic pml/RARa uncover a pathogenic role in leukemogenesis of APL through blocking promyelocytic differentiation;and this oncogenic receptor derivative pml/RARa chimera is locked in their "off" regular mode thereby constitutively repressing transcription of target genes(such as AP-1,PTEN,DAPK2,UP.1,p21WAF/CCKN1A)[204,228-230] or key enzymes(such as myeloblastin/proteinase-3, Aurora A kinase) [242-244] that are critical for differentiation of hematopoietic cells. This is first described in eukaryotes.

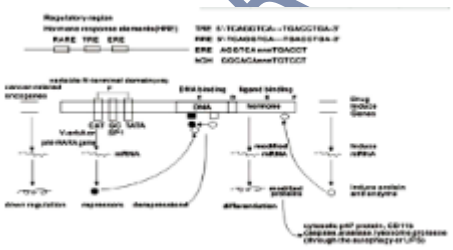

Figure 11. Molecular model of the gene regulation of retinoic acid (RA) action (George Zhu,January 1991,revised in 2012). Schematic aliganament of the receptor protein. The two highly conserved regions,identified as the putative DNA-binding (C) and hormone- binding (E), a hinge region (D) and the non-conserved variable NH2-terminus (A/B) as described above. CAT:CAAT box,CCAAT-enhancer binding proteins(or C/EBPs); GC:GC box; TATA:TATA box.(Figure from Zhu G, Curr Pharm Biotechnol,2013, 41(9):849-858) [20,241]

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