

MOLECULAR MECHANISMS OF CHEMOPREVENTION AND THERAPY OF CANCER BY RETINOIDS

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1. ABSTRACT

Chemoprevention is the use of noncytotoxic therapeutic intervention at the early stages of carcinogenesis against the development and progression of mutant clones to invasive cancer. Retinoids are the most extensively studied and one of the most prominent groups of chemopreventive agents to reach clinical trials. Acute promyelocytic leukemia is the first human malignancy that is successfully treated with all-trans retinoic acid. The t(15;17)(q22;q21) gene rearrangement and PML/RAR[alpha] fusion product in acute promyelocytic leukemia played the key role to leukemogenesis and to sensitivity to differentiation-inducing therapy of all-trans retinoic acid. This review focuses on retinoid-based chemoprevention and therapy of cancer, and use acute promyelocytic leukemia as a model to illustrate the molecular mechanisms of retinoid signaling pathway.

2. INTRODUCTION

"To win without fighting is best." - Sun Tze, Warring States Period of Ancient China - "Plan for what is difficult while it is easy, do what is great while it is small. The most difficult things in the world must be done while they are still easy. The greatest things in the world must be done while they are still small. For this reason, sages never do what is great, and this is why they can achieve that greatness." -Sun Tze- As stated in "The Art of War by Sun Tze," one of the greatest Chinese classical texts for 2500 years and is still perhaps the most prestigious and influential book of strategy in the world today (1), we can applying Master Sun's principles of military strategies to today's modern medicine, and it is obvious that to prevent a cancer occurring or to intervene in the precancerous stage is by far superior to treat a well-established or metastatic malignancy. Carcinogenesis is a multistage process of aberrance of growth, differentiation, and development. Chemoprevention is an attempt to interventions with natural and synthetic vitamins, minerals, chemicals, or pharmaceuticals at any of the multiple stages of carcinogenesis to reduce cancer incidence and mortality

both in well-defined high-risk groups as well as in the general population (2-6).

Chemoprevention is a relatively new and an emerging arena in clinical oncology. The most well known examples are, to name a few, people with diets low in animal fat and high in vegetables and fruits with rich sources of fiber, vitamin A, C, D, and E, have lower risk for many types of cancers; simply apply of sunscreens and avoid the midday sun can dramatically reducing the incidence of skin cancer; cease cigarette smoking, and eradicate the use of tobacco products can bring down the morbidity of lung cancer by an estimated 87% (5). Although it is well established that many natural and synthetic agents can prevent or halt carcinogenesis in experimental animal models both *in vivo* and *in vitro*, the number of substances with proven effectiveness in large-scale clinical trials are very limited (5, 6).

Many noncytotoxic chemopreventive agents are under clinical trials for the effectiveness of reduction in cancer incidence and mortality (6). Of the list, retinoids are the most extensively studied group of pharmacologic agents in cancer prevention and therapy (7). This review focuses on retinoid (a broad differentiation factor)-based cancer prevention and therapy. By using acute promyelocytic leukemia (APL), the first human leukemia that can be cured with retinoid maturation therapy, as a model to illustrate the pathogenesis of APL, and the explosion in discovery of molecular mechanisms underlying the biological and clinical behavior of APL is related to the important roles of coactivators and corepressors played in retinoid signaling pathway (8-12).

3. VITAMIN A, RETINOIDS AND RETINOID NUCLEAR RECEPTORS

Vitamin A (retinal) is a fat-soluble, solid terpene alcohol micronutrient that is not synthesized by human beings and must be ingested in the diet. Retinoids are a group of natural and synthetic analogues of vitamin A (7).

The structures and interconversion between naturally occurring vitamin A and commonly used retinoic acids for chemoprevention are shown in Figure 1. Vitamin A and its derivatives retinoids are modulators of cell growth, differentiation, and programmed cell death. They are essential for embryonic development, vision, hematopoiesis, bone formation, metabolism, reproduction, differentiation, maintenance of normal mucosal epithelial, induction of apoptosis (programmed cell death), and inhibition of angiogenesis (7, 14). Deficiency leads to atrophy of epithelial tissue resulting in keratomalacia, xerophthalmia, night blindness, and lessened resistance to infection of mucous membranes. In contrast, overdose and hypervitaminosis A may cause irritability, fatigue, lethargy, abdominal discomfort, painful joints, severe throbbing headache, insomnia, loss of hair, and exophthalmus.

Retinol is oxidized to retinoic acids (RA) in hematopoietic cells and isomerases can interconvert trans, 9-cis, or 13-cis-RA. Retinoids lack appreciable solubility in water and must be bound to intracellular lipid-binding proteins [termed cellular retinol-binding protein (CRBP) or cellular retinoic acid-binding protein I and II (CRABP-I and -II)] for them to be present within the cell (7). Retinoid signaling pathway includes cytoplasmic and nuclear retinoid receptors. The cytosolic retinoid receptors serve as intracellular retinoid storage sites; they can bind retinoids but not DNA. There are two families of six bona fide nuclear retinoid receptors encoded by six genes. Three retinoic acid receptors (RARs) are RAR[alpha], RAR[beta], and RAR[gamma]; three retinoic X receptors (RXRs) are RXR[alpha], RXR[beta], and RXR[gamma]. RXRs were known as orphan receptors until 9-cis-retinoic acid (9CRA) was found as a physiological ligand. Multiple RAR and RXR isoforms exist through differential splicing and multiple promoters (7, 15, 16). The RARs are the major vitamin A signal transducers and the RXRs function as enhancers of retinoid signals. Activation of the heterodimer is controlled by the RARs, and RARs require RXRs for efficient DNA binding and transactivation. All-trans retinoic acid (ATRA) can bind only to RARs, while 9CRA can bind to both RARs and RXRs (15). RARs can heterodimerize with RXRs, while RXRs can heterodimerize with other nonsteroid nuclear receptors, including the thyroid hormone receptor, the vitamin D receptor, the peroxisome proliferator-activated receptor, and nerve growth factor induced-B (NGFI-B) (15, 16).

Only the RAR-RXR heterodimers bind effectively to their specific genomic DNA recognition sequences known as retinoic acid response elements (RAREs) (16-18). RAREs are generally arranged as direct repeat that are characterized by two half sites with the consensus sequence AGGTCA separated by one to five nucleotides (15, 16). RAR bound RARE in the 3' and RXR in the 5' position. Plasma concentration of naturally occurring ATRA is $\sim 10^{-8}$ M and the physiologic intracellular concentration of ATRA is $\sim 10^{-9}$ M. The retinoids function in cells through interaction with nuclear receptor associated proteins called coactivators and corepressors to regulate transcription of target genes (7, 12,

15, 18-22). With the exception of some of the steroid receptors, DNA binding of most of the nuclear receptors is ligand independent (15). The nuclear receptors play an important role in mediate activation or repression of transcription by interacting with coactivators, corepressors, and basal transcriptional factors (20). RARs can have dual function roles operating as transcriptional repressors in the absence of the ligand (ATRA) and as transcriptional activators in the presence of the ligand (15, 19, 20).

4. PML/RAR[alpha] FUSION PROTEINS AND PATHOGENESIS OF ACUTE PROMYELOCYTIC LEUKEMIA

Acute promyelocytic leukemia (APL), a specific subset of acute myeloid leukemia (AML), is characterized by selected clonal expansion of malignant myeloid precursors in the bone marrow and blood at the promyelocyte stage of myeloid hematopoiesis (8). According to the FAB classification, APL is classified as AML-M3, and by using the WHO classification, APL is AML with recurrent cytogenetic translocation t(15;17) and t(V;17)(8-10). The typical leukemic promyelocytes are CD13+/CD33+/CD34- that containing numerous large red to purple cytoplasmic azulophilic granules and multiple Auer rods. Most patients with APL experience severe, life-threatening thrombotic or hemorrhagic manifestations related to disseminated intravascular coagulation prior to or during standard ATRA therapy (8-10). The hallmark of APL is the reciprocal and balanced translocations of t(15;17)(q22;q21): the chromosome 17q21 breakpoint is within the RAR[alpha] and the chromosome 15q22 breakpoint is within the promyelocytic leukemia (PML) gene in vast majority (99%) of cases (10). PML protein is transcriptional modulator and involved in growth suppression, differentiation, and immune response pathways. The hybrid gene resulting in the expression of a PML/RAR[alpha] fusion protein that is linked to leukemogenesis of APL in a dominant negative fashion on transcription at physiological levels of ATRA and hence blocked granulocyte differentiation at the promyelocyte stage (Figure 2).

In 1980, ATRA was reported to induce differentiation and maturation of an established AML cell line HL-60 (23). All-trans retinoic acid (ATRA) as a differentiation induction treatment regimen, administered to APL patients in the first clinical trial of retinoids in 1987, by Huang *et al.* in Shanghai, could successfully stimulating differentiation of the leukemic promyelocytes and induce long-term clinical remissions (24). APL is the first human cancer that is successfully treated with a differentiation agent direct at the causative oncogene. Advances in further refinement of standard therapies suggest that the majority of APL patients should now be cured. For example, Mandelli *et al.* reported a remarkable 95% complete remission (CR) rate with the ATRA and idarubicin (AIDA) regimen (25). A model for the molecular mechanisms of regulation of nuclear retinoid receptors functions and gene expression via transcriptional coactivator or corepressor complexes as the main leukemogenesis is

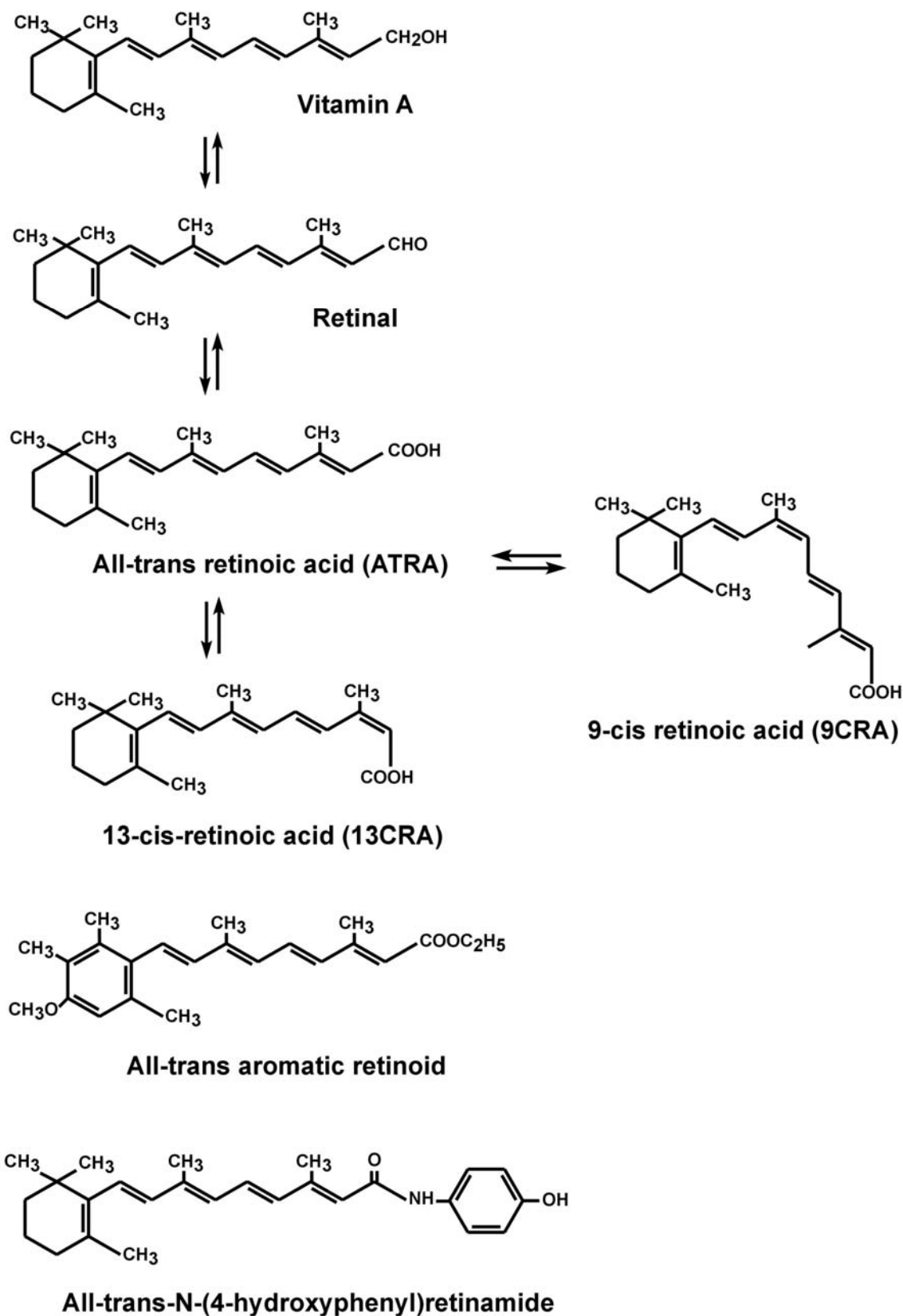


Figure 1. Structures of vitamin A (retinol), retinal, and major retinoic acids used in chemoprevention.

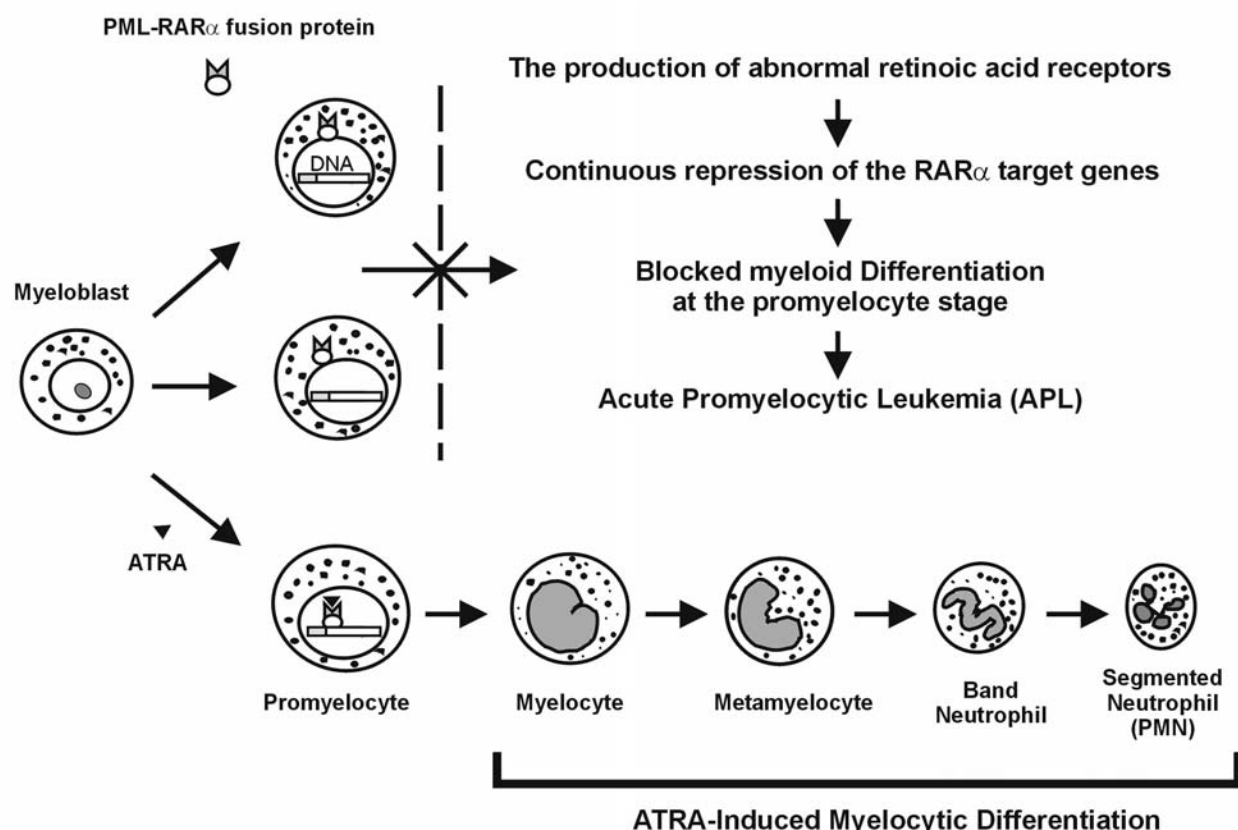


Figure 2. The pathogenesis of acute promyelocytic leukemia (APL; FAB-M3) and the responses of APL cells to ATRA-induced differentiation therapy. (Top rows): The leukemic promyelocyte with the t(15;17)(q22;q21) chromosomal translocation and the resulting PML/RAR[α] fusion gene is a unique tumor biomarker that is the hallmark of APL. The fusion protein of PML/RAR[α] hybrid gene loses part of RAR[α] transactivation domain and interferes with ATRA function. The PML/RAR[α] promyelocytes are unresponsive to the physiologic concentration of ATRA and unable to bind to ligands. The blocked granulocytic differentiation causing arrested maturation of promyelocytes. (Bottom row): A specific treatment regimen using high doses that are 1,000-fold higher than the physiologic concentration of ATRA may “outcompete” the abnormal RA receptors, with a restoration of the normal granulocytic differentiation pathway and induction of terminal maturation of granulocytes.

schematically shown in Figure 3. Chromatin remodeling is an important determinant of gene expression. In general, histone deacetylation of DNA induces a closed-chromatin configuration and repressing transcription; histone acetylation of DNA relaxes chromatin and activating transcription (15). The mechanism of action of the retinoid signaling pathway is mediated by the RXR/RAR[α] heterodimers that are transcription regulators and bind effectively to specific DNA recognition sequences in the gene promoters named retinoic acid response elements (RAREs). In APL cell, the aberrant PML/RAR[α] fusion protein and its heterodimerization partner RXR binds to RAREs, recruits and interacts with mSin3a/HDAC1 with high affinity through nuclear receptor corepressors (N-CoR) and/or silencing mediator of retinoid and thyroid hormone receptor (SMRT). Two proteins N-CoR and SMRT interact with unliganded RAR but not with liganded receptor (15). The corepressor complex with histone deacetylase (HDAC1) activity is tightly bound that is unresponsive to the physiologic concentrations of retinoids. The result is the constitutive repression of

unliganded RAR-target genes and arrested myeloid differentiation at the promyelocyte stage (Figure 3a).

Treatment of APL patients with pharmacologic doses of ATRA can induce differentiation. ATRA binds to RAR portion of the heterodimer causes a conformational change in the RAR/RXR proteins, releases the HDAC corepressor complexes from RAR[α]/RXR dimers and facilitate binding of 9-cis RA to the RXR protein. The transcriptional coactivator complex cAMP-response element binding protein [CREB]-binding protein (CBP)/P300 in the core p/CAF (p300/CBP associated factor) with histone acetyltransferase (HAT) activity then provides link between nuclear receptors and the core machinery, to activate transcription/gene expression and induce terminal differentiation of granulocytes (Figure 3b) (11-13, 15-20). Recently, a specific inhibitor of the BCR-ABL tyrosine kinase named STI 571 (STI stands for signal transduction inhibitor) can achieve complete remission responses in the blast crisis of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) with the Philadelphia chromosome (Ph) (26). APL and ATRA

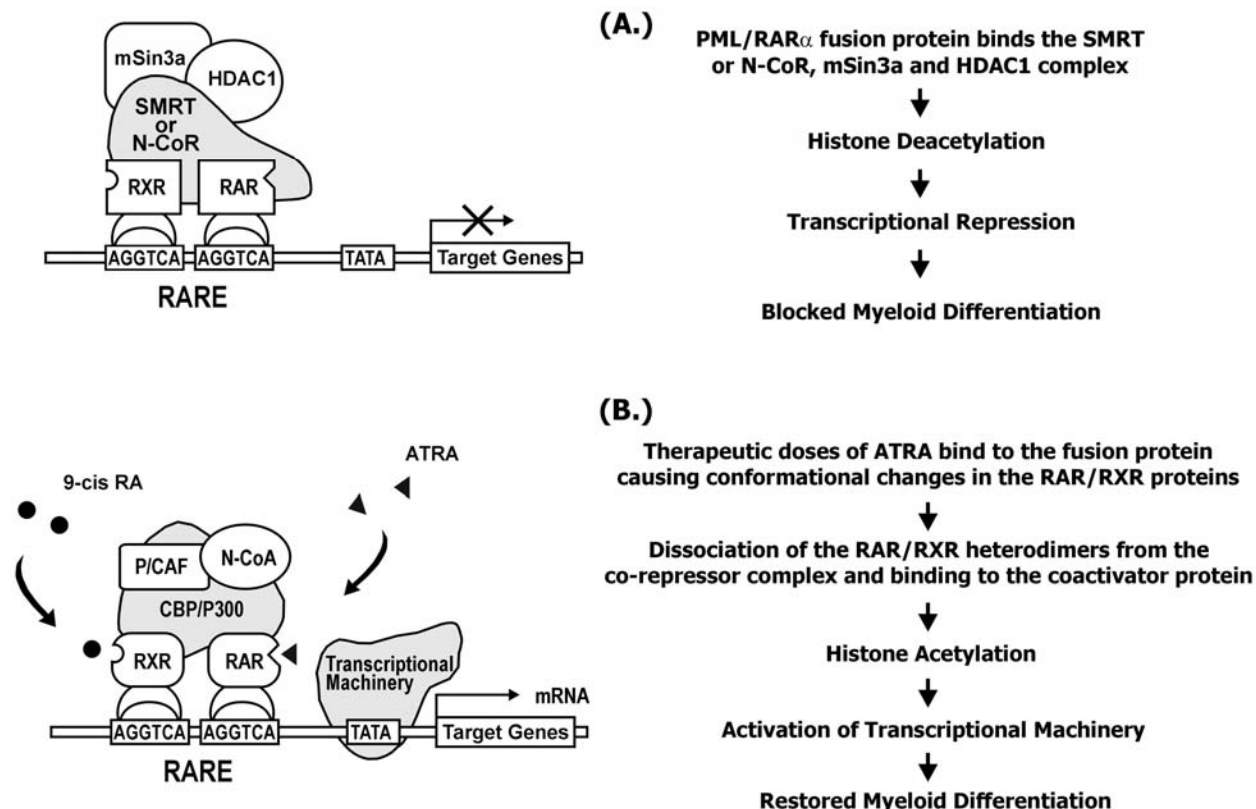


Figure 3. A model for the molecular mechanisms of regulation of nuclear retinoid receptors functions and gene expression via transcriptional coactivator or corepressor complexes. The mechanism of action of the retinoid-signaling pathway is mediated by the RXR-RAR[α] heterodimers that are transcription regulators and bind effectively to specific DNA recognition sequences in the gene promoters named retinoic acid response elements (RAREs). (3a): In APL cell, the aberrant PML/RAR[α] fusion protein and its heterodimerization partner RXR binds to RAREs, recruits and interacts with mSin3a/HDAC1 with high affinity through nuclear receptor corepressors (N-CoR) or/and silencing mediator of retinoid and thyroid hormone receptor (SMRT). The corepressor complex with histone deacetylase (HDAC1) activity is tightly bound that is unresponsive to the physiologic concentrations of retinoids. The result is the constitutive repression of unliganded RAR-target genes and arrested myeloid differentiation at the promyelocyte stage. (3b): Treatment of APL patients with pharmacologic doses of ATRA can induce differentiation. ATRA binds to RAR portion of the heterodimer causes a conformational change in the RAR/RXR proteins, releases the HDAC corepressor complexes from RAR[α]/RXR dimers and facilitates binding of 9-cis RA to the RXR protein. The transcriptional coactivator complex cAMP-response element binding protein [CREB]-binding protein (CBP)/P300/p/CAF (p300/CBP associated factor) with histone acetyltransferase (HAT) activity then provides link between nuclear receptors and the core machinery, to activate transcription/gene expression and induce terminal differentiation of granulocytes.

therapeutic regimen model clearly illustrated that by targeting the novel fusion proteins of leukemic specific translocations is the most safe and effective induction of differentiation and apoptosis in leukemic cells to achieve cure.

In addition to the classical APL with t(15;17)(q22;q21) chromosomal rearrangement of PML/RAR[α] fusion gene, four other APL-associated variable partner genes (X genes) of the RAR[α] gene have been reported. These t(V;15) are: (A). t(11;17)(q23;q21) with PLZF/RAR[α] fusion gene. (B). t(5;17)(q35;q21) with NPM/RAR[α] fusion gene, (C). t(11;17)(q13;q21) with NuMA/RAR[α] fusion gene, and (D). t(17;17)(q11;q21) with STAT 5b/RAR[α] fusion gene. These rearrangements of RAR[α] lead to

expression of PLZF (promyelocytic leukemia zinc finger)-, NPM (nucleophosmin)-, NuMA(nuclear matrix-mitotic apparatus)-, and STAT 5b (signal transducer and activator of transcription 5b) -RAR[α] fusion proteins (27, 28). The various RAR[α]-X and X-RAR[α] fusion proteins can interfere with X and/or RAR[α] function and play a critical and cooperative role in APL leukemogenesis (27-33). PLZF type APL is resistant (do not respond or respond poorly) to ATRA and was proposed to the name FAB-M3r. The PLZF leukemic promyelocytes have a regular nucleus and abundant cytoplasm with fine or coarse granules, Auer rods are occasionally seen. Few cases were natural killer (NK) cell marker CD56+ (29,32). The NPM protein is transcriptional modulator that involved in ribonucleoprotein (RNP) maturation and transport shuttle proteins between cytoplasm and nucleolus. NuMA protein

is major early target of apoptosis program for proteolysis by caspase-3 and caspase-6. STAT 5b protein is transcriptional activator implicated in hematopoietic and immune cell growth, proliferation, and function. The STAT 5b/RAR[alpha] fusion protein had a high affinity for the SMRT corepressor and only releasing it at high ATRA concentration of 10^{-6} M (29).

9CRA and ATRA inhibit activation-induced T cell receptor (TCR)/CD3-mediated apoptosis in thymocytes and T-cell hybridomas, but neither RA alone had any effect on the viability of those cells (34, 35). The apoptosis-inducing activity of ATRA and 9CRA is rather weak and may not be desired as effective apoptotic agents. However, synthetic retinoids, such as N-[4-hydroxyphenyl]-retinamide (4HPR or fenretinide) can function as potent inducer of apoptosis for cancer treatment (15, 36-39). Arsenic trioxide (As_2O_3), an ancient traditional Chinese medicine, triggers apoptosis and partial differentiation of APL cells in APL patients and APL models (40, 41). Combined arsenic and retinoic acid treatment enhances differentiation and apoptosis in arsenic-resistant NB-4 cells. Arsenic trioxide has proven to be an effective agent used in primary, refractory or relapsed patients after ATRA or chemotherapy or both (40-42).

Clinical ATRA resistance is defined as the inability to achieve or sustain complete hematological remission (CR) of APL on ATRA therapy. Nearly all cases of classical APL undergo CR with ATRA monotherapy and primary ATRA resistance is very rare. However, the development of secondary, acquired ATRA resistance is very common and many patients will develop relapse with disease (43, 44). Relapse of APL is often associated with acquired resistance to retinoid-induced differentiation while solid tumors develop intrinsic resistance to retinoids during carcinogenesis (43). Potential mechanisms of ATRA-resistance in APL include sequestration of retinoids by increased cytochrome p450 (a novel enzyme CYP26 is an RAR target and a mediator of ATRA metabolism autoregulation), induction of the cytoplasmic CRABP II, increased histone deacetylation, P-glycoprotein (Pgp)-mediated ATRA export, mutation of RAR in the RAR ligand-binding domain, persistent telomerase activity and nuclear disorganization, and alterations of coactivator or/and target gene expression (43-45).

5. CONCLUSION REMARKS

Molecular interactions between retinoid nuclear receptors and multiple coactivator and corepressor protein complexes in retinoid signal pathway serve as one of the most striking example of activation or repression of gene expression by specific t(15;17)(q22;q21) chromosomal translocation and molecular pathogenesis of APL. APL serves as a model disease for our understanding the molecular basis of cancer and help us to devise advanced therapeutic regimens in which the “cure matches the cause”(11). Substantial progress has been made in the last three decades to elucidate the molecular mechanisms of

carcinogenesis. Despite significant advances in modern cancer biology and therapy, cancer remains a leading cause of morbidity and mortality worldwide. There is an urgent need to develop a “genius” strategy in our battles with cancer. The strategy of use specific agents to suppress or reverse carcinogenesis and thereby to prevent the development of cancers certainly is toward the right direction. Master Sun Tze likens a successful force to water, which has no constant form but prevails over everything in spite of its apparent weakness. Master Sun says that: “A military force has no constant formation, water has no constant shape. The ability to gain victory by changing and adapting according to the opponent is called genius” (1). The utmost challenge for the future in chemoprevention and therapy of cancer, in author’ opinion, is to realize the “water-like” nature (as “liquid metal” character in the movies T2) of malignancy and counter-attack accordingly.

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Abbreviations: 9-cis-retinoic acid, 9CRA; acute myeloid leukemia, AML; all-trans retinoic acid, ATRA; acute promyelocytic leukemia, APL; cellular retinol-binding protein, CRBP; histone deacetylase, HDAC; nuclear corepressors, N-CoR; nuclear coactivator, N-CoA; promyelocytic leukemia, PML; retinoic acids, RA; retinoic acid receptors, RARs; retinoic X receptors, RXRs; retinoic acid response elements, RAREs; silencing mediator of retinoid and thyroid hormone receptor, SMRT

Key Words: Chemoprevention, Retinoids, All-trans retinoid acid, Acute promyelocytic leukemia, Cancer, Retinoid signal pathway, Transduction, Coactivators, Corepressors, Review

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