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Triple A therapy: The molecular underpinnings of the unique sensitivity of leukemic promyelocytes to anthracyclines, all-*trans*-retinoic acid and arsenic trioxide

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If looking for a mnemonic to remember the relevant facts about acute promyelocytic leukemia (APL), one just has to remember that APL is a disease of A's. It is acute and it is highly sensitive to treatment with anthracyclines, all-*trans*-retinoic acid (RA) and arsenic trioxide (ATO). The presence of fusions involving the retinoic acid receptor alpha (RARA) is without question the central player driving APL and dictating the response of this disease to these therapeutic agents. However, beyond this knowledge, the molecular mechanisms that contribute to the complicated pathogenesis and the response to treatment of APL are not completely defined. As more is understood about this hematological malignancy, there are more opportunities to refine and improve treatment based on this knowledge. In this review article, we discuss the response of APL to these "A" therapies.

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Introduction

Acute promyelocytic leukemia (APL) is the M3 subtype of acute myeloid leukemia (AML) according to the French American British (FAB) classification system [8]. Although representing only 5–15% of AML cases in adults [31,100], APL serves as the paradigm both for understanding the pathogenesis of leukemia and the response to differentiation-inducing agents. At the genetic level, with only one known exception [99], APL is characterized by a specific chromosomal rearrangement between the retinoic acid receptor alpha (*RARA*) on chromosome 17 and a number of partners. The majority of patients (98%) present with the 15;17 translocation, t(15;17) [92], which results in a fusion of *RARA* with the promyelocytic leukemia (*PML*) gene on chromosome 15 [25,49]. RARA is a member of the nuclear receptor (NR) superfamily and has been implicated in the fine tuning of myeloid differentiation through transcriptional activation of genes in response to physiological concentrations of its ligand, all-*trans*-retinoic acid (RA). The promyelocytic leukemia (PML) protein is a tumor suppressor ubiquitously expressed in mammalian cells, which organizes punctate nuclear structures known as PML nuclear bodies (NBs). Clinically, APL is characterized by a block in differentiation at the promyelocytic stage of myeloid development.

In APL cells, the traditional view is that leukemic effects of the chimeric protein, PML/RARA, are due to its function as a dominant negative inhibitor of normal RARA function, even at physiological RA levels. The chimera locates to promoters normally regulated by RARA, and acts as a constitutive transcriptional repressor that interferes with gene expression programs involved in granulocytic differentiation. Transcriptional deregulation stems from enhanced co-repressor binding related to the presence of the oligomerization domain of PML [27,40,42,64]. However, abolishment of the normal RARA ligand-dependent transcriptional program alone does not recapitulate the APL disease phenotype. Importantly, transgenic mice expressing an RARA mutant unable to bind RA do not develop APL [54].

It has been proposed that PML/RARA exhibits a significant gain of function. Global gene expression analysis after inducible expression of PML/RARA shows the expected down-regulation of differentiation genes, but an equivalent number of genes were up-regulated, including genes implicated in the self-renewal of HSCs, such as *LMO1* and *JAG1* [3]. *In vitro* evidence suggests PML/RARA has gained an expanded DNA binding capacity away from canonical RAREs to more widely spaced DRs [52] and can affect the transcription of genes controlled by other nuclear receptors. ChIP-seq analysis reveals a gain of function in the DNA binding repertoire for PML/RARA, as compared with wild-type RARA [72]. Furthermore, most of these additional PML/RARA binding regions are associated with epigenetic alterations, including histone acetylation and methylation and DNA methylation, indicative of functional significance. Finally, there is evidence that PML/RARA interferes with the function of transcription factors other than RARA. PML/RARA was demonstrated to form a repressive transcription complex with PU.1 [106], which has been shown to be an important transcription factor in normal hematopoiesis and in generation of myeloid leukemias through disruption of its function [79]. An alternative variation on this theme is that the co-repressor complex formed by PML/RARA may indirectly affect the activity of alternative transcription factors by depleting modulating co-factors such as RXRs or HDACs. Accordingly, genetic experiments have demonstrated that binding to RXRA, the universal partner for heterodimeric nuclear receptors, is required for cell transformation by RARA fusions [116]. This indirect mechanism may also apply to the modulation of the AP-1 transcription factor composed of Fos and Jun, which has been suggested to be of central importance in APL pathogenesis [115].

One of the signature cytological findings in APL is that PML is delocalized to a myriad of microspeckles throughout the nucleus in APL cells, rather than concentrated in discrete PML nuclear bodies (NBs) [22,34]. Treatment with RA or ATO degrades the aberrant PML/RARA fusion protein and relocalizes NB components [80,89,112,113], linking NB disruption to APL pathogenesis. Among others, NBs were associated with tuning of the p53 response through concentration and/or modification of partners such as MDM2 or CBP [87]. Enhanced self-renewal was observed upon PML loss or NB disruption [24], possibly reflecting deregulation of p53 signaling. These pathways probably cooperate to enforce the APL-specific differentiation block and acquisition of self-renewal, thus transforming a committed hematopoietic progenitor into an immortal, fully transformed cell.

Treatment of APL is more likely to induce a complete remission than the other subtypes of AML. Patients with this malignancy are more sensitive than other AML patients to anthracyclines, all-*trans*-retinoic acid, and arsenic trioxide. The presence of a chimeric fusion protein involving RARA is the only