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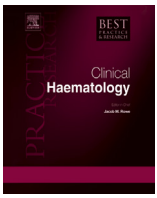

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Understanding the molecular pathogenesis of acute promyelocytic leukemia

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Acute promyelocytic leukemia (APL) is a distinct subset of acute myeloid leukemia (AML) associated with peculiar biologic and clinical features and requiring specific management. At the genetic level, APL is featured by a unique chromosome translocation t(15;17) which results in the *PML–RARα* gene fusion and chimeric protein. APL is the first example of differentiation therapy targeted to a defined genetic target i.e. PML–RARα. PML–RARα behaves as an altered retinoic acid receptor with an ability of transmitting oncogenic signaling leading to accumulation of undifferentiated promyelocytes. All-*trans*-retinoic acid (ATRA) induces disease remission in APL patients by triggering terminal differentiation of leukemic promyelocytes. More recently, arsenic trioxide (ATO) has been shown to contribute degradation of the PML–RARα oncoprotein through bonding the PML moiety and has shown excellent synergism with ATRA in clinical trials. Elucidating the oncogenic signaling of PML–RARα through various transcription factors and the study of APL mouse models have greatly helped to understand the molecular pathogenesis of APL. However, the precise molecular mechanism by which t(15;17) is formed and initiates leukemia remains unknown. While transforming oncogenic potential of PML–RARα has been described extensively, the mechanistic events important for the formation of t(15;17) have been taken from the model of Therapy-related APL (t-APL).

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Introduction

Although targeted therapies are increasingly being developed in oncology only in few instances they have resulted in significant outcome improvements. Acute promyelocytic leukemia (APL) represents one of the best paradigms of successful targeted therapy by providing the first example of chemotherapy-free cure of acute leukemia [1]. APL is in fact one of the rare forms of cancer in which targeted therapy has proven able to eradicate leukemia stem cells in the majority of patients [2,3].

APL is a distinct subset of acute myeloid leukemia (AML) associated with peculiar features and requiring specific management. The disease was initially recognized in 1957 by Hillestad [4] who described three patients with a rapidly fatal acute leukemia characterized by abundant number of abnormal promyelocytes infiltrating the marrow and a severe hemorrhagic syndrome. In the following decades, APL has become a well-recognized entity, characterized as the M3 subtype of AML within the French–American–British (FAB) morphologic classification accounting for approximately 10% of cases of AML [5]. At the genetic level, APL is characterized by a unique chromosome translocation t(15;17) which results in the *PML–RARα* gene fusion and chimeric protein [6–8]. Both moieties of the oncoprotein, whose role in leukemogenesis has been elucidated, are known to be targeted by specific agents active in the disease [9].

Biologic effects of PML–RARα

APL has served as a model disease to understand leukemogenic pathways directed by the PML–RARα oncoprotein. In addition, APL is the first example of differentiation therapy targeted to a defined genetic target i.e. PML–RARα [10]. RARα is the retinoic acid receptor alpha which binds at the nuclear level retinoic acid. Retinoids, natural or synthetic derivatives of vitamin A, are necessary dietary constituents that exert profound effects on development, cell proliferation and differentiation in normal cells and various cancer cells by regulating the expression of specific genes. Retinoids activate two classes of nuclear receptor proteins of the steroid and thyroid hormone superfamily, the RARs (α, β, and γ), and the retinoid X receptors (RXRs α, β, and γ), for gene transcriptional activation. RARs are activated by both all-*trans*-retinoic acid (ATRA) and 9-cis-RA, whereas RXRs are activated by 9-cis-RA only [11]. ATRA induces disease remission in APL patients by triggering terminal differentiation of leukemic promyelocytes [12].

RARα interacts with RXR, and the normal RARα–RXR heterodimer recruits corepressor (CoR) or coactivators (CoA) complexes at the chromatin level to differentially regulate transcription of its target genes. Physiological concentrations of RA (1×10^{-9} M) are able to release the nuclear co-repressors complex from the RAR–RXR and recruit co-activators with histone acetyltransferase activities (HAT). This results in hyperacetylation of histones at retinoic acid responsive elements (RARE) sites, chromatin remodeling and transcriptional activation of RAR-target genes [13–15].

PML–RARα behaves as an altered retinoic acid receptor with an ability of transmitting oncogenic signaling in the cell. PML–RARα acts as a constitutive repressor that is insensitive to physiological concentrations of ATRA [16]. At such concentrations of ATRA, PML–RARα binds to RXR, which may be essential for its leukemogenic potential as it facilitates binding to widely spaced direct repeats (DRs) [17] and has been shown to be a critical determinant for the transforming potential of PML–RARα complexes [18].

APL patients are treated with pharmacological doses of ATRA to overwhelm the transforming potential of PML–RARα [19]. This treatment results in the degradation PML–RARα [20] as well as in dissociation of various epigenetic enzymes from chromatin, such as histone deacetylases (HDACs) [21,22], DNMTs [19], MBDs [23,24], and histone methyltransferases [25,26]. Loss of these CoR proteins promotes the recruitment of CoA complexes at PML–RARα binding sites, creating a more accessible chromatin structure. CoA is a multi-protein complex, containing CREB binding protein (CBP)/adenoviral-E1A associated protein p300 (P300), P300/CBP associated factor (P/CAF), P300/CBP interaction protein (P/CIP), also called activator of thyroid hormone and retinoid (ACTR) and the nuclear receptors coactivator-1 (NcoA-1) or steroid hormone receptor coactivator-1 (SRC-1) or NcoA-2. All the CoA components possess histone acetylase activity [27,28].

Although ATRA induces differentiation and complete remission in virtually all APL patients it is not curative as single agent. By contrast, ATRA together with chemotherapy and/or arsenic trioxide (ATO)