Acute myeloid leukemia (AML) involves the immortalization of immature myeloid progenitors and is a heterogeneous disease. Current clinical practice separates AML into low-, intermediate-, and high-risk categories according to cytogenetic anomalies. Among the low-risk subtypes of AML is acute promyelocytic leukemia (APL). Approximately 98% of persons with APL carry a translocation of chromosomes 15 and 17, typically resulting in the fusion between RARα (retinoic acid receptor α), which encodes a retinoic acid receptor, and the promyelocytic leukemia (PML) protein. These persons are treated with all-trans retinoic acid in combination with chemotherapy; this treatment results in prolonged remission in more than 80% of patients. Patients who have a relapse are typically and often successfully treated with arsenic trioxide. A recent study by Nasr and colleagues sheds light on how these agents could control leukemia.

Cell-culture models have shown that the PML-RARα fusion protein, as well as the less common t(11;17)-associated promyelocytic leukemia zinc finger (PLZF)-RARα fusion protein, inhibits the differentiation of myeloid cell lines. This inhibition is due to the aberrant recruitment of transcription factors and histone-modifying enzymes to genes normally regulated by the retinoic acid receptor (Fig. 1). Such genes encode transcription factors that stimulate myeloid development and regulators of the cell cycle. PML-RARα also activates genes that stimulate self-renewal and perpetuation of the leukemia cell, including members of the Wnt and Notch signaling pathway. The abilities of the PML-RARα oncoprotein to encourage self-renewal and to block differentiation can be dissociated. Leukemia develops in transgenic mice expressing PML-RARα after a latent period of up to 1 year. Before then, only a very modest expansion of the myeloid compartment is noted, and PML-RARα promyelocytes have gene-expression profiles that are almost identical to normal promyelocytes. Second and perhaps other lesions, as yet unknown, collaborate with PML-RARα to block differentiation and stimulate the accumulation of malignant, self-renewing promyelocytes.

The application of all-trans retinoic acid to APL cells in culture, cell lines engineered to express the PML-RARα fusion protein, and to PML-RARα transgenic mice triggers the differentiation of malignant promyelocytes into mature granulocytes. This differentiation results in increasing numbers of maturing myeloid cells and pulmonary infiltrates — the so-called retinoic acid syndrome — which is treated with the use of corticosteroids and concomitant chemotherapy. The use of all-trans retinoic acid as a single agent in APL generally does not, however, result in durable remissions, which suggests that its ability to differentiate promyelocytes is insufficient to eliminate residual disease. Arsenic can yield an APL differentiation syndrome with manifestations similar to those of retinoic acid syndrome. Both agents can reduce the leukemia burden without the development of disseminated intravascular coagulation, greatly reducing the mortality associated with treatment in the initial phase. Although the effects of these therapies on differentiation are necessary for their success, the work of Nasr et al. indicates that the drugs have an additional effect: they reduce the number of cells capable of regenerating leukemia (known as leukemia-initiating cells or leukemic stem cells) in syngeneic mice.

Using a mouse model, Nasr et al. confirmed that during the initial phase of APL therapy, all-trans retinoic acid induces a switch in PML-RARα activity from a repressor to an activator of transcription. This switch sets off a wave of differentiation and thus the elimination of a large fraction of malignant cells and, indeed, PML-RARα itself. Components of the proteosome are engaged by the domain within the retinoic acid receptor moiety of PML-RARα that binds all-trans retinoic acid. Differentiation induced by arsenic is usually less pronounced than that observed in response to all-trans retinoic acid because arsenic does not...
directly activate PML-RARα. Instead, arsenic stimulates the addition of small ubiquitin-like modifier (SUMO) molecules to the PML moiety of the oncoprotein, marking the oncoprotein for degradation. In addition, because it can stimulate kinase pathways, arsenic modifies a critical corepressor of PML-RARα, preventing its interaction with the oncoprotein.

Nasr et al. found that neither all-trans retinoic acid nor arsenic alone completely eliminated leukemia-initiating cells. Rather, a combination of these two agents resulted in the elimination of leukemia-initiating cells — an effect correlated with the degradation and elimination of the oncoprotein from the leukemic cells. Because PML-RARα confers immortalization and self-renewal properties to cells, the persistence of even a tiny proportion of cells expressing PML-RARα will facilitate recurrence. Consistent with this point is an observation by Nasr et al. that all-trans retinoic acid induced differentiation of leukemic cells harboring the PLZF-RARα protein in mice, but it was ineffective both in eliminating leukemia-initiating cells and in curing the mice of disease. Nor can it cure humans of PML-RARα–associated leukemia. That all-trans retinoic acid cannot, on its own, eliminate leukemia-initiating cells may explain why chemotherapy must be added to this agent in order to effect long-term remission. Another study suggests that arsenic is more effective than all-trans retinoic acid in removing leukemia-initiating cells, potentially explaining its ability to induce durable remissions as a single agent in newly diagnosed APL.
The conclusions of Nasr and colleagues are consistent with those of other recent studies. Collectively, these studies reframe the field of differentiation therapy, the goal of which has been to alter the malignant phenotype of the cell, halting self-renewal and stimulating terminal differentiation. A new model must account for the leukemic stem cell, which seems immune from differentiation, can persist through some forms of therapy, and permits tumor recurrence. Treatment of both the bulk cancer-cell population and the cancer stem-cell population is therefore necessary to effect long-term remission or cure. In the future, rational combinations of agents such as all-trans retinoic acid and arsenic that effectively target the leukemic stem cell might be used without the need for conventional chemotherapy.

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From the Division of Hematology and Oncology, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago.


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