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Scientists gain important insights into acute promyelocytic leukemia

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Results from two new studies provide key mechanistic insights into the complex molecular events that cause a deadly type of leukemia. The research, published in the July issue of the journal *Cancer Cell*, published by Cell Press, illuminates specific mechanisms involved in development of acute promyelocytic leukemia (APL) and identifies promising new avenues to develop treatments for some of its variant forms.

APL is a cancer of the bone marrow that occurs when certain developing white blood cells get stuck at a highly proliferative and immature stage. The abnormal cells accumulate and eventually crowd out the normal, healthy blood cells. Most cases of APL are caused by the expression of the PML/RARA (promyelocytic leukemia/retinoic acid receptor alpha) oncogene. This oncogene is formed by an abnormal translocation between two chromosomes and gives rise to a protein called a fusion protein.

In APL, the fusion protein, always involving the transcription factor RARA, acts as a potent transcriptional repressor that interferes with gene expression and prevents normal differentiation of white blood cells. Previous work of these two groups suggested that PML/RARA self-association, called homodimerization, and posttranslational modifications are important for transformation. In addition, retinoid X receptor (RXR) has been shown to be present in the DNA-bound PML/RARA oncogenic complex and is thought to play a role in the ability of the fusion protein to bind to DNA and regulate gene expression.

Dr. Chi Wai Eric So from The Institute of Cancer Research in London and Dr. Shuo Dong from Baylor College of Medicine in Houston and their colleagues characterized the transformation mechanisms involved in APL by functionally separating homodimerization and the intrinsic DNA-binding properties of RARA fusions from transformation of primary blood cells. The researchers found that homodimerization was not sufficient for RARA fusion-mediated transformation, but higher-order RXRA/RAR fusion hetero-oligomeric complexes that aberrantly recruit transcriptional corepressors to downstream targets were essential. Importantly, disruption of RXR-dependent pathways suppressed RARA fusion-mediated transformation. The authors also suggest that disruption of homotetramers into homodimers may be sufficient to abrogate the transformation ability of RARA fusion proteins. "These findings not only identify the key elements and potential avenues for therapeutic targeting of RARA-mediated leukemia but also shed light on oligomeric transformation mechanisms reported with various leukemia-associated transcription factors," conclude Drs. So and Dong.

A separate group, led by Dr. Hugues de Thé from CNRS/University of Paris 7, investigated the role of RXR in the PML/RARA complex through a variety of experiments that revealed that, although not required for transformation of blood cells in primary culture, RXR was absolutely essential for APL development in PML/RARA transgenic mice. Pharmacological activation of RXR relieved PML/RARA-induced transcriptional repression and triggered APL differentiation only when RXR was in a complex with PML/RARA. In addition, PML/RARA promoted posttranslational modifications of RXR, including its sumoylation, a modification that triggers transcriptional repression for RXR and many other transcription factors.

"The presence of RXR in the PML/RARA complex not only greatly facilitates DNA binding but is also required for rexinoid-induced differentiation, demonstrating that RXR is not a silent partner but a

critical determinant of transformation. In addition, our observations suggest that dysregulated sumoylation induced by PML/RARA may contribute to altered gene expression and APL pathogenesis," explains Dr. de Thé.

Taken together, results from these studies indicate that formation of higher-order homotetrameric complexes and recruitment of RXR are essential components of RARA-induced transformation and that RXR is a key member of the PML/RARA-associated oncogenic response that facilitates PML/RARA-induced transformation through multiple mechanisms and participates in the differentiation response. Further, homotetrameric complexes and RXR have the potential to be useful therapeutic targets for RARA fusion-mediated cancers.

Source: Cell Press