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DECRYPTING ACUTE PROMYELOCYTIC LEUKEMIA PATHOGENESIS THROUGH THERAPY RESPONSE

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Expression of the PML/RARA fusion underlies pathogenesis of acute promyelocytic leukemia (APL), as well as its clinical response to retinoic acid (RA) and arsenic trioxide. Both agents target PML/RARA for proteasome-mediated degradation, RA targeting the RARA moiety of the fusion, while arsenic targets its PML part. Arsenic-induced degradation involves enhancement of sumolation on a specific lysine K160 in PML or PML/RARA. While previous models of PML/RARA oncogenesis were exclusively focused on enforced RARA dimerisation and enhanced corepressor recruitment, the K160 sumolation site was paradoxically shown to be absolutely required for the APL-specific differentiation block and leukemogenesis *in vivo*[1]. *Ex vivo* studies suggest that the function provided by this sumolation site is transcriptional repression, providing a clue as to why PML, rather than any self-dimerizing protein, is the recurrent translocation partner of RARA.

Activation of cAMP signaling can trigger differentiation of APL cells both *ex vivo* and *in vivo* and greatly enhances the differentiation mediated by RA or arsenic[2]. Cyclic AMP can also reverse RA-resistance conferred by a point mutation in PML/RARA[3]. Only the combination of RA and cAMP activates PML/RARA-dependent transcription in a RA-resistant leukemia, directly demonstrating a functional cooperation of these two signaling molecules on PML/RARA[3]. Activation of cAMP signaling, which can be achieved in patients, therefore constitute a third PML/RARA-targeted therapy.

Enforced RARA dimerization induces not only the tighter binding of corepressors, but also a dramatic extension of the repertoire of DNA-binding sites and hence of target genes[3]. Assessing the role of RARA dimer formation in immortalization of mouse hematopoietic progenitors, we have shown that dimerization-induced extension of the target gene repertoire is absolutely essential for transformation, demonstrating how translocation-induced dimerization transforms an unessential transcription factor into a dominant oncogene[4].

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