Acute promyelocytic leukemia (APL) is driven by the t(15;17) translocation yielding the PML/RARα oncogenic fusion protein (1). Similar to many other oncogenic proteins, PML/RARα recruits corepressors to reprogram expression of yet unidentified master regulators involved in leukemic cell self-renewal, differentiation, senescence, or apoptosis. All-trans retinoic acid (ATRA) binding onto the RARα moiety of PML/RARα yields transcriptional reactivation of these downstream targets, which foster APL differentiation to drive clinical response. It was later shown that ATRA, as well as arsenic trioxide (ATO), initiates PML/RARα degradation by arsenic trioxide (ATO) and may circumvent ATO-resistant mutants, implying a distinct molecular mechanism. Oncogenic fusion proteins are expected to be RARα–resistant mutants, implying a distinct molecular mechanism. Why is PML/RARα sensitive to hyperthermia? Because this was not observed with RARα alone, could it reflect the ability of PML to aggregate upon oxidative stress (6)? PML/RARα may be located in the nucleus or in the cytoplasm and may be degraded by the proteasome or lysosomes (8). Although some autophagic regulators have been shown in the nucleus, most of the autophagic process occurs at cytoplasm, where SIAH2 is primarily located (9). Thus, heat shock may promote export or block import of PML/RARα–corepressor complexes. More generally, this study suggests that hyperthermia may precipitate aggregation, and subsequent degradation, of other large corepressor-associated fusion proteins. The oncogenic AML1/ETO and TEL/AML1 fusions are corepressor-associated master transcriptional repressors that may be located in the nucleus or in the cytoplasm and may be degraded by the proteasome or lysosomes. These studies raise a number of intriguing biological and biochemical issues. Why is PML/RARα so sensitive to hyperthermia? Because this was not observed with RARα alone, could it reflect the ability of PML to aggregate upon oxidative stress (6)?
Hyperthermia can induce fusion oncoprotein degradation. A, In APL, targeted PML/RAR\(\alpha\) degradation occurs after ATRA/ATO treatment. In rare cases, resistant mutants can emerge that impede PML/RAR\(\alpha\) degradation. Hyperthermia first yields matrix association of the PML/RAR\(\alpha\)-corepressor complex. Then, the corepressor-bound SIAH2 E3 ligase polyubiquitinates PML/RAR\(\alpha\)-containing aggregates, leading to the degradation of the oncogenic fusion protein. Hyperthermia destabilizes wild-type or ATO-resistant PML/RAR\(\alpha\) and may synergize with ATO to drive APL response. B, Tentative generalization to other corepressor-associated oncogenic fusion proteins.

Authors' Disclosures
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PML/RARα Destabilization by Hyperthermia: A New Model for Oncogenic Fusion Protein Degradation?

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