In this issue of Blood Cancer Discovery, Maimaitiyiming and colleagues demonstrate that hyperthermia downregulates endogenous PML/RARA protein (5). Similar to ATO, hyperthermia rapidly switches PML/RARA from a soluble protein to an insoluble one (6). This can be achieved even with ATO (or ATRA)-resistant mutants, implying a distinct molecular mechanism. Oncogenic fusion proteins are expected to be prone to abnormal protein folding, particularly upon heat shock, which activates HSP-mediated protein quality control. However, hyperthermia-induced PML/RARA aggregation and downregulation cannot be reversed by HSP inhibitors, suggesting for the implication of ERAD-independent degradation mechanisms. Unexpectedly, the authors found that interaction of corepressors such as NCoR1 and SMRT is required for hyperthermia-induced PML/RARA aggregation, nuclear matrix targeting, and subsequent degradation. Accordingly, corepressor release by ATRA treatment abrogates hyperthermia-induced PML/RARA loss. PML/RARA, NCoR1, and SMRT may be nuclear matrix–associated proteins, biochemically defined as insoluble nuclear material (7). Exploring the biochemical mechanism of PML/RARA/NCoR or SMRT complex degradation, the authors demonstrate that following their coaggregation, hyperthermia promotes PML/RARA polyubiquitination through an NCoR-associated E3 ligase, SIAH2 (Fig. 1A). Then, lysosomes, and to a lesser extent, proteasomes, contribute to the degradation of PML/RARA/corepressor complexes. The authors finally demonstrate that ATO synergizes with hyperthermia to promote PML/RARA degradation. To explore any therapeutic implications of this novel degradation mechanism for therapy-resistant APL patients, the authors designed a home-based regimen combining oral arsenic with daily whole-body water bath at 42°C. The latter induced clinical APL stabilization in a relapsed patient bearing PML/RARA mutations known to confer ATRA and ATO clinical resistance. Encouraging results from two other central nervous system–relapsed APL patients also suggest that hyperthermia-ATO treatment could exert some benefit.

These studies raise a number of intriguing biological and biochemical issues. Why is PML/RARA so sensitive to hyperthermia? Because this was not observed with RARA alone, could it reflect the ability of PML to aggregate upon oxidative stress (8)? PML/RARA may be located in the nucleus or in the cytoplasm and may be degraded by the proteasome or lysosomes. 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/RARA–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 exhibit nuclear matrix attachment (10). Pilot studies in AML1/ETO– or TEL/AML1-transfected cells indeed observed their heat-induced matrix targeting (ref. 5; Fig. 1B). Oncoprotein degradation can be achieved using receptor ligands,
Hyperthermia can induce fusion oncoprotein degradation. A. In APL, targeted PML/RARα degradation occurs after ATRA/ATO treatment. In rare cases, resistant mutants can emerge that impede PML/RARα degradation. Hyperthermia first yields matrix association of the PML/RARα-corepressor complex. Then, the corepressor-bound SIAH2 E3 ligase polyubiquitinates PML/RARα-containing aggregates, leading to the degradation of the oncogenic fusion protein. Hyperthermia destabilizes wild-type or ATO-resistant PML/RARα and may synergize with ATO to drive APL response. B. Tentative generalization to other corepressor-associated oncogenic fusion proteins.

proteolysis-targeting chimera (PROTAC), or other chemical-based interventions (4). The proof-of-concept observations reported here could pave the way to further studies on hyperthermia-induced fusion oncoprotein degradation, particularly corepressor-associated ones or those whose size makes them prone to protein misfolding or aggregation. These exciting studies again emphasize how APL has opened unexpected new biological or clinical tracks of investigations.

Authors’ Disclosures

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

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