PML/RARA destabilization by hyperthermia: a new model for oncogenic fusion protein degradation?

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Summary:

In this issue, Maimaitiyiming and colleagues demonstrate thermic stress-induced PML/RARA oncogenic fusion protein destabilization driven by corepressor aggregation. Hyperthermia synergizes with PML/RARA degradation by ATO and may circumvent ATO-resistance in historical APL patients. This novel approach could be extended to other corepressor-associated oncogenic fusion proteins.

Acute promyelocytic leukemia is driven by the t(15;17) translocation yielding the PML/RARA oncogenic fusion protein (1). Similar to many other oncoprotein proteins, PML/RARA recruits co-repressors to reprogram expression of yet unidentified master regulators involved in leukemic cell self-renewal, differentiation, senescence or apoptosis. ATRA binding onto the RARA moiety of PML/RARA yields transcriptional reactivation of these downstream targets, which foster APL differentiation to drive clinical response. It was later shown that ATRA, as well as ATO, initiates PML/RARA degradation and that the latter is critical for promyelocytic blasts clearance (2). The combination of frontline ATRA and ATO has now become
the gold standard of APL therapy and cures over 95% of patients (3). Thus, APL serves as a model for leukemia cure through targeted oncoprotein degradation which has inspired novel therapeutic strategies for cancer cells elimination (4).

In this issue of *Blood Cancer Discovery*, Maimaitiyiming and colleagues demonstrate that hyperthermia down-regulates endogenous PML/RARA protein (5). Similar to ATO, hyperthermia rapidly switches PML/RARA from a soluble protein to an insoluble one (6). This can even 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 heat shock protein inhibitors, suggestive 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, corepressors 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/NCoRs or SMRT complex degradation, the authors demonstrate that following their co-aggregation, hyperthermia promotes PML/RARA poly-ubiquitination 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 in 42°C. The later induced clinical APL stabilization in a relapsed patient bearing PML and PML/RARA mutations known to confer ATRA and ATO clinical resistance. Encouraging results from 2 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? Since this was not observed with
RARA alone, could it reflect the ability of PML to aggregate upon oxidative stress (6)? PML/RARA may be located in the nucleus or in the cytoplasm and 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/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 or TEL/AML1 fusions are corepressor-associated master transcriptional repressor which may exhibit nuclear matrix attachment (10). Pilot studies in AML1/ETO or TEL/AML1 transfected cells, indeed observed their heat-induced matrix targeting (5) (Fig. 1B). Oncoprotein degradation can be achieved using receptor ligands, 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.

Reference


**Figure 1:** Hyperthermia can induce fusion oncoprotein degradation. A, In APL, targeted PML/RARA degradation occurs after ATRA/ATO treatment. In rare cases, resistant mutants can emerge that impede PML/RARA degradation. Hyperthermia first yields matrix-association of the PML/RARA-corepressors complexes. Then, the corepressor-bound SIAH2 E3 ligase polyubiquitinates PML/RARA-containing aggregates leading to the degradation of the oncogenic fusion protein. Hyperthermia destabilizes wild type or ATO-resistant PML/RARA and may synergize with ATO to drive APL response. B, Tentative generalization to other corepressor-associated oncogenic fusion proteins.
A

PML - RARα

Heat

Nuclear matrix Association

Synergy with ATO
Circumvents ATRA/ATO resistance

NCoR/SMRT

PML - RARα

Degradation

APL cure

PML-RARα mutations

ATRA

ATO

B

Heat

Fusion oncoproteins

Nuclear matrix association

Degradation?
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