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RESEARCH ARTICLES

DNMT1 Stability Is Regulated by Proteins Coordinating Deubiquitination and Acetylation-Driven Ubiquitination

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Abstract: DNA methyltransferase 1 (DNMT1) is the primary enzyme that maintains DNA methylation. We describe a previously unknown mode of regulation of DNMT1 protein stability through the coordinated action of an array of DNMT1-associated proteins. DNMT1 was destabilized by acetylation by the acetyltransferase Tip60, which triggered ubiquitination by the E3 ligase UHRF1, thereby targeting DNMT1 for proteasomal degradation. In contrast, DNMT1 was stabilized by histone deacetylase 1 (HDAC1) and the deubiquitinase HAUSP (herpes virus–associated ubiquitin-specific protease). Analysis of the abundance of DNMT1 and Tip60, as well as the association between HAUSP and DNMT1, suggested that during the cell cycle the initiation of DNMT1 degradation was coordinated with the end of DNA replication and the need for DNMT activity. In human colon cancers, the abundance of DNMT1 correlated with that of HAUSP. HAUSP knockdown rendered colon cancer cells more sensitive to killing by HDAC inhibitors both in tissue culture and in tumor xenograft models. Thus, these studies provide a mechanism-based rationale for the development of HDAC and HAUSP inhibitors for combined use in cancer therapy.

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