Histone deacetylase inhibitors (HDACi) are promising chemotherapeutic agents, but a better understanding of normal HDAC regulation will likely improve clinical outcomes. In their analysis of mouse embryonic fibroblasts (MEFs) lacking *Mule* (*Mcl-1 ubiquitin ligase E3*), Zhang and colleagues noted that *Mule*-null MEFs were resistant to cisplatin and Nutlin-3 (a small-molecule inhibitor of Mdm2 binding to p53), corresponding to decreased levels of acetylated (and thus transcriptionally active) p53. As p53 is known to be a non-histone HDAC target, the authors hypothesized that aberrant elevation of HDAC activity blocks p53 acetylation and function in *Mule*-null MEFs. Indeed, HDAC inhibition partially rescued p53 target gene expression, but *Mule*-null MEFs remained resistant to HDACi-induced apoptosis. Because these data suggested that HDAC hyperactivation was driving p53 defects and HDACi resistance, the authors screened HDAC levels in *Mule* knockout MEFs. They found that HDAC2 stability was specifically increased in Mule-deficient cells, and determined that in wild-type cells Mule binds, ubiquitinates, and targets HDAC2 for degradation. Increased HDAC2 levels were specifically responsible for the cell death defects in Mule-deficient cells, as knockdown of HDAC2, but not other known Mule substrates or HDACs, to wild-type levels restored p53 acetylation and transcriptional activity as well as cisplatin and HDACi sensitivity. Together, these results establish a role for a Mule–HDAC2–p53 axis in DNA damage- and HDACi-induced apoptosis, and identify downregulation or inactivation of Mule as a potential mechanism of HDACi resistance.


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