SUMOylation of E2F1 Regulates Expression of EZH2.

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Public Summary:

Scientific Abstract:
Elevated expression of EZH2, the enzymatic subunit of polycomb repressive complex 2 (PRC2), often occurs in cancer. EZH2 expression results in the silencing of genes that suppress tumor formation and metastasis through trimethylation of histone H3 at lysine 27 (H3K27me3) at their promoters. However, inhibitors of EZH2 enzymatic activity have not shown the expected efficacy against cancer in clinical trials, suggesting a need for other strategies to address EZH2 overexpression. Here, we show that SUMOylation, a posttranslational modification characterized by covalent attachment of small ubiquitin-like modifier (SUMO) proteins to a lysine (Lys) residue on target proteins, enhances EZH2 transcription. Either knockdown of the SUMO-activating enzyme SAE2 or pharmacologic inhibition of SUMOylation resulted in decreased levels of EZH2 mRNA and protein as well as reduced H3K27me3 levels. SUMOylation regulated EZH2 expression by enhancing binding of the E2F1 transcriptional activator to the EZH2 promoter. Inhibition of SUMOylation not only resulted in reduced EZH2 mRNA and protein levels but also increased expression of genes silenced by EZH2, such as E-cadherin, which suppresses epithelial-mesenchymal transition and metastasis. In more than 6,500 patient tumor samples across different cancer types, expression of UBA2 and EZH2 was positively correlated. Taken together, our findings suggest that inhibition of SUMOylation may serve as a potential strategy to address EZH2 overexpression and improve current cancer therapeutic approaches.

SIGNIFICANCE: These findings provide important biological insights into the mechanism of EZH2 overexpression in cancers and suggest that inhibiting SUMOylation may improve current cancer therapeutic approaches.

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