Leukemia

Major finding: Loss-of-function mutations of PRC2 complex components occur in 25% of T-ALLs.

Mechanism: NOTCH1-driven H3K27me3 loss at target promoters is potentiated by PRC2 inactivation.

Impact: EZH2 may act as a tumor suppressor or an oncogene in different cellular contexts.

EZH2 AND *SUZ12* ARE TUMOR SUPPRESSOR GENES IN T-ALL

Over half of all T-cell acute lymphoblastic leukemias (T-ALL) harbor activating *NOTCH1* mutations, but the mechanism of NOTCH1-induced transformation remains incompletely understood. Given the known role of NOTCH1 in transcriptional activation of target genes and the emerging prevalence of mutations in epigenetic modifiers in human cancers, Ntziachristos and colleagues performed microarray-based comparative genomic hybridization on 68 adult T-ALLs to identify genetic alterations in chromatin remodelers that might cooperate with oncogenic *NOTCH1* mutations in T-ALL. Loss-of-function mutations of *EZH2* or *SUZ12* were identified in 25% of the samples, the majority of which also harbored oncogenic *NOTCH1* mutations. EZH2 and SUZ12 are subunits of Polycomb repressive complex 2 (PRC2), which is responsible for the repressive histone 3 lysine 27 trimethylation (H3K27me3) chromatin modification. To better understand the relationship between NOTCH1 and PRC2, the authors analyzed epigenetic marks and protein occupancy at the promoters of canonical NOTCH1 target genes in a mouse model of T-ALL. Loss of H3K27me3 was significantly associated with NOTCH1-dependent gene upregulation and NOTCH1 binding. Furthermore, compared with normal thymocytes, *Notch1*-induced T-ALL cells exhibited decreased PRC2 occupancy at NOTCH1 target gene promoters. Collectively, these results indicate that NOTCH1 binding promotes the eviction of PRC2 and removal of the repressive H3K27me3 mark from target gene promoters, and that inactivation of PRC2 might remove a barrier for the progression of NOTCH1-driven cancers. Consistent with the concept that PRC2 loss potentiates oncogenic NOTCH signaling, silencing of EZH2 increased tumorigenicity in both a *Drosophila* Notch-driven tumor model and *NOTCH1*-mutant human T-ALL cells transplanted into immunodeficient mice. Intriguingly, gain-of-function *EZH2* mutations have also recently been reported in B-cell lymphomas, suggesting that both the mutation spectrum and interactions with other transcriptional regulators are critical determinants of the role of EZH2 in cancer.

Ntziachristos P, Tsirigos A, Van Vlierberghe P, Nedjic J, Trimarchi T, Sol Flaherty M, et al. Genetic inactivation of the polycomb repressive complex 2 in T cell acute lymphoblastic leukemia. Nat Med 2012 Jan 11. [Epub ahead of print].

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