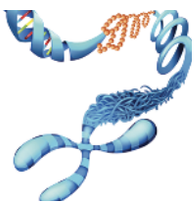
Leukemia

Major finding: The H3K27 demethylases UTX and JMJD3 have opposing roles in regulating NOTCH1-induced T-ALL growth.

Mechanism: JMJD3 interacts with NOTCH1 to regulate oncogenic genes, whereas UTX is a tumor suppressor.

Impact: The small-molecule inhibitor GSKJ4 blocks JMJD3 activity and may be a novel therapeutic for T-ALL.

HISTONE DEMETHYLASES HAVE DIVERGENT FUNCTIONS IN T-ALL



T-cell acute lymphoblastic leukemia (T-ALL) has a 25% relapse rate and an overall poor prognosis. Although drugs that target epigenetic factors have been approved for the treatment of hematopoietic disorders, they are not currently used to treat T-ALL. Recent studies have implicated histone 3 lysine 27 (H3K27) methyltransferase complexes as tumor suppressors in T-ALL; however, the role of the H3K27 demethylases lysine (K)-specific demethylase 6A (KDM6A, also known as UTX) and lysine (K)-specific demethylase 6B (KDM6B, also known as JMJD3) in T-ALL progression is unknown. Ntziachristos, Tsirigos, and colleagues found that JMJD3 expression was elevated in murine NOTCH1-induced T-ALL cells compared with untransformed T cells and was regulated by NOTCH1 and the NF-κB pathway. JMJD3 binding to the promoters of oncogenic NOTCH1 target genes was associated with co-occupancy with NOTCH1 and activating histone marks. Furthermore, JMJD3 interacted directly with the NOTCH1 transcriptional complex, suggesting that it plays a key role in regulating oncogenic programs in T-ALL. Both knockdown of JMJD3 in human T-ALL cells and *Jmjd3* knockout in mouse models resulted in reduced leukemic cell viability and improved survival rates. In contrast, silencing of UTX resulted in enhanced T-ALL cell proliferation and shorter tumor latency, whereas UTX overexpression stimulated apoptosis and inhibited tumor cell growth *in vitro*, suggesting that this enzyme may function as a tumor suppressor. Further studies demonstrated that UTX positively regulated tumor suppressor genes, and that deletions and mutations in *UTX* were found in patients with T-ALL. Importantly, the small-molecule inhibitor GSKJ4 induced cell-cycle arrest and apoptosis in human T-ALL cells and resulted in a similar gene expression and epigenetic profile as JMJD3-silenced cells, suggesting that it mainly acts by inhibiting JMJD3 demethylase activity. These results identify contrasting functions for the H3K27 demethylases JMJD3 and UTX in T-ALL, and support further studies of GSKJ4 as a potential targeted therapy for T-ALL. ■

Ntziachristos P, Tsirigos A, Welstead GG, Trimarchi T, Bakogianni S, Xu L, et al. Contrasting roles of histone 3 lysine 27 demethylases in acute lymphoblastic leukemia. Nature 2014 Aug 18 [Epub ahead of print].

Glioblastoma

Major finding: Activation of aPKC by both EGFR and paracrine TNFα signaling promotes glioblastoma progression.

Concept: Myeloid cell–derived TNFα induces EGFR inhibitor resistance and aPKC-mediated NF-κB signaling.

Impact: Targeting aPKC may inhibit tumor cell–intrinsic and non–cell-autonomous signaling in glioblastoma.

ATYPICAL PKC FUNCTIONS IN PARALLEL ONCOGENIC PATHWAYS IN GLIOBLASTOMA

Aberrant EGFR activation is frequently observed in glioblastoma, suggesting that inhibition of this receptor tyrosine kinase (RTK) may be therapeutically beneficial. However, EGFR kinase inhibitors have shown limited clinical efficacy due to activation of parallel and downstream oncogenic pathways that promote drug resistance, emphasizing the need to identify additional therapeutic strategies. Kusne, Carrera-Silva, and colleagues found that the expression of atypical protein kinase C (aPKC), a serine–threonine kinase implicated in neural development, was increased in glioblastoma samples compared with normal brain tissue and that high aPKC levels were correlated with shorter survival in patients with glioblastoma. Inhibition of aPKC reduced the growth of intracranial glioblastoma tumors in mice, including patient-derived EGFR inhibitor–resistant tumors, suggesting that aPKC promotes glioblastoma progression and that it may be a therapeutic target. aPKC was activated by EGFR as well as other RTKs in glioblastoma cells, and was also induced by TNFα produced by myeloid cells in the tumor microenvironment. Paracrine TNFα signaling stimulated NF-κB–dependent target gene expression in glioblastoma cells, enhanced glioblastoma cell proliferation and invasion, and promoted EGFR inhibitor resistance. The protumor activity of myeloid cell–derived TNFα was mediated by aPKC-dependent induction of NF-κB signaling; aPKC inhibition impaired NF-κB activation and suppressed tumor cell proliferation and invasion in coculture experiments, whereas constitutive aPKC activation was sufficient to trigger TNFα- and EGF-driven gene expression. Activation of aPKC by EGFR and TNFα resulted in the formation of distinct aPKC signaling complexes containing the scaffold proteins PAR6 or p62, respectively, resulting in specific induction of EGF and TNFα gene expression programs. These results identify a critical role for aPKC in glioblastoma progression via activation of parallel signaling pathways and suggest that targeting aPKC may facilitate inhibition of both tumor cell–autonomous and microenvironment-driven oncogenic signaling in glioblastoma. ■

Kusne Y, Carrera-Silva EA, Perry AS, Rushing EJ, Mandell EK, Dietrich JD, et al. Targeting aPKC disables oncogenic signaling by both the EGFR and the proinflammatory cytokine TNFα in glioblastoma. Sci Signal 2014;7:ra75.