Glioblastoma

Major finding: Low-level driver mutations in subventricular zone (SVZ) cells are sufficient to induce glioblastoma.

Approach: Sequencing of matched glioblastoma, tumor-free SVZ, and normal cortex samples reveals the cell of origin.

Impact: Neural stem cells in the SVZ with low-level mutations are likely the cell of origin in glioblastoma.

Glioblastoma (GBM) has been suggested to arise from neural stem cells (NSC) in the subventricular zone (SVZ) of the adult human brain. However, this has not been demonstrated directly in patients with GBM. To identify the cell of origin in GBM, Lee and colleagues performed deep sequencing of triple-matched tissue derived from tumor tissue, matched normal SVZ tissue, and matched normal cortical tissue or blood from 28 patients with IDH-wild-type GBM or other types of brain tumors. The tumors harbored an average of 80.7 somatic mutations, the tumor-free SVZ specimens had an average of 23 somatic mutations, and the normal brain or blood tissue contained an average of 4.3 somatic mutations. In 9 of 16 patients (56.3%) with wild-type IDH GBM, the normal SVZ contained low-level GBM driver mutations in the TERT promoter or in cancer driving genes (including EGFR, PTEN, or TP53) that were enriched in their matching tumors. Together with single-cell sequencing, these results demonstrated that SVZ cells clonally evolve into GBM. To determine if low-level SVZ mutations could result in GBM, Trp53, Pten, and Egfr low-level somatic mutations were introduced in mice into NSCs from the SVZ. The recurrent driver mutations were sufficient to induce GBM, with the mutant SVZ cells migrating to the dorsolateral caudal cortex to develop into malignant glioma. Collectively, these findings suggest that GBM arises from NSCs in the SVZ that acquire driver mutations and migrate to the site of gliomagenesis.


Epigenetics

Major finding: The reversible competitive KAT6A/B inhibitor WM-1119 enhanced oncogene-induced senescence.

Approach: A screen of 243,000 diverse small-molecule compounds followed by optimization yielded WM-1119.

Impact: KAT6A/B inhibition may be beneficial in lymphoma and potentially other KAT6A/B-dependent tumors.

The closely related lysine acetyltransferases KAT6A and KAT6B acetylate histones to regulate chromatin organization and function, and are also the target of recurring chromosomal translocations in cancer. KAT6A is recurrently translocated in acute myeloid leukemia (AML) and plays an essential role in normal hematopoietic stem cells, and loss of heterozygosity extends survival in mice with MYC-induced lymphoma. Similarly, KAT6B is recurrently translocated in a variety of tumor types. These findings provide a rationale for the development of KAT6A/B inhibitors for cancer therapy. To identify KAT6A inhibitors, Baell and colleagues performed a screen of 243,000 diverse small-molecule compounds, which identified a competitive KAT6A inhibitor that, after optimization, yielded WM-8014. WM-8014 inhibited both KAT6A and KAT6B, with much less activity against other KAT proteins. The crystal structure of a modified histone acetyltransferase domain in complex with WM-8014 demonstrated that the compound is a reversible competitor of acetyl coenzyme A. In mouse embryonic fibroblasts, WM-8014 induced cellular senescence with a corresponding upregulation of Cdkn2a, and downregulation of the KAT6A target gene Cdc6. WM-8014 reduced acetylation of H3K9 at KAT6 target genes specifically, and reduced acetylation of H3K14 (mediated by KAT7) throughout the genome, demonstrating on-target effects on histone acetylation. WM-8014 resulted in gene expression changes similar to KAT6A loss, including downregulation of E2f2, Ezh2, and Melk. WM-8014 enhanced oncogene-induced senescence in vitro and in a zebrafish model of hepatocellular carcinoma. A WM-8014 derivative more suitable for in vivo use, WM-1119, suppressed the growth of lymphoma in mice. In addition to developing a novel class of inhibitors targeting histone acetylation, these findings suggest that inhibiting KAT6A/B may induce senescence and suppress tumor progression.


A KAT6A/B INHIBITOR INDUCES SENESCENCE TO SUPPRESS TUMORIGENESIS

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