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LSD1 inhibition in pHGG: the key to unleashing immunotherapy?

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See the article by Bailey et al., pp. 1302–1314, in this issue.

Pediatric high-grade gliomas (pHGGs) are a heterogeneous group of aggressive tumors with a dismal prognosis. Apart from the small subgroup of anaplastic pleomorphic xanthoastrocytoma–like tumors, survival is generally less than 5 years.[1] Recent discovery of oncogenic histone gene mutations, resulting in the replacement of lysine 27 by methionine (K27M) in encoded histone H3 proteins, are detected in the majority of pHGGs and lead to global reduction of H3K27 tri- and dimethylation (H3K27me3 and K27me2), a transcriptionally repressive mark, which promote tumor growth.[2] This mutation is also associated with changes in other methyl marks, including H3K4me3 and H3K36me2, and H3K27 acetylation (H3K27ac), which are transcriptionally active chromatin marks.[3] These modifications are affected by enzymes—with mutation invariably resulting in altered regulation of gene transcription—that can be therapeutically targeted, indicating that pharmacologic inhibition of histone modifiers has intriguing potential as an approach for treatment of pHGGs. These therapies have not yet been translated into effective therapies in patients, however. In the report by Bailey et al,[4] the authors test newly developed inhibitors of lysine-specific demethylase 1 (LSD1) in pHGG models with unexpected results.

Drugs targeting epigenetic modifiers include the inhibitors of enzymatic "writers," such as DNA and histone methyltransferases, and inhibitors of enzymatic "erasers," such as histone demethylases and histone deacetylases.[3] Modulation of the epigenetic regulators known as "readers," such as bromodomain proteins that recognize and bind to covalent modifications of chromatin, has recently emerged as a therapeutic strategy in the treatment of pHGGs as well as other cancers.[5] These epigenetic targeted drugs have shown preclinical efficacy in H3K27 mutant pHGG models[5] and are actively being investigated in phase I/II clinical trials for patients with pHGGs.

The enzymatic "erasers" lysine histone demethylases (KDMs) including KDM6 (JMJD3 and UTX), KDM1A (LSD1, BHC110, AOF2), and KDM1B (LSD2) remove the methyl group(s) from a methylated lysine side chain. LSD1 has recently been shown to be critical to tumorigenesis in many cancer types, including leukemia[6] and sarcoma,[7] but its activity has not yet been evaluated in pHGG. The authors had previously investigated LSD1 inhibitors in adult glioma[8] and found limited preclinical activity as a single agent, but noticed a significant change in expression of genes related to "immune response." In the current study, the authors confirmed that this change in gene expression was also found in pHGG cell lines and correlated with improved survival in public databases of pHGG. The authors also demonstrated in vitro growth inhibition of LSD1 inhibitors against pHGG cell lines, though in vivo efficacy was not statistically significant, likely due to adaptive resistance of the tumor to sustained LSD1 treatment. Intriguingly, some of the genes upregulated by LSD1 inhibitors are natural killer (NK) cell receptors such as SLAMF7 and MICB. This led the authors to hypothesize that LSD1 inhibitors might "prime" pHGG cells for increased lysis by NK cells. After documenting this effect in vitro, the authors used an intracranial xenograft model of H3.3K27M-mutant pHGG and demonstrated that the LSD1 inhibitor successfully transports to the brain and results in a significant reduction in tumor burden when combined with NK cell infusion.

Immunotherapy of pHGG is in its infancy. Generally, pediatric central nervous system tumors are "cold" immunologically, like their adult counterparts.[9] While the subgroup of hypermutant tumors associated with congenital mismatch repair deficiency show preliminary efficacy when treated with immune checkpoint blocking antibodies,[10] there has been limited evidence that harnessing the immune system will be a successful strategy for the remaining pHGGs. NK cell infusion trials are currently under way in adult and pediatric central nervous system tumors, and the work by Bailey et al[4] in this issue provides compelling evidence to support a combination of NK cell infusion with systemic catalytic LSD1 inhibitors in subsequent trials. Additionally, this elegant preclinical study

supports further investigations in combination with chemo- and radiation therapies, in an effort to improve outcomes for children affected by these devastating malignancies.

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