New Molecular Insights and Potential Therapies for Diffuse Intrinsic Pontine Glioma

Diffuse intrinsic pontine glioma (DIPG) accounts for 10% to 15% of all pediatric central nervous system tumors, only shows transient response to external beam radiation therapy, and confers a median survival of 11 months. Multiple disappointing clinical trials with traditional chemotherapies underscore the need for new biological insights and novel therapies.

Significant recent advances in DIPG biology result from overcoming limited tumor samples and developing relevant animal models. Large-scale genomic studies showed that >70% of DIPGs contain a lysine to methionine substitution (K27M) in histone 3.1 and histone 3.3 (H3.3). This epigenetic alteration sequesters and inactivates the interacting polycomb repressive complex 2, reduces histone methylation, and causes aberrant expression of genes that are normally silenced, thereby driving tumorigenesis. Recent reports from Funato et al in Science and Hashizume et al in Nature Medicine used stem cell and DIPG-derived models to identify 2 different potential DIPG therapies.

To create candidate DIPG cells, Funato et al introduced a combination of 3 mutant genes: H3.3K27M, constitutively active platelet-derived growth factor receptor-α polypeptide (PDGFRα), and TP53 knockdown in human embryonic stem cell-derived neural progenitor cells (NPCs) (Figure 1A). H3.3K27M caused aberrant proliferation only in NPCs, but not in other cell types such as human embryonic stem cell-derived astrocytes (Figures 1D-1F). Combining H3.3K27M expression with active PDGFRα and inactive TP53 greatly increased proliferation, and DIPG resulted only from brainstem implantation of NPCs expressing this combination.

Expression profile analysis revealed that these mutant NPCs resembled a dedifferentiated neural rosette cell population, leading to the hypothesis that tumor growth could be inhibited by reducing expression of stem cell-associated genes (aberrantly overexpressed in H3.3K27M mutant cells). Small-molecule screening against the mutant NPCs identified a menin inhibitor (MI-2) with specific antiproliferative activity against H3.3K27M NPCs and patient-derived H3.3 K27 M DIPG samples but not in normal NPCs. Menin usually regulates histone methylation and is overexpressed in patient-derived DIPG cells; therefore, menin inhibition likely targets K27M tumorigenesis.

A complementary report by Hashizume et al studied 2 patient-DIPG lines with a heterozygous H3.3K27M mutation. 4 pediatric glioma lines with wild-type H3.3, and a pediatric glioma line with an H3.3 glycine to valine substitution (G34V). The 2 H3.3K27M lines had less dimethylated and trimethylated H3.3K27 compared with wild-type and H3.3G34V lines. They used GSKJ4, a small-molecule inhibitor of JMJD3 (a KDM6 demethylase that demethylates K27), a small-molecule inhibitor of JMJD3 (a KDM6 demethylase that demethylates K27), and showed GSKJ4 dose-dependent reversal of this effect on H3.3 hypermethylation in mutant H3.3K27M cell lines. GSKJ4 treatment also selectively inhibited growth of H3.3K27M mutants without affecting the wild-type or H3.3G34V cell lines. In addition, in vivo GSKJ4 treatment decreased tumor growth and improved survival of H3.3K27M-implanted...
mice. In vivo efficacy of GSKJ4 is aided by its demonstrated ability to cross the blood-brain barrier and to permeate the brainstem.

Rapid advances in understanding DIPG biology and identifying new potential therapies have resulted from discovery of the DIPG H3.3 K27M mutation. New insights into the molecular mechanisms underlying DIPG tumorigenesis have revealed promising molecular therapeutic agents that alter histone methylation biology (such as GSKJ4 and MI-2) and form a foundation for clinical trials to improve DIPG outcomes in the near future.

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REFERENCES


Buzz Kill: Neuronal Activity Promotes Glioma Proliferation

The impact of the tumor microenvironment on gliomagenesis and subsequent tumor growth is incompletely understood. Understanding the effect of surrounding cell subtypes on tumor and tumor-precursor cells is critical to understanding the mechanisms of glioma growth and is important to the search for...