DISTINCT AND SEPARABLE ROLES FOR HISTONE METHYLTRANSFERASE EZH2 IN NEUROGENIC ASTROCYTES

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BACKGROUND: The histone methyltransferase EZH2 is overexpressed in many tumors including gliomas. EZH2 catalyzes H3K27me3, which underlies Polycomb-mediated gene repression, and EZH2-inhibitors have been identified as potential therapeutic agents. In the adult brain subventricular zone (SVZ), a specialized population of astrocytes serves as neural stem cells (NSCs), generating new neurons throughout life. Understanding the epigenetic mechanisms that enable lifelong neurogenesis from SVZ NSCs, may help inform therapeutic strategies for gliomas. METHODS: We studied the expression and function of EZH2 in postnatal mouse brain with genetic strategies, gene expression, and chromatin analysis. The expression of EZH2 in the human brain SVZ was also analyzed.

RESULTS: In SVZ astroglia, EZH2 was distinctly required for both NSC self-renewal and neuronal lineage specification. By deleting the EZH2 target Ink4a/Arf, we were able to rescue NSC proliferation, but not neuronal differentiation. During adult neurogenesis from mouse SVZ astroglia, EZH2 directly targets Olig2, and repression of this bHLH transcription factor is required for neuronal differentiation. Genome-wide transcript and chromatin analyses also indicate that EZH2 prevents the inappropriate expression of transcription factors involved in non-SVZ neurogenesis. Analysis of human brain specimens indicated EZH2 expression in SVZ astrocytes as well as young migratory neurons. The cell-type expression and correlation with neurogenesis in the human SVZ was remarkably similar to that of the mouse, suggesting a conserved epigenetic mechanism for neurogenesis from this specialized population of astrocytes.

CONCLUSIONS: Our finding that EZH2 plays distinct and separable roles in this astroglial population provides novel insights into the complex role of Polycomb gene repression in both normal brain development and brain tumors. Our results, while counterintuitive, indicate that EZH2 is critical for both self-renewal proliferation via Ink4a/Arf repression and differentiation by repressing key developmental regulators, including Olig2, which is required for glioma cell proliferation. The development of EZH2 inhibitors for cancer chemotherapy may benefit from this new understanding of the multiple, distinct roles that EZH2 plays in neural cell differentiation. SECONDARY CATEGORY: Preclinical Experimental Therapeutics.