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Abstracts

HG-13. SOX9 AS A DOWN-STREAM TARGET IN RAS/MEK-DRIVEN PEDIATRIC GLIOMA

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Pediatric high-grade gliomas (pHGGs) represent approximately 8-12% of pediatric central nervous system (CNS) tumors and are associated with a dismal prognosis in patients. Genetic alterations in RAS/MEK/PI3K pathways and aberrant overexpression of receptor tyrosine kinases are a hallmark in glioma. We have recently shown that blockade of RAS/MEK, but not RAS/PI3K signaling, in oligodendrocyte progenitor cell (OPC)-derived murine HGGs block self-renewal and induces robust oligodendrocyte differentiation. To study if aberrant RAS/MEK signaling also prevents normal differentiation in astrocyte precursors, we employed a well-established astrocyte-derived HGG (GFAP-Ha^{V12}-Ras-LacZ, G-RAS) model. At birth, transgene expression (LacZ) was first identified in discrete regions, including the subventricular zone (SVZ). Expression of the transgene in SVZ neural stem cells (NSCs), but not OLIG2+ cells, resulted in an early postnatal astrocytoma formation and a progressive loss of neurogenesis. Treatment of SVZ tumorspheres from G-RAS mice and human GBMs, demonstrated that blockade of RAS/MEK, but not RAS/PI3K signaling, induced glial and neuronal differentiation. Treatment of premalignant G-RAS mice with the MEK inhibitor PD325901 completely restored neurogenesis. MEK inhibition in tumorsphere cultures effectively reduced expression of SOX9, a known barrier to neurogenesis. We confirmed that RNA interference of SOX9 induced neuronal differentiation in glioma cells. As one of the target genes of the neuronal determinant miR-124a, we demonstrate that reintroduction of miR-124a in HGG cells block SOX9 expression and induce neuronal differentiation. Our results suggest that a RAS/MEK/miR-124-SOX9 axis in the astrocyte lineage drives pediatric glioma formation.