Loss of Neurodevelopmental Transcription Factors in Glioblastoma Leads to Decreased Progression and Proliferation and Increased Survival

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Loss of Neurodevelopmental Transcription Factors in Glioblastoma Leads to Decreased Progression and Proliferation and Increased Survival

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BACKGROUND

Glioblastoma (GBM) makes up about 50% of primary brain tumors and survival has not increased notably over the last 30 years from 5% surviving past 5 years of diagnosis. Despite the inter- and intratumoral heterogeneity, key neurodevelopmental transcription factors, ASCL1 and OLIG2, have been shown to be present in GBM samples (A). Functionally, these basic-helix-loop-helix (bHLH) transcription factors form heterodimers with E-proteins (E47/TCF4) and bind to DNA to regulate transcription. ASCL1 was shown to bind to promoters and enhancer regions of genes involved in cell cycle and glial development including that of OLIG2(C). OLIG2 is able to bind to the majority of ASCL1 target genes as well as ASCL1 and OLIG2 loci (B,C). While ASCL1 and OLIG2 play roles in neuronal and glial development, their role in GBM is as of yet unknown. It has been proposed that the presence of ASCL1 and OLIG2 contribute to the neural stem cell-like properties of GBM cells which results in increased treatment resistivity and a high recurrence rate in patients.

OBJECTIVE

To assess the effects of loss or constitutive expression of ASCL1 and OLIG2 in GBM in vivo

METHODS

RESULTS

Figure 1: GBM progression following conditional knockout or constitutive expression of transcription factors.

Figure 2: Conditional knockout or constitutive expression of transcription factors results in changes to cellular composition of the tumor.

SOX10: oligodendrocytes GFAP: astrocytes

Figure 3: Conditional knockout or constitutive expression of transcription factors results in changes to cell proliferation and survival.

Figure 4: Conditional knockout or constitutive expression of transcription factors results in changes to tumor cell heterogeneity, targets of ASCL1 (Contactin 1)

CONCLUSIONS

This research shows that ASCL1 plays a role in the proliferation of cancer cells, as well, as the migration of these cells across the corpus callosum and into the parenchyma of the brain. The loss of ASCL1 alone slows tumor progression but is not enough to stop tumor growth entirely; the combined loss of ASCL1 and OLIG2 stops tumor growth and results in 100% survival of tumor mice up to 6 months.

FUTURE DIRECTIONS

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