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Abstract 3536: The role of Nuclear factor I transcription factors in glioma

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Abstract

Gliomas are the most common brain tumors in adults. Among the malignant gliomas, grade IV glioma, or glioblastoma (GBM), is the most aggressive form. Despite harsh treatments such as surgery, radiotherapy and chemotherapy, the median survival of GBM patients remains at just 12-15 months. GBM tumors could originate from cells of the glial lineage that have escaped the normal glial differentiation mechanisms. Therefore, by applying knowledge about normal glial development, we might understand how pathways that normally drive differentiation are affected in these tumors. If reactivating these pathways induces the differentiation of proliferative tumor cells, we could use this as a novel target for therapy.

Our research is focused on the Nuclear factor I (NFI) transcription factors, one of the key factors to induce glial differentiation during normal development and is implicated in glioma. In insertional mutagenesis glioma mouse models, Nfi genes are consistently disrupted, suggesting a role for NFI in glioma initiation. Furthermore, loss of NFIB is common in human astrocytoma, while loss of NFIA is associated with oligodendroglioma. To determine whether loss of Nfi alters glioma initiation, progression or tumor histology, we have crossed inducible glioma mice with conditional Nfi deletion mice to follow tumor initiation and progression using fluorescence imaging and immunohistochemistry.

Based on analyses of glioma mRNA expression data sets, NFIB expression correlates inversely with tumor grade and survival. Using immunofluorescence, we determined that both NFIA and NFIB are mainly expressed within the non-proliferative cells in GBM tissue, suggesting that NFI may play a direct role in tumor cell differentiation. To establish whether NFI expression can indeed inhibit tumor proliferation and induce differentiation, U251 GBM cells were transfected with NFI. While overexpression of NFIA and NFIB reduced cell proliferation, an NFI dominant-negative protein enhanced proliferation. We are currently validating these finding in vivo by electroporating NFI expression constructs into patient-derived GBM xenografts in mice. Our preliminary data show NFIB electroporated cells are indeed differentiated and non-proliferative.

Our data suggests that NFI-mediated glial differentiation can be induced in glioma to inhibit tumor growth and may prevent recurrence. Hence, activation of NFI could be a potential target for a glial differentiation-based approach to treat glioma.