Abstract 242: The gliogenesis initiation factor Nuclear Factor IB induces differentiation and inhibits growth of glioblastoma

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Abstract

Introduction: The phylogenetically-conserved vertebrate transcription factor, nuclear factor IB (NFIB), is a key component in the differentiation of astrocytes during the process of gliogenesis in the developing mammalian central nervous system; a process that goes awry following various genetic and epigenetic alterations during the genesis of glioblastoma (GBM), the commonest and most aggressive form of primary human adult brain cancer. We found expression of NFIB to be reduced in GBM compared to normal human brain tissue so investigated what effect increased expression of NFIB had on GBM.

Experimental procedures: Expression of NFIB was investigated by qPCR and western blot in normal human brain tissue, primary GBM surgical specimens and GBM cells lines. The Rembrandt database was interrogated for patient survival data relative to NFIB expression. GBM cell lines were derived from patient tumor tissue, following informed consent, and cultured under serum-free conditions to help preserve the phenotype of the original tumor. GBM cell lines were transfected with HA-tagged Nfib. Glial differentiation marker expression was investigated by qPCR and western blot. Stem/progenitor cell growth was investigated by neurosphere assay and by PKH26 staining. Cell proliferation was measured by MTS assay and Ki67 staining. Cell cycle analysis was performed by PI staining and FACS analysis. Apoptosis was investigated by cleaved caspase staining. Differential gene expression induced by Nfib expression was determined by microarray analysis. In vivo tumorigenicity was investigated using subcutaneous and intracranial xenografts in NOD/SCID mice.

Results: We found NFIB expression in both GBM surgical specimens and GBM cell lines to be reduced relative to normal brain tissue. Reduced NFIB expression was associated with poorer patient survival. Increased expression of Nfib in transfected GBM cell lines induced expression of glial differentiation markers, inhibited cell proliferation, reduced stem/progenitor cell growth, altered cell cycle progression, and inhibited tumor growth in murine models of GBM.

Conclusion: We have identified NFIB as a novel tumor suppressor gene in human GBM.

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