

NODAL PROMOTES GROWTH AND INVASION IN HUMAN GLIOMAS

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Uncontrolled growth and diffused invasion are major causes of mortality in patients with malignant gliomas. Nodal has been shown to play a central role in the tumorigenic signaling pathways of malignant melanomas. In this study, we show that Grade IV human glioma cell lines expressed different levels of Nodal, paralleled to the potential for cell invasiveness. Treatment of glioma cell lines with recombinant Nodal increased MMP-2 secretion and cell invasiveness. The ectopic expression of Nodal in GBM glioma cells that expressed Nodal at low level resulted in increased MMP-2 secretion, enhanced cell invasiveness, raised cell proliferation rates *in vitro*, increased tumor growth *in vivo*, and was associated with poor survival in a mice xenograft model. In contrast, the knockdown of Nodal expression in U87MG glioma cells with high Nodal expression level has reduced MMP-2 secretion, less cell invasiveness, lower tumor growth *in vivo*, and longer lifespan in mice with U87MG/shNodal cell xenografts. In addition, Nodal knockdown promoted the reversion of malignant glioma cells toward a differentiated astrocytic phenotype. Furthermore, our data support the notion that Nodal may regulate glioma progression through the induction of the leukemia inhibitory factor (LIF) via activated Smad.

Key words: Glioma; Invasion, MMP-2, Nodal

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