TITLE

Aberrant Activation of Wnt/β-catenin signaling pathway promotes tumor progression in glioma.

ABSTRACT

Gliomas account for ~30% of all brain and central nervous system tumors and 80% of all malignant brain tumors. The highly malignant grade IV glioma referred to as glioblastoma is associated with poor patient prognosis and shows median patient survival of only ~12–14 months. Glioblastoma is driven by a subpopulation of brain tumor-initiating cells, termed as glioma stem cells and presence of these cells within the tumor contributes toward cellular plasticity and heterogeneity. Presence of a distinct population of cells that drives tumor progression supports the hierarchical model of tumor development in Glioblastoma (GBM) and substantiates the cancer stem cell hypothesis. We provide direct evidence about the role of activated Wnt/β-catenin signaling pathway in malignant transformation and tumor progression in glioma. We demonstrate that Wnt ligands - Wnt1 and Wnt3a are expressed in a graded manner in glial tumors and are also over-expressed in glioma stem cell-lines. A selective inhibition of Wnt signaling pathway by selective knock-down of its ligands Wnt1 and Wnt3a in glioma-derived stem-like cell-lines leads to decreased cell proliferation, cell migration and chemo-resistance. Furthermore, silencing of Wnt signaling pathway in glioma stem cells reduces their capacity to form intra-cranial tumors *in vivo*. Next, we provide evidence about involvement of a Fbxo family member in Wnt/β-catenin signaling and glioma progression. Our studies through a myriad of experimental model systems establishes that aberrant regulation of Wnt/β-catenin signaling pathway exhibited by glioma stem cells is a key primary event in glioma progression and interference with Wnt signaling offers a novel therapeutic strategytowards management of glioblastoma.