Abstract

Inspite of the significant progress in glioma biology, the prognosis of these tumors is still dismal. One of the reasons for this is incomplete knowledge regarding the origin of these tumors and lack of information about the characteristics of cells existing in these tumors. This has led to failure in developing a cell and molecular therapy guided approach against malignant cells responsible for tumor development and therapeutic resistance.

Establishment and characterization of Glioblastoma cell lines in various grades represent an essential step to obtain better in vitro and in vivo experimental models to study glioma progression. We report here development and characterization of twenty eight long term glioma cultures, from various grades of surgical brain tumor samples and provide data supporting their usefulness as models for studying molecular events underlying glioma genesis.

Presence of brain tumor stem cell (BTSC) population in gliomas with self-renewing and tumorigenic potential are considered causal in development and propagation of tumor. Accumulating evidence suggests that BTSC might originate from the transformation of neural stem cells (NSC) and their progenitors. The presence of a CD133+/nestin+ population in brain tumors suggests that a normal neural stem cell may be the cell of origin for gliomas. In this study, we have identified human CD133-positive NSCs from adult glioma tissue and established them as long-term in vitro culture-human neuroglial culture (HNGC)-1. Replicative senescence in HNGC-1 led to a high level of genomic instability and emergence of a spontaneously immortalized clone that developed into cell line HNGC-2 with features of cancer stem cells (CSC), which includes presence of side-population, ALDH positivity, ability for self-renewal and capacity to form CD133-positive neurospheres and develop intracranial tumors. The data from my study specifies an important role of genomic instability in initiation of transformed state as well as its progression into highly tumorigenic CSC. The activated forms of Notch and Hes isoforms were found significantly over-expressed in brain tumor stem cells. These findings suggest that this model comprising of HNGC-1 and HNGC-2 cells is a useful system for studying pathways involved in self-renewal of stem cells and their transformation to cancer growth.
stem cells.

The study demonstrates a phenomenal over-expression of Wnt ligands involved in canonical Wnt signaling - Wnt1 (>900 fold) and Wnt3a (>400 fold) in malignant transformation from neural stem cell-like cells to brain tumor stem cells. A similar over-expression of Wnt1 and Wnt3a exists in GBM tumors. Enhanced expression of Wnt1 and Wnt3a, was found to promote self-renewal, tumorigenicity and invasiveness of glioma stem cells. Characteristically, inhibiting Wnt signaling by knocking down Wnt1 strongly suppressed tumor growth and cell migration in vitro while inhibiting Wnt3a completely abrogated tumor formation and ensured disease free survival.

The identification of Wnt3a as a potent glioma oncogene highlights importance of β-catenin/Wnt signalling pathway in malignant behaviour of GBM. This study imply that Wnt signalling pathway is important in tumor vascularization and invasiveness in GBM and inhibiting this pathway is a viable therapeutic option in management of chemo-resistant gliomas arising from glioma stem cells.