Malignant Gliomas Originate From Neural Stem/Progenitor Cells and Are Maintained By Cancer Stem Cells

Jian Chen Ph.D.
The University of Texas Southwestern Medical Center at Dallas, 2011
Graduate School of Biomedical Sciences
Supervising Professor: Luis F. Parada, Ph.D.

Date Available: 12/12/2013
Summer 2011
Genetics and Development Ph.D.
Bibliography: pp. 144-161

Keywords: malignant glioma; neural stem cells; cancer stem cells; mouse models; Tamoxifen; Ganlidovir; Temozolomide; combinational therapy

Malignant glioma is one of the most aggressive cancers. To study the biology of glioma, our lab previously developed a series of mouse models that phenocopy both tumor initiation and progression through stochastic tumor suppressor loss-of-heterozygosity (LOH). To determine whether the mouse models recapitulate human glioma at the molecular level, we have performed gene set enrichment analysis (GSEA) comparing the molecular signature of tumors that develop in our mouse glioma models to the gene expression profiles of a number of human tumors. Our mouse glioma models share high similarity with human GBM and showed a generally proneural marker gene expression profile. We also found that tumors from the same initial genetic mutations can be further divided into several subtypes.

Previous studies suggested a neural stem/progenitor cell (NSC) origin for gliomas, however strict exprimental evidence was still lacking. To examine the role of NSCs in glioma, we developed an NSC-specific tamoxifen-inducible nestin-cre driver mouse. When crossed to the NF/p53/Pten flox mice and induced with tamoxifen at E13.5, the Nes-Cre;Nf/p53/Pten mutant mice exhibited tumor initiation and progression similar to our previous mouse model using hGFAP-cre, with complete penetrance. All analyzed mice that were induced at 4 weeks such that only adult neural stem cells were targeted, developed malignant astrocytoma 7 - 12 months after induction. These findings indicate that despite their rarity, neural stem/progenitor cells are sufficient targets for the accumulation of mutations that initiate malignant astrocytomas.

Our highly physiological relevant mouse model also allowed us to address the question of how glioma is maintained in vivo: whether tumors are maintained by a subpopulation of cells with self-renewal capacity that supplies tumor bulk, or whether the majority of tumor cells have the capacity to maintain the tumor. In our spontaneous somatic mouse model of glioma, a Nestin-¦¤TK-IRES-GFP transgene labels the primary tumor cells that are required for tumorigenicity in allograft assays. Ablating endogenous Nes-¦¤TK-positive cells significantly extended the survival of tumor-bearing mice by decreasing tumor proliferation and infiltration. We show that the glioma drug, temozolomide, selectively targets endogenous CSC-derived proliferating cells. Furthermore, a combination therapy targeting both dividing cells and the CSCs arrests tumor progression.