Glioblastoma and Cancer Stem Cells: Why Current Therapy is Not Effective?


The theory of Cancer Stem Cells (CSCs) has been proposed for a long time ago, nevertheless demonstration of their existence has only occurred within the last decade. Regarding CSCs are tumour cells with properties that are similar to those described for adult stem cells: long-term self-renewal and ability to give rise to one or more differentiated cell lineages. The potential significance of CSCs in cancer biology has been demonstrated by several studies showing contributions to therapeutic resistance, angiogenesis, and tumor recurrence.

Moreover, Glioblastoma (GBM), a WHO-defined grade IV astrocytoma, is the most common and lethal type of primary brain tumours in adults. Despite recent therapeutic advances in other cancers, GBM treatment remains essentially palliative and patients median survival is dismal. Within GBM, CSCs referred to as Glioblastoma Stem Cells (GSCs), have the ability to self-renew, differentiate into distinct lineages within the tumour, and initiate tumour xenografts in immunocompromised mice. Furthermore, GSCs are a tumour cell subset displaying radiotherapy and chemoresistance and resistant to therapy. Therefore, targeting of GSCs may directly improve current therapies efficacy.

**Introduction**

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**Theoretical framework**

- **GSCs existence has been demonstrated by two types of assays**
  - Clonogenic assays: In vitro
  - Tumorigenic assays: In vivo

- **GSCs**
  - Have a long-term self-renewal ability
  - Share similar properties with normal neural stem cells (NSCs) and differentiate into different lineages

- **GSCs may result from genetic and epigenetic mutations in neural stem/progenitor cells or from differentiated cells such as astrocytes after a series of mutations or an epigenetic reprogrammation**

- **GSCs niche**
  - Like normal adult stem cells, GSCs also may exist in a specialized microenvironment, a stem cell niche. Several studies have shown that GSCs may be within two types of niches.

- **GSCs resistance mechanisms**
  - Current therapy for newly diagnosed GBM includes maximal tumour bulk resection followed by radiotherapy and adjutant chemotherapy with temozolomide (TMZ)

- **GSCs may exist within hypoxic niches to maintain lower levels of reactive oxygen species (ROS) and to remain out of reach of chemotherapy promoting their survival and phenotype**

- **GSCs enhance DNA damage response (DDR) as a result of DNA injury induced by radiation. DDR was measured by the activating phosphorylation of several critical checkpoint proteins (ATM, Rad17, Chk1, and Chk2)**

- **GSCs express high levels of the repair enzyme O6-methylguanine-DNA methyltransferase (MGMT), removing DNA adducts induced by TMZ. Furthermore, GSCs increased expression of drug transporters including the adenosine triphosphate–binding cassette (ABC) transporters that pump out chemotherapeutic agents.**

**Project aims**

- Summarize current state of knowledge about CSCs, focusing on GSCs and their role on GBM therapeutic resistance.
- Create a disclosure tool based on bibliographic review.
- Design a website aimed to neuro-oncology nurses and residents, and to medicine students.

**Material and methods**

Search on Pubmed database using terms such as: glioblastoma, cancer stem cells, glioblastoma stem cells, chemoresistance, radioresistance. Original and review articles were selected according to publication year and journal impact factor.

Previous to website construction it was performed an online survey to 19 subjects (9 neuro-oncology nurses, 5 neuro-oncology residents, and 5 medicine students) using the follow website www.e-encuestas.com.

Ultimately website was constructed through online platform www.wordpress.com.

**Conclusions and future perspectives**

- **CSCs are primarily responsible for tumour recurrence and therapy resistance**
- Future studies should focus on developing strategies for deplete these cells.
- **Consistent with the idea that inducing CSC differentiation might be therapeutically beneficial, it has been shown that bone morphogenetic protein 4 (BMP-4) induces the differentiation of GSCs and inhibits tumour growth in vivo when BMP4-coated beads were orthotopically transplanted together with GSCs into immunodeficient mice.**
- **MicroRNAs (miRs) can also target the Notch pathway in GBM, miR-34a targets Notch1 and Notch2 mRNAs, resulting in GSC differentiation.**
- **One of the main goals of future studies in GBM would be to develop therapies aimed at decreasing radioresistance and chemoresistance of GSCs. Therefore radio-chemoresistance molecular mechanisms should continue to be investigated.**
- **it was determined that CD133+ GSCs are primarily radioresistant, and that these cells can be sensitized by inhibition of Chk1 and Chk2.**

**References**