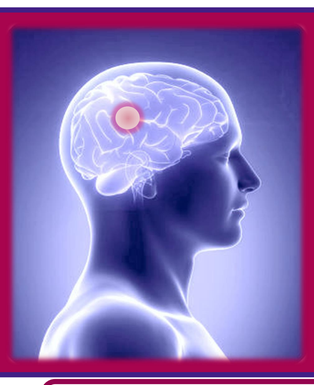

Glioblastoma and Cancer Stem Cells: Why Current Therapy is not Effective?

Garzón Chávez, Diana. Degree in Biomedical sciences. Universitat Autònoma de Barcelona. June 2015.

Introduction

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 linages. 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 chemotherapy resistant and likely contribute to rapid tumour recurrence. Thereby molecular targeting of GSCs may directly improve current therapies efficacy .

Theoretical framework

Treated patients median overall survival: 12-15 months

Affects adults preferentially (peak incidence of 45-60 years)

European and North America incidence: 3-4/100,000 person-years

Males have slight preponderance over females (male/female ratio of 3:2)

GBM

Mortality main cause in patients with GBM is tumour reoccurrence, which is attributed to treatment-resistant CSCs within and surrounding primary tumour.

GSCs

GSCs existence has been demonstrated by two types of assays

- Clonogenic assays *In vitro* — Assessing sphere-forming efficiency in non-adherent culture conditions
- Tumorigenic assays *In vivo* — Carrying out tumour-initiating assays in immunocompromised mice

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 reprogram.

GSCs share similar properties with normal neural stem cells (NSCs) including enhanced potentials for proliferation, angiogenesis, invasion and modulating immune responses.

Some important **stem cell transcription factors** involved in regulating normal stem cells (such as Sox2, Oct4, Nanog, c-Myc, Olig2 and Bmi1) are also required for the maintenance of a GSC phenotype.

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.

Hypoxic niche

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.

Perivascular niche

GSCs are located in close contact with endothelial cells (ECs) 113+, which secrete soluble factors for maintain the self-renewal and undifferentiated phenotype of GSCs (*Figure 1*).

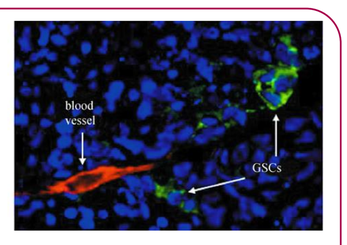

Figure 1. GBM frozen section was immuno-stained with anti-L1CAM antibody for GSCs and anti-CD31 antibody for ECs of blood vessel, and counterstained with DAPI for DNA. *Image from: Bao S, et al. Cancer Res. 2006.*

GSCs resistance mechanisms

Current therapy for newly diagnosed GBM includes maximal tumour bulk resection followed by radiotherapy and adjuvant chemotherapy with temozolomide (TMZ)

Radioresistance

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, Chk2 and Chk1).

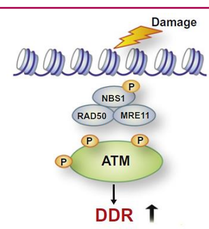

Figure 2. In GCSs DDCR is potentiated by up-regulation of Nijmegen-breakage syndrome-1 (NBS-1) protein, a critical component of the MRE11-RAD50-NBS1 (MRN) complex that activates the ataxia telangiectasia mutated (ATM) kinase. *Image from: Alison MR, et al. Cancer Treat Rev. 2012.*

Chemoresistance

GSCs express high levels of the repair enzyme O6-methylguanine-DNAmethyltransferase (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.

Results

As mentioned above before constructing website it was performed online surveys with the selected population sample. Four questions were formulated in the survey, each with only one option to response (*overall results may be consulted on memory project*).

Information gathered through the extensive bibliographic review was reflected on website adapting the concepts to population knowledge. Website design was performed according to results of previous survey. Below it is provide the website link https://glioblastomastemcells.wordpress.com/ (Fig. 3).

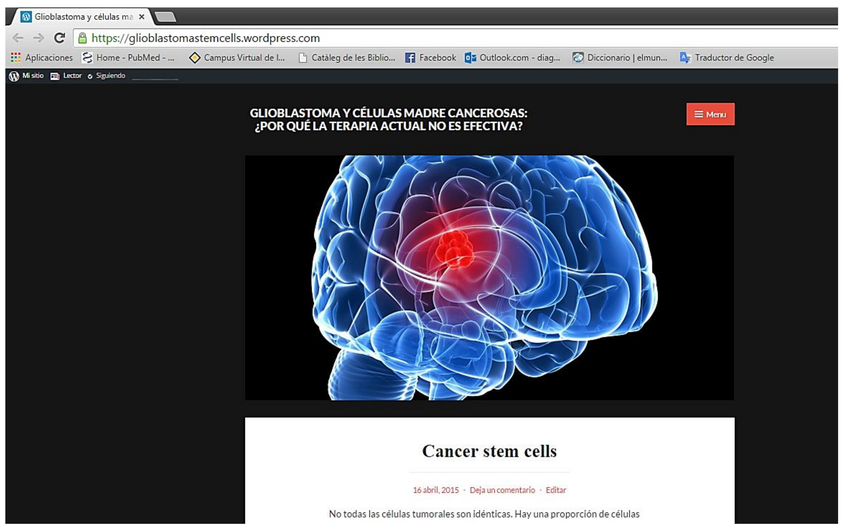

Figure 3. Snapshot of website home.

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.

Drugs could impair CSC self-renewal, induce their specific cell death, induce their differentiation or target their niche (*Figure 4*).

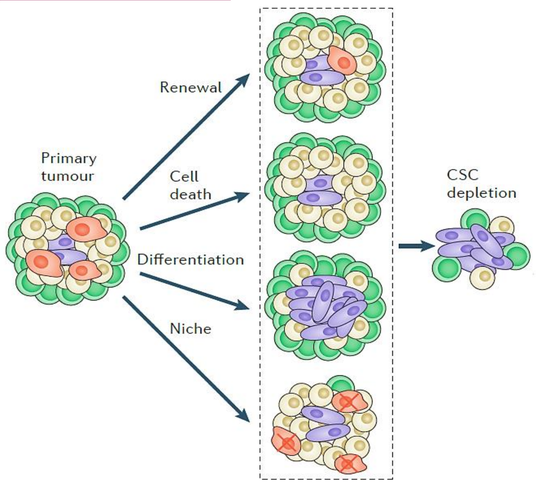

Figure 4. Strategies for deplete CSCs. Image from: Beck B, et al. Nat Rev Cancer. 2013.

- 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

1. Beck B, et al. Unravelling cancer stem cell potential. Nat Rev Cancer. 2013.
2. Ostrom QT, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. Neuro Oncol. 2014.
3. Singh SK, et al. Identification of human brain tumour initiating cells. Nature. 2004.
4. Huang Z, et al. Cancer stem cells in glioblastoma-molecular signaling and therapeutic targeting. Protein Cell. 2010.
5. Calabrese C, et al. A perivascular niche for brain tumor stem cells. Cancer Cell. 2007.
6. Heddleston JM, et al. The hypoxic microenvironment maintains glioblastoma stem cells and promotes reprogramming towards a cancer stem cell phenotype. Cell Cycle. 2009.
7. Bao S, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature. 2006.