Introduction

Malignant gliomas, and in particular high-grade astrocytomas like glioblastoma multiforme (GBM), are the most common and lethal primary tumor of the central nervous system (CNS). Although they can also be the result of the progression of lower-grade gliomas (secondary GBM), they usually appear de novo in more aggressive forms and affect older patients (primary GBM). Despite technological and medical advances of the last decades, their prognosis remains grave and current treatments can only contribute to a median survival of 14.6 months.

The question of how it is possible for a so carefully orchestrated and (initially thought) mitotically inert organ to develop such aggressive tumors has been a mystery for ages. However, since neurogenic and gliogenic events were discovered in the past three decades, the study of the origin and biology of gliomas like GBM has gained strength. This has led to the eventual identification of glioma stem cells (GSCs) and the major instauration of the Cancer Stem Cell Hypothesis in these tumors are, from the very beginning, far from being equal because of their intrinsic, stem-cell-like properties. The existence of such a population would explain why these tumors are so heterogeneous, therapy-resistant, and, importantly, display an innate tendency to relapse.

Adult Neurogenesis & Gliogenesis in the SVZ

Both the subgranular zone (SGZ) of the dentate gyrus and the subventricular zone (SVZ) are considered indispensable neurogenic areas. The SVZ lies at the wall of the lateral ventricles and is the largest germinal region in the adult CNS (figure 1). It originates from the neuroepithelial epithelium of the embryonic ventricular zone and harbors a population of several thousand astrocyte-like cells, termed 

Third

[Image]

Lateral Wall of the Lateral Ventricle

about GSCs – Main Features

- Highly angiogenic & invasive behavior
- Resistance to chemo- and radiotherapy
- Immunosuppressive potential
- Indefinite self-renewal capacity
- Ability to perpetuate the tumor in orthotopic transplants
- Ability to generate diversified neuron-like & glial-like progeny

Role of the Tumor Microenvironment

The Perivascular Niche: a Suitable Place for Hypoxia?

GSCs populating GBM are found in a microenvironment that resembles that of the NSCs, further suggesting the idea that these tumors directly arise from the SVZ. In the so-called perivascular niche (PNV), vasculature is critical for supporting and maintaining the undifferentiated state of GSCs and sets itself as a characteristic feature of high-grade gliomas. However, since these blood vessels are usually chaotic and disorganized, this results in irregular blood flow and inadequate perfusion. This leads to the emergence of necrotic areas around which new GSC-enriched, hypoxic niches arise (figure 3).

Hypoxia is Critical for GSC Maintenance & Tumor Progression

Under hypoxic conditions, cancer cells switch on an adaptive program that is fundamentally governed by the hypoxia-inducible factor (HIF) family of transcription factors: the hypoxic response (figure 4).

Why Does Antiangiogenic Therapy Fail?

- GSCs populating GBM are responsible for tumor initiation and maintenance. Although their origin is not clear, increasing evidence suggests a substantial portion of GBMs may arise from SVZ-derived NSCs or self-renewing OPCs.
- GSCs home perivascular and hypoxic niches that provide intra-tumoral tissues tumor growth, and thus arise as novel therapeutic targets.
- Since hypoxia induces cell plasticity towards a stem-like phenotype, a rigid hierarchy is not likely to be present in malignancies following the Cancer Stem Cell Model.
- Combinations of antiangiogenic drugs and HIF-1α inhibitors might prove as an effective therapeutic approach to GBM.

Concluding Remarks

Materials & Methods

Extensive literature search was performed at PubMed database. Papers were selected and reviewed according to topic relevance, time and journal of publication. Key words: Adult Neurogenesis, SVZ, Gliogenesis, Glioblastoma multiforme, Perivascular Niche, Hypoxia, HIF-1α, HIF-2α.