

Tumor Stem Cells and the Microenvironment in Glioblastoma

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Received date: March 23, 2016; Accepted date: April 01, 2016; Published date: April 04, 2016

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Keywords: Stem cells; Glioblastoma; Clonogenicity; Tumor initiating cells

Introduction

Glioblastoma stem cells (GSCs) are represented by a small group of cells with renewal and proliferation, clonogenicity, differentiation and tumorigenic capacity, responsible for tumor proliferation, invasion, recurrence and resistance to therapy [1]. They can be or not identified with the so-called tumor initiating cells (TICs). The hypothesis of the stem cell origin of gliomas includes the origin of these cells from tumor transformation of normal neural stem cells, either in the sub-ventricular zone or during and at the end of migration, at variance with the dedifferentiation either of normal adult glia by embryonic regression or of tumor cells as a consequence of mutation accumulation [2,3]. Another possible source is represented by oligodendroglial NG2 precursor cells [4-7]. It has been long discussed whether GSCs represent a special cell type or, simply, a functional status that can be acquired or lost as the consequence of microenvironment regulation [8-10]. As the stemness features can be lost with differentiation in the normal nervous cytotogenesis, so they can be progressively acquired during dedifferentiation.

In glioblastoma (GBM), a major problem, important for the therapeutic strategy, has been that of the location in the tumor of GSCs. Since therapies are ineffective when directed toward the tumor mass, constituted by differentiated inert cells, it was suggested to address them to GSCs in order to destroy the tumor source. Some hypotheses have been put forward on this matter, but very probably they reside between central necrosis and the proliferative zone of GBM, with a strict relationship with hypoxia [11,12].

The GSC regulation would be accomplished by the tumor microenvironment that is not easily definable from the phenotypic point of view; its maximum expression is believed to occur in the so-called niches which can be divided in perivascular and perinecrotic. The former are represented by cells wrapping vessels and the latter by cells around circumscribed necroses [13,14]. In both types the occurrence of GSCs is mandatory for the definition of niche.

Perivascular niches are recognized when together with tumor astrocytes, immune cells, fibroblasts or pericytes, GSCs can be demonstrated by their stemness antigens, such as Nestin, SOX2, OCT4, Musashi.1, CD133 or specific antigens [14-17]. A double signaling exchange is realized between endothelial cells and GSCs: the former generate or keep the GSC stemness by Notch for proliferation and invasion, and the latter stimulate endothelial cells to proliferate by VEGF and SDF-1 for neo-angiogenesis [13]. By this definition, not each perivascular distribution of cells is obviously a niche (Figure 1).

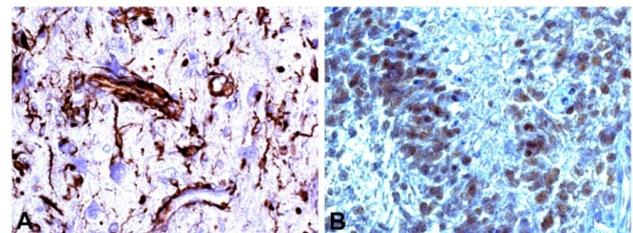


Figure 1: (A) Nestin-positive cells on capillaries, DAB, X400; (B) Development of necrosis in an area of SOX2-positive cells, DAB, X400.

Perinecrotic niches are given by the generation of GSCs by hypoxia through HIF.1/2 [16], but their genesis may have other interpretations. Circumscribed necroses are formed in hyper-proliferating areas of GBM, near central necrosis, by the imbalance between the high proliferation capacity of tumor cells and the low one of endothelial cells. An ischemia is thus realized in them as the consequence of oxygen deprivation. In our hypothesis, these areas are mainly composed of precursors/stem cells, positive to stemness antigens as deriving from the dedifferentiation of tumor cells that leads them to the acquisition of stemness properties [17]. The cells remaining to line the necrosis are those spared by it [17-19].

The regulation of the stem cell status is accomplished by the microenvironment that through its intrinsic (Notch, OCT4, Wnt/ β -catenin, BMI1, Nanog and c-Myc) and extrinsic (EGFR, PTEN, PI3K/AKT, Bmp) signaling controls the conversion of tumor cells into tumor stem cells and vice versa in a kind of cell reprogramming [20,21]. This could be important for the therapeutic strategy definition.

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