Life Sciences 89 (2011) 532–539

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Minireview

Glioblastoma cells: A heterogeneous and fatal tumor interacting with the parenchyma

Tercia Rodrigues Alves, Flavia Regina Souza Lima, Suzana Assad Kahn, Denise Lobo, Luiz Gustavo Feijó Dubois, Rossana Soletti, Helena Borges, Vivaldo Moura Neto *

Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

ARTICLE INFO

Article history:
Received 20 December 2010
Accepted 27 April 2011

Keywords:
Glioblastoma
Pathologic angiogenesis
Neoplasm invasion
Microglia
Pore forming cytotoxic proteins
Neoplastic stem cells

ABSTRACT

Glioblastomas (GBMs) are considered to be one of the deadliest human cancers, characterized by a high proliferative rate, aggressive invasiveness and insensitivity to radio- and chemotherapy, as well as a short patient survival period. Moreover, GBMs are among the most vascularized and invasive cancers in humans. Angiogenesis in GBMs is correlated with the grade of malignancy and is inversely correlated with patient survival. One of the first steps in tumor invasions is migration. GBM cells have the ability to infiltrate and disrupt physical barriers such as basement membranes, extracellular matrix and cell junctions. The invasion process includes the overexpression of several members of a super-family of zinc-based proteinases, the Metzincin, in particular a sub-group, metalloproteinases. Another interesting aspect is that, inside the GBM tissue, there are up to 30% of microglia or macrophages. However, little is known about the immune performance and interactions of the microglia with GBMs. These singular properties of GBMs will be described here. A sub-population of cells with stem-like properties may be the source of tumors since, apparently, GBM stem cells (GSCs) are highly resistant to current cancer treatments. These cancer therapies, while killing the majority of tumor cells, ultimately fail in GBM treatment because they do not eliminate GSCs, which survive to regenerate new tumors. Finally, GBM patient prognostic has shown little improvement in decades. In this context, we will discuss how the membrane-acting toxins called cytolysins can be a potential new tool for GBM treatment.

Contents

Introduction

Glioblastoma (GBM) is the most common primary malignant glioma in adults and is characterized by a high mortality rate. Clinically, gliomas are divided into four grades and the most aggressive of these, grade IV astrocytoma or GBM, is also the most common in humans (Kleihues and Cavanee, 2000).The average survival of GBM patients from the time of diagnosis is less than a

* Corresponding author at: Vivaldo Moura Neto. Instituto de Ciências Biomédicas, Bloco F, CCS, Universidade Federal do Rio de Janeiro, Av. Carlos Chagas Filho, 373. Rio de Janeiro, CEP 21949-590, Brazil. Tel.: +55 21 2562 6465; fax: +55 21 2290 0587.
E-mail address: vivaldo@anato.ufrj.br (V.M. Neto).

0024-3205
doi:10.1016/j.lfs.2011.04.022

year. Standard treatment comprises resection of the majority of the tumor mass, followed by chemotherapy and radiotherapy (Kanu et al., 2009; McCarthy, 2006; Minniti et al., 2009). However, this kind of tumor is usually highly invasive, making it extremely difficult to treat by total surgical resection or radiotherapy, which contributes to frequent recurrences and a very poor prognosis. Few anticancer drugs can modify the rapid tumor growth, and none is ultimately efficient. Therefore, most patients develop tumor recurrences or progressions after this combination of treatments (Kumar et al., 2008; Yang and Aghi, 2009). Transforming GBM into a treatable entity will require new paradigms in cancer biology and the understanding of the mechanisms underlying GBM invasion, treatment resistance and recurrence. Like most solid tumors, GBMs consist of heterogeneous cancer cells (Faria et al., 2006), as well as competent to recruit vasculature, inflammatory cells and interact with stromal elements (Hanahan and Weinberg, 2000). In this report, we will approach the interaction of GBMs with their rich tumor microenvironment. In this context, we will discuss GBM capability to interact with other cell types, to grow and invade other brain regions rapidly, as well as the possibility of using new drugs in GBM treatment and the relevance of glioblastoma stem cells (GSCs) regarding tumor progression.

Glioblastoma vascularization

The growth of solid tumors is limited to the emergence of new blood vessels (Folkman, 1972; Greene, 1961). In 1986, Dvorak classified solid tumors as wounds that do not heal, based on their requirement of the surrounding stroma to grow beyond a minimal diameter size, and also, with regard to their capability to induce a massive and continuous angiogenesis.

GBMs are among the most vascularized tumors in humans (Plate and Risau, 1995; Takano et al., 2010). In this type of tumor, malignity is often followed by endothelium proliferation (Daumas-Duport et al., 1988) and angiogenesis is correlated with aggressiveness, grade of malignancy and inversely correlated with patient survival. Indeed, the high microvessel density can be used as a prognostic postoperative indicator for patients with GBMs. Analyses from 93 sectioned formalin fixed paraffin embedded glioma samples specifically immunostained for von Willebrand factor showed a direct correlation between patients with shorter survival and higher microvessel counts, although the typical histopathological heterogeneity in GBMs could induce incorrect results (Leon et al., 1996). However, these proliferative GBM vessels exhibit abnormal morphology. Feigin et al. (1958) observed hyperplastic endothelial cells with neoplastic properties, forming a sarcomatous tissue intermingled with the pre-existing GBM mass. The endothelial cells possessed fairly large, plump, elongated or ovoid, vesicular, moderately chromatic nuclei, evidencing a high degree of variability and ultrastructural disorganization of the wall of small blood vessels (Nystrom, 1959). Morphological and phenotypical differences were observed in these vessels, such as variable diameters, permeability, tortuosity, heterogeneous distribution and an irregular basal lamina (Bart et al., 2000; Vajkoczy and Menger, 2004), including low VE-cadherin expression (Charalambous et al., 2006) and the absence of the tight junction proteins claudin-1 and -5 (Rascher et al., 2002). Moreover, endothelial cells from GBM express α-smooth muscle actin and exhibit a high proliferation and migratory capacity, and are also more resistant to apoptosis when compared to normal endothelial cells (Bian et al., 2006; Charalambous et al., 2006). All these features mentioned above result in sub-functional newly formed vessels (Bart et al., 2000; Vajkoczy and Menger, 2004) as summarized in Fig. 1. This abnormal vasculature is associated with thrombi and, consequently, with adjacent necrotic areas (Pietsch and Wiestler, 1997).

One possible explanation for this chaotic vascular organization is the overexpression of the VEGF (vascular endothelial growth factor) and poor pericyte recruitment (Bergers and Benjamin, 2003). The

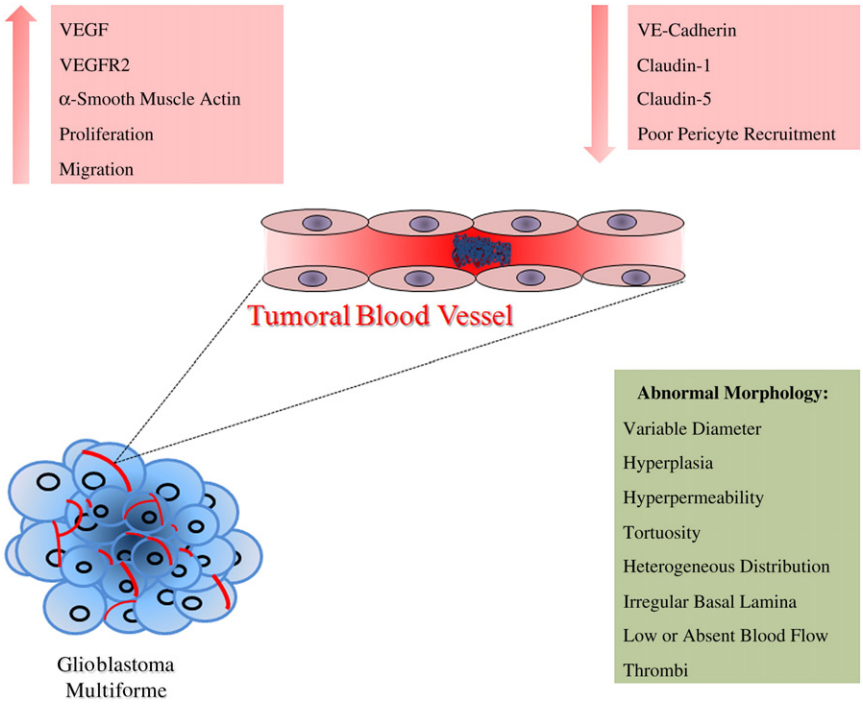

Fig. 1. Abnormal vascularization in Glioblastomas (GBM). Endothelial cells, that nourish GBMs, present morphological and molecular aberrations. Overexpression of the VEGF and its receptor, VEGFR2, can induce VE-cadherin cytoplasmic domain phosphorylation, which disrupts cell–cell contact, which then contributes to vessel hypermeability. Moreover, low levels of VE-cadherin or even the absence of the cytoplasmic tight junction proteins, claudin-1 and claudin-5, may equally result in the formation of leaky vessels. Pericytes are involved in mature blood vessel establishment, and, in GBMs, their poor recruitment can explain the immature blood vessel morphology. When compared to normal endothelial brain cells, GBM endothelial cells are more proliferative and migratory, prerequisites for angiogenesis. Finally, the angioarchitecture in GBMs is disorganized and subfunctional. GBM endothelial cells present common features such as: variable diameter, hiperplasia, hyperpermeability, tortuosity, heterogeneous distribution, irregular basal lamina, low or absent flow and thrombi.