

Angiogenesis in Brain Tumors: Gliomas and Meningiomas - A Review

Zygmunt Siedlecki¹, Karol Nowak¹, Sebastian Grzyb², Fasi A. Shaik³
and Maciej Śniegocki¹

¹Department of Neurosurgery, Neurotraumatology and Pediatric Neurosurgery, The Ludwik Rydygier Collegium Medicum in Bydgoszcz, The Nicolaus Copernicus University in Toruń

²Department of Clinical Pharmacology, The Ludwik Rydygier Collegium Medicum in Bydgoszcz, The Nicolaus Copernicus University in Toruń

³Department of Biotechnology, University of Wolverhampton, United Kingdom. Present: Jain University, India

Corresponding address:

Dr. med. Zygmunt Siedlecki Department of Neurosurgery, Neurotraumatology and Pediatric Neurosurgery,
the Ludwik Rydygier Collegium Medicum in Bydgoszcz,
ul. Skłodowskiej-Curie 9
85-094 Bydgoszcz
e-mail: siedlecki@cm.umk.pl

Abstract : Angiogenesis is a key process in cancerous tumors development. It is regulated by angiogenesis factors. Although in any type of cancer it involves the formation of new blood vessels, there are some differences between cancer types. Angiogenesis is also crucial in brain tumors development. Angiogenesis inhibitors are used in neurooncological treatment. We present an overview of the knowledge of angiogenesis in the two main types of primary brain tumors: gliomas and meningiomas. We hope that the current state of this knowledge is important in the topic of brain tumors pathology and therapy.

Keywords: angiogenesis, glioma, meningioma

Literature review

Angiogenesis in gliomas

Gliomas are differentiated in intensity of blood vessel development depending on the degree of malignancy [1]. The network of pathological blood vessels is the hallmark of glioblastoma multiforme (GBM), which is considered the most vascularized brain tumor [2,3]. However, it is not present in low-grade gliomas (LGG), in which the vascular image resembles that of the normal brain. Vascular endothelial growth factor (VEGF), is the main factor responsible for angiogenesis in glial tumors [4]. It regulates the formation of new blood vessels and their permeability, acting through the VEGFR-1 and VEGFR-2 receptors [5,6]. It has been shown that in high grade gliomas (HGG), the concentration of mRNA responsible for transcription of VEGF (VEGF mRNA) is 50-fold increased compared to normal brain tissue, in which a relatively low concentration of VEGF mRNA was found by *in situ* hybridization, as in LGG [4-6].

Neoplastic tissue hypoxia is a strong factor inducing the formation of new blood vessels within gliomas [6,7]. In the case of HGG with high growth dynamics, the rate of new vessel formation is often delayed compared to the rate of cell proliferation [8]. This results in ischemia of the tumor with areas of low oxygen saturation, low glucose and acidic pH, with consequent necrosis formation [9]. In recent decades, research in the field of molecular biology has shown a putative oxygen - dependent mechanism of induction of relevant tumor genes [10-14]. Under conditions of low oxygen concentration, the concentration of a special hypoxia - inducible factor (HIF) in the tumor cells increases, which is responsible for the expression of genes enabling growth and angiogenesis within the tumor in the event of hypoxia [15]. Based on the results of these studies, hypoxia and HIF seem to be the key factors influencing the development of tumor vasculature and malignancy. HIF was discovered in 1995, which was a milestone in understanding the mechanism of tumor response to hypoxia [15]. In addition, HIF protein synthesis is regulated by oxygen concentration and which belongs to the transcription factors. VEGF expression is strongly induced by hypoxia within GBM. VEGF synthesis is particularly intensified in periparticular GBM cells, and relatively low in oxygen - rich cells adjacent to the vessels [15].

The gene, that plays important role in hypoxia – regulated angiogenesis is *p53* gene. Hypoxia leads to cells apoptosis with an active *p53* suppressor gene, while cells lacking an active *p53* gene are more resistant to hypoxia [13,15]. Lack of the *p53* gene, in turn, leads to increased VEGF expression leading to an increase in the concentration of VEGF inside the tumor [18].

VEGFR1 and VEGFR2 play also crucial role in angiogenesis in gliomas. mRNA expression for the VEGFR2 receptor protein is restricted to HGG vascular cells, while VEGFR1 mRNA expression is both in HGG and LGG. VEGFR protein synthesis is strongly stimulated by hypoxia and HIF, which explains the presence of these receptors in HGG [15]. It is worth emphasizing that within normal brain tissue, no or only minimal VEGFR1 and VEGFR2 protein synthesis has been observed [4-7]. Comparison of the expression of both receptors and their ligands in GBM revealed correlation between the VEGF concentration and the amount of VEGFR1 and VEGFR2. This suggests that receptor - associated VEGF synthesis plays a key role in the progression of LGG to HGG [3-7,10]. Although the VEGF protein is located in the cytoplasm of GBM cells and can be marked there, it is most abundant within the blood vessels [8]. This may confirm the hypothesis about the paracrine mechanism of neoplastic angiogenesis, where VEGF produced by GBM cells binds to endothelial cells that significantly express VEGFR1 and VEGFR2 proteins [14,16]. VEGFR2 receptor activation plays a major role in the vascular of HGG. A correlation between VEGF-mRNA level and degree of vascularization of the neoplasm has been proven, although VEGF expression is also present in LGG, especially in the case of cystic degeneration [18]. This indicates the function of VEGF in the formation of neoplastic cysts within gliomas [16]. The lack of rich vascularization of LGG the content of VEGF should be explained by the lack of expression of specific receptors, which prevents this factor from inducing the formation of new vessels [17].

Proteins of angiopoietin (Ang) family, in particular Ang-1, and Ang 2 play also important role in angiogenesis in gliomas [18]. These proteins are involved in late - stage

angiogenesis in gliomas. They regulate the maturation and stabilization of newly formed pathological vessels [19]. It has been shown that hypoxia and VEGF secretion increase in cases of *in vitro* models lead to increased Ang-2 secretion in endothelial cells. The fact that Ang-2 expression is associated with VEGF secretion under the hypoxia so typical for HGG suggests that similar mechanisms take place *in vivo* within human brain gliomas [18,19].

Hepatocyte growth factor (HGF) also plays an important role in stimulating angiogenesis in gliomas [20,21]. It stimulates the mitotic division of endothelial cells as well as neoplastic cells by binding to its receptor - MET proto-oncogene, receptor tyrosine kinase (MET) [20]. Increased expression of HGF and MET proteins correlates with the degree of vascularization and the malignancy of gliomas [20].

Angiogenesis in meningiomas

The growth of meningiomas and the development of their vascularization is strongly related to the activity of various biochemical factor [22]. The results of the conducted studies on angiogenesis in meningiomas did not provide unambiguous conclusions about its mechanism and regulating factor [23]. The observations made on the angiogenesis factors in meningiomas and their activity give contradictory results. According to some reports, an increased level of VEGF in the meningioma tissue has been demonstrated, and a significant correlation was found between the degree of neoplastic vascular development and the concentration of both VEGF mRNA and the VEGF protein in meningioma cells [24]. However, according to other authors, there is no correlation between the degree of VEGF expression and tumor size, its location and histopathological subtype, and there is no correlation between the amount of VEGF and tumor vascularization [24,25]. There was no difference in the degree of VEGF expression between non-malignant meningiomas (WHO I), atypical meningiomas (WHO II) and anaplastic meningiomas (WHO III), although meningiomas WHO III are characterized by pathological vessels [26].

In the case of meningiomas, the pathophysiological mechanisms associated with hypoxia are also different. Hypoxia leading to tumor necrosis, so common in HGG, occurs in meningiomas only in the case of atypical and anaplastic forms (WHO II, III) [26]. Therefore, hypoxia and VEGF, in contrast to gliomas, does not play a regulatory role in meningiomas [24]. On the basis of animal model in female rats, it was shown that the regulation of VEGF mRNA expression takes place in both cells producing steroid hormones as well as cells sensitive to these hormones [24]. This may suggest that stimulation of receptors for female sex hormones leads to an increase in VEGF synthesis in meningiomas [27]. Studies carried out in recent decades have shown that in meningioma cells, placental growth factor (PIGF) and VEGF-B are synthesized. In the neoplastic tissue of the meningioma, the VEGFR1, which binds with high affinity to VEGF, and molecules similar to VEGF, has been found [25-27]. However, this mechanism remain unclear. It is possible that in meningiomas there may be separate receptors for VEGF and related proteins, and it is these receptors that mediate angiogenesis and formation of brain edema around the tumor in meningiomas [24].

Comparison of angiogenesis in infiltrative and expansive tumors

A diagram presenting different types of gliomas and meningiomas growth and resulting differences in the mechanisms of angiogenesis is presented in Figure 1 [28].



Figure 1. Presentation of the infiltrating glioma growth (stars) and the expansive meningioma growth (dots) [28]

The figure above shows the infiltrative nature of gliomas and the expansive, distorting growth of meningiomas [29]. The different pathomechanism of the development of these tumors results in a different type of tumor - feeding vessel formation [30]. Gliomas perform the blood vessels existing in the brain, while meningiomas require the formation of new vessels to enter inside the restricted tumor [29,30].

Abbreviations

- Ang - angiopoietin
- GBM - glioblastoma multiforme
- HGG - high grade glioma
- HIF - hypoxia-inducible factor
- LGG - low-grade gliomas
- MET - MET proto-oncogene, receptor tyrosine kinase
- PIGF - placental growth factor
- VEGF - Vascular endothelial growth factor

Declarations

- **Competing Interests:** The authors declare that they have no conflict of interest.
- **Authors' contributions:** ZS has been studying angiogenesis in brain tumors for about 10 years, as evidenced by their 2010 monography [*Siedlecki, Z. (2010). Ocena stężenia czynników angiogenezy w osoczu chorych leczonych operacyjnie z powodu nowotworów śródczaszkowych (Doctoral dissertation)*]. KN and SG joined to ZS in angiogenesis study and started own research. ZS, KN, SG have reviewed the literature, their contribution is equal. FAS as a biotechnologist also deals with angiogenesis, with particular emphasis on biotechnological drugs and techniques, brought valuable guidance to the work.

- **Zygmunt Siedlecki, Karol Nowak, Sebastian Grzyb are three equal first authors with equal contribution.**

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