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HISTORICAL OVERVIEW OF CANCER ANGIOGENESIS STUDIES IN THE ASPECT OF BRAIN TUMORS PATHOPHYSIOLOGY AND THERAPY

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Abstract

Cancer angiogenesis is a key process in the development of any cancer, including brain tumors: gliomas, meningiomas and metastatic tumors. Both neurooncology and other cancer studies have highlighted angiogenesis and have emphasizedthat inhibiting angiogenesis may be potential treatment for some neoplastic diseases. We presentthe history of research on tumor angiogenesis from the 18th century to the present day. We put emphasis , how during thedecades, new mechanisms of angiogenesis were discovered and what are the prospects for the application of anti-angiogenic drugs in brain tumors potential treatment. The presented manuscript is a review of the history of angiogenesis research over the years, in topic of brain tumors. We put attention that this topic is still relevant and may provide perspectives in neurooncology.

Keywords: Angiogenesis; Tumors; Cancer; Brain tumor

The phenomenon of neoplastic angiogenesis - introduction

Cancer cell proliferation in a newly formed tumor without its own blood vessels allows the tumor to reach a size of not more than 1 to 2 mm^3[1,2]. This phase of tumor development is called the avascular phase and the tumor grows slowly in it [2]. The cells are then supplied with oxygen and nutrients by diffusion [3]. The avascular phase of a neoplastic tumor may sometimes persist for a long time without disease progression [1-3]. Cell proliferation is then kept in balance with the rate of apoptosis, thanks to which the tumor size does not increase [2].

When diffusion becomes insufficient for tumor development, the mechanisms that enable its further growth are triggered. The most important of them is the induction and development of angiogenesis, consisting in the formation of new blood vessels from the existing ones. It is possible thanks to the secretion of pro-angiogenic factor [3]. They stimulate the proliferation and migration of endothelial cells in nearby vessels that create new capillaries from the stem. Dividing cells can also coil up to form new blood vessels in the lumen of the mother's vessels. Thus, one vessel is divided into two by creating two lights. This specific vascular formation mechanism is called intussusal angiogenesis 1-3].

The second mechanism that ensures tumor vasculature is its growth along the existing normal vessels and their use for tumor development. An example of tumors employing such a

vascularization strategy are growing invasive astrocytomas, which spread along the vessels without creating a restricted tumor mass [2,4].

Another mechanism that enables the development of tumor vasculature is vasculogenesis. It consists in creating de novo blood vessels from bone marrow-derived precursor cells.Yet another strategy for the formation of neoplastic vessels is the formation of a capillary network, which, despite the fact that it is made of endothelial cells, is formed only by neoplastic cells without the participation of other blood vessels. This phenomenon is called vascular mimicry and is observed, for example, in melanomas [4,5].

In a singletumor, more than one mechanism for the formation of new blood vessels can often be observed. It depends on the stage and grade of the tumor [2,4].

In the last three decades of the 20-century and in two decades of of the 21-century, many methods were developed to test and measure the degree of angiogenesis within neoplastic tumors, includingbrain tumors [4,5,7]. Methods measuring directly the number of proliferating and migrating endothelial cells seem to be the most important. In vitro it is possible by counting dividing cells in culture, by using radiolabeled nucleotides and by photometric measurement of mitochondrial activity [3,4]. These methods, despite their undoubted advantages, often cannot be used in clinical practice in patients due to the need to use advanced, often inaccessible laboratory procedures [3]. A much more accessible method of measuring the advancement of neoplastic angiogenesis seems to be the determination of the concentration of proangiogenic substances in the blood of patients or in neoplastic tissue [1,3,4].

Historical overview of tumor angiogenesis research

The term "angiogenesis" was introduced in 1787 by John Hunter, a British surgeon. The development of research and observations on the existence of pathological vascularization of neoplastic tumors, however, took place only 100 years later, i.e. in the second half of the 19th century [5].

Scientific reports from this period mainly describe persistent intraoperative hemorrhages during tumor resection and the existence of pathological dilated blood vessels identified during the procedurę [6,7]. The reasons for such pathological vascularization of neoplasms were vasodilation, inflammatory reaction, necrosis of neoplastic cells, increased metabolism within the tumor and the related increase in the concentration of acid metabolites,

uric acid and hypoxia [8]. Some research studies in animal models of mice and rats have focused on the development of vascularization of tumors transplanted from one organ to another region of the body, and the secretion of substances that stimulate the formation of new vessels [6-8].

A turning point in the history of research on neoplastic angiogenesis was the year 1971, when M. J. Folkman published the thesis that the development of a neoplastic tumor depends on the development of blood vessels [8]. In his dissertation Tumor angiogenesis: therapeutic implications, published in the New England Journal of Medicine, determined that a tumor cannot reach a size greater than 1-2 mm^3 without the existence of vessels feeding it, and that there are chemicals diffusing between the tumor cells that stimulate the formation of a capillary network [5-8]. He also emphasized that inhibition of angiogenesis with the use of pro-angiogenic factor antagonists may be a potential, effective method of oncological treatment. In 1984, Yuen Shing and Michael Klagsbrun, using the chromatography technique, isolated from a tumor a substance that is mitogenic for endothelial cells [9]. This substance turned out to be identical in molecular structure with the fibroblast growth factor (FGF) [5,8], which had already been isolated in bovine pituitary gland cells by D. Gospodarowicz and was characterized by mitogenic properties for fibroblasts and prolonged their survival [10].

In 1989, independently of each other, Rosalind Rosenthal and Ferrara isolated a protein different from FGF with strong properties that stimulate the proliferation of vascular endothelial cells [11]. It was named by Ferrara vascular-endothelial growth factor (VEGF) and soon was assigned the greatest role in neoplastic angiogenesis, including brain tumors [5,8,11]. In 1990, the VEGF molecule was found to be identical to the vascular permeability factor discovered by Senger and Dvorak in 1983 [12]. This fact made it clear that VEGF has a multidirectional biological action and in the case of brain tumors, apart from angiogenesis, it may play a role in the development of cerebral edema [9,8,12].

The following years brought further rapid development of research on neoplastic angiogenesis and the discovery of further factors of angiogenesis [5]. The current direction of research is aimed at to determine whether there are sensitive and specific ways to determine the stage of tumor development by measuring the concentration of factors responsible for its vascularization [8-12]. This applies in particular to biochemical factors that can be tested in a simple, minimally invasive way, e.g. in blood or urine [13,14]. Just as an increase in blood calcitonin concentration is a sensitive marker of the development of medullary thyroid

carcinoma, the question of whether there are appropriate markers that can indicate the development of neoplastic disease in the preclinical stage is important [15]. These premises constitute an important reason for undertaking research on the importance of the concentration of angiogenesis factors in the blood of patients with intracranial neoplasms [14-16].

Anti - angiogenic agents as a future of brain tumor treatment - review

Already M. J. Folkman in his dissertation from 1971, describing the dependence of the development of neoplastic disease on the developmentof pathological blood vessels, pointed out that substances inhibiting angiogenesis may become effective drugs preventing the development of cancer [4-11]. They may prove to be an effective form of treatment of intracranial neoplasms. This is especially true of high-grade glial tumors, which, firstly, are characterized by high angiogenic activity and, secondly, due to the infiltrative growth in the brain, they often cannot be radically removed during surgery [9,13]. Therefore, angiogenic treatment may become a biological treatment complementary to surgical treatment of gliomas [13]. The results of preclinical studies using angiogenesis inhibitors are very promising, but have not yet been confirmed by clinical trials [5,8].

Agents that antagonize angiogenesis include, for example, bevacizumab, which is an anti-VEGF monoclonal antibody [8]. It has been studied in the treatment of kidney cancer patients. However, it did not significantly extend the survival time of patients. It is also being analyzed in the treatment of GBM [17]. Studies on the use of bevacizumab in the treatment of recurrent glioblastoma were in Phase III clinical trials in 2009 [5,8,17]. In May 2009, the US Food and Drug Administration approved bevacizumab for use in high-grade gliomas [8,17]. In addition to bevacizumab, angiogenesis inhibitors include thalidomide, an antagonist of VEGF and bFGF [18]. It has been shown to be effective in the treatment of malignant gliomas as monotherapy and in combination with chemotherapy [17]. The angiogenesis inhibiting substances also include interferon, which exerts its anti-angiogenic effect by inhibiting the expression of bFGF [18,19]. Certainly, the use of angiogenesis inhibitors in the oncological treatment of brain tumors seems to be a potentially effective method supporting surgery, radiotherapy and chemotherapy [19]. This is one of the important reasons for examining the concentration of angiogenesis factors and the dynamics of their changes in the plasma of patients with brain tumors for the use of appropriate antagonists in clinical practice [17,20].

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References

1. Folkman, J. (1971). Tumor angiogenesis: therapeutic implications. New england journal of medicine, 285(21), 1182-1186.
2. Mariotti, M., & Maier, J. A. (2006). Angiogenesis: an overview. In New frontiers in angiogenesis (pp. 1-29). Springer, Dordrecht.
3. Enholm, B., Paavonen, K., Ristimäki, A., Kumar, V., Gunji, Y., Klefstrom, J., ... & Alitalo, K. (1997). Comparison of VEGF, VEGF-B, VEGF-C and Ang-1 mRNA regulation by serum, growth factors, oncoproteins and hypoxia. Oncogene, 14(20), 2475-2483.
4. Folkman, J. (1990). Tumors Are Angiogenesis Dependent?. Journal of the National Cancer Institute: JNCI., 82(1), 4.
5. Lenzi, P., Bocci, G., & Natale, G. (2016). John Hunter and the origin of the term “angiogenesis”.
6. Folkman, J. (1972). Anti-angiogenesis: new concept for therapy of solid tumors. Annals of surgery, 175(3), 409.
7. Folkman, J. (1995). Clinical applications of research on angiogenesis. New England Journal of Medicine, 333(26), 1757-1763
8. Folkman, J. (2008). History of angiogenesis. In Angiogenesis (pp. 1-14). Springer, Boston, MA.
9. Shing, Y., Folkman, J., Haudenschild, C., Lund, D., Crum, R., & Klagsbrun, M. (1985). Angiogenesis is stimulated by a tumor-derived endothelial cell growth factor. Journal of cellular biochemistry, 29(4), 275-287.
10. Gospodarowicz, D. E. N. I. S. (1975). Purification of a fibroblast growth factor from bovine pituitary. Journal of Biological Chemistry, 250(7), 2515-2520.
11. Rosenthal, R. A., Megyesi, J. F., Henzel, W. J., Ferrara, N., & Folkman, J. (1990). Conditioned medium from mouse sarcoma 180 cells contains vascular endothelial growth factor. Growth Factors, 4(1), 53-59.
12. Senger, D. R., Galli, S. J., Dvorak, A. M., Perruzzi, C. A., Harvey, V. S., & Dvorak, H. F. (1983). Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science, 219(4587), 983-985.

13. Folkman, J. (1990). Tumors Are Angiogenesis Dependent?. Journal of the National Cancer Institute: JNCI., 82(1), 4.
14. Cimpean, A. M., & Raica, M. (2021). Historical Overview of In Vivo and In Vitro Angiogenesis Assays. In Vascular Morphogenesis (pp. 1-13). Humana, New York, NY.
15. Ollauri-Ibáñez, C., & Astigarraga, I. (2021). Use of Antiangiogenic Therapies in Pediatric Solid Tumors. Cancers, 13(2), 253.
16. Seeger, D. R., Golovko, S. A., Grove, B. D., & Golovko, M. Y. Cyclooxygenase inhibition attenuates brain angiogenesis and independently decreases mouse survival under hypoxia. Journal of Neurochemistry.
17. Lugano, R., Ramachandran, M., & Dimberg, A. (2020). Tumor angiogenesis: Causes, consequences, challenges and opportunities. Cellular and Molecular Life Sciences, 77(9), 1745-1770.
18. Ahir, B. K., Engelhard, H. H., & Lakka, S. S. (2020). Tumor development and angiogenesis in adult brain tumor: glioblastoma. Molecular Neurobiology, 1-18.
19. Kickingereder, P., Brugnara, G., Hansen, M. B., Nowosielski, M., Pflüger, I., Schell, M., ... & Bendszus, M. (2020). Noninvasive characterization of tumor angiogenesis and oxygenation in bevacizumab-treated recurrent glioblastoma by using dynamic susceptibility MRI: secondary analysis of the European Organization for Research and Treatment of Cancer 26101 Trial. Radiology, 297(1), 164-175.
20. Teleanu, R. I., Chircov, C., Grumezescu, A. M., & Teleanu, D. M. (2020). Tumor angiogenesis and anti-angiogenic strategies for cancer treatment. Journal of Clinical Medicine, 9(1), 84.
21. Viallard, C., & Larrivée, B. (2017). Tumor angiogenesis and vascular normalization: alternative therapeutic targets. Angiogenesis, 20(4), 409-426.
22. Li, T., Kang, G., Wang, T., & Huang, H. (2018). Tumor angiogenesis and anti-angiogenic gene therapy for cancer. Oncology letters, 16(1), 687-702.