ScienceDirect

International Journal of Biological Macromolecules

Volume 311, Part 1, June 2025, 143838

Review

The role of biological macromolecules in the regulation of angiogenesis in glioblastoma: Focus on vascular growth factors, integrins, and extracellular matrix proteins

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Abstract

Glioblastoma, classified as a grade 4 brain tumor, accounts for approximately half of all malignant central nervous system cancers. Despite extensive research and aggressive treatment modalities, much about this disease remains elusive. The proliferation of blood vessels within glioblastoma tumors significantly contributes to their invasive nature, primarily due to the influence of vascular endothelial growth factor-A (VEGF-A). As a result, the past decade has seen a concentrated effort to explore angiogenesis, especially the VEGF signaling pathway, as a therapeutic target for glioblastoma. This investigation led to the FDA approval of bevacizumab, a monoclonal antibody against VEGF-A, for the treatment of recurrent glioblastoma. However, despite promising clinical trials and theoretical research, bevacizumab has not significantly improved patient survival rates. Furthermore, other anti-angiogenic agents targeting the VEGF signaling pathway have shown limited efficacy. This suggests the existence of multiple alternative angiogenic pathways that facilitate vascularization, even when VEGF signaling is inhibited.

In this study, we aim to assess the current landscape of anti-angiogenic agents, explore potential resistance mechanisms to such therapies, and suggest strategies to improve the effectiveness of these therapeutic interventions. Our goal is to provide a comprehensive understanding of the limitations of current treatments and to identify new avenues for enhancing therapeutic

outcomes in glioblastoma patients.

Introduction

Glioblastoma multiforme (GBM) is the most aggressive and lethal form of primary brain tumor, accounting for nearly half of all malignant gliomas. It is marked by rapid cellular proliferation, diffuse infiltration into surrounding brain tissue, high levels of angiogenesis, and notable resistance to standard therapies such as surgical resection, radiation, and chemotherapy [1,2]. Despite intensive treatment protocols, the median survival of patients remains disappointingly low, typically ranging between 12 and 15 months [3].

The concept of tumor angiogenesis as a hallmark of cancer was first proposed by Judah Folkman in the early 1970s, who hypothesized that tumor growth is angiogenesis-dependent [114]. His pioneering work laid the foundation for the development of anti-angiogenic therapies, particularly in highly vascularized tumors such as glioblastoma. In GBM, angiogenesis is not merely a consequence of tumor growth, but a driving force that facilitates tumor expansion, invasiveness, and treatment resistance [5,6]. Among the key molecular drivers of angiogenesis in GBM are vascular endothelial growth factor (VEGF) and its receptors, integrins, and components of the extracellular matrix (ECM). These biological macromolecules orchestrate complex signaling cascades that remodel the tumor microenvironment, promote neovascularization, and suppress anti-tumor immune responses [[7], [8], [9]]. This review aims to provide a comprehensive overview of the angiogenic processes in glioblastoma, with a specific focus on the role of VEGF signaling, integrin-mediated adhesion, and ECM remodeling. A better understanding of these mechanisms is essential for developing novel therapeutic strategies to combat this devastating disease.

Having established the background and the rationale for this study, the following section describes the methods employed to gather and analyze the relevant data.

Keywords: The literature search was conducted using keywords such as “anti-angiogenic therapy,” “glioblastoma,” “VEGF inhibitors,” “TKI,” and “tumor angiogenesis.”

Databases: The search was performed across multiple databases, including PubMed, Scopus, and Web of Science.

Articles were selected based on their relevance to the impact of anti-angiogenic therapies on glioblastoma. Priority was given to original research articles, while review articles were used sparingly for background information.

Initial Search Results: The initial search yielded 1200 articles. Titles and abstracts were screened to identify relevant studies.

Full-Text Review: 300 articles were downloaded for full-text review.

Exclusion Criteria: 200 articles were excluded due to reasons such as lack of relevance to glioblastoma or anti-angiogenic therapy, absence of original data, or being review articles.

Final Selection: 100 original research articles were selected for detailed analysis.

Qualitative Analysis: The selected articles were analyzed qualitatively to assess the impact of various anti-angiogenic therapies on tumor growth and metastasis in glioblastoma.

Section snippets

Neovascularization

The formation of new blood vessels, or angiogenesis, significantly enhances the blood supply to tumor cells, thereby accelerating disease progression and facilitating the spread to adjacent tissues [1]. Hypoxia—oxygen deficiency—stimulates the upregulation of vascular endothelial growth factor (VEGF) and its receptor (VEGFR), which promotes angiogenesis and supports tumor cell survival [2]. Additionally, stem cells capable of differentiating into endothelial cells play a pivotal role in …

Neovascularization mechanisms in glioblastoma

In glioblastoma (GBM), as in most cancers, the demand for oxygen and nutrients becomes more pronounced under hypoxic conditions. This hypoxia activates VEGF gene expression through the hypoxia-inducible factor (HIF) pathway [5]. VEGF plays a central role in promoting angiogenesis by binding to its receptors—VEGFR-1, VEGFR-2, and VEGFR-3—on endothelial cells, thereby initiating signaling cascades that drive endothelial proliferation, migration, and vascular permeability. In GBM, the …

Anti-angiogenic treatment in glioblastoma

A variety of small molecules, antibodies, and other therapeutic strategies have been developed to inhibit the formation of new blood vessels and target multiple angiogenic pathways. This section critically evaluates the efficacy of these treatments, highlighting both successes and limitations. These agents are employed in the treatment of various cancers, including brain cancer. For instance, in the United States, there have been over fifty clinical trials aimed at treating brain cancer by …

Angiogenesis

Angiogenesis is essential for tumor growth by supplying oxygen and nutrients through blood vessels. Inhibition using agents like endostatin and angiostatin has shown promising results in preclinical studies, demonstrating reduced tumor growth and vasculature [113,114]. These findings underscore the complexity of angiogenic pathways and the molecular signaling underlying anti-angiogenic therapies. A significant challenge in glioblastoma treatment is understanding the mechanisms of resistance to …

Vascular co-option in glioblastoma

Beyond VEGF-mediated angiogenesis, glioblastoma also exploits vascular co-option—whereby tumor cells hijack existing vasculature rather than inducing new vessel formation. This allows the tumor to infiltrate surrounding tissues while evading anti-angiogenic therapies [101]. Emerging research suggests vascular co-option plays a pivotal role in tumor progression and therapeutic resistance. …

The role of multifaceted therapies and treatment pathways in the future

The complexity of glioblastoma biology demands multi-targeted therapeutic strategies. The limited efficacy of monotherapy with anti-VEGF agents [22,93] has prompted investigation into agents targeting multiple pathways simultaneously. ANGIOPOIETIN-2 in conjunction with VEGFR inhibition has shown potential [17], and similar strategies are being evaluated in other cancers [102,103]. Furthermore, combining EMP2 inhibition with bevacizumab has yielded encouraging results [32,102].

Targeting tyrosine …

Conclusions

Despite recent therapeutic advancements, glioblastoma remains the most prevalent and aggressive form of brain tumor, with its treatment and prevention still posing significant challenges. One of the hallmark features of glioblastoma is its high vascularization, which has driven considerable interest in targeting angiogenic pathways. However, monotherapies such as bevacizumab have shown inconsistent clinical efficacy, underscoring the need for a more comprehensive understanding of the intricate …

CRediT authorship contribution statement

Abbas Zabihi: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. …

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. …

Declaration of competing interest

Abbas Zabihi declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

Acknowledgments

Not applicable. ...

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