ScienceDirect

International Immunopharmacology

Volume 150, 26 March 2025, 114173

Review

Novel neutrophil targeting platforms in treating Glioblastoma: Latest evidence and therapeutic approaches

Rui Zhong, Hongmei He, Xiande Wang

Department of Neurosurgery, The First People's Hospital of Lin'an District, Hangzhou 311300, China

Received 8 October 2024, Revised 22 January 2025, Accepted 23 January 2025, Available online 11 February 2025, Version of Record 11 February 2025.

What do these dates mean?

Show less

Share Cite

https://doi.org/10.1016/j.intimp.2025.114173

Get rights and content

Highlights

- Neutrophils have a dual pro and anti-tumor in GBM.
- Neutrophils can cross the BBB naturally.
- Targeting neutrophils could be effective in GMB treatment.
- Nanosystem-based neutrophil targeting platforms are effective in GBM treatments.

Abstract

Glioblastoma (GBM) is the most aggressive and lethal type of primary brain tumor, characterized by its rapid growth, resistance to conventional therapies, and a highly immunosuppressive tumor microenvironment (TME). Recent studies have highlighted the critical role of neutrophils in the progression of GBM, where they contribute to tumor growth, invasion, and treatment resistance. As a result, neutrophils have emerged as a promising target for therapeutic intervention in GBM. Various strategies are being investigated to specifically target neutrophils within the GBM environment, including using small molecules, antibodies, and nanoparticle-based methods. These approaches aim to regulate neutrophils' recruitment, activation, and functions. This study reviews the latest findings regarding the involvement of neutrophils in GBM, explores potential techniques targeting neutrophils for therapeutic purposes, and discusses current clinical studies and prospects in this rapidly evolving field. By studying the diverse functions of neutrophils in GBM, these innovative therapeutic strategies can help address some of the most significant challenges in treating this malignancy.

Introduction

Glioblastoma (GBM) is the predominant and highly malignant kind of primary brain tumor, including over 48% of all primary malignant brain tumors [1]. Despite the progress made in surgical methods, radiation, and chemotherapy, the outcome for patients with GBM is still relatively poor, with an average survival time of around 15 months after being diagnosed [2]. The treatment of GBM is complex due to various factors, including the tumor's invasive characteristics, its capacity to avoid immune detection, and the development of a protective blood–brain barrier (BBB) that restricts the effectiveness of many drugs [3]. Neutrophils, a tumor microenvironment (TME) component, have lately been recognized for their dual function in promoting and restraining tumor growth, contributing to the aggressive nature of GBM [4].

Neutrophils, the most prevalent leukocytes in the human body, are mostly known for their involvement in acute inflammation and innate immunity. Nevertheless, recent findings indicate that neutrophils have a multifaceted impact on cancer, specifically in GBM, where they frequently correlate with unfavorable prognosis [5]. Neutrophils are recruited to the GBM microenvironment using several chemokines and cytokines, such as interleukin-8 (IL-8) and granulocyte colony-stimulating factor (G-CSF). These immune mediators are released by both tumor cells and other stromal components [6]. Following the recruitment and infiltration, neutrophils can promote tumor growth and invasion by secreting pro-tumorigenic substances, such as matrix metalloproteinases (MMPs) and reactive oxygen species (ROS), which modify the extracellular matrix and stimulate the formation of new blood vessels (angiogenesis) [7], [8], [9].

In addition, neutrophils create an immunosuppressive environment in GBM by interacting with other immune cells, including macrophages and regulatory T cells (Tregs), to inhibit anti-tumor immune responses. Neutrophils can conduct neutrophil extracellular trap (NET) formation or NETosis [10], [11]. This mechanism can trap and shield tumor cells from immune-mediated death while supporting invasiveness, further complicating their immunosuppressive role [12]. Given these multifaceted roles, targeting neutrophils in GBM presents both a challenge and an

opportunity for therapeutic intervention [13].

Various tactics have been devised to specifically target neutrophils in cancer treatment, encompassing the inhibition of their recruitment as well as the modulation of their activation and function [14], [15], [16]. One strategy entails utilizing small molecule inhibitors or antibodies to obstruct crucial chemokine receptors, such as CXCR2, which plays a role in attracting neutrophils into the TME [17]. Another practical approach entails utilizing nanoparticles specifically engineered to transport therapeutic substances directly to neutrophils, augmenting medication selectivity and minimizing unintended side effects [18], [19]. Furthermore, there is an increasing fascination with specifically targeting the process of NETosis, either by inhibiting the development of NETs or by disrupting already formed NETs to decrease the advancement of tumors and metastasis [13], [20]. Although there have been significant breakthroughs, translating approaches that target neutrophils from the laboratory to clinical use is still in its first phases. Current clinical trials are investigating the safety and effectiveness of these methods in patients with GBM, aiming to discover new therapeutic techniques that can enhance existing treatments and patient outcomes [21]. This review offers a thorough discussion of the most recent information regarding the involvement of neutrophils in GBM. It will also summarize the existing therapeutic strategies that focus on neutrophils and explore potential future developments in this rapidly progressing area of research.

Section snippets

Glioblastoma

GBM is the most aggressive and lethal kind of primary brain neoplasm [22], [23], [24]. This cancer is characterized by fast proliferation, diffuse infiltration, and resistance to traditional treatments [25]. The etiology of GBM is intricate and encompasses various genetic, epigenetic, and microenvironmental variables that stimulate tumor development, progression, and recurrence [26]. …

Role of neutrophils in the TME of Glioblastoma

Neutrophils, conventionally identified as the initial responders in acute inflammation and infection, have emerged as crucial factors in the TME of several cancers, including GBM [47] (Fig. 1). In GBM, neutrophils play a significant role in tumor development, immune regulation, and therapeutic resistance, highlighting their intricate function within the TME [48], [49], [50]. The GBM microenvironment is defined by chronic inflammation, which is crucial for recruiting neutrophils to the tumor …

Neutrophil targeting/affecting platforms

As discussed, GBM is a prevalent brain tumor that presents significant obstacles in

pharmacological administration [86]. This section comprises two parts: the initial section examines treatments utilizing immunotherapy and targeted therapy, while the subsequent section assesses nanosystem-based therapies (Table 1, Table 2). …

Mechanisms of neutrophil-induced resistance to ICIs

As discussed, neutrophils are essential in the GBM TME, supporting immune tolerance, tumor growth, and treatment resistance [132]. TANs support the immune evasion of cancer cells by secreting anti-inflammatory cytokines such as IL-10 that inhibit $CD8^+$ T cell cytotoxicity, downregulate MHC-I molecules on tumors and APCs, and are associated with resistance to ICIs [133], [134]. TANs also control the expression of PD-L1 on GBM cells via cytokines such as TNF-α and IL-6, where they initiate the …

Advantages of neutrophil targeting in Glioblastoma therapy

Neutrophil-targeting strategies in GBM therapy offer several advantages. One of the primary benefits is the ability to penetrate the BBB [149]. Conventional therapies face significant challenges in penetrating the BBB [150]. Neutrophils can naturally traverse this barrier, allowing drug delivery systems utilizing neutrophils as carriers to reach the tumor site more effectively [151]. Neutrophil-mediated drug delivery systems, such as nanoparticle-loaded neutrophils, exemplify this capability …

Concluding remarks and future directions

Neutrophil-targeting technologies for GBM treatment constitute a new and rapidly advancing domain. Neutrophils' capacity to traverse the BBB and their inherent tendency to localize at inflammatory regions present distinctive prospects for directly delivering medicines to the TME. Recent advancements in nanoparticle-based delivery systems and genetically modified neutrophils have demonstrated potential in preclinical models, suggesting avenues for enhancing the efficacy of GBM therapies. …

Authors' contributions

X W: Conception, design, and inviting co-authors to participate. R Z and H H: Writing the original manuscript draft.XW: Review and edit the manuscript critically for important intellectual content and provide comments and feedback for the scientific contents of the manuscript. All authors read, revised, and approved the final manuscript. …

CRediT authorship contribution statement

Rui Zhong: Writing – original draft. **Hongmei He:** Writing – original draft. **Xiande Wang:** Writing – review & editing, Supervision, Conceptualization. …

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

Acknowledgments

None. …

Recommended articles

References (166)

R. Stupp *et al.*
Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial
Lancet Oncol. (2009)

C.M. Todd *et al.*
The effects of a CXCR1/CXCR2 antagonist on neutrophil migration in mild atopic asthmatic subjects
Pulm. Pharmacol. Ther. (2016)

T.T. Lah *et al.*
Brain malignancies: Glioblastoma and brain metastases, Seminars in cancer biology
Elsevier (2020)

T.R. Alves *et al.*
Glioblastoma cells: a heterogeneous and fatal tumor interacting with the parenchyma
Life Sci. (2011)

R.P. Nagarajan *et al.*
Epigenetic mechanisms in glioblastoma multiforme, Seminars in cancer biology
Elsevier (2009)

F. Hajizadeh *et al.*
Hypoxia inducible factors in the tumor microenvironment as therapeutic targets of cancer stem cells
Life Sci. (2019)

M.R. Galdiero *et al.*
Tumor associated macrophages and neutrophils in cancer
Immunobiology (2013)

H. Hosseinalizadeh *et al.*
Neutrophil mediated drug delivery for targeted glioblastoma therapy: A comprehensive review
Biomed. Pharmacother. (2022)

H.-C. Tsai *et al.*
Acrolein produced by glioma cells under hypoxia inhibits neutrophil AKT activity and suppresses anti-tumoral activities
Free Radic. Biol. Med. (2023)

H. Bi *et al.*
Extrinsic factors associated with the response to immunotherapy in glioblastoma
Cancer Lett. (2021)

View more references

Cited by (0)

View full text

© 2025 Elsevier B.V. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

ELSEVIER

All content on this site: Copyright © 2025 or its licensors and contributors. All rights are reserved, including those for text and data mining, AI training, and similar technologies. For all open access content, the relevant licensing terms apply.
RELX™