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Emerging strategies for targeting tumor-associated macrophages in glioblastoma: A focus on chemotaxis blockade

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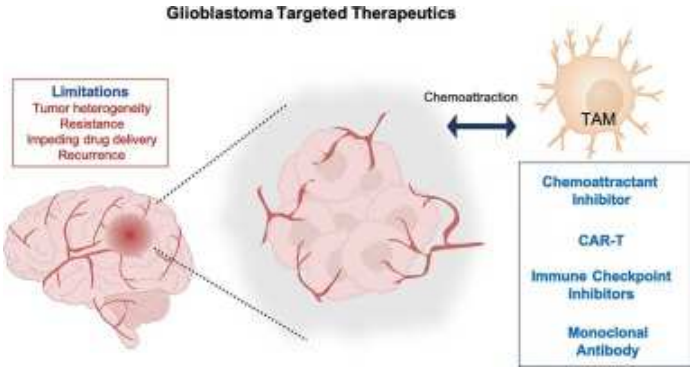
Abstract

Glioblastoma (GBM) remains one of the most aggressive and treatment-resistant brain tumors, with poor prognosis for affected patients. A key player in the GBM tumor microenvironment is the tumor-associated macrophage (TAM), which promotes tumor progression, immune evasion, and therapeutic resistance. The recruitment of TAMs to the tumor site is driven by specific chemotactic signals, including CSF-1/CSF-1R, CXCR4/CXCL12, and HGF/MET pathways. This review explores the current understanding of these chemotaxis mechanisms and their role in GBM progression. It highlights the potential therapeutic benefits of targeting TAM chemotaxis pathways to disrupt TAM infiltration, reduce immunosuppression, and enhance the efficacy of conventional treatments. Additionally, we discuss the preclinical and clinical evidence surrounding key inhibitors, such as PLX3397, AMD3100, and Crizotinib, which have shown promise in reprogramming TAMs and improving treatment outcomes in GBM. While these strategies offer hope for overcoming some of the challenges of GBM therapy, the review also addresses the limitations and obstacles in clinical translation, emphasizing the need for further research and the development of combination therapies to achieve sustained therapeutic benefit.

Graphical abstract



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Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive primary malignant brain tumor, defined by rapid proliferation, diffuse invasion, and poor prognosis [1]. Despite progress in surgical resection, radiotherapy, and chemotherapy, GBM remains highly resistant to treatment. Patients typically survive only 12 to 14months after diagnosis [2]. This poor outcome reflects the tumor's capacity for immune evasion, its heterogeneity, and the presence of a highly immunosuppressive tumor microenvironment (TME). A key component of this TME is tumor-associated macrophages (TAMs), a heterogeneous immune cell population that includes resident microglia and infiltrating monocyte-derived macrophages.

TAMs play a central role in GBM progression. They influence immune suppression, angiogenesis, and resistance to therapy. TAMs are recruited to the TME through specific chemotactic cues, such as CSF-1/CSF-1R, CXCR4/CXCL12, and HGF/MET pathways. Upon entry, they predominantly polarize into the immunosuppressive M2 phenotype [3]. These M2-like TAMs promote tumor progression by enhancing the recruitment of regulatory T cells and myeloid-derived suppressor cells. They also support tumor cell growth, metastasis, and resistance to conventional therapies.

Because of their central role in GBM pathogenesis, TAMs are an attractive therapeutic target. Disrupting their recruitment and polarization pathways may limit immune suppression and enhance treatment efficacy [4]. This review outlines current knowledge on TAM chemotaxis in GBM, with emphasis on the signaling pathways that regulate their infiltration and phenotype. We also assess the therapeutic potential of targeting TAMs using agents such as CSF-1R inhibitors (e.g., PLX3397), CXCR4 antagonists (e.g., AMD3100), and other molecular inhibitors aimed at reprogramming the TME. Although early findings are promising, clinical translation remains challenging. Further investigation into combination strategies is needed to optimize therapeutic outcomes and address the complexity of GBM biology.

Section snippets

Glioblastoma multiforme

GBM is the most common and aggressive form of primary malignant brain tumor, with an annual incidence of fewer than 10 cases per 100,000 people [5]. It accounts for over half of all gliomas and is the deadliest form of brain cancer. Symptoms vary by tumor location and may include headaches, focal deficits, confusion, memory loss, personality changes, or seizures [6].

The cause of GBM is largely unknown, with hereditary factors involved in only about 5% of cases [7]. Most are sporadic. Malignant …

Chemotaxis-inhibiting drugs for chemotactic interaction between TAMs and GBM

TAMs play a central role in GBM by promoting tumor growth, survival, and invasion. These cells are actively recruited to the TME, where they can comprise up to 50% of the total cell population. Widely distributed throughout the tumor mass, TAMs contribute to disease progression. By secreting immunosuppressive cytokines, they help establish a “cold tumor” environment that weakens immune surveillance and facilitates immune evasion. Combined with GBM's intrinsic aggressiveness, TAM activity …

Conclusion

Glioblastoma (GBM) remains one of the most aggressive and therapeutically challenging cancers, with tumor-associated macrophages/microglia (TAM) playing a pivotal role in its progression, immune evasion, and metastasis. The chemotactic interactions between TAMs and GBM, particularly via the CSF-1/CSF-1R, CXCR4/CXCL12, and HGF/MET pathways, highlight critical targets for novel therapeutic strategies.

Targeting these pathways with small molecules, monoclonal antibodies, and kinase inhibitors …

CRediT authorship contribution statement

Chaelin Lee: Conceptualization, Formal analysis, Investigation, Resources, Visualization, Writing – original draft, Writing – review & editing. **Jaehyun Lee:** Writing – original draft, Visualization, Resources, Investigation, Conceptualization. **Moongyu Jeong:** Writing – original draft, Resources, Investigation, Conceptualization. **Dayoung Nam:** Writing – original draft, Resources, Investigation, Conceptualization. **Inmoo Rhee:** Writing – review & editing, Writing – original

draft, Visualization, …

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. …

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