

The Tumour Immune Microenvironment in Glioblastoma: Implications for Immunotherapy Failure and Future Directions

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Abstract

Glioblastoma accounts for 14.5% of all central nervous system (CNS) tumours. Current immunotherapeutic strategies include surgery, radiotherapy, and chemotherapy, with an increased focus on checkpoint inhibitors and CAR-T cell therapy. However, these have demonstrated limited clinical effectiveness due to the tumour's ability to generate and sustain pro-tumourigenic immune microenvironments (TIME), T-cell exhaustion, and myeloid-derived suppressor cell activity. In order to overcome these limitations, future directions emphasise multimodal approaches, including oncolytic virotherapy and nanoparticle-based delivery systems, to improve therapeutic outcomes.

Keywords: Glioblastoma, high-grade glioma, tumour immune microenvironments, immunotherapy, CART cell therapy, nanoparticle-based delivery.

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Introduction

Glioblastoma (GBM), formerly known as glioblastoma multiforme, represents a WHO grade 4 adult-type diffuse glioma characterised by rapid growth and marked biological aggressiveness.¹ It is the most common primary brain tumour, accounting for 14.5% of all central nervous system (CNS) tumours.² Immunotherapy seeks to elicit a tumour-specific immune response capable of selectively eliminating malignant cells. The success of checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapy in both solid and haematologic malignancies has driven interest in applying these approaches to GBM. However, the CNS is considered an immunoprivileged environment, and GBM suppresses immune responses as it is maintained by microglial surveillance.³

Tumours actively generate and sustain pro-tumourigenic tumour immune microenvironments (TIME), consisting of

host immune cells that drive immunosuppression and enhance tumour expansion. It is a dynamic and continuously evolving system that adapts to specific tumour type, surrounding cells, and local conditions. The host immune system functions to recognize and eliminate non-self entities, such as foreign antigens. However, tumours can exploit this system to shape the TIME by selectively favouring cancer cell variants that resist, evade, or suppress anti-tumour immunity.⁴

This review critically examines the mechanisms underlying immunotherapy failure in glioblastoma, particularly the role of tumour immune microenvironment, and considers emerging therapeutic strategies and future directions to overcome these challenges.

Literature Review

The tumour immune microenvironment in glioblastoma is a complex, heterogeneous system composed of endothelial cells, neurones, glial cells, and immune cells such as microglia, tumour-associated macrophages, and tumour-infiltrating lymphocytes. Glioma cells actively regulate these components via signalling networks that promote tumour growth, immune modulation, and therapy resistance. This dysregulated microenvironment is the biological basis for profound immunosuppression and a key determinant of poor response to immunotherapeutic strategies.⁴

Within this context, Wang et al. (2021) demonstrated that immunosuppressive myeloid populations and impaired T cell activation dominate the immune microenvironment in glioblastoma. Cytotoxic T-cell response is suppressed by the anti-inflammatory phenotype of tumour-associated macrophages characterised by interleukin-10 and transforming growth factor beta secretions.⁵ Furthermore, T-cell activity within the tumour microenvironment is pronouncedly reduced, enabling immune escape. Expanding on this, Yu and Quail (2021) showed marked microenvironment heterogeneity and immune-evasive signalling pathways in glioblastoma that exhibit significant immunotherapy resistance.⁶ Together, these findings indicate that glioblastoma does not merely contain immune cells but actively reprograms them into disruptive states, resulting in failure of checkpoint-based therapies.

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Woroniecka et al. (2018) reported that limited anti-tumour immunity is because glioblastoma displays a severely exhausted phenotype of tumour-infiltrating lymphocytes.⁷ There is reduced proliferation, impaired cytokine secretion, diminished cytotoxic function, and increased expression of inhibitory receptors such as PD-1, TIM-3, and CTLA-4, in these T-cells. This T-cell exhaustion is more severe in glioblastoma and is primarily irreversible, even with sustained antigen exposure. This persistent dysfunction contributes significantly to therapeutic failure.

A study highlighted that primary mediators of immune suppression and tumour progression are myeloid-derived suppressor cells (MDSCs). De Leo et al. (2021) reported that within the tumour microenvironment and peripheral circulation, there's a marked elevation in MDSCs.⁸ These cells cause metabolic disruption through reactive oxygen species production and nutrient depletion. Moreover, an immunosuppressive tumour microenvironment is sustained through interaction between MDSCs and other myeloid populations. Collectively, these findings indicate that MDSCs play a primary role in maintaining immune evasion in glioblastoma.

Meanwhile, tumour cells and other components of the glioblastoma microenvironment act synergistically to reinforce immunosuppression through the secretion of indoleamine 2,3-dioxygenase 1 (IDO1), interleukin-10 (IL-10), C-C motif chemokine ligand 2 (CCL2) and transforming growth factor beta (TGF-beta) that collaboratively favour the expansion and recruitment of regulatory T cells (Tregs) infiltrating into glioblastomas. Liu et al. (2024) reviewed that these Tregs enhance immune escape by expressing inhibitory checkpoint molecules such as PD-1 and CTLA-4, leading to suppression of effector T-cell activation and sustaining a self-amplifying immunosuppressive loop.⁹

Although the immunosuppressive tumour microenvironment in glioblastoma is greatly understood, current immunotherapeutic strategies have shown limited clinical effectiveness. This is due to T-cell exhaustion, regulatory T-cell activity, tumour-associated macrophages, and MDSCs, which suppress effective anti-tumour immune responses. Recent studies have investigated the combination of immune checkpoint inhibitors with standard treatments such as radiotherapy and chemotherapy to enhance the immune response against tumours and facilitate immune cell infiltration into tumour sites. In addition, strategies to aim at components of the tumour microenvironment, including tumour-associated immune cells, are currently being investigated to diminish immunosuppressive signalling.

Advancing strategies like chimeric antigen receptor (CAR)

T-cell therapy and vaccines designed for specific tumours are also currently being tested and demonstrate high potential to improve tumour recognition and therapeutic specificity.³ Other strategies that are still in early development include oncolytic virotherapy, which infects and causes lysis of tumour cells in a selective manner while promoting immunogenic cell death and enhancing the presentation of tumour antigens. In addition, nanoparticle-based delivery systems are also being investigated to achieve better therapeutic penetration into the blood-brain barrier as well as selective manipulation of the tumour immune microenvironment, making it possible to increase treatment specificity and decrease systemic toxicity.⁹ Together, these strategies indicate greater emphasis on multi-modal immunotherapeutic strategies to address the challenges associated with glioblastoma.

Conclusion

Glioblastoma's tumour microenvironment represents a highly coordinated immunosuppressive network driven by exhausted T cells, MDSCs, tumour-associated macrophages, and regulatory T cells, collectively rendering current immunotherapies ineffective. Addressing this requires multi-modal strategies that simultaneously target multiple axes of immune evasion. Emerging approaches, including CAR T-cell therapy, oncolytic virotherapy, and nanoparticle-based delivery systems, offer promise. Continued translational research remains essential to achieving meaningful clinical outcomes.

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