





Review

Chimeric antigen receptor T cell therapy for glioblastoma: overcoming current barriers and strategies to enhance efficacy for therapeutic implications

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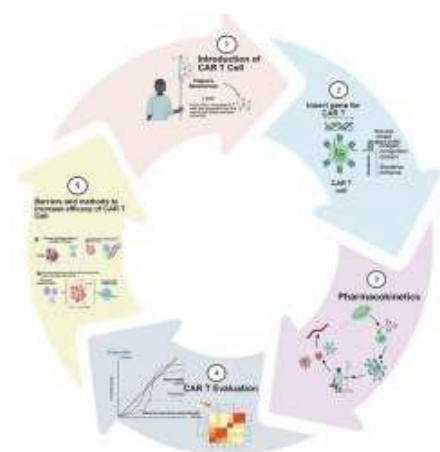
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Abstract

Glioblastoma (GBM) is a highly malignant primary brain tumor, characterized by limited therapeutic options and poor survival outcomes. Nevertheless, its treatment is significantly hampered by the immunosuppressive tumor microenvironment, tumor antigen heterogeneity, the risks of antigen escape, and on-target/off-tumor toxicity. To address these barriers, chimeric antigen receptor (CAR-T) cell therapy has emerged as a promising immunotherapeutic approach,

showing potential in early clinical trials targeting epidermal growth factor receptor variant III (EGFRvIII), human epidermal growth factor receptor 2 (HER2), and interleukin-13 receptor alpha 2 (IL13R α 2). However, the efficacy of CAR-T cells for GBM is constrained by their limited persistence, tumor infiltration, and functional activity. This review therefore highlights key engineering methods to modify CAR-T cells for GBM, including enhancing resistance to immunosuppressive cytokines through transforming growth factor-beta (TGF- β) inhibition or signal conversion, blocking inhibitory checkpoints with gene editing, promoting tumor infiltration by chemokine receptor engineering or localized delivery, improving viability via cytokine support, delaying T cell exhaustion through modulation of exhaustion drivers, metabolic reprogramming to sustain function in nutrient-poor environments, and enriching memory phenotypes for long-term persistence. Future studies are required to develop multimodal approaches that combine next-generation CAR designs with enhanced delivery methods to simultaneously target multiple resistance pathways. Accordingly, this review aims to provide knowledge and pathways to overcome the pharmacological obstacles that have hindered CAR-T cell success in GBM, creating a roadmap for future research and clinical development.

Graphical abstract



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Introduction

Glioblastoma (GBM) is the most aggressive primary brain tumor, with rapid proliferation, diffuse infiltration, and strong resistance to traditional methods. Despite multimodal treatment strategies, which consist of maximal surgical resection, radiotherapy, and temozolomide chemotherapy, the median patient survival remains only 15 to 18 months, with a five-year survival rate below 10% [1], [2]. Treatment failure and tumor recurrence are primarily driven by a highly immunosuppressive tumor microenvironment (TME), inter- and intratumoral heterogeneity, and the protective blood-brain barrier (BBB) [3]. These obstacles highlight the need for new therapeutic modalities capable of addressing the shortcomings of existing

standard-of-care regimens.

Immunotherapy represents an innovative strategy in oncology, with particularly impressive results in hematologic malignancies. Among these approaches, chimeric antigen receptor T (CAR-T) cell therapy has demonstrated significant effectiveness against refractory B-cell leukaemias and lymphomas [4], [5]. CAR-T cells are engineered to express synthetic receptors that target tumor-associated antigens (TAAs), regardless of major histocompatibility complex (MHC) restriction, enabling potent, targeted cytotoxicity [6]. However, applying CAR-T cells therapy to GBM faces specific challenges, including antigen heterogeneity, immunosuppressive cytokines, T cell exhaustion, and poor traffic across the BBB [7]. Early-stage clinical trials targeting GBM-specific antigens, e.g., interleukin-13 receptor alpha 2 (IL13R α 2), human epidermal growth factor receptor 2 (HER2), and epidermal growth factor receptor variant III (EGFRvIII) have shown promising but limited efficacy due to antigen escape and short-lived persistence [8], [9]. To overcome these challenges, new methods are being explored. These include engineering CAR-T cells to resist immunosuppression; providing cytokine support to improve persistence; chemokine receptor co-expression to promote tumor infiltration; targeting transcriptional regulators to prevent exhaustion; reprogramming cell metabolism to maintain effector function in nutrient-deprived TMEs; and finally, enriching memory phenotypes to establish long-term immunity [8], [10].

This review examines current barriers to CAR-T cell therapy in GBM and highlights emerging methods to enhance its efficacy. We summarize the current state of CAR-T cell therapy for GBM, beginning with an overview of barriers and culminating in a critical analysis of the most innovative engineering solutions to overcome them. Instead of merely describing the studies, we evaluate the field's status and limitations through the lens of pharmacology. Ultimately, we aim to identify critical research opportunities and logical follow-up steps with the purpose of sketching a path towards the next generation of CAR-T cell therapies that can elicit durable responses in GBM. By integrating advances in genetic engineering, immunometabolism, and multimodal delivery, next-generation CAR-T therapies may finally overcome the formidable defenses of GBM, offering new hope for patients.

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Section snippets

Epidemiological features of GBM

Gliomas are heterogeneous brain tumors that arise from glial cells or their precursors, including

astrocytomas and oligodendrogliomas [11]. They are classified into four grades by the World Health Organization (WHO), with grade I being localized and grades II-IV showing a diffuse growth pattern and increasing invasiveness [12]. The most common and aggressive type is glioblastoma (GBM). GBM is a grade IV diffuse astrocytoma that can arise from any part of the central nervous system (CNS), most ...

Challenges and advances in CAR T-cell therapy

Despite progress in medicine, malignant tumors remain a major therapeutic challenge. This is largely due to the invasiveness, systemic toxicity, and acquired resistance nature of conventional therapeutic strategies, including surgery, chemotherapy, and radiotherapy [33], [34].

Immunotherapy has been recognized as a promising alternative, leveraging the body's immune system against neoplastic cells, and cell-based therapy is among its most promising approaches [35]. For example, while ...

Chimeric antigen receptor T cell therapy for GBM

Despite the advances in structure, the clinical use of CAR-T cells in GBM remains limited to a few target antigens, each with its own profile of expression and clinical results. Because tumor-specific antigens have not yet been discovered, CAR-T cell therapy remains limited in GBM. However, with the development of 2nd and 3rd-generation CAR-T cells, it is now possible to overcome the significant heterogeneity of GBM tumor antigens and obtain superior clinical outcomes. In current clinical ...

Barriers of CAR-T cell in the treatment of GBM

In the current therapeutic landscape of glioblastoma, chimeric antigen receptor (CAR) T-cell therapy continues to face significant obstacles (Fig. 5). Many factors, such as the high tumor-antigen heterogeneity, antigen-escape mechanisms, and a highly suppressive tumor microenvironment (TME), prevent the ability of CAR-T cells to produce long-lasting and efficient anti-tumor responses [43]. ...

Methods to improve the efficacy of CAR-T cells against GBM

The limited clinical efficacy of early CAR-T cell therapies in GBM is a direct result of the profound pharmacokinetics and biodistribution challenges imposed by the brain tumor microenvironment [87], [92]. Inefficient tumor trafficking, poor persistence due to T cell exhaustion, and functional suppression necessitate novel engineering approaches to improve the in vivo performance of cellular therapeutics. Therefore, the approaches outlined in Fig. 6 share the common goal of overcoming these ...

Therapeutic implications of CAR-T cell therapy in GBM

The translation of promising engineering methods from pre-clinical models to clinical application in GBM patients has been hampered by a significant translational gap. Many studies showing the efficacy of approaches such as TGF- β inhibition [95], IL-12 secretion [49], or metabolic reprogramming [132], [133] were initially established in subcutaneous regional tumor models or non-CNS cancer models (e.g., prostate, melanoma). They can be utilized in initial trials, since these models have no ...

Conclusion and perspectives

CAR-T cell therapy for GBM has moved beyond an intuitive idea of targeted killing into a pharmacological quandary of idealizing cellular bio-distribution, lifespan, and functionality in a hostile disease environment. Early clinical trials targeting IL13R α 2, HER2, and EGFRvIII suggested that CAR-T cells can traffic to CNS tumors, engage their target, and cause significant regression. However, these trials consistently identified two major barriers: the profound immunosuppression of the TME which ...

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CRediT authorship contribution statement

Muhammad Abid Hayat: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Si Yu:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Conceptualization. **Guo Tao:** Writing – review & editing, Validation, Methodology, Data curation. **Muhammad Usman Ghani:** Writing – review & editing, Visualization, Validation, Resources, Methodology, Data curation. **Jiabo Hu:** Writing – review & editing, ...

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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