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Review Article

The immunosuppressive microenvironment modulated by glioma-associated mesenchymal stem cells: Current status and potential strategies

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Highlights

- GA-MSCs play a crucial role in shaping the immunosuppressive microenvironment of gliomas.
- GA-MSCs interact with immune cells to regulate immune responses.
- GA-MSCs enhance the stemness, proliferation, and tumorigenicity of glioma stem cells.
- GA-MSCs can be genetically engineered to counteract tumor-induced immunosuppression.

- GA-MSCs can serve as drug delivery vehicles, reducing off-target effects.

Abstract

Glioma, the most prevalent primary malignant tumor of the central nervous system, exhibits aggressive progression and poor prognosis, largely due to its highly immunosuppressive tumor microenvironment (TME). Glioma-associated mesenchymal stem cells (GA-MSCs), a key component of the glioma TME, play a dual and context-dependent role in tumor biology. On one hand, GA-MSCs actively shape immunosuppression by interacting with various immune cells—including T cells, B cells, natural killer (NK) cells, dendritic cells (DCs), and macrophages—via soluble factors (e.g., TGF-β, PGE2, miR-21) and cell-contact mechanisms, thereby facilitating tumor immune evasion. They also promote glioma progression by enhancing the stemness, invasiveness, and chemoresistance of glioma stem cells (GSCs) through pathways such as IL-6/STAT3 and mitochondrial transfer, while contributing to pathological angiogenesis via differentiation into pericytes and secretion of pro-angiogenic factors like VEGF. On the other hand, GA-MSCs possess therapeutic potential: genetically engineered GA-MSCs can secrete pro-inflammatory cytokines (e.g., IL-12, IFN-β) or immune checkpoint blockers (e.g., scFv-PD1) to reverse immunosuppression, serve as carriers for targeted delivery of chemotherapeutics, miRNAs, suicide genes, or oncolytic viruses, and enhance anti-tumor immune responses. However, clinical translation is hindered by challenges including residual immunosuppressive activity, unstable transgene expression, limited migration efficiency, and safety concerns. This review summarizes the complex mechanisms by which GA-MSCs modulate the glioma TME, highlights their bidirectional roles in tumor progression and immunotherapy, and discusses potential strategies to overcome current limitations, aiming to provide insights for developing novel therapies targeting GA-MSCs and their interactions within the glioma microenvironment.

Introduction

Glioma, which originates from undifferentiated glial cells or neural precursor cells, is the most common primary tumor of the central nervous system, accounting for approximately 81% of intracranial malignant tumors. Among these, malignant gliomas (WHO grade III anaplastic astrocytoma and WHO grade IV glioblastoma) represent the majority and are associated with high mortality rates [1,2]. Gliomas are characterized by rapid proliferation, invasive growth, resistance to complete resection, and a high recurrence rate. Despite aggressive treatment strategies, the prognosis for glioma patients remains poor. For instance, the median survival time for glioblastoma (GBM) is approximately one year, with a five-year survival rate of only 9.8% [3,4]. The blood-brain barrier (BBB) significantly limits the effective delivery of therapeutic concentrations of drugs to the tumor tissue, while tumor heterogeneity complicates targeted therapy [5].

For many years, research on anti-glioma treatments has primarily focused on the tumor cells themselves. However, tumors are not merely solid aggregates of malignant cells; they also include the microenvironment that surrounds these cells. The immune microenvironment of glioma comprises GSCs, endothelial cells, immune cells, astrocytes, neural stem cells/precursor cells (NPCs), MSCs, and various biochemical factors [6]. Among these components, myeloid-derived cells represent 40% to 70% of the total immune cell population and typically exhibit immunosuppressive phenotypes [7]. Glioma cells employ various mechanisms to evade immune system attacks, including immune editing and the establishment of an inhibitory immune microenvironment. They secrete chemokines that recruit regulatory T cells (Tregs) into the tumor microenvironment. Tregs subsequently release TGF-β, a cytokine that inhibits the activity of CD8+ cytotoxic T lymphocytes, thereby aiding glioma cells in evading immune surveillance [8]. Moreover, glioma cells can escape immune recognition by modulating antigen expression, altering the surface levels of MHC-I molecules, and modifying the mechanisms of antigen presentation and processing [9].

GA-MSCs employ various soluble and cell-mediated mechanisms to suppress effective tumor-specific immune responses, leading to decreased T-cell infiltration within their immunosuppressive microenvironment and a lack of effector responses. Although immunostimulants such as interleukin-12 (IL-12), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-alpha (TNF-α), and interferon-beta (IFN-β) have been explored, their effectiveness in reversing immunosuppression in patients remains limited [10,11]. These characteristics indicate that the immunosuppressive microenvironment shaped by GA-MSCs and glioma cells is both highly complex and heterogeneous. Therefore, a multifaceted approach that combines several strategies is essential to overcome these immunosuppressive mechanisms and enhance therapeutic efficacy. Understanding the interaction between GA-MSCs and immune cells is essential for the development of effective immunotherapies. This review examines the role of GA-MSCs in shaping the immunosuppressive TME, the underlying mechanisms involved, and potential therapeutic strategies to counteract these effects.

Section snippets

Mesenchymal stem cells

MSCs are a type of non-hematopoietic stem cell that were first identified in bone marrow more than 40years ago [12]. These cells are capable of adhering to bone marrow and have since been found in various tissues, including the brain, adipose tissue, lungs, heart, umbilical cord, fetal

tissue, and other organs [13,14]. In 2006, the International Society for Cell Therapy (ISCT) established criteria for the identification of MSCs: they are adherent cells that are negative for hematopoietic …

T cell

T cells, particularly $CD8^+$cytotoxic T cells and $CD4^+$Th1 cells, are crucial in anti-tumor immune responses. Upon recruitment to the tumor site, MSCs exert a significant influence on T-cell responses, modulating their activity to shape the tumor immune microenvironment [33]. Sandra Cascio's research has shown that MSCs contribute to the “immune-tumor rejection” phenomenon by sequestering $CD8^+$cytotoxic T cells from the tumor periphery [34]. This sequestration disrupts effector cell-cancer cell …

Regulation of the tumor microenvironment

GA-MSCs can play a key role in immune regulation through genetic engineering modification (Fig. 3), holding promise for reversing the tumor-induced immunosuppressive microenvironment. (See Table 2.) Using lentivirus or adeno-associated virus (AAV)-mediated gene transduction technology, GA-MSCs can stably express proinflammatory cytokines and immune-stimulatory molecules such as IL-12, IL-2, and IFN-γ. Among these, IL-12, due to its significant proinflammatory properties, can effectively reverse …

Challenges and limitations

Therapies based on GA-MSCs and existing ICIs show significant differences yet complementarity in glioma treatment. ICIs relieve T cell suppression by blocking immunosuppressive pathways such as PD-1/PD-L1; however, their efficacy depends heavily on the presence of functional T cells within the TME, leading to low response rates in “cold tumors” like gliomas. Moreover, the blood-brain barrier restricts drug delivery to the tumor site, and systemic immune-related toxicities remain a concern.

In …

Conclusion

As a key regulatory component of the glioma TME, GA-MSCs perform complex, highly context-dependent functions that critically influence tumor progression, immune evasion, and therapeutic responses. As reviewed here, GA-MSCs actively shape an immunosuppressive TME through multiple mechanisms: they suppress anti-tumor effector populations—including $CD8^+$ T cells, NK cells, and DCs — while simultaneously promoting the recruitment and activation of regulatory cell subsets such as Tregs, M2 …

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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