Glioma tumor immune microenvironment

- TMEM115: a promising marker for glioma immunotherapy and prognosis
- Patient-Derived Glioblastoma Explants Empower Rapid and Personalized Drug Assessment: Harnessing the Potential of 3D Perfusion Bioreactors in Glioblastoma Drug Discovery
- Machine learning-driven SLC prognostic signature for glioma: predicting survival and immunotherapy response
- Interrogation of macrophage-related prognostic signatures reveals a potential immune-mediated therapy strategy by histone deacetylase inhibition in glioma
- Novel fusion superkine, IL-24S/IL-15, enhances immunotherapy of brain cancer
- Unlocking glioblastoma: breakthroughs in molecular mechanisms and next-generation therapies
- Palmitoylation-driven immune dysregulation and prognostic signature in low-grade glioma: a multi-omics and functional validation study
- Adoptive cell therapy with macrophage-drug conjugates facilitates cytotoxic drug transfer and immune activation in glioblastoma models

The glioma tumor immune microenvironment (TIME) is a complex ecosystem comprising tumor cells, stromal cells, immune cells, and extracellular matrix components. This microenvironment plays a critical role in glioma progression, immune evasion, and resistance to therapies, particularly in aggressive types like glioblastoma.

Key Components

Immune Cells

Microglia and Macrophages:

Dominant immune cell population in gliomas, comprising up to 30-50% of the tumor mass.

Often exhibit an M2-like phenotype (anti-inflammatory, pro-tumoral).

Secrete cytokines like IL-10, TGF-β, and pro-angiogenic factors such as VEGF.

T Cells

Predominantly exhausted T cells, characterized by high expression of immune checkpoint molecules such as PD-1, CTLA-4, and TIM-3.

Few effector T cells due to the immunosuppressive environment.

Regulatory T Cells (Tregs)

Overrepresented in gliomas, contributing to immune suppression through secretion of IL-10 and TGF-β.

Myeloid-Derived Suppressor Cells (MDSCs)

Accumulate in gliomas and suppress T cell activity.

Natural Killer (NK) Cells

Their activity is limited due to low expression of activating ligands and high levels of immunosuppressive cytokines.

Cytokines and Chemokines

Immunosuppressive factors dominate

IL-10, TGF-β: Suppress effector immune responses.

CCL2, CXCL12: Recruit macrophages and Tregs to the tumor site.

Pro-inflammatory cytokines (e.g., IL-6, TNF-α) may also be present but are often neutralized by the immunosuppressive environment.

Extracellular Matrix (ECM)

Gliomas remodel the ECM to support invasion and immune evasion.

Components like hyaluronic acid and tenascin-C promote immune cell dysfunction and tumor progression.

Tumor-Associated Endothelium:

Gliomas induce an abnormal, “leaky” vasculature that impairs immune cell trafficking.

Express PD-L1 and other molecules that suppress T cell infiltration.

Mechanisms of Immune Evasion in Gliomas

Immune Checkpoint Expression:

Glioma cells and immune cells express checkpoint molecules like PD-L1 and CTLA-4, which inhibit T cell activation.

Low Immunogenicity:

Gliomas exhibit a low mutational burden, reducing neoantigen presentation and immune recognition.

Downregulation of MHC class I molecules further limits antigen presentation.

Tumor-Derived Metabolites:

IDH-mutant gliomas produce 2-hydroxyglutarate (2-HG), which suppresses T cell activation and promotes immunosuppression. Hypoxia-driven production of adenosine and lactate inhibits effector T cells and promotes Treg activity.

Recruitment of Immunosuppressive Cells:

Chemokines like CCL2 and CXCL12 recruit macrophages, Tregs, and MDSCs, which sustain an immunosuppressive microenvironment.

Epigenetic Modifications:

Gliomas modify the epigenome of immune cells, rendering them dysfunctional or pro-tumoral.

Therapeutic Implications

Immune Checkpoint Inhibitors (ICIs):

Drugs targeting PD-1/PD-L1 and CTLA-4 have shown limited success due to the highly immunosuppressive environment.

Combination strategies are being explored (e.g., ICIs with vaccines or radiotherapy).

Cancer Vaccines:

Designed to enhance the presentation of glioma-specific antigens.

Examples: EGFRvIII-targeted vaccines.

Adoptive Cell Therapies:

CAR-T cells targeting glioma-specific antigens (e.g., IL13Rα2, EGFRvIII).

NK cell-based therapies are under investigation.

Reprogramming the Microenvironment:

Agents that shift macrophages/microglia from an M2 to an M1 phenotype.

Examples: CSF-1R inhibitors.

Oncolytic Viruses:

Engineered viruses that selectively infect glioma cells, releasing tumor antigens and stimulating an immune response.

Targeting IDH Mutations:

Blocking 2-HG production to restore T cell function and reduce immunosuppression.

Current Challenges

Blood-Brain Barrier (BBB): Limits immune cell infiltration and therapeutic delivery.

Tumor Heterogeneity: Gliomas vary widely in immune composition, making uniform therapeutic strategies difficult.

Immunosuppressive Milieu: High levels of TGF-β, IL-10, and other factors suppress immune responses even with aggressive therapies.

Shan et al. established a gene signature associated with ROS to explore its influence on prognosis and immune microenvironment in gliomas.

The Reactive Oxygen Species (ROS)-related gene expression profile dichotomized patients into two groups with different clinicopathological features and prognoses. A 19-gene ROS-related signature was used to robustly predict prognosis in both training and validation datasets. Functional analysis indicated an association between ROS levels and the immune microenvironment. The expression of immune checkpoints and M2-type markers was upregulated in the high-risk group, which suggested the immunosuppressive function of ROS.

ROS-related signature is an independent glioma prognosis factor and could potentially exert immunosuppressive effects on the tumor microenvironment [1)].

Dysregulated cholesterol metabolism is implicated in the immunosuppressive tumor immune microenvironment and promotes tumor progression. Dong et al. found that cholesterol levels in GBM tissues are abnormally high, and glioma-supportive macrophages (GSMs), an essential “cholesterol factory”, demonstrated aberrantly hyperactive cholesterol metabolism and efflux, providing cholesterol to fuel GBM growth and induce CD8+ T cells exhaustion. Subsequent bioinformatics analysis confirmed that high 7-Dehydrocholesterol reductase (DHCR7) level in GBM tissues was concomitant with increased cholesterol biosynthesis, suppressed tumoricidal immune response, and poor patient survival and DHCR7 expression level was significantly elevated in GSMs. Therefore, they reported an intracavitary sprayable nanoregulator-encased hydrogel system to modulate the cholesterol metabolism of GSMs. The degradable nanoregulator-mediated ablation of DHCR7 in GSMs effectively suppressed cholesterol supply and activated T-cell immunity. Moreover, the combination of Toll-like receptor 7/8 (TLR7/8) agonists significantly promoted GSM polarization to antitumor phenotypes and ameliorated the immunosuppressive TME. Treatment with the hybrid system exhibited superior antitumor effects in the orthotopic GBM tumor model and postsurgical recurrence model. Altogether, our findings unravel the role of GSMs DHCR7/cholesterol signaling in the regulation of immunosuppressive TME, presenting a potential GBM treatment strategy that warrants further clinical trials [2)].

To identify a more efficient strategy to treat glioma, in recent years, the influence of the inflammatory microenvironment on the progression of glioma has been studied. Various immunophenotypes exist in microglial cells, each of which has a different functional property. In this review, references about the phenotypic conversion of microglial cell polarity in the microenvironment were briefly summarized, and the differences in polarized state and function, their influences on glioma progression under different physiological and pathological conditions, and the interactive effects between the two were mainly discussed. Certain signaling molecules and regulatory pathways involved in the microglial cell

polarization process were investigated, and the feasibility of targeted regulation of microglial cell conversion to an antitumor phenotype was analyzed to provide new clues for the efficient auxiliary treatment of neural glioma [3].

The tumor immune microenvironment (TIME) in high-grade glioma (HGG) exhibits high spatial heterogeneity. Though the tumor core and peripheral regions have different biological features, the cause of this spatial heterogeneity has not been clearly elucidated. Here, we examined the spatial heterogeneity of HGG using core and peripheral regions obtained separately from the patients with HGG. We analyzed infiltrating immune cells by flow cytometry from 34 patients with HGG and the transcriptomes by RNA-sequencing analysis from 18 patients with HGG. Peripheral region-infiltrating immune cells were in vitro cultured in hypoxic conditions and their immunophenotyping. They analyzed whether the frequencies of exhausted CD8+ T cells and immunosuppressive cells in the core or peripheral regions are associated with the survival of patients with HGG. They found that terminally exhausted CD8+ T cells and immunosuppressive cells, including regulatory T (TREG) cells and M2 tumor-associated macrophages (TAMs), are more enriched in the core regions than the peripheral regions. Terminally exhausted and immunosuppressive profiles in the core region significantly correlated with the hypoxia signature, which was enriched in the core region. Importantly, in vitro culture of peripheral region-infiltrating immune cells in hypoxic conditions resulted in an increase in terminally exhausted CD8+ T cells, CTLA-4+ TREG cells, and M2 TAMs. Finally, they found that a high frequency of PD-1+CTLA-4+CD8+ T cells in the core regions was significantly associated with decreased progression-free survival of patients with HGG. The hypoxic condition in the core region of HGG directly induces an immunosuppressive TIME, which is associated with patient survival [4].

In a study, both U118 cell and GSC23 cell exhibited good printability and cell proliferation. Compared with 3D-U118, 3D-GSC23 had a greater ability to form cell spheroids, to secrete VEGFA, and to form tubule-like structures in vitro. More importantly, 3D-GSC23 cells had a greater power to transdifferentiate into functional endothelial cells, and blood vessels composed of tumor cells with an abnormal endothelial phenotype was observed in vivo. In summary, 3D bioprinted hydrogel scaffold provided a suitable tumor microenvironment (TME) for glioma cells and GSCs. This bioprinted model supported a novel TME for the research of glioma cells, especially GSCs in glioma vascularization and therapeutic targeting of tumor angiogenesis [5].

Tumor-associated microglia and macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) are potent immunosuppressors in the glioma tumor microenvironment (TME). Their infiltration is associated with tumor grade, progression and therapy resistance.

This resiliency of glioma stem cells (GSCs) is, in part, due to self-remodeling of their supportive niche also known as the tumor microenvironment [6] [7] [8] [9].

The tumor and the surrounding microenvironment are closely related and interact constantly. Tumors can influence the microenvironment by releasing extracellular signals, promoting tumor angiogenesis and inducing peripheral immune tolerance, while the immune cells in the microenvironment can affect the growth and evolution of cancerous cells.

The tumor microenvironment contributes to tumour heterogeneity.

Tumor microenvironment has been shown to be an important source for therapeutic targets in both adult and pediatric neoplasms.

To characterize the glioma tumor microenvironment, a mixed collective of nine glioma patients underwent [18F]DPA-714-PET-MRI in addition to [18F]FET-PET-MRI. Image-guided biopsy samples were immuno-phenotyped by multiparameter flow cytometry and immunohistochemistry. In vitro autoradiography was performed for image validation and assessment of tracer binding specificity.

They found a strong relationship ($r = 0.84$, $p = 0.009$) between the [18F]DPA-714 uptake and the number and activation level of glioma-associated myeloid cells (GAMs). TSPO expression was mainly restricted to HLA-DR+ activated GAMs, particularly to tumor-infiltrating HLA-DR+ MDSCs and TAMs. [18F]DPA-714-positive tissue volumes exceeded [18F]FET-positive volumes and showed a differential spatial distribution.

[18F]DPA-714-PET may be used to non-invasively image the glioma-associated immunosuppressive TME in vivo. This imaging paradigm may also help to characterize the heterogeneity of the glioma TME with respect to the degree of myeloid cell infiltration at various disease stages. [18F]DPA-714 may also facilitate the development of new image-guided therapies targeting the myeloid-derived TME. [10].

Low-grade glioma tumor immune microenvironment

Low-grade glioma tumor immune microenvironment

Glioblastoma tumor microenvironment

Glioblastoma tumor microenvironment.

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