Hallmarks of the Tumour Microenvironment of Gliomas

Subjects: Oncology

Contributor: Christian A. Linares , Anjana Varghese , Aruni Ghose , Sayali D. Shinde , Sola Adeleke , Elisabet Sanchez , Matin Sheriff , Cyrus Chargari , Elie Rassy , Stergios Boussios

Gliomas are aggressive, primary central nervous system tumours arising from glial cells. Glioblastomas are the most malignant. They are known for their poor prognosis or median overall survival. The advent of immunotherapy with its various modalities—immune checkpoint inhibitors, cancer vaccines, oncolytic viruses and chimeric antigen receptor T cells and NK cells—has shown promise.

gliomas tumour microenvironment immunotherapy

1. Introduction

The central nervous system (CNS) can be broadly divided into two cell types, neurons and glial cells, and gliomas originate from the glial cells, which include astrocytes, oligodendrocytes, ependymal cells and microglia. Gliomas comprise one of the most prevalent types of primary CNS tumours (PCNSTs), which are classified as Grade I to IV according to the World Health Organization (WHO) classification, taking into account histological, molecular and genomic features in their grading [1][2]. Glioblastoma, a WHO Grade IV glioma previously known as glioblastoma multiforme (GBM), is the commonest malignant PCNST, representing 49% of them and having an incidence of 3.23 per 100,000 of the population [1]. With a median overall survival (mOS) of 14.6 months and a 5-year survival rate of 5% despite surgical resection and adjuvant therapies, glioblastoma is certainly the centre of attention among PCNSTs [1][2][3].

2. Cellular Armoury

Cancer is a disease that can arise in almost any tissue of the human body. Cancer arises when normal healthy cells transform into cancer cells that proliferate uncontrollably, leading to the formation of tumours. It is a leading cause of mortality worldwide, and the predicted risk of a cancer diagnosis is around 50% for individuals born post 1960 in the United Kingdom (UK) [4][5]. The hallmarks of cancer describe a set of characteristics acquired by healthy cells as they transform into neoplastic entities. The interaction between glioma cells and the TME is key for tumour proliferation and migration [6][7][8], and understanding the immunoregulatory entities and processes in the TME has uncovered many viable targets for developing antitumour strategies [9]. Glioma cells constitutively secrete C–C motif chemokine ligand 2 (CCL2), which converts T_h2 lymphocytes into immunosuppressive T regulatory (T_{reg}) cells and macrophages into the pro-neoplastic M2 phenotype [10]. In addition, glioma cells release C-X-C motif ligand 8 (CXCL8), which modifies the extracellular matrix through activating matrix metalloproteinases within in the TME [10][11][12]. Furthermore, through activation of tumour growth factor beta (TGF-β) and epidermal growth factor receptor (EGFR) signalling pathways, glioma cells can enhance their invasiveness [12].

A major part of the tumour bulk is comprised of immune cells such as tumour-associated myeloid cells (TAMCs) [12], subtypes of which include tumour-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), neutrophils and microglia. Whilst not all myeloid cells are immunosuppressive, these TAMCs promote cancer growth directly by enhancing tumour cell proliferation and indirectly by generating an immunosuppressive microenvironment (**Table 1**) [12][13][14]. Microglia are present throughout the CNS and are key in regulating the cerebral immunological homeostasis [15]. Microglia are the resident CNS TAMs [16], which can secrete either immunosuppressive factors such as interleukin 10 (IL-10) and TGF-β or antitumour-stimulating cytokines such as IL-12 and TNF-α, according to the state of TME, whether ‘hot’ and highly infiltrated or ‘cold’ and poorly infiltrated [17].

Table 1. Principal cells of the tumour microenvironment of gliomas.

Cell Type	Function within the Tumour Microenvironment (TME)	References
Glioma cells	• Secrete immunosuppressive cytokines • Downregulate major histocompatibility complex (MHC) class I expression • Upregulate programmed death-ligand 1 (PD-L1) expression • Remodel the extracellular matrix • Release growth factors that promote angiogenesis, proliferation, invasion and immune evasion	[12][13][14]
Tumour-associated macrophages and microglia (TAMs)	• Mostly M2 phenotype promoting glioma growth and immune suppression • Release interleukin 10 (IL-10), tumour growth factor beta (TGF-β) and IL-12 • Suppress T-cell and NK-cell activity	[12][13][14]
Regulatory T (T_{reg}) cells	• Inhibit effector T-cell activity and promote immune evasion	[12][13][14]

Cell Type	Function within the Tumour Microenvironment (TME)	References
	• Increase cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programme cell death protein 1 (PD-1) expression, suppressing anti-tumour pathways	
Natural killer (NK) cells	• Recognise and kill glioma cells • Produce interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α) and IL-12, promoting anti-tumour immune responses	[12][13][14]
Dendritic cells (DCs)	• Antigen-presenting cells (APCs) that can active T cells and initiate anti-tumour immune response	[12][13][14]
Myeloid-derived suppressor cells (MDSCs)	• Immunosuppressive cells that inhibit the activity of T cells and NK cells, promoting immune evasion	[12][13][14]

s tumour- type was correlated with a higher tumour grade and lower mOS or poor outcomes in recurrent glioblastoma [15][18]. TAMs have a high degree of plasticity and, therefore, can be reprogrammed, thus providing opportunities for their exploitation in treatment options.

DCs are ‘professional’ antigen-presenting cells (APCs) linking innate and adaptive immunity. They capture antigens and present them to T cells [14]. DC development comprises two distinct stages: immature and mature. Immature DCs predominantly reside in peripheral tissues, where they exhibit antigen-capturing abilities via phagocytosis and receptor-mediated endocytosis. In contrast, mature DCs are mainly found within lymph nodes and the spleen, displaying an enhanced antigen-presenting capacity with the elevated expression of co-stimulatory molecules like CD80 and CD86. These mature DCs effectively activate naive T cells, priming them to differentiate into effector T cells. DCs are usually present in the meninges and choroid plexus but are not seen within the normal brain parenchyma [12]. On the contrary, in a glioma-infiltrated brain, they are harboured within the parenchyma [19]. Some animal studies have demonstrated that these are recruited to the TME in a similar way to NK cells via chemokines CCL5 and XCL1 [19]. DCs are also essential in the activation of antitumour immune responses and interact with other immune cells through integration of the various TME signals [14]. They can secrete cytokines such as IL-12, leading to the increased recruitment of $CD8^+$ T cells. However, they are still affected by TME immunosuppression, thus becoming regulatory DCs, which subsequently activate T_{reg} [20]. This leads to downregulation of $CD8^+$ T-cell recruitment [21]. Increased IL-10 secretion by macrophages leads to reduced IL-12 production and results in the containing of DCs within the TME [19]. These mechanisms lead to inefficient DC differentiation and the formation of impaired DCs in immature cellular states, causing immunosuppressive conditioning of the TME [21]. DC-based vaccines against glioblastoma are presently under construction, and significant progress has been made over the past year [22][23].

The immune cells and the blood–brain barrier (BBB) are key to the TME's adaptive alterations [8]. The BBB comprises a semipermeable membrane with endothelial cells, astrocyte foot processes and pericytes. This disconnects the brain from the peripheral immune system as evidenced by nil acute rejection of implanted grafts [24][25]. Naïve T cells cannot cross the BBB, but activated T cells can [24]. The BBB, thus, tightly regulates leukocyte entry into the brain parenchyma, due to which gliomas experience an overall decreased immune surveillance as compared to other tumours [15]. Furthermore, this tight regulation accounts for the poor therapeutic effectiveness of lipophobic intravenous treatments. In gliomas, the tumour physically distorts the BBB and induces inflammation, which then causes the surrounding blood vessels to become leaky and compromised [24]. The inadequate blood flow creates hypoxic regions within the tumour due to insufficient oxygen delivery, and these areas then attract macrophages, which further enhances the tumourigenicity of gliomas [20].

3. The Lymphocytic Milieu

Physiologically, the cytokine environment of the CNS is regulated towards helper T cell lymphocytes (T_h2) to shield the brain against inflammatory destruction [20]. Gliomas exploit this response by enhancing tumour-infiltrating lymphocyte (TIL) production of T_h2 cytokines [12][13].

Regulatory T cell (T_{reg}) suppress the activity of effector T cells and DCs. Whilst no T_{reg} are found in normal brain tissue, increased numbers of T_{reg} cells are seen in a glioma-infiltrated brain. This offers the key ability of a glioma to evade the immune system, as will be discussed in onward sections [12]. These cells are recruited to the TME by the secretion of chemokines such as CCL2 and CXCL12 by glioma cells. The number of T_{reg} present is linked to the location and grade of the tumour [12][20]. They induce compromised APCs, which have decreased ability to activate tumour reactive T cells [20]. In addition, T_{reg} secrete factors such as IL-10 and TGF-β, which inhibit the activity of other immune cells [14]. M2-phenotype macrophages and T_{reg} infiltrating the glioblastoma also leads to suppression of T-cell function [7]. A study showed that this concept was successful in treating ovarian cancer [26].

Natural killer (NK) cells are $CD3^-$, $CD56^+$ and $CD16^+$ innate lymphocytes that induce cytotoxic apoptosis in cells, therefore playing a vital role in the immune response [17]. NK cells are characterised by the expression of specific receptors, including killer cell immunoglobulin-like receptors (KIR) and killer cell lectin-like receptors (KLR), also known as killer activation receptors (KAR). NK cells can recognise virally infected or malignant cells by their absent major histocompatibility complex (MHC) class I and cause apoptosis by exhibiting a combination of inhibitory as well as stimulatory receptors [12][13][14]. Studies have shown that NK-cell deficiencies were correlated with an increased incidence of certain cancers, including glioblastoma [27][28]. Furthermore, glioblastoma expresses human leukocyte antigen G (HLA-G), which further limits the action of NK cells, providing protection from NK-cell-mediated death [17]. HLA-G interacts with inhibitory receptors on NK cells, suppressing cytotoxicity and inhibiting the ability to recognise and attack tumour cells. This immune evasion mechanism provides protection from NK-cell-mediated death, contributing to tumour resistance and disease progression. NK-cell activity is also hindered by MDSCs through the production of arginase and reactive oxygen species (ROS) [7].

4. Immunosuppressive Factors and Immune Evasion

The glioma microenvironment secretes a variety of immunosuppressive factors, such as TGF-β2, prostaglandin E2 (PGE2), IL-1, IL-10 and fibrinogen-like protein 2 (FGL2). These factors collectively further suppress effector T cell activity [12]. In addition, T_{reg} cells and MDSCs further prevent the normal NK-cell- and cytotoxic T lymphocyte (CTL)-mediated cytotoxic reactions [14][15]. TGF-β1 and IL-10 skew TAMCs toward the immunosuppressive M2 phenotype, which then along with T_{reg} secrete further TGF-β1 and IL-10, hence suppressing the immune system [13]. This immunosuppressive phenotype enables aggressive tumour proliferation and invasion, while inhibiting the normal antitumour immune responses [14].

Gliomas also express programmed death-ligand 1 (PD-L1), which is the primary ligand of programmed cell death protein 1 (PD-1), resulting in T-cell exhaustion and anergy [20].

Chronic antigenic stimulation in the TME induces T-cell exhaustion, characterised by impaired cytokine production, cytotoxicity and proliferation. This exhaustion is mediated by immune checkpoint molecules such as PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Immune checkpoint inhibitors (ICIs) targeting these pathways have revolutionised cancer treatment by reinvigorating exhausted T cells.

T-cell anergy is a common tolerance mechanism in which T cells are functionally inactivated, thus unable to coordinate a response after encountering an antigen, but remain in a prolonged, hyporesponsive state. Both types of anergies, i.e., clonal/in vitro and adaptive/in vivo, are seen in glioblastoma [29]. In clonal anergy, ineffective Ras/mitogen-activated protein kinase (Ras/MAPK) pathway activation and defective co-stimulation leads to impaired T-cell activation. Adaptive anergy, on the other hand, has persistent low-level antigen stimulation causing T-cell desensitisation, which leads to defective nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), decreased IL-2 release and impaired T-cell amplification [13][29].

The ability of glioma cells to evade the immune system is key in allowing them to proliferate. This mechanism depends on the anatomical site of the tumour within the CNS and the intrinsic cell-to-cell interactions among the tumour and the immune cells [12][13][14]. One of the most effective ways in which glioma cells cause immunosuppression is by reducing the overall recruitment of immune cells, while increasing the recruitment of microglial cells [15]. These microglia appear like immature APCs, lacking the ability to provide T-cell-mediated immunity. In addition, gliomas release immunosuppressant cytokines such as TGF-β, IL-10 and cyclooxygenase 2 (COX-2), while simultaneously inhibiting signal transducer and activator of transcription 3 (STAT3), thus enhancing the immunosuppressive microenvironment [20]. Hypoxia within TME due to impaired blood vessels and greater usage of oxygen by tumour cells results in the activation of the immunosuppressive STAT3 pathway. This STAT3 pathway leads to the creation of hypoxia-inducible factor-1 alpha (HIF-1α), the stimulation of T_{reg} cells and the synthesis of vascular endothelial growth factor (VEGF), and VEGF then further alters the vasculature and inhibits DC development, antigen presentation and T-cell infiltration into tumours [21].

Antigen recognition following presentation is essential for T-cell-mediated immunity, and this relies on the expression of MHC molecules [6]. Invading gliomas downregulate the expression of MHC proteins and costimulatory molecules such as CD80 and CD86 on their surface, leading to reduced immune recognition and the activation of cytotoxic T cells (CTLs) [7][13]. As mentioned above, the IL-10 and TGF-β enriched immunosuppressive TME of gliomas leads to loss of MHC expression on microglia [20]. Furthermore, reduced expression of MHC class I proteins was also present in glioma stem cells, in turn adding to T-cell-mediated immunity resistance and leading to increased tumour proliferation [15].

The blockage of chemotactic agents with antibodies or therapeutic drugs supresses the recruitment of suppressor cells. TGF-β is key in the development of T_{reg} cells and is upregulated in gliomas [13][20]. Antisense phosphorothioate oligodeoxynucleotide trabedersen (AP 12009) has been shown to successfully inhibit TGF-β expression in vitro, and in animal models the inhibition of TGF beta pathways among gliomas helped to re-establish immune surveillance [30]. Thus, inhibiting the cytokine production of glioma cells decreases their ability to proliferate, thus reducing their capacity to recruit immunosuppressive cells [31].

References

1. Ostrom, Q.T.; Cioffi, G.; Waite, K.; Kruchko, C.; Barnholtz-Sloan, J.S. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018. Neuro-Oncol. 2021, 23, iii–iii105.
2. Louis, D.N.; Perry, A.; Wesseling, P.; Brat, D.J.; Cree, I.A.; Figarella-Branger, D.; Hawkins, C.; Ng, H.K.; Pfister, S.M.; Reifenberger, G.; et al. The 2021 WHO Classification of Tumors of the Central Nervous System: A summary. Neuro-Oncol. 2021, 23, 1231–1251.
3. Stupp, R.; Hegi, M.E.; Mason, W.P.; van den Bent, M.J.; Taphoorn, M.J.; Janzer, R.C.; Ludwin, S.K.; Allgeier, A.; Fisher, B.; Belanger, K.; et al. European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009, 10, 459–466.
4. Cancer Research UK. Cancer Risk Statistics. Available online: https://www.cancerresearchuk.org/health-professional/cancer-statistics/risk#heading-Zero (accessed on 24 March 2023).
5. Cancer Research UK. Survival. Available online: https://www.cancerresearchuk.org/about-cancer/brain-tumours/survival#glioma (accessed on 24 March 2023).
6. Rolle, C.E.; Sengupta, S.; Lesniak, M.S. Mechanisms of immune evasion by gliomas. Adv. Exp. Med. Biol. 2012, 746, 53–76.

7. Magaña-Maldonado, R.; Chávez-Cortez, E.G.; Olascoaga-Arellano, N.K.; López-Mejía, M.; Maldonado-Leal, F.M.; Sotelo, J.; Pineda, B. Immunological Evasion in Glioblastoma. Biomed. Res. Int. 2016, 2016, 7487313.
8. Gieryng, A.; Pszczolkowska, D.; Walentynowicz, K.A.; Rajan, W.D.; Kaminska, B. Immune microenvironment of gliomas. Lab. Investig. 2017, 97, 498–518.
9. van Weverwijk, A.; de Visser, K.E. Mechanisms driving the immunoregulatory function of cancer cells. Nat. Rev. Cancer 2023, 23, 193–215.
10. Groblewska, M.; Litman-Zawadzka, A.; Mroczko, B. The Role of Selected Chemokines and Their Receptors in the Development of Gliomas. Int. J. Mol. Sci. 2020, 21, 3704.
11. Chen, Z.; Mou, L.; Pan, Y.; Feng, C.; Zhang, J.; Li, J. CXCL8 Promotes Glioma Progression by Activating The JAK/STAT1/HIF-1α/Snail Signaling Axis. Onco Targets. Ther. 2019, 12, 8125–8138.
12. Dapash, M.; Hou, D.; Castro, B.; Lee-Chang, C.; Lesniak, M.S. The Interplay between Glioblastoma and Its Microenvironment. Cells 2021, 10, 2257.
13. DeCordova, S.; Shastri, A.; Tsolaki, A.G.; Yasmin, H.; Klein, L.; Singh, S.K.; Kishore, U. Molecular Heterogeneity and Immunosuppressive Microenvironment in Glioblastoma. Front. Immunol. 2020, 11, 1402.
14. Chen, H.; Li, M.; Guo, Y.; Zhong, Y.; He, Z.; Xu, Y.; Zou, J. Immune response in glioma’s microenvironment. Innov. Surg. Sci. 2021, 5, 20190001.
15. Brown, N.F.; Carter, T.J.; Ottaviani, D.; Mulholland, P. Harnessing the immune system in glioblastoma. Br. J. Cancer 2018, 119, 1171–1181.
16. Pombo Antunes, A.R.; Scheyltjens, I.; Duerinck, J.; Neyns, B.; Movahedi, K.; Van Ginderachter, J.A. Understanding the glioblastoma immune microenvironment as basis for the development of new immunotherapeutic strategies. eLife 2020, 9, e52176.
17. Price, G.; Bouras, A.; Hambardzumyan, D.; Hadjipanayis, C.G. Current knowledge on the immune microenvironment and emerging immunotherapies in diffuse midline glioma. EBioMedicine 2021, 69, 103453.
18. Lu-Emerson, C.; Snuderl, M.; Kirkpatrick, N.D.; Goveia, J.; Davidson, C.; Huang, Y.; Riedemann, L.; Taylor, J.; Ivy, P.; Duda, D.G.; et al. Increase in tumor-associated macrophages after antiangiogenic therapy is associated with poor survival among patients with recurrent glioblastoma. Neuro-Oncol. 2013, 15, 1079–1087.
19. Böttcher, J.P.; Reis e Sousa, C. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. Trends Cancer 2018, 4, 784–792.

20. Grabowski, M.M.; Sankey, E.W.; Ryan, K.J.; Chongsathidkiet, P.; Lorrey, S.J.; Wilkinson, D.S.; Fecci, P.E. Immune suppression in gliomas. J. Neurooncol. 2021, 151, 3–12.
21. Hetze, S.; Sure, U.; Schedlowski, M.; Hadamitzky, M.; Barthel, L. Rodent Models to Analyze the Glioma Microenvironment. ASN Neuro. 2021, 13, 17590914211005074.
22. Lieberman, N.A.P.; DeGolier, K.; Kovar, H.M.; Davis, A.; Hoglund, V.; Stevens, J.; Winter, C.; Deutsch, G.; Furlan, S.N.; Vitanza, N.A.; et al. Characterization of the immune microenvironment of diffuse intrinsic pontine glioma: Implications for development of immunotherapy. Neuro-Oncol. 2019, 21, 83–94.
23. Liau, L.M.; Ashkan, K.; Brem, S.; Campian, J.L.; Trusheim, J.E.; Iwamoto, F.M.; Tran, D.D.; Ansstas, G.; Cobbs, C.S.; Heth, J.A.; et al. Association of Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination with Extension of Survival Among Patients with Newly Diagnosed and Recurrent Glioblastoma: A Phase 3 Prospective Externally Controlled Cohort Trial. JAMA Oncol. 2023, 9, 112–121.
24. Dubois, L.G.; Campanati, L.; Righy, C.; D’Andrea-Meira, I.; Spohr, T.C.; Porto-Carreiro, I.; Pereira, C.M.; Balça-Silva, J.; Kahn, S.A.; DosSantos, M.F.; et al. Gliomas and the vascular fragility of the blood brain barrier. Front. Cell. Neurosci. 2014, 8, 418.
25. Daneman, R.; Prat, A. The blood-brain barrier. Cold Spring Harb. Perspect. Biol. 2015, 7, a020412.
26. Fecci, P.E.; Mitchell, D.A.; Whitesides, J.F.; Xie, W.; Friedman, A.H.; Archer, G.E.; Herndon, J.E., 2nd; Bigner, D.D.; Dranoff, G.; Sampson, J.H. Increased regulatory T-cell fraction amidst a diminished CD4 compartment explains cellular immune defects in patients with malignant glioma. Cancer Res. 2006, 66, 3294–3302.
27. Fares, J.; Fares, M.Y.; Fares, Y. Natural killer cells in the brain tumor microenvironment: Defining a new era in neuro-oncology. Surg. Neurol. Int. 2019, 10, 43.
28. Zhang, L.; Yu, H.; Xue, Y.; Liu, Y. Decreased natural killer cells in diffuse intrinsic pontine glioma patients. Childs Nerv. Syst. 2020, 36, 1345–1346.
29. Zarek, P.E.; Huang, C.T.; Lutz, E.R.; Kowalski, J.; Horton, M.R.; Linden, J.; Drake, C.G.; Powell, J.D. A2A receptor signaling promotes peripheral tolerance by inducing T-cell anergy and the generation of adaptive regulatory T cells. Blood 2008, 111, 251–259.
30. Jaschinski, F.; Rothhammer, T.; Jachimczak, P.; Seitz, C.; Schneider, A.; Schlingensiepen, K.H. The antisense oligonucleotide trabedersen (AP 12009) for the targeted inhibition of TGF-β2. Curr. Pharm. Biotechnol. 2011, 12, 2203–2213.
31. Christofides, A.; Kosmopoulos, M.; Piperi, C. Pathophysiological mechanisms regulated by cytokines in gliomas. Cytokine 2015, 71, 377–384.

Retrieved from https://encyclopedia.pub/entry/history/show/111134