# Part 1: Detailed Report – Immune Pathway Markers in Glioma

Gliomas, especially high-grade glioblastomas, create an immunosuppressive tumor microenvironment (TME) characterized by skewed cytokine/chemokine profiles, immune checkpoint upregulation, metabolic reprogramming, and a unique composition of immune cells[[1]](https://www.nature.com/articles/s41698-024-00717-4?error=cookies_not_supported&code=0b451d28-15ea-4d97-a122-f71059e2973e#:~:text=The%20glioma%20immune%20microenvironment%20consists,com)[[2]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=and%20T%20lymphocytes,regulatory%20lymphocytes%20to%20the%20tumor). Below we comprehensively detail key immune-related molecules and cell markers under several categories (cytokines, chemokines, checkpoints, metabolic markers, immune cell markers, and functional regulators), emphasizing their pro- or anti-inflammatory roles, the cellular context, and known glioma-specific relevance.

## Cytokines in the Glioma Microenvironment

**Pro-inflammatory Cytokines (Tumor-Promoting in Gliomas):** Glioma-associated myeloid cells often produce “classic” pro-inflammatory cytokines like **interleukin-1β (IL-1β)**, **IL-6**, and **tumor necrosis factor-α (TNF-α)**, but in the TME these can paradoxically support tumor progression. Tumor-associated macrophages (TAMs) in gliomas secrete IL-1β, IL-6, and TNF-α as part of the innate immune response[[3]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=,mechanisms%20of%20immune%20surveillance%2C%20including). These cytokines are typically pro-inflammatory and would promote T cell activation in normal contexts. However, in glioma, chronic IL-6 and IL-1β signaling can drive a **mesenchymal** tumor phenotype and support angiogenesis and invasion, thereby aiding tumor growth[[4]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=IL,NOX3%20and%20increase%20ROS%20production)[[5]](https://biosignaling.biomedcentral.com/articles/10.1186/s12964-023-01255-5#:~:text=NLRP3%20inflammasome%20has%20shown%20that,cell%20line%20causes%20augmented%20NLRP3). For example, NLRP3 inflammasome-driven IL-1β release in gliomas has been shown to activate NF-κB and promote glioma cell proliferation, invasion, and epithelial-to-mesenchymal transition (EMT)[[5]](https://biosignaling.biomedcentral.com/articles/10.1186/s12964-023-01255-5#:~:text=NLRP3%20inflammasome%20has%20shown%20that,cell%20line%20causes%20augmented%20NLRP3). **Interferon-γ (IFN-γ)**, a Th1 cytokine from activated T/NK cells, is strongly pro-inflammatory and can have anti-tumor effects; indeed IFN-γ (and TNF-α) signaling in gliomas can reduce MDSC abundance and push the microenvironment toward a more inflammatory (anti-tumor) state[[6]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1252%20Different%20cytokines,downregulation%2C%20promoting%20the%20secretion%20of). However, gliomas often induce T cell dysfunction such that IFN-γ production is limited. Type I interferons (IFN-α/β) are part of innate anti-tumor immunity and can penetrate the CNS; therapeutic trials delivering IFN-α or TNF-α have shown potential to partly reverse glioma-induced immunosuppression[[7]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=particularly%20immunomodulatory%20cytokines%2C%20as%20a,%CE%B1%20to%20counteract).

**Anti-inflammatory (Immunosuppressive) Cytokines:** Gliomas abundantly express **interleukin-10 (IL-10)** and **transforming growth factor-β (TGF-β)**, which are key anti-inflammatory, immunosuppressive cytokines. TAMs and microglia in the glioma TME secrete IL-10 and TGF-β to dampen anti-tumor immunity[[8]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=immunity%20homeostasis%20in%20the%20brain,is%20impaired%20but%20showed%20increased). IL-10 is primarily produced by M2-polarized macrophages and regulatory T cells (Tregs); it inhibits pro-inflammatory cytokine release and impairs antigen presentation, fostering tolerance. High IL-10 levels in glioblastoma correlate with influx of Tregs and poor prognosis[[9]](https://pmc.ncbi.nlm.nih.gov/articles/PMC9206138/#:~:text=The%20immunosuppressive%20role%20of%20indoleamine,can%20worsen%20the%20prognosis). TGF-β, produced by both glioma cells and TAMs, is a potent suppressor of immunity: it drives macrophages towards an M2 phenotype, promotes Treg differentiation, and directly inhibits cytotoxic T lymphocyte (CTL) and natural killer (NK) cell effector functions[[8]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=immunity%20homeostasis%20in%20the%20brain,is%20impaired%20but%20showed%20increased)[[10]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=cytokines%2C%20and%20upregulate%20co,microenvironment%2C%20in%20particular%20composition%20and). These cytokines contribute to the “cold” immune status of gliomas, wherein immune responses are blunted. Notably, **TGF-β and IL-10 signaling in GBM can induce systemic immunosuppression** – for example, tumor-antigen presentation in cervical lymph nodes can trigger IL-10/TGF-β–mediated expansion of peripheral Tregs that then home to the tumor[[11]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=impacting%20pathways%20such%20as%20TGF,gut%20microbiota%20can%20undergo%20metabolic).

**Other Cytokines:** Several additional cytokines influence glioma immunity. **IL-12** and **IL-15** are pro-inflammatory cytokines (produced by dendritic cells, macrophages) that support CTL and NK cell activity (IL-12 drives Th1 responses/IFN-γ, IL-15 is crucial for NK and memory T cell survival); these are generally anti-tumorigenic, but in gliomas their levels are often low. **IL-2**, a T cell growth factor, is also low in the glioma milieu, except when delivered by therapies (e.g. some CAR T regimens), leading to poor T cell proliferation on site. **IL-4** and **IL-13** (Th2 cytokines) can appear in the TME and push macrophages toward the M2 state; IL-13 in particular is exploited by some glioma therapies as a target (IL13Rα2 is a glioma-restricted receptor). **Colony-stimulating factors (CSFs)** are important in glioma as well: **M-CSF (CSF1)** is often secreted by glioma cells to recruit and differentiate macrophages via CSF1R, promoting immunosuppressive TAM accumulation. **GM-CSF (CSF2)** and **G-CSF (CSF3)** can be produced in gliomas; paradoxically, while GM-CSF might stimulate dendritic cell activity in some contexts, in gliomas these factors tend to support the recruitment and proliferation of **myeloid-derived suppressor cells (MDSCs)** and TAMs[[12]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=MDSCs%20infiltrate%20the%20TME%20under,in%20maintaining%20metabolic%20reprogramming%2C%20proliferation). Elevated CSF1/CSF2 levels sustain the immunosuppressive, pro-tumor myeloid populations in glioblastoma. In summary, gliomas skew the cytokine milieu: *pro*-inflammatory cytokines are present but often co-opted for tumor promotion or kept ineffective, whereas *anti*-inflammatory cytokines like IL-10 and TGF-β dominate and enforce immune suppression.

## Chemokines and Their Receptors

Chemokines in gliomas orchestrate the trafficking of various immune cells into (or out of) the tumor, shaping the immune landscape. Glioma cells and associated stromal cells secrete numerous chemokines (CC and CXC families) to recruit immunosuppressive myeloid cells and sometimes exclude effector lymphocytes[[13]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=Glioma%20cells%20secrete%20numerous%20chemokines%2C,directing%20the%20immune%20system%20into)[[14]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=in%20GBM,cell%20proliferation%20and%20activation). Below are key examples:

* **CCL2 (MCP-1)** – *Monocyte/MDSC recruiter, pro-tumor.* CCL2 is highly expressed in gliomas (especially mesenchymal subtype) and binds CCR2 on Ly6C^hi monocytes and MDSCs, driving their influx into the tumor. CCL2 from the glioma microenvironment is essential for attracting immunosuppressive CCR2^+ monocytes/MDSCs and also **CCR4^+ Tregs**[[15]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=CCL12%2C%20CCL2%2C%20and%20CCL7,instead%20of%20conventionally%20fractionated%20radiotherapy)[[16]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=421,2016%3B76%2819%29%3A5671%E2%80%9382). High CCL2 correlates with worse patient survival; GBM patients with lower CCL2 expression survive significantly longer, highlighting its pro-tumor role[[17]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L2654%20exacerbating%20the,of%20the%20CCL2%2FCCR2%20axis%20inhibited). In murine models, disrupting the CCL2–CCR2 axis reduces MDSC and Treg infiltration and inhibits glioma growth[[18]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=exacerbating%20the%20TIME%20in%20GBM,of%20the%20CCL2%2FCCR2%20axis%20inhibited).
* **CXCL12 (SDF-1α)** – *Treg and myeloid recruiter, pro-tumor.* CXCL12 is secreted by glioma cells and signals via CXCR4 (and atypical receptor CXCR7) on immune cells. The **CXCL12–CXCR4 axis** helps retain T cells in the perivascular niche and can preferentially attract Tregs and monocytes rather than effector T cells. It also aids glioma cell invasion and survival. In many cancers, CXCL12-rich TMEs exclude CTLs; in glioma, high CXCL12 is associated with an immune-excluded “cold” tumor. Preclinically, blocking CXCL12/CXCR4 can enhance T cell entry. (Notably, CAR-NK cells engineered to overexpress CXCR4 have shown improved homing to CXCL12-secreting GBM[[19]](https://www.nature.com/articles/s41698-024-00717-4?error=cookies_not_supported&code=0b451d28-15ea-4d97-a122-f71059e2973e#:~:text=match%20at%20L889%20expressed%20on,This%20occurs%20because%20NK)[[20]](https://www.nature.com/articles/s41698-024-00717-4?error=cookies_not_supported&code=0b451d28-15ea-4d97-a122-f71059e2973e#:~:text=123,Cancer%2016%2C%207%E2%80%9319%20%282015).)
* **CX3CL1 (Fractalkine)** – *Microglia-interacting chemokine.* CX3CL1 is expressed by neurons and glioma cells; its receptor **CX3CR1** is highly expressed on microglia. CX3CL1 can mediate attraction and adhesion of microglia to tumor cells. In gliomas, CX3CL1 may help tether resident microglia (which are CX3CR1^+) to the tumor, influencing their activation state. (Microglia also express *P2RY12* and *TMEM119*, see later, which distinguish them from blood monocytes[[21]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=or%20macrophages,Functions%20of%20those%20putative%20discriminating).)
* **CCL5 (RANTES)** – *Mixed effects (T cell recruitment but also tumor support).* CCL5 can attract effector T cells via CCR5, which might sound beneficial; however, glioma cells and TAMs produce CCL5 in response to certain signals (e.g. bradykinin B1 receptor activation[[22]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L804%20cytokines%20secretion%2C,319)). Glioma-derived CCL5 often acts in concert with immunosuppressive factors to shape a protumor TME. It may recruit **CCR5^+ TAMs and Tregs** as well. Elevated CCL5 in GBM has been linked to mesenchymal transition and worse outcomes in some studies.
* **CCL22** – *Treg recruiter, pro-tumor.* Although not as well studied in GBM as in some other tumors, CCL22 from TAMs or glioma cells can attract **CCR4^+ regulatory T cells** into the tumor. Treg recruitment via CCL2/CCL22 is one mechanism by which GAMs (glioma-associated microglia/macrophages) and MDSCs suppress immunity[[10]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=cytokines%2C%20and%20upregulate%20co,microenvironment%2C%20in%20particular%20composition%20and).
* **CXCL8 (IL-8)** and **CXCL5** – *Neutrophil/MDSC recruiters, pro-tumor.* IL-8 (CXCL8) is secreted by glioma cells and GAMs; it binds CXCR1/2 on neutrophils and granulocytic MDSCs, promoting their migration. It is one of the factors that mobilize MDSCs[[23]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1156%20,crucial%20mediator%20that%20establishes%20the). IL-8 in GBM has been associated with angiogenesis and tumor progression as well. CXCL5 is another CXCR2 ligand possibly upregulated in gliomas. These CXC chemokines contribute to the accumulation of **tumor-associated neutrophils (TANs)**, which often adopt pro-tumor (N2) functions (described later).
* **CXCL10 (IP-10)** and **CXCL9 (MIG)** – *Th1 chemoattractants, potentially anti-tumor.* These interferon-inducible chemokines bind CXCR3 on effector T cells and NK cells, attracting them to sites of inflammation. If GBM tissue produces CXCL9/10 (e.g. in response to IFN-γ), it could promote infiltration of CTLs and Th1 cells. Indeed, in brain metastases, CXCL10 is crucial for recruiting anti-tumor T cells[[24]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=,crucial%20mediator%20that%20establishes%20the). However, many GBMs have low levels of these chemokines or an environment that favors other signals, so CTL infiltration remains sparse.
* **Others:** **CXCL1/CXCL2** (via CXCR2) can also attract neutrophils to gliomas. **CXCL11** (another CXCR3 ligand) was noted in one study to be secreted by GBM cells along with IL-6, CCL5, and IL-8 under certain stimuli, collectively **promoting monocyte infiltration**[[22]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L804%20cytokines%20secretion%2C,319). **CCL3 and CCL4** (MIP-1α/β) may recruit various myeloid cells as well. The net effect of chemokines in glioma is an attraction of immunosuppressive myeloid cells (monocytes, MDSCs, neutrophils) and regulatory lymphocytes, while effective recruitment of cytotoxic lymphocytes is minimal. This chemokine-guided trafficking is a major reason glioblastomas are considered immunologically “cold” tumors.

## Immune Checkpoint Regulators

Gliomas upregulate numerous immune checkpoint molecules to suppress T cell activity. These include well-known inhibitory receptors and ligands that either diminish T cell responses or promote T cell “exhaustion.” Major checkpoint pathways in glioma include:

* **PD-1 (Programmed cell death-1, a.k.a. PDCD1)** on T cells and **PD-L1 (PD-1 ligand, a.k.a. CD274 or B7-H1)** on tumor cells and myeloid cells. PD-1 is highly expressed on the small population of CD8^+ and CD4^+ T cells that infiltrate GBM, indicating an exhausted phenotype[[25]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=TME%20express%20various%20co,1%2B%2C%20CD39%2B%2C%20and%20CD45RO%2B%5B87%5D.%20Through). PD-L1 is frequently upregulated on glioma cells and TAMs, especially in more aggressive cases[[26]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=and%20secreting%20IL,35%5D.%20They%20have). The PD-1/PD-L1 interaction transmits an inhibitory signal that reduces T cell proliferation and cytokine release. In glioblastoma, PD-L1 not only inhibits effector T cells but also can **induce and maintain regulatory T cells** within the tumor[[27]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L7737%20immune%20checkpoint,2018%3B7%287%29%3A%20e1448329). This contributes to immune evasion. Clinically, **high PD-L1 expression in GBM is associated with poorer prognosis**, and trials of PD-1/PD-L1 blocking antibodies have so far shown limited success, in part due to the highly suppressive milieu[[28]](https://www.nature.com/articles/s41698-024-00717-4?error=cookies_not_supported&code=0b451d28-15ea-4d97-a122-f71059e2973e#:~:text=The%20challenges%20outlined%20above%20become,broadly%2C%20the%20TME%20includes%20the)[[29]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=,3).
* **CTLA-4 (Cytotoxic T-lymphocyte antigen-4, CD152)** on T cells (particularly Tregs). CTLA-4 competes with the costimulatory receptor CD28 for B7 ligands (CD80/CD86) on antigen-presenting cells. In gliomas, CTLA-4 is upregulated on intratumoral Tregs and some exhausted T cells, leading to suppressed priming and expansion of anti-tumor T cells. Tregs rely on CTLA-4 to downregulate B7 on dendritic cells, thus broadly dampening T cell activation. CTLA-4^+ Treg infiltration in GBM further contributes to poor immune response. (While CTLA-4 blockade has revolutionized melanoma treatment, in GBM a trial of ipilimumab showed negligible benefit, reflecting the formidable immunosuppression in GBM.)
* **TIM-3 (T cell immunoglobulin and mucin-domain containing-3, or HAVCR2)** on T cells *and* myeloid cells. TIM-3 is widely upregulated in GBM’s immune compartment: on exhausted CD8 T cells, on dysfunctional NK cells, and even on TAMs/microglia[[30]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=%5B73%5D.%20TIM,metabolite%20lactate%20from%20GBM%20can). It binds ligands like Galectin-9 and phosphatidylserine. TIM-3 in GBM T cells marks a state of severe exhaustion often co-expressing PD-1 and LAG-3. Importantly, TIM-3 can directly modulate macrophages: TIM-3 activation on TAMs was found to induce their migration and polarize them to an **anti-inflammatory, pro-tumor M2 phenotype via IL-6 secretion**[[31]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L785%20%5B73%5D.%20TIM,metabolite%20lactate%20from%20GBM%20can). Thus, TIM-3 contributes to both adaptive and innate immunosuppression. Blocking TIM-3 in preclinical GBM models has shown restoration of T cell and microglia activity, increased NK and CD8 T cell presence, and slowed tumor growth[[32]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L854%20from%20T,CD8%2B%20T%20cells%2C%20and%20microglias). TIM-3 is considered one of the most upregulated co-inhibitory receptors in GBM and correlates with poor prognosis[[33]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1612%20immune%20cells%2C,only%20inhibited%20its%20induction%20of).
* **LAG-3 (Lymphocyte activation gene-3)** on T cells. LAG-3 binds MHC class II molecules and negatively regulates T cell activation. In GBM, LAG-3 is co-expressed with PD-1 on exhausted T cells[[34]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=immune%20checkpoint%20family%2C%20particularly%20in,correlated%20with%20poorer%20survival%20in). It may also be found on certain tumor-infiltrating regulatory T cells. High LAG-3 in gliomas has been linked to immune escape, and it is a target of emerging combination therapies (e.g., PD-1 plus LAG-3 blockade).
* **VISTA (V-domain Ig suppressor of T cell activation,** also known as **VSIR)** on myeloid cells and T cells. VISTA is an immune checkpoint receptor typically expressed on APCs and some T cells, functioning somewhat analogous to PD-L1/CTLA-4 in suppressing T cell responses. Studies show VISTA is upregulated in GBM myeloid infiltrates; it can inhibit T cells by binding to an unknown ligand or receptor on T cells. High VISTA expression in gliomas is associated with T cell dysfunction and may predict poor outcome. (VISTA is being investigated as a target in other cancers, but in GBM it remains to be clinically exploited.)
* **TIGIT (T cell Ig and ITIM domain)** on T and NK cells. TIGIT binds CD155 (PVR) on dendritic cells or tumor cells, delivering an inhibitory signal to T and NK cells. It often co-exists with PD-1 and TIM-3 on exhausted T cells in GBM. TIGIT^+ NK cells in glioma are also functionally impaired. In a mouse GBM model, combined TIGIT and PD-1 blockade outperformed PD-1 alone, improving CD8 T cell function and reducing MDSC levels[[35]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1607%20production%20of,MDSCs%20and%20DCs%20amount). This suggests TIGIT contributes to the suppressive network in glioma.
* **ICOS (Inducible T cell co-stimulator, CD278)** on activated T cells, especially T\_FH and Tregs. Unlike the above, ICOS is a *positive* costimulatory receptor (member of CD28 family) – its ligand ICOSL can be on APCs or tumor cells. In gliomas, ICOS is noteworthy because Tregs in tumors often highly express ICOS. ICOS signaling supports the maintenance and suppressive function of Tregs. Indeed, correlations have been observed between ICOS and immunosuppressive markers in GBM (e.g., a fusion analysis found ICOS expression correlating with other checkpoints PD-1, TIM-3, LAG-3 and IDO in mesenchymal GBM)[[34]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=immune%20checkpoint%20family%2C%20particularly%20in,correlated%20with%20poorer%20survival%20in). This indicates ICOS^+ Tregs are part of the immunosuppressive milieu. Some experimental therapies aim to deplete or modify ICOS^+ Tregs to relieve immunosuppression.
* **B7-H3 (CD276)** and **B7-H4 (VTCN1)** on tumor cells. These B7 family checkpoints are overexpressed in gliomas. B7-H3 (also called CD276) inhibits T cell function and is highly expressed in many GBM specimens; it correlates with poor survival and has prompted development of B7-H3–targeted CAR-T cells. B7-H4 is another inhibitory ligand on tumor cells that can suppress T cell proliferation; it’s also found in GBM. Both are emerging immunotherapy targets.

In summary, gliomas exploit multiple checkpoint pathways (some redundantly) to shut down T cell immunity. The infiltrating T cells often co-express several checkpoints (PD-1^+TIM-3^+LAG-3^+ etc.), indicative of “exhaustion”[[25]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=TME%20express%20various%20co,1%2B%2C%20CD39%2B%2C%20and%20CD45RO%2B%5B87%5D.%20Through). Meanwhile, tumor and myeloid cells express the ligands (PD-L1, Gal-9, CD155, B7-H3, etc.) that engage these receptors. This extensive upregulation underscores why single-agent checkpoint blockade (like anti–PD-1 alone) has had limited efficacy – the glioma TME presents many simultaneous roadblocks to immune attack.

## Immunometabolic Markers

Gliomas induce metabolic changes that have immunological consequences. Certain enzymes and metabolic regulators become crucial “immunometabolic” markers – they modulate metabolism in a way that affects immune cell function or survival. Key examples relevant to glioma include:

* **IDO1 (Indoleamine 2,3-dioxygenase 1):** IDO1 is a tryptophan-catabolizing enzyme often upregulated in glioma cells and myeloid cells. It depletes tryptophan and produces kynurenine, an immunosuppressive metabolite that activates the aryl hydrocarbon receptor (AHR) in T cells. **High IDO1 expression is a hallmark of immunosuppressive tumors; in gliomas, elevated IDO1 is associated with increased Treg infiltration and worse prognosis**[[9]](https://pmc.ncbi.nlm.nih.gov/articles/PMC9206138/#:~:text=The%20immunosuppressive%20role%20of%20indoleamine,can%20worsen%20the%20prognosis). IDO1 essentially starves effector T cells (which require tryptophan) and induces Tregs and MDSCs, contributing to anergic T cells. In GBM models, IDO1 knockdown led to reduced CD8^+ T cell exhaustion and enhanced anti-tumor immunity[[36]](https://www.sciencedirect.com/science/article/abs/pii/S1567576924015832#:~:text=Indoleamine%202%2C3,down%20in%20glioblastoma%20cells). IDO1 is a target of interest (small-molecule IDO inhibitors have been tested in trials, though not yet successful in GBM).
* **GPX4 (Glutathione peroxidase 4):** GPX4 is a key antioxidant enzyme that protects cells from lipid peroxidation and prevents ferroptotic cell death. Its immunometabolic relevance lies in ferroptosis and inflammation: **GPX4 activity is linked to chronic inflammation** and tumor progression[[37]](https://pmc.ncbi.nlm.nih.gov/articles/PMC9273259/#:~:text=Ferroptosis%20in%20Glioma%20Immune%20Microenvironment,that%20glioma%20progression%20is). In gliomas, tumor cells with high GPX4 are resistant to ferroptosis. Inducing ferroptosis via GPX4 inhibitors (like RSL3) has been shown to kill glioma cells and can potentially release damage signals to stimulate immunity[[38]](https://pmc.ncbi.nlm.nih.gov/articles/PMC10659054/#:~:text=PMC%20pmc,accumulation%20of%20lipid%20peroxides). However, glioma cells often maintain high GPX4 to avoid ferroptosis and the pro-inflammatory effects of lipid peroxidation. There is also evidence that *targeting GPX4 might help overcome the immunosuppressive TME*: ferroptotic cancer cell death can release HMGB1 and other alarmins that activate dendritic cells and T cells[[39]](https://www.nature.com/articles/s41419-024-06963-5#:~:text=Intracellular%20C5aR1%20inhibits%20ferroptosis%20in,ERK1%2F2%2C%20thereby%20promoting%20glioma). Thus, GPX4 is both a metabolic vulnerability and a marker of an immune-resistant metabolic state.
* **GFPT1/2 (Glutamine–fructose-6-phosphate transaminase 1 and 2):** These are the rate-limiting enzymes of the **hexosamine biosynthesis pathway (HBP)**, which generates UDP-GlcNAc for protein glycosylation. Enhanced HBP flux in tumors can drive aberrant glycosylation of immune-regulatory proteins. Indeed, **GFPT1 has been shown to promote tumor immune evasion via increased glycosylation of PD-L1**, effectively protecting PD-L1 from degradation and enhancing its checkpoint function[[40]](https://www.frontiersin.org/journals/genetics/articles/10.3389/fgene.2024.1482929/full#:~:text=expression%20enhance%20the%20EMT%20and,drug%20sensitivity%20have%20not%20been). Overexpression of GFPT1 in cancer correlates with poor survival, elevated M2 macrophage infiltration, and immune escape signatures[[41]](https://www.frontiersin.org/journals/genetics/articles/10.3389/fgene.2024.1482929/full#:~:text=Results%3A%20Elevated%20GFPT1%20expression%20was,migration%2C%20along%20with%20enhanced%20apoptosis)[[42]](https://www.frontiersin.org/journals/genetics/articles/10.3389/fgene.2024.1482929/full#:~:text=%28Zhang%20et%20al,drug%20sensitivity%20have%20not%20been). GFPT2 is an isozyme more expressed in neural tissues; recent studies in other cancers found **high GFPT2 associated with immunosuppressive cell infiltration and T-cell exhaustion** in the tumor microenvironment[[43]](https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2022.811559/full#:~:text=in%20focal%20adhesion%2C%20ECM%20receptor,a%20certain%20class%20of%20drugs). While specific data in glioma is limited, these findings suggest gliomas with elevated GFPT1/2 might have more glycosylation-mediated immune suppression (e.g., heavily glycosylated PD-L1, CD44, etc.) and could be more aggressive. The hexosamine pathway thus represents a link between tumor metabolism and immune modulation.
* **NLRP3 (NOD-, LRR- and Pyrin domain-containing protein 3):** NLRP3 is an innate immune sensor that forms the NLRP3 inflammasome, which activates caspase-1 to mature IL-1β and IL-18. In normal contexts, NLRP3 triggers pro-inflammatory responses against danger signals. In gliomas, NLRP3 can be expressed by microglia or even glioma cells. Paradoxically, **overactivation of the NLRP3 inflammasome in glioma has been linked to tumor-promoting inflammation**. Patient-derived glioma cells show aggressive NLRP3 activity, which is considered a marker of glioma progression[[44]](https://biosignaling.biomedcentral.com/articles/10.1186/s12964-023-01255-5#:~:text=match%20at%20L412%20investigated,of%20NLRP3%20in%20glioma%20was)[[45]](https://biosignaling.biomedcentral.com/articles/10.1186/s12964-023-01255-5#:~:text=investigated,of%20NLRP3%20in%20glioma%20was). NLRP3-driven IL-1β release, as noted, can aid invasion and growth of glioma cells[[46]](https://biosignaling.biomedcentral.com/articles/10.1186/s12964-023-01255-5#:~:text=exhibited%20that%20the%20NLRP3%20inflammasome,dependent). Furthermore, inflammasome activity might induce an immunosuppressive feedback: for instance, chronic IL-1β can attract MDSCs and enhance PD-L1 expression in the TME. There is ongoing research into NLRP3 inhibitors (like MCC950) to see if tamping down this aberrant inflammation can curb glioma progression[[47]](https://biosignaling.biomedcentral.com/articles/10.1186/s12964-023-01255-5#:~:text=match%20at%20L434%20In%20addition,127%5D.%20WP1066). Notably, *the dual nature of NLRP3 means it could potentially stimulate anti-tumor immunity if properly harnessed*, but in GBM it appears to mostly contribute to a pathological inflammation that the tumor exploits.
* **SREBP1/2 (Sterol regulatory element-binding proteins 1 and 2) and SCAP (SREBP cleavage-activating protein):** SREBP1 and SREBP2 are master transcription factors that regulate lipid biosynthesis (fatty acids by SREBP1; cholesterol by SREBP2). SCAP is the chaperone that escorts SREBPs to the Golgi for activation. Tumor cells often have upregulated SREBP pathways to sustain rapid growth, and this has **immunological consequences**. High lipid production by tumors can create an immunosuppressive milieu (via acidosis, nutrient competition, and recruiting lipid-loving suppressive cells). In hepatocellular carcinoma, *tumor-intrinsic SREBP1 activity correlated with an immune-excluded TME*[[48]](https://pubmed.ncbi.nlm.nih.gov/40518290/#:~:text=Multiomics%20identifies%20tumor,tumor%20cells%2C%20elevated%20immunosuppressive). In gliomas, a similar effect is plausible – e.g., excess cholesterol/lipids can be shuttled to TAMs, inducing a more suppressive phenotype. Indeed, the **SREBP pathway in TAMs is critical for their function**: research showed that *Treg cells promote the SREBP1-dependent metabolic fitness of tumor-associated macrophages* by curbing IFN-γ in the microenvironment[[49]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-023-01498-2#:~:text=match%20at%20L3179%20Vignali%20KM%2C,397%20e386). This allows TAMs to accumulate lipids and thrive as M2 cells. Conversely, blocking SREBP1 in macrophages can impair their immunosuppressive “M2-like” functions and even sensitize tumors to therapy[[50]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-023-01498-2#:~:text=preclinical%20study%20showed%20that%20the,that%20dietary%20intake%20enriched%20with)[[51]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-023-01498-2#:~:text=which%20is%20dependent%20on%20the,suppressive%20effect). SREBP1 also prevents ferroptosis in tumor cells by upregulating monounsaturated fatty acid synthesis (via SCD1)[[52]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-023-01498-2#:~:text=match%20at%20L418%20cells%20from,AKT%20signaling%20may%20prove), thus helping tumor cells avoid a form of cell death that would release immunostimulatory signals. **SREBP2**, on the other hand, controls cholesterol uptake/export. Hypoxic, acidic glioma regions activate SREBP2 to increase cholesterol synthesis and uptake, which has been associated with reduced overall survival[[53]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-023-01498-2#:~:text=match%20at%20L521%20Additionally%2C%20an,is%20associated%20with%20reduced%20overall). In summary, SREBP1/2 (with SCAP) are crucial metabolic regulators that link to immune suppression: they ensure tumor and TAM cells have abundant lipids to support growth and suppressive functions. Targeting the SREBP pathway (e.g., with drugs like fatostatin or by diet modification) is being explored as a way to hit both metabolism and immunity in cancer[[54]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-023-01498-2#:~:text=match%20at%20L1174%20their%20effects,with%20vemurafenib%20therapy%20enhances%20the)[[50]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-023-01498-2#:~:text=preclinical%20study%20showed%20that%20the,that%20dietary%20intake%20enriched%20with).
* **Other Immunometabolic Factors:** **Arginase-1 (ARG1)** and **iNOS (NOS2)** are metabolic enzymes in myeloid cells that we will detail below as functional effectors, but worth noting here: they modulate arginine metabolism, profoundly affecting T cells (through nutrient deprivation and NO production). **COX-2 (PTGS2)**, an enzyme in prostaglandin synthesis, is often up in gliomas and TAMs, leading to high PGE\_2, which is immunosuppressive. **VEGF-A**, while a growth factor for blood vessels, is also an immunomodulator (it can impair dendritic cell maturation and attract MDSCs). Elevated VEGF in gliomas (partly due to HIF-1α) thus has dual protumor roles: angiogenesis and immune suppression. **AHR (aryl hydrocarbon receptor)**, activated by metabolites like kynurenine (from IDO1) or lactate, is another immunometabolic node that drives regulatory phenotypes in TAMs and T cells. For instance, AHR activation in TAMs can induce more IL-10 and suppressive genes. **Glutamate metabolism** is also relevant – gliomas release excess glutamate which can kill T cells or neurons; the enzyme **GDH** and glutaminases link to this. Overall, the metabolic environment of gliomas – high lactate, low glucose, high lipids, altered amino acids – is carefully tuned by the tumor to inhibit effective immunity.

## Immune Cell-Specific Markers and Subtypes in Gliomas

The glioma immune microenvironment contains various immune cells, though in proportions very different from peripheral tumors due to the brain’s “immune privilege.” Below we outline each major immune cell type, their key markers for identification, their functional role (pro- or anti-inflammatory), and their glioma-specific behavior or relevance.

### T Cells (CD4⁺ Helper, CD8⁺ Cytotoxic, and Tregs)

**Tumor-Infiltrating T Lymphocytes (TILs)** in gliomas are notably sparse. High-grade gliomas are considered “T cell cold” – infiltrating T cells are low in number (often <5% of cells) and typically dysfunctional[[1]](https://www.nature.com/articles/s41698-024-00717-4?error=cookies_not_supported&code=0b451d28-15ea-4d97-a122-f71059e2973e#:~:text=The%20glioma%20immune%20microenvironment%20consists,com).

* **CD3⁺ T Cells:** A pan-T cell marker, indicating the presence of any T cell. In glioblastoma, CD3^+ T cells are present but at low density. Many are found in perivascular spaces or at the tumor margins rather than deeply infiltrating all tumor regions.
* **CD4⁺ T Helper Cells:** These include various subsets: Th1, Th2, Th17, and Tregs (which also express CD4). In gliomas, **CD4^+FoxP3⁺ T regulatory cells** are a significant subset of CD4 TILs (discussed below). The CD4^+ T\_effector cells that are present often exhibit an exhausted or anergic phenotype. Key markers like **CD40L (CD154)** or cytokines (IFN-γ, IL-2) are low in these cells. Many CD4 TILs in GBM produce IL-10 or other suppressive signals instead of pro-inflammatory cytokines.
* **CD8⁺ Cytotoxic T Cells:** These are the main effectors against tumors in immunocompetent contexts. In GBM, CD8 T cells are present but typically at very low frequency. Studies have found that **T cells in GBM (both CD4 and CD8) show markers of exhaustion such as PD-1, TIM-3, LAG-3, CD39, and an effector-memory phenotype (CD45RO⁺) without proliferation**[[25]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=TME%20express%20various%20co,1%2B%2C%20CD39%2B%2C%20and%20CD45RO%2B%5B87%5D.%20Through). They often fail to produce granzyme B or IFN-γ in meaningful quantities. The few CD8 TILs may be restricted in specificity (possibly reacting to CMV antigens or mutant neoantigens, but tumor heterogeneity and IDH-wildtype GBMs having low neoantigen load limit their efficacy). **Markers:** Aside from CD8, these TILs express exhaustion markers as noted; some express tissue-resident marker **CD69** or **CXCL13** (in CD4 T\_fh-like cells), indicating they’ve been in the tumor a while. Functionally, they are usually ineffective at killing tumor cells due to checkpoint inhibition and lack of co-stimulation. The **ratio of CD8 T cells to immunosuppressive cells** (like Tregs or MDSCs) is often unfavorable in GBM.
* **Regulatory T Cells (Tregs):** These are a critical component in glioma. Identified by **FOXP3** transcription factor, and surface markers **CD25 (IL-2Rα)**^high and often **CTLA-4**, **ICOS**, **CCR4**, etc. Tregs are actively recruited to gliomas (via CCL2, CCL22, etc.)[[16]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=421,2016%3B76%2819%29%3A5671%E2%80%9382). **Glioblastomas have a higher fraction of Tregs among CD4 T cells than normal brain or low-grade gliomas**. Tregs are strongly immunosuppressive: they secrete IL-10, TGF-β and granzyme, consume IL-2, and express checkpoint molecules (PD-1, CTLA-4) that inhibit dendritic cells and Teff cells. Functionally, Tregs in GBM directly suppress CD8 and CD4 effector function and may promote TAM M2 polarization. Markers to note: FOXP3 is definitive for Tregs (in humans, >90% of FOXP3^+ CD4 T cells are suppressive). High FOXP3^+ Treg infiltration in GBM is correlated with worse outcomes and is part of the “immunosuppressive signature” in aggressive tumors[[10]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=cytokines%2C%20and%20upregulate%20co,microenvironment%2C%20in%20particular%20composition%20and). Indeed, strategies like CCNU-Temozolomide chemotherapy have been noted to transiently reduce Tregs, and experimental Treg depletion enhances immune responses to glioma. In sum, the T cells in glioma are mostly rendered ineffective: a few exhausted CD8s and CD4s are present, alongside a notable subset of Tregs that dominate the T cell compartment’s function.

**Glioma-specific context:** Because of the low baseline immunogenicity of gliomas, the presence of even small numbers of TILs can be significant. Some studies suggest that a slightly higher CD8 T cell infiltration or an elevated CD8:Treg ratio might correlate with improved survival or response to immunotherapy[[55]](https://pmc.ncbi.nlm.nih.gov/articles/PMC8962431/#:~:text=The%20Immune%20System%20against%20Glioblastoma%E2%80%94How,of%20these%20cells%20to). Conversely, abundant Tregs and exhausted T cells signify an immunologically cold tumor. Notably, neoadjuvant PD-1 blockade (giving anti–PD-1 before surgery) was shown to increase TIL numbers and induce a type I interferon response in GBM, hinting that T cells *can* be activated given the right conditions[[56]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=immune%20checkpoint%20protein%20PD,2018%3B7%287%29%3A%20e1448329). Markers like **CD3, CD8, CD4, FOXP3, PDCD1 (PD-1)** are often used in GlioVis or other expression datasets to gauge T cell presence and state. For instance, a high FOXP3/CD3 mRNA ratio would imply a Treg-rich environment. Overall, T cells provide the potential for anti-tumor immunity, but gliomas severely constrain this potential via multiple suppressive mechanisms.

### B Cells

B lymphocytes are typically rare in glioma microenvironments. The CNS has few B cells under normal conditions, and gliomas do not elicit strong B cell responses in most cases. **Markers:** Pan-B cell markers include **CD19** and **CD20 (MS4A1)**. In immunohistochemistry of GBM, **CD20⁺ B cells are infrequent – often <1% of immune cells**[[57]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=INF,26). Flow cytometry studies (e.g., by Kmiecik et al.) found ~0.5–1% of cells in GBM are B cells[[57]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=INF,26). They are usually located in perivascular or lymphoid-like clusters when present.

Despite being few, B cells in gliomas can form **tertiary lymphoid structures (TLS)** in a subset of patients – essentially lymphoid aggregates with B cell follicles and T cells. Recent research indicates a minority of GBM (especially IDH-mutant or lower grade) can have TLS, and their presence might be associated with a less immunosuppressive microenvironment or better prognosis (as seen in other cancers). B cells in TLS can act as antigen-presenting cells and support T cell responses. In most GBMs, however, TLS are absent and B cells are scattered if present at all.

Functional role of B cells in GBM is not well characterized. They might produce antibodies against some tumor antigens or viruses (e.g., CMV, if one subscribes to the theory of CMV in GBM). But given the immune privilege of the brain, intratumoral antibodies are not a major factor. Some B cells could differentiate into plasma cells – markers like **CD138 (SDC1)** might indicate that – but again, low frequency.

In summary, **B cells are an infrequent component of glioma immunity**, often neglected in favor of myeloid and T cell dynamics. However, their presence (even if rare) can be noted via CD19/CD20 expression. If using GlioVis or expression data, one might include *MS4A1* (CD20 gene) or *CD19* in analyses, but generally their expression is very low in GBM samples. The consensus is that gliomas do not provoke a strong humoral immune infiltration, and any B-cell presence is likely a consequence of general inflammation rather than a directed anti-tumor response.

### Natural Killer (NK) Cells

NK cells are cytotoxic innate lymphocytes that can attack tumor cells lacking MHC class I. In gliomas, NK cells are present but typically in low numbers. They also face barriers such as limited CNS entry and immunosuppressive signals in the TME.

**Markers:** Classic NK markers include **NCAM1 (CD56)** and **FCGR3A (CD16)**, as well as **NCR1 (NKp46)**, **NKG2D (KLRK1)**, and transcription factor **Eomes**. In GBM tissue, NK cells often exhibit a **CD56^dim CD16^– phenotype** (per Kmiecik et al.)[[57]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=INF,26), meaning they are the subset specialized for cytotoxicity but here lacking CD16 (which might indicate reduced antibody-dependent cellular cytotoxicity capability). They also express activating receptors like NKG2D (~57% of NKs in one GBM study expressed NKG2D)[[57]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=INF,26). However, many GBM NK cells upregulate inhibitory receptors (like NKG2A, TIGIT) and downregulate some activating receptors, reflecting an exhausted state.

**Functional role:** NK cells can kill glioma cells (especially if glioma cells downregulate HLA molecules or express stress ligands like MIC-A/B for NKG2D). Indeed, presence of **activated, CD16⁺ NK cells in GBM correlates with improved survival** in patients[[58]](https://www.nature.com/articles/s41698-023-00356-1#:~:text=Advances%20in%20NK%20cell%20therapy,The). A meta-analysis found that higher NK gene signatures were associated with lower risk of death in GBM[[55]](https://pmc.ncbi.nlm.nih.gov/articles/PMC8962431/#:~:text=The%20Immune%20System%20against%20Glioblastoma%E2%80%94How,of%20these%20cells%20to). This suggests that NK cells, when they do infiltrate, provide a beneficial anti-tumor effect. Unfortunately, gliomas actively suppress NK cells: TGF-β in the TME can downregulate NK cytotoxicity receptors; MDSCs and TAMs can secrete nitric oxide and peroxynitrite that impair NK viability. Additionally, physical barriers (dense extracellular matrix, poor perfusion) limit NK cell infiltration from the bloodstream[[59]](https://www.sciencedirect.com/science/article/pii/S1525001625001686#:~:text=Natural%20killer%20cell%20therapy%20targeting,reach%20and%20eliminate%20tumor). It’s reported that *higher grade gliomas have fewer infiltrating NK cells than lower grades*, indicating NK infiltration inversely correlates with malignancy[[60]](https://pmc.ncbi.nlm.nih.gov/articles/PMC6868035/#:~:text=CAR,Therefore%2C%20differences%20in).

Glioma NK cells also interact with microglia/macrophages. Some microglia express ligands like CD155 (for TIGIT) or HLA-E (for NKG2A) that can inhibit NK cells. The net result is many NK cells in GBM are functionally anergic or even have features of “adaptive NK cells” that are less aggressive.

In the lab, enhancing NK cells has shown promise: e.g., CAR-NK cells and NK cells overexpressing CXCR4 (to migrate to CXCL12) improved GBM killing[[19]](https://www.nature.com/articles/s41698-024-00717-4?error=cookies_not_supported&code=0b451d28-15ea-4d97-a122-f71059e2973e#:~:text=match%20at%20L889%20expressed%20on,This%20occurs%20because%20NK)[[20]](https://www.nature.com/articles/s41698-024-00717-4?error=cookies_not_supported&code=0b451d28-15ea-4d97-a122-f71059e2973e#:~:text=123,Cancer%2016%2C%207%E2%80%9319%20%282015). Markers such as **NCR1, TBX21 (T-bet), EOMES, KLRK1**, and cytotoxic mediators **GZMB** (Granzyme B) and **PRF1** (Perforin) can indicate NK cell presence/function in datasets. Typically, GBM shows low PRF1/GZMB expression due to low T and NK activity.

In summary, NK cells are a potentially potent but underutilized component of glioma immunity. Their low numbers and suppressed state in GBM underscore the challenge. Nonetheless, patients with even modest NK cell infiltration tend to do better, highlighting them as a key cell type to monitor (and possibly augment) in immune correlation studies.

### Macrophages (M1/M2) and Microglia (Glioma-Associated Macrophages, GAMs)

**TAMs (Tumor-Associated Macrophages)** and **microglia** together form the most abundant immune population in gliomas – often comprising 30–50% of the tumor mass[[61]](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1393173/full#:~:text=of%20tumors,proliferation%20and%20possess%20a%20highly). These are the principal orchestrators of the glioma immune environment, usually playing a pro-tumor, immunosuppressive role.

**Origins and definitions:** Microglia are the resident CNS myeloid cells (arising from embryonic yolk sac), whereas macrophages here refer to infiltrating monocyte-derived macrophages from the bloodstream. In gliomas, both are present and often collectively termed **glioma-associated microglia/macrophages (GAMs)**. They are difficult to distinguish by standard markers since they overlap (both express many myeloid markers). However, some markers are enriched in each: - **Microglia-specific markers:** *P2RY12*, *TMEM119*, *GPR34*, *SIGLEC-H* – these genes are **exclusively or highly expressed in microglia, not in peripheral macrophages**[[21]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=or%20macrophages,Functions%20of%20those%20putative%20discriminating). For example, **P2RY12** and **TMEM119** are commonly used to identify microglia in human tissue[[21]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=or%20macrophages,Functions%20of%20those%20putative%20discriminating). If these are high, the myeloid population is largely resident microglia. - **Peripheral macrophage markers:** There’s no single unique marker, but *CCR2* (receptor for CCL2) is on infiltrating monocytes, and *CX3CR1* is on both but to different extents. Some use *CD45* intensity (microglia are CD45^low vs blood macrophages CD45^high in flow cytometry). Also, microglia tend to have homeostatic genes like *TREM2*, *HEXB*, while infiltrating macrophages express more *HLA-DR* and *CCR2*.

**M1 vs M2 polarization:** This is a spectrum rather than binary, but: - **M1-like (classically activated) macrophages**: pro-inflammatory, anti-tumorigenic in theory. They produce IL-12, TNF-α, IL-1β, high reactive oxygen species, and express markers like **NOS2 (iNOS)**, **HLA-DR^high**, **CD86**, **CD80**, and transcription factor **STAT1**. In gliomas, true M1 macrophages are scarce. The hypoxic, IL-10/TGF-β–rich TME prevents stable M1 polarization. However, some localized M1-like activity can occur (e.g., at tumor edges or after treatments like poly-ICLC). Generally, GBM TAMs lack co-stimulatory molecules CD80/CD86 and have impaired antigen presentation[[3]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=,mechanisms%20of%20immune%20surveillance%2C%20including). - **M2-like (alternatively activated) macrophages**: immunosuppressive, pro-tumoral. They secrete IL-10, TGF-β, VEGF, arginase-1, and express **CD163**, **CD206 (MRC1)**, **SEPP1**, **STAT3/6** activity, etc. Glioma TAMs largely exhibit an M2-like phenotype[[8]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=immunity%20homeostasis%20in%20the%20brain,is%20impaired%20but%20showed%20increased)[[10]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=cytokines%2C%20and%20upregulate%20co,microenvironment%2C%20in%20particular%20composition%20and). Markers like **CD163** and **CD206** are highly expressed in GAMs within GBM, indicating an immunosuppressive state. These cells scavenge debris (CD163 is hemoglobin scavenger receptor) and promote tissue remodeling and tumor growth (secreting growth factors, **MMPs** for matrix remodeling, **EGF** to stimulate tumor invasion, etc.). They also potently suppress T cells via IL-10, TGF-β and **arginase-1 (ARG1)** which depletes arginine needed by T cells.

**Markers to identify TAMs in data:** - Pan-macrophage markers: **CD68** (lysosomal protein), **CD14**, **ITGAM (CD11b)**, **AIF1 (IBA-1)**. CD68 and IBA1 are commonly used to stain TAMs in tissue (they mark both microglia and macros). **CD11b (integrin αM)** is widely expressed on myeloid cells (microglia, macros, neutrophils) in brain; it was used historically as a “microglia” marker, but actually labels all brain myeloid cells[[62]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=Microglia%20are%20myeloid%20cells%20residing,Generally%2C%20markers). - M2 markers: **CD163**, **MRC1 (CD206)**, **ARG1**, **CHI3L1 (YM1)**, **IL10**, **TGFβ1**, **PTGS2 (COX-2)**, **SEPP1**, **Stabilin-1**, **CLEC7A (Dectin-1)**. Many of these are elevated in GBM TAMs. - M1 markers: **NOS2 (iNOS)**, **TNF**, **IL1B**, **IL12B**, **HCST**, **FCGR3A (CD16)**. These are generally low in glioma TAMs, except perhaps NOS2 in some peri-necrotic areas.

**Functions in glioma:** TAMs/Microglia serve as “double agents” – initially, microglia might attempt a defense (secreting TNF, IL-1, etc.), but glioma cells quickly educate them into a tumor-supportive mode. GAMs then facilitate tumor growth by: - **Immunosuppression:** releasing IL-10, TGF-β, expressing PD-L1 and **FasL**, which induce T cell apoptosis or exhaustion[[26]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=and%20secreting%20IL,35%5D.%20They%20have). They also attract Tregs by CCL2/5[[63]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=immunosuppressive%20cytokines%20and%20chemokines%20shaping,derived%20signals%20and%20mechanisms). They **lack** co-stimulatory CD80/CD86 needed to activate T cells, as noted[[3]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=,mechanisms%20of%20immune%20surveillance%2C%20including). - **Angiogenesis:** producing VEGF-A, TGF-β, and matrix metalloproteinases (MMP9) to help new vessel formation. - **Tumor invasion:** secreting EGF and HGF that stimulate tumor cell motility, and TGF-β that induces glioma cell mesenchymal transition. Also, TAMs clear away extracellular matrix barriers. - **Metabolic support:** supplying nutrients via scavenging, providing glutamate that glioma can use, and dampening harmful inflammation (preventing buildup of cytotoxic NO or ROS that could harm tumor cells).

Glioma TAM density correlates inversely with survival[[2]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=and%20T%20lymphocytes,regulatory%20lymphocytes%20to%20the%20tumor). The mesenchymal GBM subtype in particular shows **high TAM infiltration** and immunosuppressive gene signatures[[64]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=cell%20subtypes%20include%20mesenchymal,33%20%5B%2017%5D%20are%20employed). Clinically, imaging and biomarker studies suggest that more macrophages = more aggressive tumor. This is why CSF1R inhibitors (targeting TAMs) and other myeloid modulators are in trials.

**Microglia vs macrophages in GBM:** Early in tumor development, **microglia** (resident) are first responders. They get activated and can phagocytose tumor debris, perhaps present antigens. But glioma-secreted factors (like CSF-1, CX3CL1, periostin, etc.) quickly polarize microglia to an M2-like state (sometimes called MG2). As tumor grows and BBB becomes leaky, **monocytes from blood** are recruited by CCL2, CCL7, etc. These monocyte-derived macrophages often outnumber microglia in later stages. They especially localize around necrotic regions and pseudopalisading cells where hypoxia drives VEGF and more recruitment. Both microglia and macros converge to a similar immunosuppressive TAM phenotype in GBM, often called **GAMs** collectively. However, recent single-cell RNA-seq shows subtle differences: microglia-origin GAMs may express higher *P2RY12* (though still lower than normal microglia) until fully polarized, while monocyte-origin GAMs express *CCR2* and high *HLA-DR*. But functionally, both are pro-tumor.

**Markers summary:** For correlation studies, one might use *CD68* or *AIF1* for total GAM content; *CD163* or *MRC1* for M2 TAMs; *P2RY12* or *TMEM119* specifically for microglia-origin; *CCR2* for monocyte-macrophages. Also, *CHI3L1* (encoding YKL-40) is a secreted protein by TAMs in GBM that’s a known prognostic marker – it correlates with M2 TAM presence and poor survival. Importantly, *high expression of M2 markers (CD163, ARG1, etc.) alongside low T cell markers defines an immunosuppressive glioma microenvironment*.

### Dendritic Cells (DCs)

Dendritic cells are the professional antigen-presenting cells critical for initiating T cell responses. In gliomas, true DCs are relatively rare. The brain has few resident dendritic cells, and recruitment of DCs into gliomas is limited by factors such as the blood–brain barrier and tumor-secreted cytokines that skew monocytes away from DC differentiation (driving them to TAM instead).

**Markers:** Conventional DCs can be identified by **CD11c (ITGAX)** along with **HLA-DR** and co-stimulatory molecules. Subsets: cDC1 (BATF3-dependent, CD8α^+ in mice, CLEC9A^+ in human, marker XCR1), cDC2 (CD11b^+ DCs, marker CD1c in human), and pDC (plasmacytoid DC, markers CD303/BDCA2, TCF4, produces IFN-α). In glioma tissue, *CD11c* mRNA is present at low levels, and immunohistochemistry shows sparse CD11c^+ cells. Many of those could actually be macrophages (since macrophages can upregulate CD11c when activated). That said, a small population of bona fide DCs does infiltrate or reside in gliomas – some near blood vessels or in leptomeningeal areas.

**Function:** The presence of functioning DCs in glioma is thought to be one limiting factor for effective anti-tumor T cell priming. Gliomas sequester antigen behind the BBB; any tumor antigens reaching lymph nodes have to be carried by DCs or other APCs that travel from the brain to cervical lymph nodes. It’s been noted that GBM patients often have impaired DC function systemically (likely due to tumor factors like IL-10, prostaglandin E2). Within the tumor, any DCs present likely struggle to mature, as indicated by low CD80/CD86. They may present antigen but without co-stimulation, inducing T cell tolerance. Additionally, **glioma-derived VEGF and IL-6 can inhibit DC differentiation**.

Nonetheless, some DC-related phenomena: *Migratory monocyte-derived cells with DC-like phenotype* can be found. Also, if a strong adjuvant is given (e.g., poly-ICLC or CpG in a vaccine), some infiltrating monocytes can become tipDCs (TNF/iNOS-producing DCs) or other activated DCs that support T cells. In general, however, **GBM has an insufficiency of functional DCs**, contributing to poor priming of anti-tumor immunity.

**Markers to analyze:** *ITGAX (CD11c)*, *HLA-DPA1/B1* (MHC-II genes), *CD86*, *CCR7* (for migratory DC), *CLEC9A*, *IRF8* for cDC1, *CLEC10A (CD301)* or *CD1c* for cDC2, *TCF4* (E2-2 TF) or *IRF7* for pDCs, *NRP1* (BDCA4) for pDCs. In GBM data, these are generally low. A notable point: a study found that “mature DC signature” (high MHC and co-stim genes) in GBM correlates with better survival and a more inflammatory microenvironment[[65]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=including%20immune%20checkpoint%20blockade%20,specific%20antigens%20with%20vaccines%20and). That suggests that even though DCs are rare, their presence could be beneficial.

Finally, therapeutic vaccines using patient-derived DCs loaded with tumor antigens have been attempted in GBM (e.g., DCVax trial). These aim to compensate for the tumor’s lack of good DC function.

### Neutrophils (Polymorphonuclear Leukocytes) and MDSCs

We group neutrophils and MDSCs here because they share some overlap (granulocytic MDSCs are essentially neutrophils with immunosuppressive phenotype). Both are myeloid cells that in glioma contribute to immunosuppression and tumor progression.

**Tumor-Associated Neutrophils (TANs):** Neutrophils were historically underestimated in GBM, but recent evidence highlights their importance. They are **recruited by glioma-secreted chemokines such as CXCL8 (IL-8), CXCL1/2, G-CSF, and IL-1β**[[66]](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1393173/full#:~:text=,chemokine%20ligand%203)[[67]](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1393173/full#:~:text=They%20show%20complex%20and%20dual,15). Although peripheral blood has ~50-70% neutrophils, the normal brain has virtually none. In GBM, neutrophils infiltrate from circulation (including via newly discovered pathways from skull bone marrow to brain[[68]](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1393173/full#:~:text=Neutrophils%20migrate%20to%20the%20brain,not%20adequately%20compensate%20for%20the)). TANs might constitute a smaller fraction than macrophages, but still significant: one report suggests a monocyte:neutrophil ratio of 1:7–1:10 inside GBM, opposite to blood ratio[[69]](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1393173/full#:~:text=Associated%20Neutrophils%20,The%20rarity%20of). If true, neutrophils could be ~10% of immune cells in some tumors (though estimates vary). Markers for neutrophils include **CD15 (SSEA-1)**, **CD66b (CEACAM8)**, **MPO (myeloperoxidase)**, **ELANE (neutrophil elastase)**. In tissue, they can be seen by MPO or neutrophil elastase staining.

**N1 vs N2 polarization:** Similar to M1/M2 for macrophages, neutrophils can polarize: - **N1 (anti-tumor)** – more cytotoxic to tumor, produce ROS and kill tumor cells, secrete pro-inflammatory cytokines (TNF-α, etc). N1 can support T cells by secreting chemokines like CCL3. - **N2 (pro-tumor)** – immunosuppressive, pro-angiogenic. N2 neutrophils produce arginase-1 (like MDSCs), IL-10, and suppress T cell proliferation. They also release MMPs that help tumor invasion and VEGF for angiogenesis.

Glioma TME tends to induce an **N2-like phenotype** in neutrophils[[70]](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1393173/full#:~:text=lymphocytes%20,They%20contribute%20to). TANs in GBM can promote tumor proliferation, invasion, and **immunosuppression**[[70]](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1393173/full#:~:text=lymphocytes%20,They%20contribute%20to). For instance, neutrophils can form NETs (neutrophil extracellular traps) that were recently implicated in glioma progression and resistance. TANs also interact with macrophages and T cells – they can supply chemokines that bring more suppressive myeloid cells and can inhibit T cell responses by arginase and PD-L1 expression.

Clinical data: High **neutrophil-to-lymphocyte ratio (NLR)** in peripheral blood of GBM patients is correlated with worse prognosis[[71]](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1393173/full#:~:text=neutrophils%20within%20the%20central%20nervous,classification%20method%20of%20N1%2FN2%20in), suggesting that systemic inflammation and neutrophilia accompany aggressive disease. Also, some GBMs with postoperative infections (which elevate neutrophils) paradoxically had better survival – hypothesized that activated neutrophils could attack tumor under certain conditions. But generally, **neutrophil infiltration in GBM is associated with tumor aggressiveness** and poor outcomes[[72]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=match%20at%20L2598%20with%20neutrophil,Immunology%202011%3B132%3A39%E2%80%9348). Some studies specifically link high tumor IL-8 or G-CSF (neutrophil attractants) to lower survival.

**Myeloid-Derived Suppressor Cells (MDSCs):** These are a heterogeneous population of immature myeloid cells that potently suppress T cells. Two main subtypes: - **Monocytic MDSCs (M-MDSCs):** phenotypically CD11b^+ CD14^+ HLA-DR^low in humans (or simply termed CD14^+HLA-DR^low monocytes). They resemble monocytes but with immunosuppressive gene expression (high ARG1, iNOS). They can differentiate into tumor-associated macrophages. - **Polymorphonuclear MDSCs (PMN-MDSCs):** essentially neutrophil-like (CD11b^+ CD15^+ CD14^– low HLA-DR). They resemble TANs and share markers with neutrophils (high CD66b, etc.), but are defined more by function (suppressing T cells via arginase, ROS).

Gliomas induce expansion and recruitment of MDSCs. **CD33** is a pan-MDSC myeloid marker often used (CD33^+CD11b^+ cells). Studies show **circulating CD33^+ MDSCs are elevated in GBM patients** compared to healthy controls[[73]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=characteristics%20of%20M1%20and%20M2,37). Glioma-derived factors (CCL2, CXCL8, GM-CSF, etc.) drive MDSC accumulation[[12]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=MDSCs%20infiltrate%20the%20TME%20under,in%20maintaining%20metabolic%20reprogramming%2C%20proliferation)[[74]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=such%20as%20CXCR4,deficiency%20has%20been%20associated%20with). Within the tumor, MDSCs further differentiate into TAMs or continue to suppress immune responses.

**Markers and function:** MDSCs in GBM express **ARG1**, **NOS2 (iNOS)**, **PD-L1 (CD274)**, and **COX2**, among others. They suppress T cells by: - Depleting *L-arginine* via ARG1, which causes T cell cell-cycle arrest and downregulation of the CD3ζ chain. - Producing *NO* and *ROS* (from iNOS and NADPH oxidase) that nitrate T cell receptors and inactivate them[[75]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1348%20cells%2C%20nitrating,the%20TIME%20to%20some%20extent). - Expressing *PD-L1* to directly inhibit T cells (and inducing Tregs). - Releasing *IL-10* and *TGF-β* (like TAMs) to generally suppress immunity[[76]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=have%20been%20discovered%20at%20higher,%CE%B2%2C%20and). MDSCs also inhibit NK cells and impair dendritic cell maturation[[77]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=immunosuppressive%20cytokines%20and%20chemokines%20shaping,cells%20and%20cytotoxic%20CD8%2B%20T).

In GBM models, MDSCs have been shown to induce apoptosis of activated T cells via the **Fas/FasL pathway** and PD-L1[[78]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=natural%20killer%20cells%20,20). Co-culture of normal monocytes with GBM cells can turn them into MDSC-like cells, upregulating PD-L1, IL-10, TGF-β and gaining the ability to kill T cells[[79]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=characteristics%20of%20M1%20and%20M2,37). This highlights how glioma factors actively convert infiltrating monocytes to suppressors.

MDSC abundance in tumors correlates with immunosuppression and poor patient prognosis. High expression of MDSC-related genes in GBM (e.g., S100A8/A9, ARG1) is associated with shorter survival[[80]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1067%20cytokines%20like,with%20the%20promoter%20of%20ARG1). Conversely, strategies that reduce MDSCs (like inhibiting CSF3R or using chemotherapy at specific doses) can boost anti-tumor immunity.

**In data analysis:** One might gauge MDSCs by markers *CD14* (monocytes) with low *HLA-DRA*, or *CD33*, *S100A8/S100A9*, *ARG1*, *NOS2*. A gene like *IL1R2* is also high in MDSCs. *CXCR2* ligands (CXCL1/2/5/8) favor PMN-MDSCs, whereas *CCR2* ligands (CCL2/7) favor M-MDSCs[[74]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=such%20as%20CXCR4,deficiency%20has%20been%20associated%20with)[[15]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=CCL12%2C%20CCL2%2C%20and%20CCL7,instead%20of%20conventionally%20fractionated%20radiotherapy). GBMs often express both, hence recruiting both subtypes. Notably, **GBM with high MDSC and TAM infiltration have very few T cells and are immunologically cold**[[81]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=and%20T%20lymphocytes,cells%20and%20cytotoxic%20CD8%2B%20T). MDSCs and TAMs together form a powerful suppressive network: they attract Tregs, block CTLs and NK, and nurture each other with cytokines.

### Functional Regulators: Transcription Factors and Effector Enzymes

Finally, it’s important to recognize key **intracellular regulators** and **effector molecules** that control immune function in gliomas:

* **NF-κB (Nuclear Factor kappa-B):** A transcription factor complex that drives many inflammatory genes (IL-1, IL-6, TNF, etc). In glioma TAMs, NF-κB signaling is aberrantly activated in some contexts (e.g., via TLRs or tumor necrosis) but the tumor often subverts it toward supporting tumor growth. NF-κB can induce both pro-inflammatory mediators and pro-survival signals. For example, TNF-α from TAMs can activate NF-κB in tumor cells, promoting their survival and invasion[[82]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=crosstalk%20among%20genetic%20alterations%2C%20epigenetic,Moreover%2C%20individuals%20with%20GBM). On the flip side, NF-κB activity in immune cells is required for an effective response; gliomas produce A20 and other inhibitors that keep NF-κB in check in dendritic cells. Nonetheless, **NF-κB is a central hub**: therapies that activate NF-κB in immune cells (like TLR agonists) can break immunosuppression, whereas constitutive NF-κB in tumor cells/TAMs fosters an immunosuppressive cytokine loop. In MDSCs, NF-κB drives iNOS expression, a key suppressive enzyme[[83]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1240%20certain%20proinflammatory,another%20crucial%20factor%20activated%20by).
* **STAT3:** Perhaps the most critical immunosuppressive TF in gliomas. STAT3 is activated by IL-6, IL-10, and growth factors abundant in GBM. It is sometimes called the “master regulator” of the glioma TME. **In TAMs and MDSCs, STAT3 promotes the M2 program and suppressive functions**[[84]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=cytokines%20like%20IL,with%20the%20promoter%20of%20ARG1). STAT3 upregulates **ARG1**, **VEGF**, **IL-10** and downregulates pro-inflammatory mediators. It also upregulates *S100A8/A9* which recruits more MDSCs. Many GBMs show a STAT3 gene signature (especially mesenchymal subtype). In T cells, tumor-driven STAT3 activation can impede Th1 differentiation. Because of this, STAT3 is a therapeutic target: drugs inhibiting STAT3 signaling (e.g., JAK inhibitors or STAT3 decoy) aim to tilt the balance toward anti-tumor immunity.
* **HIF-1α (Hypoxia-inducible factor-1):** A transcription factor stabilized in hypoxic regions of glioma. HIF-1 upregulates **VEGF** (angiogenesis) and **CXCL12** (attracting immunosuppressive cells via CXCR4). It also induces **PD-L1** on tumor and myeloid cells, directly linking hypoxia to immune evasion. HIF-1 skews macrophages to an M2-like phenotype (hypoxia-conditioned macrophages often express more ARG1 and VEGF, less IL-12). Therefore, HIF-1 is a key driver of the “alternatively activated” milieu in necrotic/hypoxic tumor zones. HIF-2α may also play a role similarly. Targeting HIF or alleviating hypoxia (with oxygenation strategies) could improve immune response.
* **STAT1 and IRFs:** These are more associated with pro-inflammatory (M1/Th1) responses. STAT1, activated by IFN-γ, drives iNOS and IL-12. IRF5, IRF8 help M1 polarization. In gliomas, STAT1/IRF activation is relatively muted except perhaps at the tumor edge. Notably, nitration of STAT1 by MDSC-derived peroxynitrite can impair its function[[75]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1348%20cells%2C%20nitrating,the%20TIME%20to%20some%20extent). Also, tumors with a “STAT1^high” signature (which would mean more Th1/M1 presence) are relatively rare and may correlate with slightly better survival.
* **C/EBPβ:** A transcription factor induced by IL-6/IL-10 that is crucial for MDSC development. High C/EBPβ in myeloid cells leads to the production of ARG1 and IL-10. Gliomas likely exploit this; for instance, G-CSF and IL-6 activate C/EBPβ in neutrophils to create PMN-MDSCs.
* **AHR (Aryl hydrocarbon receptor):** Mentioned earlier, it’s activated by tryptophan metabolites (kynurenine from IDO). In TAMs, AHR activation reinforces an immunosuppressive phenotype, including more IL-10 production. In T cells, AHR can promote differentiation into Tregs or Tr1 cells in the presence of certain cues. Thus, it’s an immunometabolic sensor.
* **FOXP3:** The defining transcription factor of Tregs. FOXP3 is a master regulator that turns a CD4 T cell into a suppressor. It induces CTLA-4, IL-2 receptor, and other suppressive elements. High FOXP3 mRNA in a glioma sample indicates significant Treg presence. Mutations in FOXP3 are not relevant here (that’s IPEX syndrome), but the level of FOXP3 is a gauge of Treg-mediated immunosuppression in the tumor.

Moving to **effector enzymes and molecules**:

* **Arginase-1 (ARG1):** As discussed, it breaks down arginine to ornithine and urea. Arginine depletion starves proliferating T cells (they cannot sustain protein synthesis or express CD3ζ chain). **ARG1 is highly expressed by MDSCs and M2 macrophages in GBM**[[77]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=immunosuppressive%20cytokines%20and%20chemokines%20shaping,cells%20and%20cytotoxic%20CD8%2B%20T). It’s a signature of immunosuppressive myeloid cells. A strong inverse correlation exists between ARG1 expression and T cell activity in tumors. In fact, ARG1+ macrophages in GBM co-localize with areas of T cell exclusion.
* **Inducible Nitric Oxide Synthase (iNOS/NOS2):** Produces nitric oxide from arginine. In moderate amounts, NO can kill microbes and tumor cells (M1 macrophage role). But in the chronic context of tumors, NO reacts to form peroxynitrite, which nitrates amino acids on TCRs and chemokines like CCL2, rendering them nonfunctional[[75]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1348%20cells%2C%20nitrating,the%20TIME%20to%20some%20extent). **MDSCs in GBM use iNOS to suppress T cells** – e.g., nitrotyrosine residues are found on T cells in tumors with high MDSC activity. iNOS is generally an M1 marker, but in tumors it paradoxically contributes to immune suppression due to these byproducts.
* **NOX2 (NADPH oxidase complex):** This enzyme in neutrophils/MDSCs produces reactive oxygen species (superoxide). **NOX2 in PMN-MDSCs leads to H\_2O\_2 and peroxynitrite formation, which cause T cell dysfunction**[[4]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=IL,NOX3%20and%20increase%20ROS%20production). STAT3 can upregulate NOX2 subunits in MDSCs[[84]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=cytokines%20like%20IL,with%20the%20promoter%20of%20ARG1). ROS from NOX2 can also induce T cell apoptosis in close contact.
* **Fas/FasL:** Many GBMs exploit the Fas pathway. Tumor cells or TAMs can express **Fas Ligand (CD95L)**, which engages Fas on T cells and triggers their apoptosis. Indeed, GBM TAMs expressing FasL can eliminate infiltrating effector T cells. This is a mechanism of “immune privilege” similarly used in other organs like the eye. It’s not an enzyme per se, but a death factor.
* **Granzyme B (GZMB) and Perforin (PRF1):** These are produced by CTLs and NK cells to kill targets. In GBM, as noted, T and NK cells are exhausted so their GZMB/PRF1 expression is low. If immunotherapy reinvigorates T cells, these would increase. They are effectors of anti-tumor immunity – thus often absent in immunosuppressed tumors. Some immunogram studies use GZMB or PRF1 mRNA as a readout of active cytotoxic immunity.
* **Enzymes in metabolic pathways:** e.g., **IDO1** (already covered), **COX-2 (PTGS2)** which leads to PGE2 (a suppressive prostaglandin affecting DCs and T cells), **PTGES (PGE synthase)**, etc. **PTGS2** is expressed by both tumor cells and TAMs in GBM and PGE2 skews TAMs to M2 and recruits MDSCs. Inhibitors like aspirin or celecoxib could counteract that.
* **Effector cytokines:** not enzymes but worth mentioning as functional outputs – **IFN-γ, TNF-α by effector cells** (low in GBM), **IL-2 by T cells** (virtually absent intratumor, which is why Tregs survive well since IL-2 is all captured by them externally).
* **Enzymes degrading neurotransmitters or others:** e.g., **CD39** and **CD73** which generate adenosine (a potent immunosuppressant) from ATP. These are up on Tregs and some tumor cells (CD73 also known as NT5E, highly expressed in GBM vasculature). Adenosine then signals through A2A receptors on T cells to inhibit them. So CD39/CD73 axis is another metabolic checkpoint.

In conclusion, the glioma immune environment is orchestrated by these factors: transcriptional regulators like STAT3 and NF-κB shape the polarization of myeloid cells, while effector enzymes like arginase and iNOS execute the suppression of lymphocytes. A balance between pro-inflammatory and anti-inflammatory signals is heavily tilted toward the latter in GBM. **Pro-inflammatory TFs (e.g., NF-κB, STAT1) are kept at bay, whereas immunosuppressive TFs (STAT3, C/EBPβ) are highly active**. Correspondingly, **effector molecules from immune cells (granzymes, IFN-γ) are scarce, whereas suppressive molecules (ARG1, PD-L1, IL-10, TGF-β) are abundant**[[10]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=cytokines%2C%20and%20upregulate%20co,microenvironment%2C%20in%20particular%20composition%20and). Effective immunotherapy in glioma will likely require reprogramming these regulatory networks – for example, blocking STAT3 and checkpoints to enable NF-κB and STAT1-driven anti-tumor activity, and inhibiting enzymes like arginase and IDO to restore T cell function.

Overall, this detailed report has outlined critical immune pathway components relevant to gliomas, with an emphasis on whether they promote (pro-inflammatory/anti-tumor) or suppress (anti-inflammatory/pro-tumor) immune responses, what cells they are associated with, and specific findings in glioma research. These insights set the stage for big-data analyses (e.g., using GlioVis) where expression of these markers can be correlated with glioma molecular subtypes, patient survival, or therapy response, potentially identifying patterns such as “immune-hot” vs “immune-cold” tumors. For a quick reference, a summary table is provided below.

# Part 2: Summary Table – Immune Markers in Glioma

Below is a concise table summarizing key immune molecules and cell markers in glioma, categorized by type, with their roles (pro- vs anti-inflammatory), typical cellular context, and glioma-specific relevance:

| **Category** | **Marker (Gene)** | **Role & Immune Function** | **Cellular Context** | **Glioma Relevance** |
| --- | --- | --- | --- | --- |
| **Cytokine (Pro-inf.)** | **IL-1β** | Pro-inflammatory cytokine; drives IL-6, NF-κB | M1 macrophages, microglia | Present in GBM; promotes tumor invasiveness via NF-κB[[5]](https://biosignaling.biomedcentral.com/articles/10.1186/s12964-023-01255-5#:~:text=NLRP3%20inflammasome%20has%20shown%20that,cell%20line%20causes%20augmented%20NLRP3). |
| **Cytokine (Pro-inf.)** | **IL-6** | Pro-inflammatory, acute phase cytokine | TAMs, tumor cells | Highly expressed in GBM; correlates with mesenchymal transition and immune suppression[[85]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=cytokines%20secretion%2C%20like%20CCL5%2C%20IL,319). |
| **Cytokine (Pro-inf.)** | **TNF-α** | Pro-inflammatory; can induce apoptosis or NF-κB | TAMs, microglia, T cells | Present in GBM TAMs[[3]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=,mechanisms%20of%20immune%20surveillance%2C%20including); chronic TNF aids tumor cell survival via NF-κB. |
| **Cytokine (Pro-inf.)** | **IFN-γ** | Th1 cytokine, activates macrophages & CTLs | CD8⁺ T cells, NK cells | Low in GBM (few T\_h1 cells); *exogenous IFN-γ can counter GBM-induced suppression*[[7]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=particularly%20immunomodulatory%20cytokines%2C%20as%20a,%CE%B1%20to%20counteract). |
| **Cytokine (Anti-inf.)** | **IL-10** | Anti-inflammatory; inhibits Th1, APCs | M2 TAMs, Tregs | **High in GBM TAMs**[[8]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=immunity%20homeostasis%20in%20the%20brain,is%20impaired%20but%20showed%20increased); recruits Tregs, worse prognosis when elevated[[9]](https://pmc.ncbi.nlm.nih.gov/articles/PMC9206138/#:~:text=The%20immunosuppressive%20role%20of%20indoleamine,can%20worsen%20the%20prognosis). |
| **Cytokine (Anti-inf.)** | **TGF-β** | Potent immunosuppressive cytokine | Tumor cells, TAMs, Tregs | **Abundant in GBM**; drives Treg, M2 polarization, blocks CTLs[[8]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=immunity%20homeostasis%20in%20the%20brain,is%20impaired%20but%20showed%20increased). |
| **Cytokine (Growth)** | **CSF-1 (M-CSF)** | Macrophage colony-stimulating factor | Tumor cells | High in GBM; recruits & **polarizes monocytes to M2 TAMs** (targeted by CSF1R inhibitors). |
| **Cytokine (Growth)** | **CSF-2 (GM-CSF)** | GM-CSF; can stimulate DCs or MDSCs contextually | Tumor, stromal cells | Present in some GBM; supports MDSC expansion[[12]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=MDSCs%20infiltrate%20the%20TME%20under,in%20maintaining%20metabolic%20reprogramming%2C%20proliferation); used in some vaccines to attract DCs. |
| **Chemokine (CC)** | **CCL2 (MCP-1)** | Recruits CCR2⁺ monocytes/MDSCs (pro-tumor) | Tumor cells, GAMs | **Key monocyte attractant** in GBM; high CCL2 = more TAMs/Tregs, worse survival[[17]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L2654%20exacerbating%20the,of%20the%20CCL2%2FCCR2%20axis%20inhibited)[[14]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=in%20GBM,cell%20proliferation%20and%20activation). |
| **Chemokine (CC)** | **CCL5 (RANTES)** | Recruits T cells, monocytes (context-dependent) | Tumor cells, GAMs | Elevated in GBM; part of immunosuppressive secretome (with IL-6, IL-8) promoting monocyte infiltration[[22]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L804%20cytokines%20secretion%2C,319). |
| **Chemokine (CC)** | **CCL22** | Recruits CCR4⁺ Tregs (anti-inflammatory) | TAMs (M2), DCs | Likely up in GBM TAMs; helps accumulation of **Tregs** in tumor (similar to CCL2 action). |
| **Chemokine (CXC)** | **CXCL8 (IL-8)** | Recruits neutrophils & PMN-MDSCs (pro-tumor) | Tumor cells, GAMs | **High in GBM**; drives TAN infiltration, angiogenesis; induces MDSC mobilization[[23]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1156%20,crucial%20mediator%20that%20establishes%20the). |
| **Chemokine (CXC)** | **CXCL10 (IP-10)** | Recruits CXCR3⁺ Th1 and CTLs (anti-tumor) | Microglia, Th1 cells (IFN-γ induced) | Typically low in GBM; if present can attract effector T cells (brain mets use this; GBM less so)[[24]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=,crucial%20mediator%20that%20establishes%20the). |
| **Chemokine (CXC)** | **CXCL12 (SDF-1α)** | Recruits CXCR4⁺ cells (Tregs, monocytes); retains cells in niche | Tumor cells, stroma | **High in GBM niches**; attracts Tregs/MDSCs, guides tumor cell invasion. Blocking CXCL12 improves T cell entry. |
| **Checkpoint (T cell)** | **PD-1 (PDCD1)** | Inhibitory receptor on T cells (exhaustion marker) | TILs (CD8 and CD4) | **Upregulated on GBM T cells** (exhausted phenotype)[[25]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=TME%20express%20various%20co,1%2B%2C%20CD39%2B%2C%20and%20CD45RO%2B%5B87%5D.%20Through); blockade alone has limited success in GBM. |
| **Checkpoint (Ligand)** | **PD-L1 (CD274)** | Ligand inhibiting PD-1; suppresses T cell activity | Tumor cells, TAMs | **Highly expressed in GBM**; correlates with poor prognosis, fosters Treg induction[[27]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L7737%20immune%20checkpoint,2018%3B7%287%29%3A%20e1448329). |
| **Checkpoint (T cell)** | **CTLA-4 (CD152)** | Inhibitory receptor, suppresses early T cell activation | Tregs, activated T cells | **Expressed by GBM-infiltrating Tregs**; competes for CD80/86 on APC, contributing to T cell anergy. |
| **Checkpoint (T cell)** | **TIM-3 (HAVCR2)** | Inhibitory receptor, marks deep exhaustion; also on myeloid cells | CD8 T cells, Tregs, TAMs | **Common in GBM TME**; drives TAM M2 polarization via IL-6 pathway[[30]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=%5B73%5D.%20TIM,metabolite%20lactate%20from%20GBM%20can). Targeting TIM-3 can revive T/NK cells[[32]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L854%20from%20T,CD8%2B%20T%20cells%2C%20and%20microglias). |
| **Checkpoint (T cell)** | **LAG-3** | Inhibitory receptor binding MHC-II, limits T cell expansion | CD4 & CD8 T cells | Co-expressed with PD-1 on GBM TILs[[34]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=immune%20checkpoint%20family%2C%20particularly%20in,correlated%20with%20poorer%20survival%20in); contributes to T cell exhaustion and therapy resistance. |
| **Checkpoint (T cell)** | **TIGIT** | Inhibitory receptor (binds CD155), suppresses T/NK | CD8 T, NK, Tregs | Upregulated in GBM T & NK cells; blocking TIGIT + PD-1 synergistically improved survival in GBM models[[35]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1607%20production%20of,MDSCs%20and%20DCs%20amount). |
| **Checkpoint (Ligand)** | **VISTA (VSIR)** | Checkpoint ligand/receptor, broadly suppressive | Myeloid cells (APCs), some T cells | Overexpressed in GBM myeloid compartment; associated with T cell suppression (emerging target). |
| **Co-stimulator** | **ICOS (CD278)** | Positive costimulatory receptor (enhances T cell function, esp. Tfh/Treg) | Activated CD4 T cells (Tregs) | **High on GBM Tregs**; ICOS⁺ Tregs contribute to immunosuppression (correlates with other checkpoints)[[34]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=immune%20checkpoint%20family%2C%20particularly%20in,correlated%20with%20poorer%20survival%20in). |
| **Immunometabolic** | **IDO1** | Tryptophan-catabolizing enzyme; creates immunosuppressive kynurenine | Tumor cells, TAMs, pDCs | **Elevated in GBM**; depletes tryptophan, recruits Tregs. High IDO1 = more Tregs, worse outcome[[9]](https://pmc.ncbi.nlm.nih.gov/articles/PMC9206138/#:~:text=The%20immunosuppressive%20role%20of%20indoleamine,can%20worsen%20the%20prognosis). |
| **Immunometabolic** | **ARG1 (Arginase-1)** | Depletes L-arginine, impairs T cells (via cell cycle arrest, ↓CD3ζ) | MDSCs, M2 TAMs | **Highly expressed by GBM TAMs/MDSCs**[[77]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=immunosuppressive%20cytokines%20and%20chemokines%20shaping,cells%20and%20cytotoxic%20CD8%2B%20T); marker of M2 polarization and strong T cell suppression. |
| **Immunometabolic** | **NOS2 (iNOS)** | Generates NO; high NO/ROS kill microbes but chronically suppress T cells (via peroxynitrite) | M1 Macs, MDSCs | Found in some GBM myeloid cells; peroxynitrite from iNOS **nitrates TCRs & chemokines**, aiding tumor immune evasion[[75]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=match%20at%20L1348%20cells%2C%20nitrating,the%20TIME%20to%20some%20extent). |
| **Immunometabolic** | **GPX4** | Glutathione peroxidase; prevents lipid peroxidation/ferroptosis | Tumor cells (some TAMs) | **Upregulated in GBM cells**; resists ferroptosis. GPX4 links to chronic inflammation[[37]](https://pmc.ncbi.nlm.nih.gov/articles/PMC9273259/#:~:text=Ferroptosis%20in%20Glioma%20Immune%20Microenvironment,that%20glioma%20progression%20is); targeting it may release immunogenic cell death. |
| **Immunometabolic** | **GFPT1** | Rate-limiting enzyme in hexosamine pathway; drives protein glycosylation (e.g., PD-L1) | Tumor cells, some immune cells | Overexpressed in aggressive tumors; **O-GlcNAcylates PD-L1 → immune evasion**[[40]](https://www.frontiersin.org/journals/genetics/articles/10.3389/fgene.2024.1482929/full#:~:text=expression%20enhance%20the%20EMT%20and,drug%20sensitivity%20have%20not%20been). High GFPT1 associated with M2 TAM infiltration[[41]](https://www.frontiersin.org/journals/genetics/articles/10.3389/fgene.2024.1482929/full#:~:text=Results%3A%20Elevated%20GFPT1%20expression%20was,migration%2C%20along%20with%20enhanced%20apoptosis). |
| **Immunometabolic** | **GFPT2** | Hexosamine pathway enzyme (isozyme); similar to GFPT1 | Tumor cells (especially neural origin) | In cancer, high GFPT2 correlates with immunosuppressive TME and T cell exhaustion[[43]](https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2022.811559/full#:~:text=in%20focal%20adhesion%2C%20ECM%20receptor,a%20certain%20class%20of%20drugs). In glioma, GFPT2 might be relevant given neural expression patterns. |
| **Immunometabolic** | **NLRP3** | Inflammasome sensor; triggers IL-1β/IL-18 release | Microglia, macrophages, tumor cells | **Overactive in GBM**; NLRP3 inflammasome drives IL-1β → promotes tumor proliferation/invasion[[46]](https://biosignaling.biomedcentral.com/articles/10.1186/s12964-023-01255-5#:~:text=exhibited%20that%20the%20NLRP3%20inflammasome,dependent). Potential target to reduce tumor-promoting inflammation. |
| **Immunometabolic** | **SREBP1/2** | Master lipid synthesis transcription factors | Tumor cells, TAMs (when activated) | **Active in GBM** for high lipid demand. **SREBP1 supports M2 TAM survival** (Tregs foster this)[[49]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-023-01498-2#:~:text=match%20at%20L3179%20Vignali%20KM%2C,397%20e386); SREBP2 in hypoxia linked to poor survival[[53]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-023-01498-2#:~:text=match%20at%20L521%20Additionally%2C%20an,is%20associated%20with%20reduced%20overall). |
| **Immunometabolic** | **SCAP** | SREBP cleavage-activating protein; required for SREBP function | Ubiquitous (tumor, TAMs) | Enables SREBP1/2 activity. By supporting SREBP, SCAP indirectly contributes to the lipid-rich, immunosuppressive milieu of gliomas (targetable via SREBP pathway inhibitors). |
| **T Cell Marker** | **CD3D/E** | CD3 complex (pan-T cell marker) | T cells (all) | Low-to-moderate in GBM; indicates overall T cell presence. GBM generally has sparse CD3^+ infiltrate[[1]](https://www.nature.com/articles/s41698-024-00717-4?error=cookies_not_supported&code=0b451d28-15ea-4d97-a122-f71059e2973e#:~:text=The%20glioma%20immune%20microenvironment%20consists,com). |
| **T Cell Marker** | **CD4** | Helper T cell marker (also on Tregs) | CD4⁺ T cells, Tregs | Low in GBM; many tumor-infiltrating CD4s are **FOXP3⁺ Tregs** rather than Th1 effectors. |
| **T Cell Marker** | **CD8A** | Cytotoxic T cell marker | CD8⁺ T cells (CTLs) | Low in GBM; CD8 TILs exist but often exhausted. Higher CD8 density is linked to slightly better outcomes, but GBM is generally “CD8-cold.” |
| **T Cell Marker** | **FOXP3** | Treg lineage-defining transcription factor | CD4⁺ Tregs | **Enriched in GBM TILs**; Tregs can be 30–50% of CD4 cells in GBM. High FOXP3 indicates strong immunosuppression. |
| **B Cell Marker** | **CD19** | Pan-B cell marker (part of BCR complex) | B cells (naive, memory) | Very low in GBM (B cells ~0.5–1% of immune cells)[[57]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=INF,26); notable if tertiary lymphoid structures present. |
| **B Cell Marker** | **MS4A1 (CD20)** | Marker for mature B cells (common target for rituximab) | B cells | Very low in GBM; a few CD20^+ cells might cluster in TLS. Not a prominent feature of most gliomas. |
| **NK Cell Marker** | **NCAM1 (CD56)** | NK cell adhesion molecule (also on some T cells) | NK cells (CD56^bright/dim subsets) | NKs in GBM are CD56^dim mainly[[57]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=INF,26). Presence of CD56^+ cells (~2% in GBM) correlates with better survival[[57]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=INF,26)[[55]](https://pmc.ncbi.nlm.nih.gov/articles/PMC8962431/#:~:text=The%20Immune%20System%20against%20Glioblastoma%E2%80%94How,of%20these%20cells%20to). |
| **NK Cell Marker** | **FCGR3A (CD16)** | IgG Fc receptor III (ADCC mediator) | NK cells (CD56^dim subset) | Often **downregulated on GBM-infiltrating NK**[[57]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=INF,26) (they tend to be CD16^–), indicating reduced ADCC function. |
| **NK Cell Marker** | **NKG2D (KLRK1)** | Activating receptor recognizing stress ligands | NK cells, CD8 T cells | Expressed on GBM NK (57% in one study)[[57]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=INF,26), but tumors shed NKG2D ligands to impair this pathway. |
| **Macrophage Marker** | **CD68** | Lysosomal glycoprotein (pan-macrophage/microglia) | All GAMs (microglia & macros) | **Highly expressed in GBM** (TAM load); indicates total myeloid infiltrate. Higher CD68 = more TAMs, correlates with grade. |
| **Macrophage Marker** | **CD163** | Scavenger receptor (M2 marker) | M2-polarized macrophages | **Upregulated on GBM TAMs** (M2)[[10]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=cytokines%2C%20and%20upregulate%20co,microenvironment%2C%20in%20particular%20composition%20and); associated with immunosuppression and poor prognosis. |
| **Macrophage Marker** | **MRC1 (CD206)** | Mannose receptor (M2 marker) | M2 macrophages, dendritic cells | High on GBM TAMs; often co-expressed with CD163 on tumor-promoting macrophages. |
| **Microglia Marker** | **P2RY12** | Purinergic receptor (microglia-specific in CNS) | Microglia (resting & active) | **Specific to resident microglia**[[21]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=or%20macrophages,Functions%20of%20those%20putative%20discriminating); in GBM, P2RY12 is downregulated when microglia become tumor-educated, but still indicates microglial origin. |
| **Microglia Marker** | **TMEM119** | Microglia-specific membrane protein | Microglia only (not macros) | **Specific microglia marker**[[21]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=or%20macrophages,Functions%20of%20those%20putative%20discriminating); used to distinguish microglia vs blood-derived macrophages in glioma tissues. |
| **Dendritic Cell Marker** | **ITGAX (CD11c)** | Integrin αX, pan-DC marker (also on some Macs) | Conventional dendritic cells, some TAMs | Low in GBM (few true DCs); some CD11c^+ cells are present but many may be macrophages. |
| **Dendritic Cell Marker** | **HLA-DR (MHC-II)** | MHC-II antigen-presenting molecule | DCs, macrophages, B cells | Expressed on TAMs and any DCs. GBM TAMs have impaired upregulation of HLA-DR[[3]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=,mechanisms%20of%20immune%20surveillance%2C%20including) (often HLA-DR^low MDSC phenotype). |
| **Neutrophil Marker** | **CD15 (Lewis X)** | Carbohydrate antigen on neutrophils (SSEA-1) | Neutrophils, PMN-MDSCs | Marks TANs in GBM (along with CD66b). Neutrophils comprise a smaller but significant fraction; high neutrophils correlate with tumor progression[[70]](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1393173/full#:~:text=lymphocytes%20,They%20contribute%20to). |
| **Neutrophil Marker** | **CEACAM8 (CD66b)** | GPI-linked protein on granulocytes | Neutrophils, PMN-MDSCs | **Specific to neutrophils**; used to identify TAN infiltration. TAN density is linked with immunosuppression and poor outcome. |
| **MDSC Marker** | **CD14^+HLA-DR^lo** | Classical phenotype of monocytic MDSCs | M-MDSCs (immature monocytes) | **Expanded in GBM** (blood & tumor)[[73]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=characteristics%20of%20M1%20and%20M2,37); these cells suppress T cells via ARG1, PD-L1, IL-10. |
| **MDSC Marker** | **CD15^+CD33^+ (PMN-MDSC)** | Phenotype of granulocytic MDSCs (overlaps with neutrophils) | PMN-MDSCs (immature neutrophils) | **Present in GBM**; high G-MDSC infiltration associates with “cold” tumor and T cell exclusion[[86]](https://www.nature.com/articles/labinvest201719?error=cookies_not_supported&code=1aa23676-f074-40bd-9338-fe2093c7d94e#:~:text=immunosuppressive%20cytokines%20and%20chemokines%20shaping,microenvironment%2C%20in%20particular%20composition%20and). |
| **Effector Enzyme** | **Granzyme B (GZMB)** | Cytotoxic serine protease (kills target cells) | CTLs, NK cells | Very low in GBM (few active CTLs); higher if adaptive immunity engaged (e.g. post-immunotherapy). Used as a readout of cytotoxic activity. |
| **Effector Enzyme** | **Perforin (PRF1)** | Pore-forming protein for delivering granzymes | CTLs, NK cells | Low in GBM for same reasons as GZMB. A baseline for CTL presence; an increase would signal reinvigorated T/NK function. |
| **Transcription Factor** | **STAT3** | TF promoting M2 polarization, suppressive phenotype | TAMs, MDSCs, tumor cells | **Constitutively active in GBM TAMs/MDSCs**; central to immunosuppression (ARG1, IL-10 production)[[84]](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-024-01544-7#:~:text=cytokines%20like%20IL,with%20the%20promoter%20of%20ARG1). Target for reversing TAM-mediated suppression. |
| **Transcription Factor** | **NF-κB** | TF complex driving inflammatory genes (or survival signals) | Broad (immune cells, tumor) | Active in GBM cells (promotes growth) and some myeloid cells; however, **tumor factors modulate NF-κB** to avoid full inflammation. NF-κB-induced IL-1β, IL-6 present but lead to tumor-promoting inflammation[[5]](https://biosignaling.biomedcentral.com/articles/10.1186/s12964-023-01255-5#:~:text=NLRP3%20inflammasome%20has%20shown%20that,cell%20line%20causes%20augmented%20NLRP3). |
| **Transcription Factor** | **FOXP3** | (Listed above under T cell markers) Master regulator of Tregs | Treg cells | (See FOXP3 above) – indicates presence of regulatory T cells which are abundant in GBM. |
| **Transcription Factor** | **HIF-1α** | Oxygen-sensing TF; induces hypoxia-response genes | Tumor cells, TAMs in hypoxia | **Stabilized in GBM necrotic areas**; increases VEGF, CXCL12, and **PD-L1**, thus linking hypoxia to immunosuppression. |
| **Transcription Factor** | **C/EBPβ** | TF that cooperates with STAT3 in MDSC gene expression | MDSCs, TAMs | Induced by IL-6/IL-10; drives **ARG1, IL-10** in MDSCs. Important for MDSC generation in GBM; potential target to cut off MDSC supply. |

Each of these markers can be explored in GlioVis (or similar platforms) to analyze gene expression in glioma datasets, correlate with immune cell infiltration estimates, and identify patterns (e.g., tumors with high *CCL2*, *CD163*, *PD-L1* and *FOXP3* vs those with higher *CD8A*, *GZMB*, *M1* markers). Such analyses aid in understanding the immune landscape of gliomas and could guide development of immunotherapeutic strategies or biomarkers for patient stratification.

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