Cheng *et al. Journal of Translational Medicine* (2026) 24:432
https://doi.org/10.1186/s12967-026-07873-0

Journal of Translational Medicine

REVIEW Open Access

# Decoding myeloid heterogeneity in glioblastoma: spatial insights from transcriptomics

Yilun Cheng[1†], Wenwen Zhao[1†], Mingyuan Xie[1†], Xiangrong Zheng[1*], Feng Ding[1*] and Jianyang Du[1*]

## Abstract

**Background** Glioblastoma represents the most aggressive primary brain malignancy, characterized by a profoundly immunosuppressive microenvironment that limits therapeutic efficacy and drives disease progression. Myeloid cells—comprising tumor-associated macrophages, myeloid-derived suppressor cells, and dendritic cells—serve as central regulators of this milieu. However, their profound heterogeneity in origin, function, and localization has historically complicated efforts to neutralize their protumoral effects using conventional bulk analyses.

**Main body** This review synthesizes emerging insights from single-cell and spatial transcriptomics to decode myeloid dynamics across distinct glioblastoma anatomical compartments. We delineate how ontogeny and niche-specific cues sculpt cellular identity: microglia-derived macrophages predominate at the invasive leading edge to facilitate tumor dissemination, whereas monocyte-derived populations cluster in perivascular and necrotic zones to support angiogenesis and proliferation. Furthermore, the analysis highlights the hypoxic core as a critical niche where myeloid-derived suppressor cells and reprogrammed macrophages form immunosuppressive hubs, sequestering cytotoxic T cells and sustaining glioma stemness through specific signaling axes such as hypoxia-inducible factors and chemokine gradients.

**Conclusions** By mapping these spatially segregated mechanisms, this review offers a blueprint for next-generation precision oncology. Integrating spatial resolution into the understanding of myeloid heterogeneity supports a paradigm shift from uniform immunomodulation to niche-targeted interventions. Strategies that selectively disrupt compartment-specific interactions—ranging from invasion inhibitors at the periphery to metabolic modulators in the hypoxic core—hold the potential to dismantle the structural resilience of the glioblastoma microenvironment and overcome therapeutic resistance.

†Yilun Cheng, Wenwen Zhao and Mingyuan Xie contributed equally to this work.

*Correspondence:
Xiangrong Zheng
zhengxiangrong2008@163.com
Feng Ding
slyydf6352@163.com
Jianyang Du
jianyangdu@126.com

Full list of author information is available at the end of the article

**Keywords** Glioblastoma, Tumor microenvironment, Myeloid cells, Single-cell transcriptomics, Spatial transcriptomics, Immunosuppression

## Introduction

Glioblastoma (GBM) is the most aggressive primary brain malignancy. It features an immunosuppressive tumor microenvironment (TME) that is associated with immune evasion, tumor progression, and therapeutic resistance. Myeloid cells, including tumor-associated macrophages (TAMs) (resident microglia and infiltrating monocyte-derived macrophages), myeloid-derived suppressor cells (MDSCs), and dendritic cells (DCs), are central regulators of this milieu [1], [2–5]. TAMs predominate, associated with immunosuppression and tumor growth [1]. MDSCs are linked to amplified suppression and associated with chemotherapy resistance [3, 6–8]. DCs possess dual potential for immune activation but are often associated with subversion by the TME, contributing to tolerance [4, 5]. The interplay among their origins, functional plasticity, and spatial organization underpins GBM complexity, rendering uniform therapies inadequate.

Recent advances in single-cell transcriptomics, spatial transcriptomics, and multimodal imaging have revolutionized our understanding of myeloid spatial dynamics and functional heterogeneity across GBM anatomical compartments: leading edge (LE), cellular tumor (CT), pseudopalisades (PAN), and microvascular proliferation (MVP) zones [5, 9]. Yet, these technologies face constraints, including limited single-cell spatial resolution, dissociation-induced artifacts, and inability to capture temporal dynamics, underscoring the need for integrative methods [5, 9, 10]. These approaches reveal niche-specific roles: microglia-derived TAMs at the invasive periphery correlate with invasion, monocyte-derived macrophages in the vascular core contribute to angiogenesis, MDSCs in hypoxic rims support stem-like cells, and DCs distributed variably may indicate latent immune activation [5, 9]. Such functions correlate with location via pathways like CCL2–CCR2, MIF-CXCR4, and VEGF-VEGFR. However, spatial omics data yield primarily correlations, with functional studies implicating causal roles for cues like hypoxia [11, 12] (Fig. 1).

Spatial data refines molecular inferences by merging gene expression (e.g., HIF1A upregulation in TAMs) with proximity (e.g., TAM-stem cell colocalization), inferring roles like tumor sustenance; yet, these rely on associations, demanding validation via inhibitors or perturbations [13]. Besides, key assumptions—that proximity denotes direct interactions (overlooking diffusive signals) and expression equates to function (despite post-transcriptional regulation)—require causal inference methods like Mendelian randomization or perturbations to address biases [5, 9, 14, 15]. These patterns show consistency across GBM cases in multi-patient cohorts, though interpatient variability (e.g., from IDH mutations or subtypes) modulates adaptations [5, 9, 16–18]. Derived from integrated omics in 5–20 samples per study, augmented by animal models, these maps offer representative insights, with consistent patterns validated orthotopically, albeit tempered by sample limitations [5, 9, 10].

This review synthesizes TAM, MDSC, and DC origins, subtypes, and spatial distributions in GBM, merging cutting-edge omics and imaging to chart their roles in progression and modulation. By integrating these researches, we offer a blueprint for spatially tailored therapies that dismantle the TME, surpassing uniform approaches for this fatal disease. Specifically, spatial insights translate into targeted therapies by pinpointing niche-specific molecular targets, enabling the development of interventions that selectively reprogram myeloid cells in distinct compartments, such as edge-directed invasion inhibitors or core-focused hypoxia modulators, providing possibilities for precise treatment.

**What this review adds**: Unlike prior narrative reviews that primarily focused on general interactions between GBM and myeloid cells or the broader TME without explicit spatial context, such as the overview of glioma-microenvironment crosstalk by or the discussion of GBM microenvironment biology and therapy, this synthesis emphasizes a compartment-specific lens (LE, CT, PAN, MVP). By integrating recent spatial transcriptomics data, it maps myeloid niche-dependent functions, such as hypoxia-driven TAM reprogramming and MDSC-stem cell interactions, while highlighting therapeutic opportunities like niche-targeted interventions.

## Technological advances in single-cell and spatial multiomics

The immunosuppressive TME of GBM poses unique challenges for dissecting myeloid cell heterogeneity, necessitating advanced tools to resolve cellular states and interactions at high resolution. Single-cell RNA sequencing (scRNA-seq) marked an initial breakthrough, evolving to multiomic methods that jointly profile transcriptomes with DNA and epigenomics [1, 5]. These developments have been instrumental in GBM research, allowing delineation of TAM lineages and MDSC subtypes by capturing co-expression of markers [1, 5]. For example, scRNA-seq has revealed functional myeloid heterogeneity, including immunosuppressive TAM states, in GBM progression [5, 19]. However, such

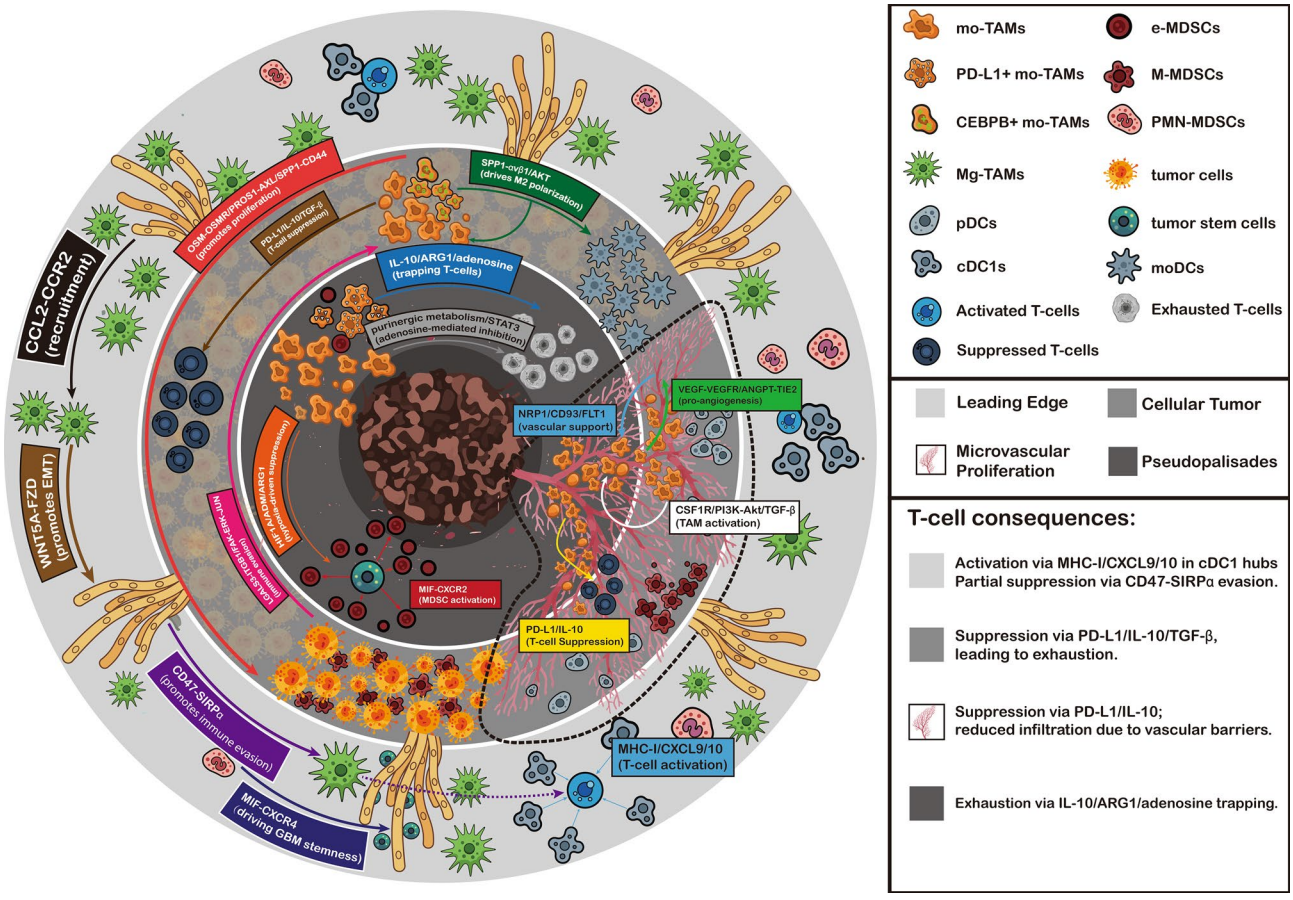


**Fig. 1** Spatially compartmentalized myeloid heterogeneity and immunosuppressive networks in the glioblastoma microenvironment. The schematic illustrates the functional adaptation of myeloid lineages across four distinct anatomical niches in glioblastoma (GBM). Leading edge (LE): at the invasive periphery, microglia-derived tumor-associated macrophages (TAMs) and polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) drive tumor dissemination via WNT4-EMT signaling and immune evasion (CD47-SIRPα). While cDc1s establish local activation hubs for T-cell priming (MHC-II/CXCL9/10), their efficacy is dampened by checkpoint signals. Cellular tumor (CT): in the proliferative core, monocyte-derived TAMs (Mo-TAMs) and monocytic MDSCs (M-MDSCs) sustain tumor growth and stemness through SPP1-αvβ1/Akt and MIF-CXCR2 axes, respectively, fostering T-cell exhaustion via PD-L1/IL-10. Microvascular proliferation (MVP): perivascular niches feature Mo-TAM clusters that support angiogenesis (VEGF/ANGPT/TIE2) and reprogramming (CSF1R/TGF-β). Plasmacytoid DCs (pDCs) and monocyte-derived DCs (moDCs) reinforce vascular barriers to restrict T-cell infiltration. Pseudopalisades (PAN): the hypoxic perinecrotic rim sequesters early-stage MDSCs and PD-L1$^{+}$ TAMs. This niche mediates profound T-cell trapping and exhaustion through hypoxia-driven metabolic pathways (purinergic metabolism/adenosine/ARG1) and chemokine recruitment (CCL2/CCR2)

methods omit spatial context, curtailing insights into niche adaptations—a void filled by spatial technologies

### Defining spatial context

In this context, "spatial" denotes the fusion of molecular data (e.g., transcriptomics) with cellular positioning in tumor tissue, encompassing localization (e.g., myeloid relative to tumor/stroma/immune cells), niches (hypoxic core, invasive periphery, vascular zones), and architecture (e.g., compartmental structures like LE, CT, PAN, MVP). By preserving this spatial information, these approaches reveal how local signaling and interactions drive myeloid heterogeneity and GBM progression. Such spatial approaches, often based on datasets from 10 to 30 human GBM samples across multiple studies or integrated with preclinical models (e.g., syngeneic mouse gliomas), enable the delineation of representative compartment-specific adaptations, though they primarily capture snapshots from resected tumors and may underrepresent rare subpopulations or longitudinal dynamics [5, 9, 10].

### Advantages over bulk analyses

Compared to non-spatial (bulk) analyses, which homogenize tissue samples and average molecular signals across all cells, thereby masking subpopulation differences and location-dependent variations, spatial heterogeneity profoundly influences our understanding of myeloid cell function. For instance, bulk RNA sequencing might detect overall immunosuppressive signatures in TAMs but fail to distinguish how hypoxia in PAN reprograms TAMs toward enhanced PD-L1 expression and IL-10

secretion, while peripheral leading-edge TAMs retain more surveillant, pro-inflammatory traits [5, 9, 10]. Spatial approaches, by contrast, uncover these niche-specific functional adaptations—such as differential activation of pathways like HIF1A in hypoxic cores versus CCL2–CCR2 at invasive edges—revealing dynamic crosstalk that drives GBM progression and resistance. This granularity enables identification of targeted interventions that bulk methods overlook, such as disrupting spatially segregated immunosuppressive hubs.

Spatial data supports molecular conclusions from scRNA-seq (e.g., gene expression signatures of immunosuppressive states) by adding proximity information (e.g., colocalization in PAN), inferring functions like PD-L1-mediated suppression primarily from both; however, these inferences reflect correlations, and causal evidence is provided by functional experiments (e.g., pathway inhibitors) [10, 20]. Underlying assumptions in these interpretations posit that spatial colocalization equates to functional crosstalk, which may not account for non-contact-mediated signaling, and that observed expression gradients imply causal drivers of phenotypes, assumptions that must be tested against potential confounders like tissue heterogeneity. Causal inferences, therefore, demand complementary approaches such as Mendelian randomization or in vivo perturbations to distinguish correlation from causation [5, 9, 10, 14].

#### Advances in spatial multiomics

The field has advanced to spatial multiomics, using array-based transcriptomics and microfluidic barcoding for resolved profiling of poly(A) RNA and analytes [10]. These methods illuminate intercellular mechanisms in GBM, revealing myeloid niche-specific roles, e.g., hypoxia-driven TAM reprogramming in PAN. While these spatial technologies primarily capture correlations between positioning and functional states, complementary mechanistic experiments (e.g., pathway inhibitors) support causal inferences, highlighting the need for integrated approaches to establish direct causation [10]. Despite these advancements, current spatial and molecular technologies face several limitations, including suboptimal resolution in early platforms (e.g., capturing multiple cells per spot, leading to averaged signals), difficulties in integrating large multimodal datasets, and restrictions in gene detection due to preselected panels or spectral overlap in imaging-based methods. Furthermore, they predominantly provide static snapshots, limiting the capture of temporal dynamics in GBM progression, and may introduce biases from tissue processing, such as dissociation artifacts in scRNA-seq or nucleic acid degradation in formalin-fixed samples [5, 9, 10, 14]. By complementing scRNA-seq with spatial context, these tools bridge the gap between cellular identity and TME architecture, as demonstrated in studies integrating spatial transcriptomics to decode glioma cellular heterogeneity and myeloid-tumor interactions [5, 9]. Recent applications include mapping the GBM spatial architecture from core to edge, revealing myeloid contributions to tumor organization and therapeutic resistance [4, 5]. Such integrated analyses have revealed consistent spatial patterns across diverse GBM cases, including conserved myeloid distributions in hypoxic and vascular niches, despite variations in individual tumor profiles [5, 9, 10].

#### Technological synergies and challenges

Single-cell RNA sequencing (scRNA-seq) provides high-resolution transcriptomic profiling of individual cells, enabling the identification of myeloid subtypes (e.g., immunosuppressive TAM states) and heterogeneity, but it requires tissue dissociation, losing spatial information [1, 5]. Spatial transcriptomics complements this by preserving tissue architecture, mapping gene expression to specific niches (e.g., hypoxia-driven TAM reprogramming in PAN via array-based methods), thus revealing location-dependent functions like immunosuppression in hypoxic cores [9, 10]. Multimodal imaging (e.g., imaging mass cytometry) further integrates by offering visual and protein-level data, validating RNA findings and capturing morphological/cellular interactions (e.g., TAM-T cell colocalization in perivascular niches) at subcellular resolution [5, 9]. Together, these technologies synergize: scRNA-seq defines cellular states, spatial transcriptomics assigns them to anatomical compartments, and imaging confirms spatial organization and adds non-transcriptomic layers, as seen in integrated studies decoding GBM TME resilience, where functions are inferred from gene expression enriched in specific niches and validated by proximity-driven interactions [4, 5, 9, 21] (Fig. 2).

However, these synergies rest on assumptions that proximity-based inferences capture true functional dependencies, potentially underestimating dynamic or indirect effects, and that static snapshots from spatial data suffice for causal modeling, highlighting the need for time-resolved or perturbation-based validations to refine interpretations [4, 5, 9, 15]. Nonetheless, these synergies are tempered by ongoing challenges, such as computational demands for deconvoluting mixed signals in low-resolution spatial data and the inability to fully resolve subcellular interactions or causal mechanisms without functional validation [4, 5, 9]. Building on these methodological synergies, the following sections explore myeloid cell types, starting with TAMs, where origins inform functional plasticity and spatial roles in GBM progression.

**Key Takeaways:** The progression from scRNA-seq to integrated spatial multiomics has revolutionized the

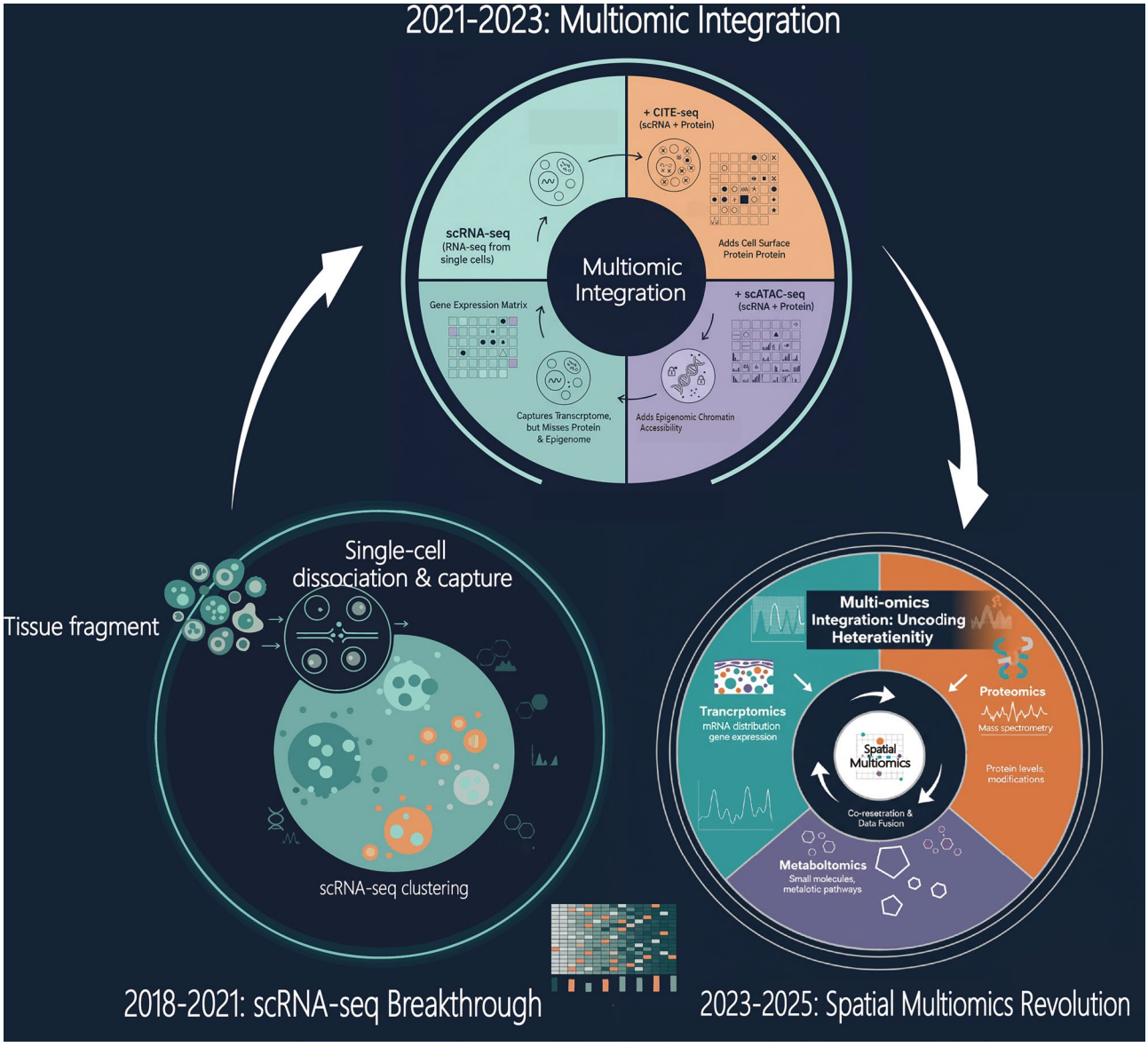


**Fig. 2** Evolution of single-cell and spatial multiomics technologies for decoding the glioblastoma microenvironment. The timeline delineates three transformative paradigms in resolving myeloid complexity. scRNA-seq breakthrough (2018–2021): droplet-based microfluidics enabled the high-throughput profiling of dissociated tissues, establishing foundational atlases that first unveiled the extent of myeloid heterogeneity. Multiomic integration (2021–2023): the simultaneous capture of transcriptomes, cell-surface proteomics (CITE-seq), and chromatin accessibility (scATAC-seq) within single cells added critical epigenomic and protein-level dimensions, refining the definition of functional states beyond RNA expression alone. Spatial multiomics revolution (2023–2025): current platforms preserve native tissue architecture while integrating spatial transcriptomics, proteomics, and metabolomics. This allows the direct mapping of niche-specific programs—such as hypoxia-driven reprogramming in pseudopalisades (PAN) and pro-angiogenic signaling in microvascular proliferation (MVP) zones—shifting the analytical paradigm from dissociated cellular inventories to spatially organized ecosystems

dissection of myeloid heterogeneity in GBM, preserving spatial context to reveal niche-specific adaptations and functional states that bulk analyses obscure. By synergizing transcriptomic, proteomic, and imaging modalities, these tools uncover immunosuppressive mechanisms and intercellular crosstalk, though limitations in resolution and causal inference underscore the need for multimodal validations and perturbations to guide targeted therapies, setting the stage for exploring myeloid subsets' roles in tumor progression.

## Tumor-associated macrophages: origins, functions, and spatial roles

TAMs constitute a substantial fraction of the cellular composition of GBM, accounting for 30–50% of the tumor mass in single-cell studies of IDH-wild-type GBM [1, 22–25]. TAMs are instrumental in shaping the

immunosuppressive TME. Unlike monolithic entities, TAMs display remarkable diversity in their origins, functional states, and spatial distribution within the tumor. This section traces their lineages, functional plasticity, and spatial dynamics, which is the key to their tumor-promoting roles.

#### Developmental lineages and identities

TAMs in GBM originate from two primary lineages. Microglia derive from yolk sac progenitors during embryogenesis, express high levels of P2RY12, TMEM119, CX3CR1, and SALL1, and dominate early transformation and periphery in edge zones, whereas monocyte-derived macrophages arise from bone marrow hematopoietic stem cells, express elevated CD45, CCR2, CD49D, and TGFBI, and infiltrate in advanced stages, favoring core zones with the blood–brain barrier (BBB) disruption [5, 26–28]. Regarding how these dimensions relate, lineage origins partially determine initial spatial localization (e.g., microglia in edges due to resident nature), but the TME can reprogram cells regardless of origin toward shared functional states, as evidenced by omics data showing convergent immunosuppressive traits in both lineages under hypoxia [5, 26].

These molecular distinctions extend to their proportional representation in GBM, where dynamic shifts during tumor evolution reflect underlying pathological processes. In IDH-wild-type GBM single-cell studies, TAMs constitute 50–85% monocyte-derived macrophages and 15–50% microglia [1, 22–25], with the composition evolving during progression: microglia dominate early transformation and infiltration phases, whereas advanced stages, marked by hypoxia, necrosis, and BBB breach, favor monocyte-derived macrophage infiltration [5]. Genetic subtypes are associated with distribution: IDH-wild-type GBM shows increased macrophage infiltration, IDH-mutant lower-grade gliomas enrich microglia [1]. These differences likely reflect lineage-specific or spatial patterns. In IDH-wild-type GBM, macrophage infiltration predominates, leading to greater immune cell infiltration compared to IDH-mutant gliomas [16–18, 22], whereas IDH-mutant lower-grade gliomas enrich microglia linked to preserved BBB integrity, 2-HG-associated inhibition of immune responses, and chemokine hypermethylation (e.g., reduced CXCL1/CXCL2 expression) [16–18].

Collectively, this lineage diversity not only is associated with priming TAMs for their functional roles in GBM but also underscores the association of developmental origins on TME responses. This foundational diversity primes TAMs for their functional role in GBM. As we shift our focus from their origins to their behavior within the tumor, it becomes evident that their developmental lineage shapes their response to the TME, setting the stage for a deeper insight of their functional states and spatial dynamics (Fig. 3).

#### Functional plasticity and heterogeneity

Upon recruitment to the GBM microenvironment, TAMs exhibit plasticity. They adopt a continuum of functional states that defy binary classification. The M1/M2 polarization model frames this traditionally: M1-like TAMs show proinflammatory and anti-tumor traits, they release reactive oxygen species, nitric oxide, and cytokines such as IL-1β, IL-6, TNF-α via NF-κB and STAT1 activation (experimentally validated as drivers of proinflammatory function in preclinical models, such as inhibitor studies) [29]. Conversely, M2-like TAMs adopt anti-inflammatory, protumoral roles. They express ARG1, CD163, CD206 while secreting IL-10 and TGF-β through STAT6 and PI3K/Akt pathways (inferred from spatial expression patterns in scRNA-seq data, with functional validation in TAM polarization assays) [1, 5, 27, 29]. This dichotomous model offers a foundational understanding. However, limitations arise in GBM's complex TME. Their different lineage origins seem to influence initial functional predispositions (e.g., microglia show more pro-inflammatory features), but the TME reprograms both origins toward immunosuppressive states in core zones, overriding origin-specific traits as shown in single-cell studies [1, 5, 27]; this interplay suggests TME dominance over lineage in driving functional convergence [30].

In GBM, the TME influences, ranging from hypoxia to exosomal signaling, consistently skew TAMs toward immunosuppressive phenotypes. For example, tumor-secreted MIF sustains M2-like states via CD74 (inferred from expression data); GBM stem cells release β2-microglobulin to recruit TAMs via CCL2 and CXCL10, engaging PI3K/AKT for M2 marker expression (experimentally validated as drivers of polarization in GBM cell co-culture models) [27, 31]. Mesenchymal-like tumor cells reinforce M2 polarization through CSF1–CSF1R, ANXA1–FPR1/3, CCL3/4-CCR1 axes (inferred from spatial co-expression in multiomics data, with partial validation via pathway inhibition) [27, 31]. Hypoxia exacerbates this via CAIX and cholesterol metabolites, increasing CD36 and PD-L1 (experimentally validated in hypoxic culture systems) [5, 27] In single-cell RNA-seq analyses of GBM, 66% TAMs co-express M1/M2 markers, forming a spectrum: microglia-derived TAMs retain homeostatic features but upregulate inflammation, whereas monocyte-derived TAMs branch into interferon-responsive, hypoxic, and immunosuppressive subtypes [1, 5, 22, 27, 32].

Pseudotime analyses provide dynamic insights into TAM trajectories, uncovering transitional states that bridge surveillant origins to immunosuppressive end points. Pseudotime analyses delineate transitions:

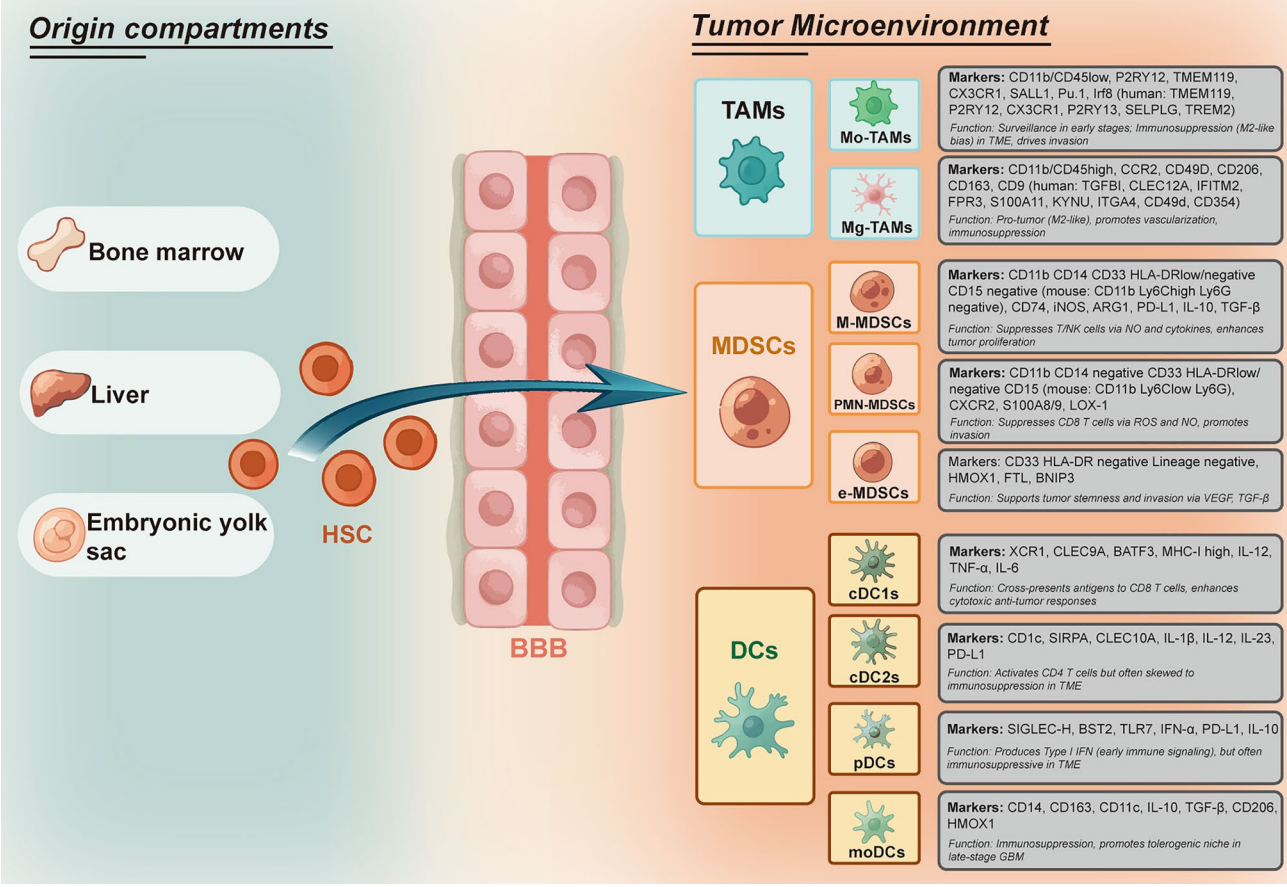


**Fig. 3** Developmental origins and functional diversification of myeloid lineages in the glioblastoma microenvironment. The schematic maps the trajectory of myeloid cells from distinct ontogenic reservoirs to their intratumoral phenotypic states. Origin compartments (left): progenitor pools from the embryonic yolk sac, liver, and bone marrow (hematopoietic stem cells, HSCs) converge upon the tumor microenvironment (TME), traversing the blood–brain barrier (BBB) to replenish the myeloid landscape. Phenotypic landscape (right): within the TME, these lineages differentiate into three functional categories defined by unique molecular signatures: (1) TAMs, encompassing resident microglia-derived (Mg-TAMs; e.g., P2RY12$^{+}$, TMEM119$^{+}$) and infiltrating monocyte-derived (Mo-TAMs; e.g., CD49d$^{+}$, CCR2$^{+}$) subsets that modulate invasion and surveillance; (2) MDSCs, divided into monocytic (M-MDSCs), polymorphonuclear (PMN-MDSCs), and early-stage (e-MDSCs) subtypes that drive immunosuppression via effectors like ARG1 and ROS; and (3) DCs, including cDc1s/cDc2s and pDcs, which balance antigen cross-presentation with TME-induced tolerance. This framework highlights how lineage plasticity (e.g., monocyte-to-TAM transitions) and niche-specific cues shape functional heterogeneity, identifying vulnerabilities for therapeutic interventions such as STAT3 blockade

microglia evolve from surveillant to activated/immunosuppressive states, downregulating P2RY12 and upregulating CD163, APOE, HIF1A; monocyte-derived TAMs advance from inflammatory monocytes to PD-L1$^{+}$ immunosuppressive macrophages [1, 27, 33, 34]. Notable subtypes include SIGLEC9$^{+}$ TAMs, which curb T-cell activation and are linked to PD-1 resistance [35], and lipid-laden macrophages/microglia (LLMs), which express GPNMB, LPL, ZFYVE27 to support tumor growth [36]. In lower-grade gliomas, TAMs favor immune activation, shifting to immunosuppression in high-grade gliomas with STAT1 downregulation and Spp1/Gpnmb upregulation [37]. These findings emphasize the profound linkage between TAM lineage and functional evolution, a theme that acquires additional depth when viewed through the lens of spatial distribution within the TME, where niche-specific cues could be exploited for reprogramming.

These functional states are inferred primarily from gene expression (e.g., co-expression of M1/M2 markers like IL-10 and TNF-α from scRNA-seq) supported by spatial proximity in later analyses, with spatial data enhancing molecular conclusions by revealing niche-specific adaptations, though these represent correlations, and causal links require functional experiments like pathway inhibitors [1, 5, 27, 32]. However, there are still limitations of current technologies, which often fail to capture real-time dynamics or subcellular resolution, potentially overlooking transient states or rare interactions in the GBM TME [1, 5, 27].

The interplay between TAM origins and their functional evolution is essential. As we explore their spatial

distribution, this heterogeneity represents a new dimension, revealing how the TME architecture orchestrates TAM behavior in GBM.

### Spatial distribution and dynamics

The spatial organization of TAMs provides a critical perspective for understanding their contribution to tumor biology. This reflects their origins, functional states, and interactions with the TME. Advances in spatial transcriptomics and imaging have implied these patterns.

Microglia-derived TAMs, marked by P2RY12, TMEM119, SALL1, predominate at the invasive edges and white matter tracts, where they promote invasion via matrix remodeling through pathways like WNT5A-FZD and retain more pro-inflammatory traits [5, 38]. Monocyte-derived TAMs, identified by CD49D, TGFBI, CLEC12A, cluster in the tumor core, particularly around blood vessels and necrotic zones, enabling them to drive angiogenesis through VEGF-VEGFR pathways and immunosuppression via PD-L1 expression, contributing to T-cell exhaustion [5, 10, 26, 39, 40]. These distinctions are supported by genetic lineage tracing, showing differential interactions with TME components; their lineage partially determines localization (e.g., resident microglia in edges), but TME reprograms cells across origins, enabling similar immunosuppressive functions in core zones regardless of lineage [5, 9, 10]. Spatial transcriptomics further refines this: immunosuppressive macrophages are concentrated in hypoxic regions and perivascular niches, correlating with formation of immune-suppressive hubs associated with poor prognosis through mechanisms like IL-10 secretion, though experimental validation is needed to confirm causality [9, 41]. SIGLEC9$^+$ monocyte-derived TAMs are enriched in the tumor core and interact with exhausted T cells to bolster immunosuppression [35]. LLMs, tied to lipid metabolism, localize to myelin-rich areas, supporting MES-like GBM cells [36]. A VSIG4$^+$ S100A10$^+$ TAM subtype resides near T cells in both core and invasive edges and expresses PD-L1 to inhibit T-cell function [42]. This distribution is dynamic: in immunocompetent hosts, TAMs shift from perivascular clustering early in tumor growth to hypoxic pseudopalisading patterns later, highlighting interactions with adaptive immunity [10]. These spatial distributions demonstrate consistency across GBM cases, with microglia-derived TAMs reliably enriched at invasive edges and monocyte-derived TAMs in core regions in multiple cohorts, though interpatient heterogeneity, such as in IDH-wild-type versus mutant tumors, can modulate these patterns [5, 9, 16–18, 26] (Table 1).

The signaling pathways underlying these distributions are spatially segregated. In the hypoxic core, TAMs activate purinergic metabolism, converting ATP to adenosine to suppress T cells, tied to EGFR amplification and hypoxia (inferred from spatial expression patterns in transcriptomics and experimentally validated as drivers of immunosuppression via CD39/CD73 inhibition in mouse models) [39]. This process involves sequential enzymatic steps where CD39 hydrolyzes ATP to AMP, followed by CD73 converting AMP to adenosine, ultimately leading to A2A receptor-mediated suppression of T-cell activation and effector functions (experimentally validated in receptor blockade studies) [39]. The STAT3–BLIMP1 pathway drives IL-10 production in immunosuppressive TAMs, reinforcing suppression (experimentally validated as a functional driver in CRISPR-based studies) [43]. In myelin-rich regions, the liver X receptor pathway upregulates lipid efflux in LLMs, transferring cholesterol esters to tumor cells (inferred from spatial multiomics data, with validation in lipid transfer assays) [36]. Perivascular monocyte-derived TAMs activate CSF1R, PI3K-Akt, TGF-β pathways, promoting angiogenesis (inferred from perivascular expression patterns and experimentally validated in CSF1R inhibitor models) [5]. Multiomics analyses revealed four core programs—systemic inflammation, scavenging, complement suppression, glucocorticoid response—differentially activated across niches, reflecting TME-driven reprogramming (inferred from spatial transcriptomics) [44]. Hypoxic TAMs in pseudopalisading zones express adrenomedullin, BNIP3, CSTB, increasing vascular permeability (experimentally validated in hypoxic culture and mouse models) [45]. The "pathway–space–phenotype" model underscores how local signals tailor TAM functions.

Spatial interactions further amplify TAM impact. At the tumor periphery, P2RY12$^+$ microglia-derived TAMs colocalize with CD8+ T cells and DCs, potentially aiding antigen presentation [5]. In the core, SIGLEC9$^+$ monocyte-derived TAMs neighbor exhausted T cells and secrete IL-10 and TGF-β [35]. LLMs transfer lipids to MES-like GBM cells via CD36, upregulating PD-L1 and downregulating MHC-II [36]. Perivascular TAMs secrete VEGFA and angiopoietin-2, driving angiogenesis, whereas CD73$^+$ tumor cells and CD39$^+$ TAMs collaborate to increase adenosine levels [39]. In hypoxic zones, CCL8 from GBM cells recruits TAMs, reprogramming them to express CD206 and ARG1 and trapping cytotoxic T lymphocytes in an exhausted state [12].

These spatial patterns, elucidated from spatial transcriptomics datasets encompassing 10–20 human GBM samples and corroborated by lineage-tracing in mouse models, indicate representative niche preferences, with microglia-derived TAMs enriched at edges and monocyte-derived TAMs in cores across diverse patient profiles [5, 9, 26, 41]. Immunosuppressive and protumoral functions here are inferred from both gene expression (e.g., upregulated PD-L1 and VEGF) and spatial

**Table 1** Comparative overview of microglia-derived and monocyte-derived tumor-associated macrophages (TAMs) in glioblastoma

| Category | Microglia-Derived TAMs (Mg-TAMs) | Monocyte-Derived TAMs (Mo-TAMs) | Key References |
|---|---|---|---|
| Developmental Origins | Derived from yolk sac progenitors during embryogenesis; self-renew via local proliferation in the CNS; dominate early tumor transformation and infiltration phases, especially in IDH-mutant lower-grade gliomas due to preserved BBB integrity and chemokine hypermethylation (e.g., reduced CXCL1/CXCL2). | Arise from bone marrow hematopoietic stem cells; differentiate into circulating monocytes that infiltrate the CNS in advanced GBM via BBB disruption, driven by CCL2–CCR2 signaling; predominate in IDH-wild-type GBM with hypoxia, necrosis, and increased immune infiltration. | [1, 5, 16–18, 22–25, 28] |
| Proportional Representation in GBM | ~15–50% of TAMs in IDH-wild-type GBM; higher in IDH-mutant gliomas (~30–50% overall TAMs); decreases in advanced stages as monocyte infiltration increases. | ~50–85% of TAMs in IDH-wild-type GBM; lower in IDH-mutant gliomas due to 2-HG-mediated immune inhibition; increases with tumor progression and BBB breach. | [1, 5, 16–18, 22–25] |
| Molecular Markers | High: P2RY12, TMEM119, CX3CR1, SALL1, PU0.1, IRF8; retain core microglial signatures (e.g., TMEM119, P2RY12 in humans); downregulate surveillant markers (e.g., P2RY12) during transition to activated states. | High: CD45, CCR2, CD49D, CD206, CD163, CD91, TGFBI, CLEC12A, IFITM2; branch into subtypes with upregulated CD163, APOE, HIF1A, PD-L1 in immunosuppressive states. | [5, 26, 27] |
| Dominant Spatial Niches | Predominate at invasive leading edge (LE), white matter tracts, and infiltrative periphery; surveillant phenotype in early phases; colocalize with $CD8^+$ T cells and DCs for potential antigen presentation. | Cluster in tumor core (CT), perivascular niches (MVP), hypoxic pseudopalisades (PAN), and necrotic zones; form immunosuppressive hubs in hypoxic and vascular areas. | [1, 5, 9, 10, 26, 41, 42] |
| Functional States and Plasticity | Retain homeostatic features but upregulate inflammation (e.g., via pseudotime transitions from surveillant to activated/immunosuppressive); promote invasion at edges via matrix remodeling, WNT5A-FZD/CD146, and purinergic metabolism (ATP to adenosine via CD39/CD73, suppressing T/NK cells); less skewed to M2-like compared to Mo-TAMs. | Exhibit greater plasticity with interferon-responsive, hypoxic, and immunosuppressive subtypes; skewed to M2-like (ARG1, CD163, CD206, IL-10, TGF-β via STAT6/PI3K/Akt); promote angiogenesis (VEGF-VEGFR), immunosuppression (PD-L1, IL-10 via STAT3–BLIMP1), and lipid transfer (LLMs via CD36); coexpress M1/M2 markers (>50% in scRNA-seq). | [1, 5, 27, 29, 31–34, 36, 39, 43, 44] |
| Key Signaling Pathways | TGF-β for transition to tumor-associated states; purinergic (CD39/CD73–A2A); WNT5A-FZD for angiogenesis/migration; less hypoxia-driven; systemic inflammation and complement suppression programs. | Hypoxia-driven (HIF1A, CAIX, adrenomedullin, BNIP3, CSTB for vascular permeability); CSF1–CSF1R, ANXA1–FPR1/3, CCL3/4-CCR1 for M2 polarization; PI3K/AKT for M2 markers; glucocorticoid response and scavenging programs. | [5, 9, 10, 12, 29, 31, 36, 39, 43–45] |
| Cellular Interactions and Contributions to GBM Resilience | Colocalize with astrocyte-like tumor cells and $CD8^+$ T cells/DCs at edges; promote EMT/invasion via GPNMB-EGFR; early immunosuppression via adenosine; interact with adaptive immunity in immunocompetent hosts. | Neighbor exhausted T cells in core ($SIGLEC9^+$ secrete IL-10/TGF-β); transfer lipids to MES-like GBM cells (LLMs via CD36, upregulating PD-L1); collaborate with $CD73^+$ tumor cells for adenosine hubs; drive angiogenesis (VEGFA, angiopoietin-2) and T-cell exhaustion in hypoxic zones. | [5, 9, 10, 12, 35, 36, 39, 42, 44] |
| Therapeutic Implications | Target edge-specific recruitment (e.g., CCL2–CCR2 blockade) or reprogram via metabolic inhibitors (e.g., cyclocreatine disrupting ATP/CKB); enhance antigen presentation for immunotherapy. | Disrupt core/hypoxic programs (e.g., STAT3/HDAC inhibitors for IL-10/ARG1; anti-CSF1R for depletion); combine with anti-PD-1 to counter PD-L1; nanoparticle delivery for vascular niches. | [5, 43, 46–54] |

*Notes: This table synthesizes developmental, spatial, and functional distinctions from single-cell and spatial transcriptomics data, emphasizing niche-dependent adaptations. Proportions vary by GBM subtype (e.g., IDH status) and progression stage. Abbreviations: BBB, blood-brain barrier; CNS, central nervous system; CT, cellular tumor; LE, leading edge; LLM, lipid-laden macrophage; MES, mesenchymal; MVP, microvascular proliferation; PAN, pseudopalisades; scRNA-seq, single-cell RNA sequencing

proximity (e.g., colocalization with exhausted T cells in hypoxic regions), where spatial transcriptomics supports cellular conclusions by correlating expression with anatomical context, but these are associations, with causality suggested by functional studies such as genetic lineage tracing or pathway perturbations [5, 9, 10, 35, 55].

This spatial perspective not only deepens our understanding of TAM heterogeneity but also highlights its therapeutic potential. These spatial insights into TAM roles pave the way for integrating observational data with therapeutic strategies, as detailed later.

### Therapeutic translation roadmap

**Targets by niche:** Hypoxic core—MIF-CXCR2/adenosine axis [39, 56, 57]; perivascular—VEGF/ANGPT-TIE2 [45, 46]; edge—CCR2 blockade + cDC1 support [27, 58, 59].

**Modalities:** Small-molecule STAT3/TGF-β inhibitors [30, 43, 60, 61], CSF1R/CCR2/CXCR2 antagonists [27, 62, 63], oncolytic or in situ DC priming [64, 65], and combination with checkpoint inhibitors [47, 66].

**Trial design hints:** Spatial biomarkers/endpoints (e.g., imaging mass cytometry scores [9, 20]; spatial transcriptomic signatures [9, 10, 67]).

**Key Takeaways:** TAMs in GBM exhibit lineage-dependent origins, with microglia enriching invasive edges and

monocyte-derived macrophages dominating hypoxic cores, driving functional plasticity toward immunosuppression via TME cues like hypoxia and MIF signaling. Spatial multiomics reveals niche-specific adaptations and interactions that amplify tumor progression, underscoring therapeutic opportunities through targeted modalities such as STAT3 inhibitors or niche-directed blockade to reprogram the immunosuppressive landscape and overcome resistance.

## Myeloid-derived suppressor cells: origins, subtypes, and spatial interactions

MDSCs are pivotal orchestrators of the immunosuppressive TME of GBM. MDSCs, originating from myeloid progenitors and modulated by tumor-derived signals, not only suppress immune responses but also contribute to chemotherapy resistance and tumor progression [3]. This section explores the origins and recruitment of MDSCs in GBM, their diverse subtypes and transformations, and their spatial distribution within the tumor, providing a comprehensive view of their role in this lethal disease. By integrating these dimensions, we aim to highlight how MDSCs drive immune evasion and how their spatial interactions might unlock novel therapeutic opportunities.

### Origins and recruitment mechanisms

MDSCs originate from the bone marrow as heterogeneous immature myeloid progenitors that normally differentiate into DCs, macrophages, or granulocytes. In GBM, dysregulated myelopoiesis, driven by chronic inflammation or tumor-derived signals, promotes their expansion and accumulation [3]. Additionally, normal monocytes can be induced into immunosuppressive MDSCs within the GBM TME via factors such as TGF-β. This dual origin underscores the adaptability of MDSCs to tumor demands.

Tumor-derived chemoattractants, including CD200, MIF, IDO1, CCL20, draw MDSCs from the bone marrow to the tumor site [3, 56, 68, 69]. Hypoxia enhances this via CCL26 upregulation, targeting $CX3CR1^+$ MDSCs, alongside VEGF and HIF1α induction, elevating ENTPD2 and 5'-AMP [69]. Glioma stem cells secrete glutamate to promote MDSC maturation and infiltration through NMDA receptors, with glutamine-derived α-ketoglutarate amplifying expansion [3, 70].

Post recruitment, MDSC activation occurs via tumor-derived factors (IFN-γ, STAT3, IL-6, IL-4Rα, PGE2, TGF-β, S100A8/A9) that upregulate immunosuppressive effectors ARG1, iNOS, PD-L1, NO, ROS. In GBM, IL-6 and PGE2 activate JAK/STAT3 to elevate ARG1 and PD-L1 (experimentally validated as drivers of MDSC activation in cytokine stimulation assays); TGF-β promotes ROS and IDO1 (inferred from expression data and validated in TGF-β inhibitor studies); S100A8/A9 reinforce expansion via RAGE/NF-κB (inferred from expression data and validated in TGF-β inhibitor studies) [3, 71–73]. Glioma stem cells (GSCs) secrete MIF, binding CD74/CXCR2/4 on MDSCs, triggering PI3K/AKT to upregulate ARG1 and suppress T cells (inferred from spatial co-expression and experimentally validated in co-culture and PI3K inhibitor experiments) [11].

This foundational diversity primes MDSCs for their functional roles in GBM. As we shift our focus from their origins to their behavior within the tumor, it becomes evident that their developmental lineage shapes their response to the TME, setting the stage for a deeper insight of their functional states and spatial dynamics

### Subtypes and functional transformations

MDSCs encompass monocytic (M-MDSCs), polymorphonuclear (PMN-MDSCs), and early-stage (e-MDSCs) subtypes, each with distinct markers and functions in GBM. M-MDSCs ($CD11b^+$ $CD14^+$ $CD33^+$ HLA-DRlow/-$CD15^-$ in humans; $CD11b^+$ $Ly6ChighLy6G^-$ in mice) suppress T and NK cells via iNOS, ARG1, PD-L1, NO, IL-10, TGF-β, and metabolic reprogramming [3]. PMN-MDSCs ($CD11b^+$ $CD14^-$ $CD33^+$ HLA-DRlow/-$CD15^+$ or $CD66b^+$ in humans; $CD11b^+$ $Ly6ClowLy6G^+$ in mice) inhibit $CD8^+$ T cells through ROS and NO, induce tolerogenic T cells, and differentiate into tumor-associated neutrophils [3, 74]. e-MDSCs ($CD33^+$ HLA-$DR^-$ $Lineage^-$) are immature precursors expressing HMOX1, FTL, BNIP3, supporting stemness via VEGF and TGF-β [11, 75].

In GBM, subtypes adapt: M-MDSCs accumulate via CCL2/CCL7–CCR2, upregulated by radiotherapy-induced type I IFN via cGAS-STING (experimentally validated as recruitment drivers in CCR2 knockout and STING agonist models) [62, 69, 70]. PMN-MDSCs express S100A8/9 and LOX-1, correlating with poor prognosis (inferred from spatial expression and validated in prognostic cohort studies) [74, 76, 77]. e-MDSCs are recruited by CXCL1/CXCL2–CXCR2, with MIF-CXCR2 activating ARG1 (experimentally validated in CXCR2 inhibitor experiments); itaconic acid blocks T-cell metabolism, weakened by 2-HG in IDH-mutant GBM (inferred from metabolic profiling and validated in IDH-mutant cell lines) [78–80]. Their suppressive functions (e.g., T-cell inhibition via ARG1 and ROS) are inferred primarily from gene expression (e.g., upregulated effectors like PD-L1) in scRNA-seq, enhanced by spatial data in subsequent sections that add proximity context, with these observations indicating correlations; causal relationships demand functional validation, such as through inhibitor studies [3, 74, 78–80]. These correlative insights underscore technological constraints, including the loss of spatial context in scRNA-seq and the need for higher-resolution spatial methods to disentangle mixed cellular

signals in heterogeneous GBM tissues [3, 74, 78]. These transformations underscore MDSC contributions to resistance, transitioning to spatial dynamics.

#### Spatial distribution and tumor interactions

MDSCs exhibit niche-specific localization in GBM, amplifying immunosuppression through proximity to tumor elements. M-MDSCs concentrate in core, perivascular, and hypoxic niches, predominant in male GBM models, where they are associated with local immunosuppression by proliferating via STAT3/NF-κB and suppressing T cells through ARG1 and PD-L1, while also promoting angiogenesis in perivascular areas via VEGF secretion [22, 81]. They colocalize with GSCs, secreting cytokines that suppress T cells and promote stemness [11].

PMN-MDSCs are abundant at invasive edges and infiltration zones, colocalizing with EGFR+ tumor cells, correlating with formation of a positive feedback loop that appears to enhance tumor expansion and immune evasion via EGFR signaling and chemokines like CXCL2/CXCL3; while observational data support this association, genetic and functional studies (e.g., Mendelian randomization on myeloid phenotypes) suggest underlying causal links [55, 82]. In pseudopalisading regions of IDH-wild-type GBM, e-MDSCs are near metabolically adapted tumor cells, protecting glioma stem cells by bolstering stemness through VEGF and TGF-β secretion, thereby contributing to therapeutic resistance [79]. This interaction is diminished in IDH-mutant gliomas due to hypermethylation of chemokine genes and 2-hydroxyglutarate accumulation, highlighting genetic basis for spatial differences [79].

MDSCs and GSCs cluster in specific TME niches. GSCs secrete MIF, attracting and activating MDSCs via CXCR2, prompting ARG1 and immunosuppressive factors that shield GSCs from T-cell attack [11, 80]. This MIF-mediated network forms functional synergy reinforcing local immunosuppression, with spatial proximity enhancing signal efficiency [11].

In male GBM models, M-MDSCs predominate within tumor tissue, whereas in females, PMN-MDSCs are enriched in peripheral blood [81]. These patterns shift with progression: e-MDSCs decline in GBM as they differentiate into mature MDSCs within the tumor; late-stage PMN-MDSCs increase, aligning with EGFR+ cells at margins to promote invasion [82, 83]. Furthermore, emerging evidence underscores sex-specific disparities in MDSC composition and spatial distribution, which may influence GBM progression and therapeutic responses. In preclinical models and human cohorts, males exhibit elevated intratumoral monocytic MDSCs (mMDSCs), which cluster preferentially in the tumor core and MVP zones, correlating with enhanced local immunosuppression, accelerated tumor growth, and poorer survival. In contrast, females display higher circulating polymorphonuclear MDSCs (PMN-MDSCs), potentially limiting their infiltration into central niches and conferring a relative survival advantage. These differences are mechanistically linked to sex hormones and cytokine profiles, such as IL-1β-driven mMDSC expansion in males and FLT3-mediated PMN-MDSC predominance in females, highlighting the need for sex-stratified analyses in spatial omics studies to refine niche-targeted therapies [18, 81, 84, 85].

These localization patterns, derived from single-cell and spatial analyses of multiple GBM patient cohorts (e.g., 8–15 samples) and supported by sex-stratified preclinical models, reflect representative sex- and stage-dependent distributions, although further large-scale validation is required to account for interindividual heterogeneity [11, 79, 81, 82]. Overall, MDSC spatial patterns show consistency across GBM cases, with M-MDSCs predominating in core niches and PMN-MDSCs at edges in diverse patient samples, albeit with variations linked to sex, IDH status, and disease stage [11, 79, 81, 82].

Molecular underpinnings include S100A8/9 in PMN-MDSCs for chemotactic capabilities (inferred from expression patterns and validated in migration assays), LOX-1 in progression (experimentally validated as a prognostic marker in clinical samples) [86, 87], and Ki-67/Cyclin D in M-MDSCs via STAT3/NF-κB (experimentally validated in STAT3 inhibitor studies) [81]. The CCL2–CCR2 axis recruits M-MDSCs, augmented by CCL20 and osteoprotegerin (inferred from chemokine profiling); radiotherapy-induced type I interferon via cGAS-STING drives $CCR2^{+}$ MDSC infiltration (experimentally validated in radiation models and STING knockouts) [69, 88]. These spatially defined interactions contribute to chemotherapy resistance by ROS/NO from PMN-MDSCs and cytokine suppression by M-MDSCs [3, 74] (Table 2).

Niche-specific functions like local immunosuppression are inferred from both gene expression (e.g., STAT3/NF-κB activation in M-MDSCs) and spatial proximity (e.g., colocalization with GSCs in core niches), with spatial data supporting molecular conclusions by revealing interaction patterns, though these are primarily correlations, and causality is suggested by genetic studies like Mendelian randomization [11, 79, 81, 82].

This spatial orchestration underscores MDSC complexity in GBM. These observational patterns in MDSC distribution inform potential therapeutic disruptions, explored in subsequent sections. Building on this, DCs emerge as potential immune activators often subverted, holding promise for reprogramming.

**Table 2** Subtypes of myeloid-derived suppressor cells (MDSCs) in glioblastoma: recruitment axes, Dominant niches, and immune-evasion mechanisms

| Subtype | Molecular Markers (Human/Mouse) | Recruitment Axes and Activation Factors | Dominant Spatial Niches | Immune-Evasion Mechanisms and Functions | Key References |
|---|---|---|---|---|---|
| Monocytic MDSCs (M-MDSCs) | Human: $CD11b^+$ $CD14^+$ $CD33^+$ HLA-DRlow/-$CD15^-$; Mouse: $CD11b^+$ $Ly6ChighLy6G^-$; Upregulate ARG1, PD-L1, Ki-67/Cyclin D. | CCL2/CCL7–CCR2 (augmented by RT-induced type I IFN via cGAS-STING); CCL20, osteoprotegerin; Activation: IL-6/PGE2-JAK/STAT3, TGF-β-ROS/IDO1, S100A8/A9-RAGE/NF-κB, MIF-CD74/CXCR2/4-PI3K/AKT. | Tumor core (CT), perivascular (MVP), and hypoxic niches (PAN); Predominant in male GBM models; Radiate from necrosis; Colocalize with GSCs. | Suppress T/NK cells via iNOS, ARG1, PD-L1, NO, IL-10, TGF-β, metabolic reprogramming (e.g., ARG1 depletes L-arginine); Promote stemness (VEGF, TGF-β); Confer chemotherapy resistance via cytokines; Positive feedback with GBM cells (e.g., MIF-CXCR2 loop). | [3, 11, 69, 71–73, 79–81, 88] |
| Polymorphonuclear MDSCs (PMN-MDSCs) | Human: $CD11b^+$ $CD14^-$ $CD33^+$ HLA-DRlow/-$CD15^+$ or $CD66b^+$; Mouse: $CD11b^+$ $Ly6Clow$-$Ly6G^+$; Express S100A8/9, LOX-1. | TGFA/HBEGF-EGFR, CXCL2/CXCL3; S100A8/A9 for chemotaxis; Hypoxia via CCL26–CX3CR1, VEGF/HIF1α-ENTPD2/5′-AMP. | Invasive edges (LE) and infiltration zones; Colocalize with $EGFR^+$ tumor cells; Enriched in peripheral blood in female GBM models; Increase in late-stage progression. | Inhibit $CD8^+$ T cells via ROS, NO, ARG1; Induce tolerogenic T cells; Differentiate into tumor-associated neutrophils; Enhance tumor expansion/invasion via positive feedback loops; Correlate with poor prognosis. | [3, 74, 76, 77, 82, 86, 87, 89, 90] |
| Early-Stage MDSCs (e-MDSCs) | Human: $CD33^+$ HLA-$DR^-$ $Lineage^-$; Express HMOX1, FTL, BNIP3. | CXCL1/CXCL2–CXCR2, MIF-CXCR2; Glutamate-NMDA receptors (from GSCs); Itaconic acid blocks T-cell metabolism; Diminished in IDH-mutant GBM by 2-HG/hypermethylation. | Pseudopalisading regions (PAN) near metabolically adapted tumor cells; Decline in advanced GBM as they differentiate; Colocalize with GSCs in hypoxic rims. | Support stemness via VEGF, TGF-β; Suppress T cells via ARG1, IDO1; Amplify expansion via glutamine-derived α-ketoglutarate; Weaken T-cell metabolism; Reciprocate with tumor cells (e.g., CXCL1/2-CXCR2 loop). | [11, 75, 78–80, 83, 91–93] |

*Notes: MDSC subtypes exhibit sex-specific disparities (e.g., M-MDSCs intratumoral in males, PMN-MDSCs circulating in females) and shift with progression/IDH status. Recruitment and evasion mechanisms are niche-dependent, with hypoxia amplifying suppression. Therapeutic targets include CXCR2/MIF inhibitors to disrupt axes. Abbreviations: ARG1, arginase 1; CT, cellular tumor; GSC, glioma stem cell; IDO1, indoleamine 2,3-dioxygenase 1; LE, leading edge; MVP, microvascular proliferation; NF-κB, nuclear factor kappa B; NO, nitric oxide; PAN, pseudopalisades; PGE2, prostaglandin E2; ROS, reactive oxygen species; RT, radiotherapy

#### Therapeutic translation roadmap

**Targets by niche:** Hypoxic core—MIF-CXCR2/adenosine axis [9, 10, 56, 57]; perivascular—VEGF/ANGPT-TIE2 [45, 46]; edge—CCR2 blockade + cDC1 support [58, 59, 74, 81].

**Modalities:** Small-molecule STAT3/TGF-β inhibitors [30, 43, 60, 61], CSF1R/CCR2/CXCR2 antagonists [62, 74, 94], oncolytic or in situ DC priming [64, 65], and combination with checkpoint inhibitors [48, 66, 94].

**Trial design hints:** Spatial biomarkers/endpoints (e.g., imaging mass cytometry scores [9, 20, 95]; spatial transcriptomic signatures [9, 10, 67]).

**Key Takeaways:** MDSCs in GBM arise from bone marrow progenitors and adapt via tumor signals like MIF and CCL2, differentiating into *M*-, PMN-, and e-MDSC subtypes that mediate immunosuppression through ARG1, ROS, and PD-L1, with niche-specific functions driving resistance. Spatial analyses reveal subtype localization—core/hypoxic for M-MDSCs, edges for PMN-MDSCs—and sex/genetic influences, highlighting targeted disruptions of axes such as CXCR2 or STAT3 to reprogram the TME and enhance therapeutic efficacy.

## Dendritic cells: subtypes, spatial patterns, and functional implications

DCs occupy a pivotal position at the interface of innate and adaptive immunity, orchestrating responses that can counteract or facilitate GBM progression. Within this landscape, DCs exhibit remarkable heterogeneity, shaped by subtype diversity, molecular signaling, cellular interactions, and spatial positioning. This section explores DCs in GBM, integrating subtypes, differentiation pathways, functional transformations, and spatial distribution.

### Subtypes and functional evolution

Diverse DC subtypes in GBM include conventional DCs (cDCs), plasmacytoid DCs (pDCs), and monocyte-derived DCs (moDCs). cDCs subdivide into cDC1s and cDC2s. cDC1s cross-present tumor antigens to $CD8^+$ T cells via MHC-I, eliciting cytotoxic responses, and secrete proinflammatory cytokines to promote T-cell differentiation and NK-cell activation [4, 9, 37, 96]. cDC2s activate $CD4^+$ T cells through cytokines but often shift to immunosuppression in GBM TME [5, 82].

pDCs produce type I IFN-α via TLR7/9-IRF7 to enhance innate immunity [64, 97]. GBM factors such as TGF-β subvert them, upregulating PD-L1 and IL-10 to suppress T cells [98]. MoDCs emerge in late-stage GBM, secreting IL-10 and TGF-β to reinforce immunosuppression [99, 100]. Additional subsets include $CCR7^+$ migratory DCs and IL-1β/TNF-rich systemic inflammatory cDCs, indicating TME adaptations [5, 44].

DC differentiation originates from bone marrow myeloid progenitors, guided by cytokines: GM-CSF increases generation, IL-4 favors immature DCs, TNF-α promotes maturation. GBM disrupts this via IL-6, IL-10, TGF-β, reducing costimulatory molecules and MHC-II, impairing antigen presentation [65, 101]. These different functions (e.g., activation vs. suppression) are inferred primarily from gene expression (e.g., MHC-I and PD-L1 levels) in scRNA-seq, with spatial data later enhancing these by adding proximity-based insights, representing associations that require causal confirmation via mechanistic assays [4, 5, 37, 96]. The interplay between DC origins and their functional evolution is crucial. As we explore their spatial distribution, this heterogeneity acquires additional depth when viewed through the lens of TME architecture.

### Spatial distribution and microenvironmental influences

Spatial distribution of DCs in GBM profoundly influences function, revealed by spatial transcriptomics, imaging mass cytometry, and single-cell spatial transcriptomics. Each subtype occupies distinct niches, reflecting tumor's manipulation of immune responses. cDC1s predominate at invasive edges and T-cell-rich zones, forming activation hubs that promote anti-tumor immunity by cross-presenting antigens to $CD8^+$ T cells via MHC-I and recruiting effectors through CXCL9/10 chemokines, countering invasion [37, 38, 102]. Their colocalization likely reinforces antigen cross-presentation [9, 103].

cDC2s concentrate in tumor core and perivascular regions, where hypoxia drives their shift to immunosuppression, fostering tolerance near regulatory T cells and TAMs via PD-L1 and IL-10 expression, which supports tumor proliferation and angiogenesis [82, 104]. Hypoxic core activates HIF-1α, polarizing cDC2s toward suppressive phenotype, associated with vascular structures [105]. pDCs scatter near periphery and blood vessels, linked to CCL21–CCR7 signaling [98]. They exhibit dual potential: IFN-α secretion suggests early signaling, yet immunosuppressive markers limit efficacy [97]. MoDCs enrich in necrotic and hypoxic regions, expressing CD206, HMOX1, S100A8/A9, IL-10, TGF-β, revealing tolerogenic population sculpted by TME [100, 105]. SI-cDCs cluster in hypoxic/inflammatory niches, secreting IL-1β and TNF, tracing to peripheral monocytes [44].

This spatial segregation—cDC1s at frontlines, cDC2s/moDCs in suppressive core, pDCs as sentinels—underscores how GBM exploits topography to thwart immunity. Chemokine gradients and metabolic cues, such as *R*-2-hydroxyglutarate in IDH-mutant GBM, dictate patterns and inhibit DC maturation [105]. These spatial distributions, mapped from multimodal datasets of 5–12 human GBM samples integrated with mouse models, provide representative insights into DC compartmentalization, revealing activation gradients that are conserved across studies but influenced by tumor genetics such as IDH status. These patterns are consistent across GBM cases, as evidenced by multimodal analyses of patient cohorts revealing conserved activation gradients, although tumor genetics like IDH mutations introduce variability [5, 9, 44, 82, 105] (Table 3).

Such location-dependent functions like tolerance in the core are inferred from both gene expression (e.g., upregulated IL-10 under hypoxia) and spatial proximity (e.g., colocalization with Tregs and TAMs), where spatial transcriptomics and imaging support cellular conclusions by mapping microenvironmental influences, but these inferences are correlative, necessitating functional validation for causality [5, 9, 44, 82]. However, these mappings are limited by current technologies' resolution, which may average signals across cells, and their inability to capture live-cell dynamics, thus requiring integration with emerging tools for more precise GBM analyses [5, 9, 44].

This spatial narrative reveals a gradient of immune competence, with activation at edges yielding suppression inward. Understanding these offers therapeutic possibilities, altering DC positioning or countering cues to shift toward antitumor immunity.

### Signaling pathways and cellular interactions

Functional fate of DCs is governed by signaling and dialogs deftly by TME. cDC1s rely on STAT1–IRF8 axis, active at periphery, for antigen presentation and IL-12 secretion (experimentally validated as drivers of DC maturation in IRF8 knockout models) [4, 37, 106]. cDC2s influenced by STAT6–IRF4, under hypoxia promote PD-L1 (inferred from hypoxic expression patterns and validated in STAT6 inhibitor studies) [82]. TLR7/9-IRF7 in pDCs fuels IFN-α, yet TGF-β shifts to IL-10 (experimentally validated in TLR agonist and TGF-β blockade

**Table 3** Subsets of Dendritic cells (DCs) in glioblastoma: spatial localization and net effect on antitumor immunity

| Subset | Molecular Markers and Differentiation Pathways | Spatial Localization and Microenvironmental Influences | Net Effect on Antitumor Immunity and Functional Implications | Key References |
|---|---|---|---|---|
| Conventional DCs Type 1 (cDC1s) | Cross-presentation markers: MHC-I, IL-12; Driven by STAT1–IRF8 axis; Proinflammatory cytokines (e.g., CXCL9/10); From bone marrow progenitors via GM-CSF/IL-4/TNF-α. | Predominate at invasive edges (LE) and T-cell-rich zones; Form activation hubs; Colocalize with $CD8^+$ T cells; Influenced by peripheral chemokine gradients; Less affected by core hypoxia. | Generally antitumor: Cross-present antigens to $CD8^+$ T cells; Recruit CTLs via CXCL9/10; Promote T-cell differentiation and NK activation; Potential for immunotherapy enhancement (e.g., via NDV priming); Subverted in advanced GBM by TME cues. | [4, 9, 37, 38, 44, 96, 102, 103, 106] |
| Conventional DCs Type 2 (cDC2s) | $CD4^+$ T-cell activation markers: MHC-II, cytokines; Driven by STAT6–IRF4; Often shift to PD-L1/IL-10 in TME; Differentiation disrupted by IL-6/IL-10/TGF-β (reduced costimulatory molecules). | Concentrate in tumor core (CT) and perivascular regions (MVP); Near Tregs and TAMs; Characterized by hypoxia (HIF-1α polarization to suppressive states); Associated with vascular structures. | Dual, often immunosuppressive: Activate $CD4^+$ T cells initially but foster tolerance via PD-L1/IL-10; Interact with Tregs/TAMs through PD-L1-PD-1/IL-1β; Contribute to resistance; Net suppressive in hypoxic core. | [5, 9, 44, 82, 104, 105] |
| Plasmacytoid DCs (pDCs) | Type I IFN-α producers: TLR7/9-IRF7; Upregulate PD-L1/IL-10 under TGF-β; Dual potential; From progenitors, subverted by GBM factors (e.g., CCL21–CCR7 signaling). | Scatter near periphery (LE) and blood vessels (MVP); Linked to CCL21–CCR7; Influenced by peripheral blood recruitment; Exhibit sentinel-like distribution. | Dual: Enhance innate immunity via IFN-α (early activation of NK/T cells); But subverted to tolerance (PD-L1/IL-10 suppress T cells); Net immunosuppressive in GBM TME; Therapeutic restoration via TGF-β inhibition. | [4, 64, 97, 98, 105] |
| Monocyte-Derived DCs (moDCs) | Immunosuppressive markers: CD206, HMOX1, S100A8/A9, IL-10, TGF-β, IDO1/PD-L1; Driven by NF-κB/MAPK in hypoxia; Emerge late-stage from monocytes. | Enrich in necrotic/hypoxic regions (PAN); Trace to peripheral monocytes (SI-cDCs); Influenced by metabolic cues (*R*-2-HG in IDH-mutant, hypoxia); Colocalize with TAMs/Tregs. | Predominantly immunosuppressive: Secrete IL-10/TGF-β to reinforce tolerance; Block costimulatory expression; Impair antigen presentation; Net contribution to T-cell exhaustion and resistance. | [4, 44, 99, 100, 104, 105] |
| Migratory DCs (MigDCs) | $CCR7^+$ markers for migration; Express costimulatory molecules (e.g., CD80/86); Driven by CCL21–CCR7 signaling; From cDC precursors, adapted for antigen transport to lymph nodes. | Predominantly at tumor periphery (LE) and perivascular zones (MVP); Influenced by chemokine gradients (e.g., CCL21 from GBM cells); Colocalize with T cells; Facilitate migration to draining lymph nodes, but often impaired in GBM TME. | Potentially antitumor: Facilitate antigen presentation to T cells in lymphoid tissues; Promote T-cell priming and migration back to tumor; However, GBM-induced dysfunction (e.g., via IDH mutations or immunosuppressive signals) limits efficacy; Enhance DC vaccines by boosting migration. | [5, 44, 98] |
| Systemic Inflammatory cDCs (SI-cDCs) | IL-1β/TNF-rich inflammatory markers; Express proinflammatory cytokines (e.g., IL-1β, TNF-α); Trace to peripheral monocytes; Driven by systemic inflammation signals (e.g., TLR agonists). | Cluster in hypoxic/inflammatory niches (PAN/CT); Influenced by TME cytokines and monocyte infiltration; Colocalize with TAMs and Tregs; Reflect broader systemic immune activation but localized to tumor. | Dual with inflammatory bias: Secrete IL-1β/TNF to amplify inflammation and potentially activate T/NK cells; But in GBM, often contribute to chronic inflammation that supports tumor progression; Net effect immunosuppressive due to TME subversion; Targetable for reprogramming in immunotherapy. | [5, 44] |

*Notes: DC subsets show a spatial gradient of immune competence (activation at edges, suppression in core/hypoxic zones), modulated by TME cues like *R*-2-HG/hypoxia/IL-6/VEGF/CD47. Net effects are context-dependent, with opportunities for reprogramming (e.g., STAT3/TGF-β blockers). MigDCs ($CCR7^+$ migratory DCs) and SI-cDCs (IL-1β/TNF-rich systemic inflammatory cDCs) have been added as additional subsets, based on multiomics data indicating TME adaptations and their roles in migration/inflammation. Abbreviations: CTL, cytotoxic T lymphocyte; CT, cellular tumor; IDO1, indoleamine 2,3-dioxygenase 1; IRF, interferon regulatory factor; LE, leading edge; MHC, major histocompatibility complex; MVP, microvascular proliferation; NDV, Newcastle disease virus; NK, natural killer; PAN, pseudopalisades; SI-cDC, systemic inflammatory cDC; STAT, signal transducer and activator of transcription; TAM, tumor-associated macrophage; TME, tumor microenvironment; Treg, regulatory T cell

experiments) [97, 98]. MoDCs, driven by NF-κB/MAPK in hypoxic zones, upregulate IDO1/PD-L1 (inferred from spatial transcriptomics and validated in MAPK inhibitor assays) [99, 104].

These intersect cellular interactions. cDC1s engage CD8+ T cells via MHC-I/CD80/86, increasing cytotoxicity (experimentally validated in co-culture models). cDC2s/moDCs interact with Tregs/TAMs through PD-L1-PD-1/IL-1β, reinforcing suppression (inferred from spatial proximity data) [44, 82]. pDCs enhance NK via IFN-α but diminished under tumor influence [64]. Tumor cells deploy CD47 to evade phagocytosis (validated in CD47 blockade studies), secrete IL-6/VEGF to impair maturation (experimentally validated in cytokine neutralization assays) [101, 105]. These intersect TAM/MDSC suppression, highlighting DCs as key nodes.

TME amplifies via metabolic cues. *R*-2-HG/hypoxia stimulate DC development, IL-10/TGF-β block costimulatory expression [99, 105]. Therapeutic prospects: inhibiting TGF-β restores pDC function, STAT3 blockers counter IL-6, targeting CCL21–CCR7 reduces infiltration [97–99].

Integrating subtypes, spatial patterns, signaling, interactions positions DCs as victims and potential victors. Their transformation reflects tumor ingenuity but highlights intervention avenues. These spatial and functional insights from DCs, alongside TAMs and MDSCs, form

the basis for cross-compartmental synthesis and therapeutic translation in the following sections.

#### Therapeutic translation roadmap

**Targets by niche:** Hypoxic core—MIF-CXCR2/adenosine axis [9, 10, 56]; perivascular—VEGF/ANGPT-TIE2 [45, 46]; edge—CCR2 blockade + cDC1 support [58, 59, 64, 96, 107].

**Modalities:** Small-molecule STAT3/TGF-β inhibitors [30, 43, 60, 61], CSF1R/CCR2/CXCR2 antagonists [62], oncolytic or in situ DC priming [64, 65, 96, 108], and combination with checkpoint inhibitors [47, 66].

**Trial design hints:** Spatial biomarkers/endpoints (e.g., imaging mass cytometry scores [9, 20]; spatial transcriptomic signatures [9, 10, 67]).

**Key Takeaways:** DCs in GBM display subtype-specific plasticity, with edge-localized cDC1s enabling antigen presentation and core/hypoxic cDC2s/moDCs fostering immunosuppression through TME cues like HIF-1α and TGF-β. Integrated spatial analyses uncover signaling pathways and interactions that orchestrate immune evasion, positioning DCs as reprogrammable targets via modalities such as STAT3/TGF-β inhibitors or in situ priming to shift the balance toward antitumor immunity and overcome resistance.

## Myeloid cells in glioblastoma compartments: a spatially resolved view

Recent advances in single-cell transcriptomics, spatial transcriptomics, and multimodal imaging have delineated spatial distribution, subtypes, signaling pathways, and interactions of myeloid cells in GBM. Laser microdissection and RNA sequencing define four key compartments: LE, CT, PAN, MVP zones, each with unique profiles and roles [5, 9]. This section reviews myeloid contributions across these, informing therapeutic targets. This framework highlights adaptive versatility, beginning with LE where invasion initiates.

#### Leading edge: invasion and early immunosuppression

LE is GBM's infiltrative frontier. It supports matrix degradation, EMT, chemotaxis to drive invasion [9]. Myeloid cells promote dissemination. Specifically, microglia-derived TAMs at this frontier drive invasion by remodeling matrix and inducing early immunosuppression via adenosine production (CD39/CD73 pathway), dampening T-cell responses and facilitating tumor spread [9, 39]

Homeostatic microglia transition to tumor-associated microglia via TGF-β signaling (inferred from spatial expression and validated in TGF-β blockade models) [9]. MES-like cells intermingle with M2-like TAMs [5]. GPNMBhigh macrophages cluster, promoting MES states via EGFR and suppressing T cells. TAM-Mgs engage astrocyte-like tumor cells via WNT5A-FZD/CD146, fostering angiogenesis/migration (inferred from co-expression data) [38]. Microglia convert ATP to adenosine via CD39/CD73, suppressing T/NK (experimentally validated as immunosuppressive drivers in enzyme inhibition assays) [39]. Early MDSCs support stemness through CCL5–CCR1, CXCL8–CXCR1 and MIF-CXCR4 (experimentally validated in chemokine receptor knockouts) [11, 79, 109, 110]. PMN-MDSCs localize with EGFR+ tumor cells. They are recruited by TGFA/HBEGF and CXCL2/CXCL3. This suppresses CD8+ T-cells via ROS/IFN-γ/STAT1/NO (inferred from spatial patterns and validated in ROS scavengers and STAT1 models) [56, 79, 89, 90, 111]. P2RY12+ Mg-TAMs colocalize with CD8+ T-cells/DCs for antigen presentation [5]. cDC1s form activation hubs and cross-present via MHC-I/CXCL9/10 (experimentally validated in T-cell priming assays) [9]. This network primes invasion, suggesting targeting chemokine gradients (Fig. 4A).

This transitions to CT zone, where proliferative demands reshape myeloid contributions.

#### Cellular tumor zone: proliferation and vascular support

CT zone forms proliferative core, densely packed with dividing cells, moderate vascularity, minimal necrosis, supporting stem-like regeneration under normoxia [9]. Myeloid cells enhance proliferative signaling, establish perivascular immunosuppressive niches, promoting M2 polarization, inhibiting antigen presentation.

Monocyte-derived TAMs constitute ~85%, diversifying into SEPP1high, APOEhigh, RPL13high, CD83high/HLA-DRAhigh subtypes, recruited via CCL2–CCR2, clustering perivascularly [5, 9, 38, 45]. CEBPB+ subgroups secrete SPP1/CCL2 with M2 TAMs in niches, MES-like cells interact with MDMs via LGALS3–ITGB1, inducing M2 polarization. Lipid-rich LLMs express PD-L1high/CD39high in MES areas [36], hybrid neutrophils activate T cells via IFN, countered by mo-TAM signals.

Subtypes engage signaling for proliferation/vascularity: proangiogenic mo-TAMs via VEGF-VEGFR/ANGPT-TIE2, amplified by HIF1A (experimentally validated in angiogenesis assays and HIF inhibitors) [12, 112], SPP1–CD44 stabilizing tumors/suppressing immunity (inferred from ligand-receptor analysis and validated in CD44 knockouts) [36]. DCs vary: cDC2s foster tolerance near Tregs/TAMs; cDC1s engage CD8+ via MHC-I/CD80/86 (validated in co-culture); moDCs/Tregs via PD-L1-PD-1/IL-1β (inferred from spatial data) [44]. pDCs enhance NK via IFN-α but diminish (validated in IFN blockade) [64], tumor evade phagocytosis via CD47 (validated in anti-CD47 therapy models), impair DC via IL-6/VEGF (experimentally validated in neutralization studies) [101] (Fig. 4B).

Mo-TAMs as suppressors via IL-10/TGF-β/PD-L1, intersecting TAM/MDSC networks [5]. This includes

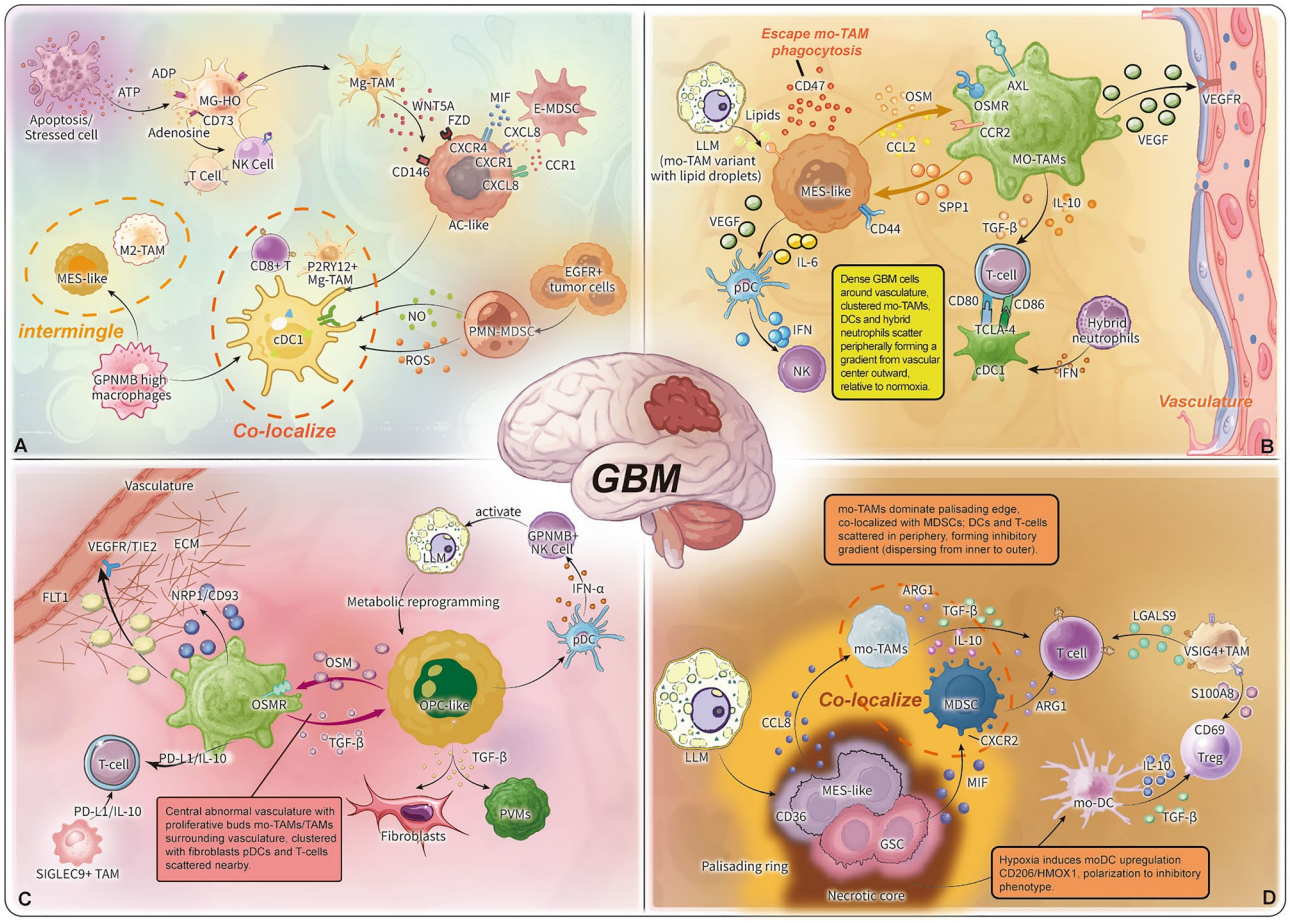


**Fig. 4** Spatially resolved signaling networks and metabolic adaptations of myeloid cells across glioblastoma compartments. This schematic delineates the distinct intercellular crosstalk and functional reprogramming of myeloid subsets within four defining niches. (**A**) Leading edge (LE): in the invasive periphery, stressed tumor cells release ATP/adenosine, activating microglia-derived TAMs (Mg-TAMs) via purinergic (CD73) and chemokine (CXCR4/CXCR8) axes. Despite the presence of cDc1s, effective immunity is subverted by PMN-MDSCs and GPNMB-high macrophages through NO/ROS secretion and the CD47-SIRPα "don't eat me" signal. (**B**) Cellular tumor (CT): the dense proliferative core is characterized by immune evasion, where tumor cells escape Mo-TAM phagocytosis via CD47/SIRPα. Lipid-laden Mo-TAM variants engage mesenchymal (MES)-like cells through OSMR/CCL2/SPP1 signaling, while perivascular neutrophils are modulated by VEGF/EGFR gradients to support tumor survival. (**C**) Pseudopalisading necrosis (PAN): hypoxic rims drive profound metabolic reprogramming, inducing lipid-laden (LLM) and perivascular (PVM) phenotypes in macrophages. A collaborative network involving Mo-TAMs, MDSCs, and Tregs orchestrates immune exclusion via ARG1/TGF-β/IL-10, protecting MES-like stemness under hypoxic stress. (**D**) Microvascular proliferation (MVP): aberrant vascular buds recruit Mo-TAM clusters via NRP1/VEGFR/FLT1 signaling to drive angiogenesis. Crosstalk with OPC-like cells and fibroblasts establishes a physical and immunologic barrier (TGF-β/PD-L1) that impedes T-cell infiltration and reinforces the vascular niche. Collectively, these zone-specific adaptations highlight therapeutic vulnerabilities, supporting the use of CD47 inhibitors, STAT3 blockers, or hypoxia modulators to dismantle compartment-specific resilience

adenosine hubs formed by $CD73^+$ tumor cells and $CD39^+$ TAMs, contributing to A2A-mediated T-cell suppression (as detailed in TAM spatial dynamics).

These proliferative and vascular interactions set the stage for the angiogenic dynamics in MVP zones, where myeloid-driven neovascularization further supports tumor growth.

### Microvascular proliferation zones: angiogenesis and perivascular niches

Microvascular zones feature aberrant vessels with endothelial hyperplasia, sustaining nutrients, correlating recurrence. Vascular chaos recruits myeloid to amplify neovascularization, establish immunosuppressive hubs, modulating endothelial interactions/matrix remodeling.

Proangiogenic TAMs cluster vessels [12]; mo-TAMs express FTL for adaptation, remodel ECM via NRP1/CD93. LLMs support metabolism/suppress via PD-L1high [36]. In recurrent GBM, PVMs/lytic cells aggregate with decorin-rich fibroblasts, pDCs scatter near vessels via CCL21–CCR7, secreting IFN-α but upregulating suppressors [105].

Subtypes drive angiogenesis signaling: VEGF-VEGFR/ANGPT-TIE2 amplified HIF1A (experimentally validated in endothelial co-culture and HIF knockdown) [12], CSF1R/PI3K-Akt/TGF-β (inferred from perivascular

patterns and validated in PI3K inhibitors) [5]. CD73+ tumor/CD39+ TAMs increase adenosine (validated in purinergic blockade) [39]; SIGLEC9+ inhibit T, overlapping hypoxic TAMs with VEGFA-FLT1/TNFRSF1B-GRN (inferred from multiomics) [10, 12, 35]. TAMs interact OPC-like via OSM-OSMR for stemness (experimentally validated in OSM neutralization) [10, 12, 35]. This symbiosis shields anti-angiogenics, suggesting combined vascular-myeloid targeting (Fig. 4C).

These vascular-driven dynamics contrast with the hypoxic adaptations observed in pseudopalisading zones.

#### Pseudopalisades: hypoxic adaptation and stemness protection

PAN encircle necrotic foci with migrating cells under hypoxia. Markers include HIF-1α, glycolytic enzymes and vascular permeability genes. Cells acquire stem-like phenotypes in IDH-wildtype GBM [79]. Hypoxic gradients prompt myeloid accumulation. This enhances tumor survival via immunosuppressive factors and supports stemness. It exacerbates vascular disruption and T-cell exhaustion.

Hypoxia-TAMs/mo-TAMs dominate rims [10, 45]. VSIG4+ S100A10+ TAMs inhibit T cells near necrotic areas (see TAM spatial details) [42]. HMOX1+ TAMs exhaust T cells via IL-10/JAK/STAT3 [43]. E-MDSCs colocalize with stem-like cells and respond to VEGF/TGF-β, while recruitment occurs by CXCL1/CXCL2–CXCR2 [79, 91–93]; MDSCs cluster GSCs via MIF [11, 113]. M-MDSCs radiate from necrosis via CCL5–CCR1/CXCL8–CXCR1/VCAN-CD44 [66, 79]. MoDCs enrich necrotic/hypoxic; SI-cDCs trace monocytes [44].

Distributions activate pathways that perpetuate hypoxia/suppression: TAMs use purinergic metabolism tied to EGFR/hypoxia [39], involving CD39/CD73 enzymatic steps and A2A-mediated T-cell suppression. They express ADM/BNIP3/CSTB for permeability (inferred from hypoxic expression and validated in gene knockdown) [45]. SIGLEC9+ mo-TAMs secrete IL-10/TGF-β near exhausted T (validated in cytokine assays) [35]. LLMs transfer lipids via CD36 to upregulate PD-L1 and downregulate MHC-II (experimentally validated in lipid uptake studies). CCL8 recruits TAMs to express CD206/ARG1 and trap CTLs (inferred from chemokine data). GSCs secrete MIF to activate MDSCs (ARG1+) via CXCR2 and shield from T attack (validated in CXCR2 antagonists) [11]. Hypoxic gradients weaken in IDH-mutant due hypermethylation/2-HG (validated in IDH-mutant xenografts) [79]. HIF inhibitors may disrupt these. This attenuation in IDH-mutant GBM reduces myeloid infiltration and immunosuppressive networks compared to IDH-wild-type, where enhanced chemokine signaling (e.g., CCL2–CCR2) drives greater MDSC and TAM accumulation in core/hypoxic zones, potentially explaining differences in disease aggressiveness and therapeutic responses [16–18]. (Fig. 4D).

Having examined individual myeloid types, we now integrate these observational data into a unified spatial view across GBM compartments, setting the stage for therapeutic implications.

**Key Takeaways:** Myeloid cells exhibit compartment-specific adaptations in GBM, driving invasion at LE through TGF-β/WNT5A signaling and early immunosuppression, proliferation in cellular cores via SPP1–CD44 and VEGF axes, angiogenesis in microvascular zones with CSF1R/PI3K pathways, and stemness protection in hypoxic PAN via MIF-CXCR2 and purinergic metabolism. Multiomics mapping reveals these niche-dependent interactions and immunosuppressive hubs, offering translational roadmaps for targeted interventions such as adenosine blockers or chemokine antagonists to reprogram the TME and surmount resistance.

## Integrative analysis: Cross-zone patterns and interactions

This synthesizes spatially resolved insights, bridging compartment-specific observations into cohesive framework elucidating myeloid dynamics. Integration highlights patterns of crosstalk/signaling convergence. Myeloid cells orchestrate immunosuppressive TME across zones, adapting local cues while sustaining global resilience. This perspective informs disrupting networks for immunotherapy/targeted interventions. Synthesis begins with cross-compartmental distribution. This integrative framework, synthesizing data from multiple human samples and models, underscores the representative nature of these spatial patterns while highlighting the need for causal validation through perturbations such as CRISPR-based editing in organoids [10, 45].

#### Cross-compartmental distribution and adaptation

Myeloid cells exhibit zone-specific enrichment correlating with TME gradients, with phenotypic shifts underscoring adaptability. Importantly, while spatial transcriptomics data in this review primarily demonstrate correlations between positioning and functions (e.g., hypoxia correlating with immunosuppressive TAM states), emerging evidence from functional perturbations (e.g., HIF1A inhibition) and genetic causal inference (e.g., Mendelian randomization linking myeloid immunophenotypes to GBM risk) supports causal roles for niche cues in driving these adaptations [10, 45, 55]. Nevertheless, these data are constrained by technological limitations, such as incomplete single-cell resolution in spatial platforms and challenges in longitudinal sampling, which may bias interpretations toward static associations in GBM [10, 45]. Future studies using spatial CRISPR

or organoid models are needed to definitively establish causation.

Microglia-derived TAMs predominate LE, transitioning homeostatic to activated for invasion; mo-TAMs dominate core/microvascular, diversifying proangiogenic/lipid-laden under normoxic/vascular cues [5, 9]. In PAN, hypoxia drives immunosuppressive convergence, upregulating HIF1A/ADM/ARG1 [10, 45]. MDSCs bias: PMN-MDSCs peripherally for ROS suppression, M-MDSCs/e-MDSCs centrally shielding stem-like via CXCL1/CXCL2–CXCR2 [11, 79]. DCs graded: cDC1s activating peripherally (MHC-I+/CXCL9/10+), tolerogenic core/hypoxic (PD-L1+/IL-10+) [44]; moDCs necrotic with CD206/HMOX1/S100A8/A9.

Patterns reveal continuum: peripheral surveillance to central suppression, modulated hypoxia/chemokines/metabolites [39]. Multiomics identified conserved programs differentially activated, highlighting plasticity as GBM progression hallmark [44]. VSIG4+ S100A10+ TAMs accumulate hypoxic cores, correlated poor prognosis/PD-1 nonresponsiveness [42]. This adaptability transitions to intercellular networks sustaining patterns.

This cross-zone framework reveals consistent spatial architectures across GBM cohorts, where myeloid adaptations follow conserved gradients, though patient-specific factors such as hypoxia levels and genetic alterations contribute to variability [10, 44, 45].

#### Key networks and myeloid–tumor crosstalk

Myeloid interactions form feedback loops amplifying support. LE, TAMs/E-MDSCs engage tumor via WNT5A-FZD/MIF-CXCR4 promoting EMT/stemness [11, 38]; GPNMB-EGFR enhancing MES/suppressing T. Infiltrating macrophages recruited CCL2–CCR2 interact GBM secreting VEGF for angiogenesis [5]. Centrally, mo-TAMs fuel proliferation OSM-OSMR/PROS1-AXL/SPP1–CD44; CEBPB+ polarize M2 via SPP1-αvβ1/AKT; MES deploy LGALS3–ITGB1/FAK-ERK-JUN evasion.

In PAN, crosstalk intensifies: MDSCs/GSCs via MIF-CXCR2, MDSCs secreting ARG1/VEGF/TGF-β protecting stem [11]; TAMs exhaust T via IL-10/JAK/STAT3/purinergic [43]. HMOX1+ TAMs release IL-10 mediating exhaustion [43]. Extend microvascular, proangiogenic TAMs interact endothelial VEGF-VEGFR/ANGPT-TIE2 [12]; recurrent niches PVMs/lytic with fibroblasts TGF-β. DCs intersect: cDC1s recruit CTLs CXCL9/10 peripherally [9]; moDCs suppress centrally PD-L1-PD-1 [44]. Hybrid neutrophils activate T via IFN, overridden hypoxic.

Networks self-reinforcing, myeloid as hubs: TAMs bridge invasion/angiogenesis, MDSCs sustain stemness/resistance, DCs modulate adaptive. Shared motifs chemokine axes/metabolic reprogramming, attenuated IDH-mutant due hypermethylation/2-HG [79]. For example, invasive edges MES-like intermingle M2 TAMs bolstering infiltration NF-κB/TNF-α.

This cross-zone integration of observational insights naturally leads to therapeutic strategies that target these interconnected networks.

**Key Takeaways:** Integrative spatial analyses reveal cross-compartmental myeloid adaptations in GBM, with peripheral surveillance yielding to central suppression through gradients of hypoxia, chemokines, and metabolites, underpinned by self-reinforcing networks like MIF-CXCR2 and SPP1–CD44 that sustain tumor stemness, angiogenesis, and immune evasion. This cohesive framework highlights causal roles for niche cues—validated by perturbations—while acknowledging technological limitations, guiding precision therapies such as axis-specific inhibitors to disrupt myeloid orchestration and enhance TME reprogramming.

## Therapeutic implications of spatially resolved myeloid heterogeneity in glioblastoma

The spatial heterogeneity of myeloid cells in GBM, as revealed by single-cell and spatial transcriptomics, offers a possible blueprint for niche-targeted therapies that address immunosuppressive networks and overcome resistance to conventional treatments [1, 10, 114]. This approach shifts from uniform immunomodulation, which has shown limited clinical success, to precision strategies that exploit compartment-specific vulnerabilities within the TME.

By mapping myeloid distributions, functional states, and interactions across GBM zones—such as the invasive LE, proliferative CT, hypoxic PAN, and MVP regions—these technologies convert descriptive insights into actionable interventions. For instance, selective inhibition of hypoxia-driven TAM reprogramming in PAN or blockade of perivascular MDSC recruitment in microvascular zones can disrupt protumoral networks, enhancing anti-tumor immunity and therapeutic efficacy [10, 45, 115]. Preclinical models demonstrate the feasibility of such disruptions using hypoxia-activated prodrugs or nanoparticle-based delivery systems that leverage niche-specific cues like pH gradients and vascular permeability, potentially repolarizing TAMs toward pro-inflammatory states and diminishing MDSC-mediated stemness support [2, 3, 49, 50].

Further, single-cell analyses underscore how hypoxic niches sequester and reprogram myeloid cells immunosuppressively, indicating that targeted alterations in recruitment and polarization could amplify immune responses [10].

#### Niche-specific therapeutic targets

Spatial transcriptomics reveals distinct myeloid adaptations across GBM compartments, informing

niche-specific targeting to dismantle immunosuppressive circuits.

**Leading Edge:** This infiltrative zone involves microglia-derived TAMs and PMN-MDSCs promoting invasion via WNT4-EMT and CD47-SIRPα evasion. Spatial insights here translate to therapies by identifying peripheral enrichment of surveillant microglia, enabling targeted delivery of CCL2–CCR2/MIF-CXCR4 inhibitors to block recruitment and enhance cDC1 function, directly disrupting invasion-supporting networks revealed by colocalization data. Target CCL2–CCR2/MIF-CXCR4 to block TAM/MDSC recruitment and stemness support, while enhancing cDC1 antigen presentation to boost adaptive immunity and curb dissemination [5, 49, 79, 116]. Metabolic inhibitors like cyclocreatine disrupt astrocyte-derived ATP/CKB fueling, drawing from neurodegenerative parallels to halt peripheral growth [51, 52].

**Cellular Tumor:** Proliferative core dominated by mo-TAMs and M-MDSCs sustains tumor via SPP1–CD44 proliferation and VEGF-VEGFR/ANGPT-TIE2 vascular support. These spatial patterns inform therapies by highlighting perivascular clustering, allowing selective inhibition of SPP1–CD44 or VEGF pathways to reprogram TAMs and overcome resistance, as guided by normoxic adaptation maps from spatial omics. Inhibit these pathways to reprogram TAMs, mitigate immunosuppression, and counter resistance; PI3K/AKT/mTOR inhibitors restore antitumor states in preclinical models, though pathway redundancy challenges monotherapy [5, 9, 50, 51, 60, 117].

**Pseudopalisades:** Hypoxic rim features e-MDSCs and PD-L1$^+$ TAMs correlating with trapping of T cells via IL-10/ARG1/adenosine (purinergic/STAT3). Spatial transcriptomics translates to targeted approaches by delineating hypoxic gradients and colocalizations, facilitating the design of MIF-CXCR2/HIF1A inhibitors that specifically address stemness protection in this niche, transforming correlative maps into causal disruption strategies. Targeting cells in hypoxic niches is feasible using agents like adrenomedullin antagonists or hypoxia-inducible factor inhibitors, which have shown in orthotopic models to normalize vasculature, reduce TAM accumulation, and shift myeloid functions toward anti-tumor activity by decreasing immunosuppressive cytokine secretion and enhancing phagocytic capacity [118]. Additional preclinical studies demonstrate that inhibiting creatine metabolism in myeloid cells within hypoxic niches blunts tumor growth by disrupting myeloid-to-tumor metabolic support, further supporting feasibility and potential to reprogram immunosuppressive myeloid functions. In particular, monocyte-derived TAMs (Mo-TAMs) in hypoxic niches are attracted and reprogrammed via adrenomedullin, and disrupting this could normalize vasculature while shifting Mo-TAM functions from immunosuppressive to anti-tumor, reducing cytokine secretion like IL-10 [119]. M-MDSCs secrete creatine in hypoxic niches to fuel GBM progression; disrupting this via Ckb knockout reduces M-MDSC metabolic support, impairing their protumoral functions and enhancing anti-tumor immunity [57]. Early MDSCs (E-MDSCs) adapt to hypoxia by upregulating metabolic pathways; targeting these disrupts E-MDSC accumulation and stemness support, while exosome inhibition reduces MDSC proliferation via miR-1246, reversing T-cell suppression [120]. Disrupting the MIF-CXCR2/HIF1A/adenosine axes possibly reduces stemness protection and exhaustion; HDAC inhibitors target bevacizumab resistance through neurodegenerative-enriched pathways (e.g., Alzheimer's genes), despite hypoxia-driven drug efflux [11, 46–48, 53, 54, 79]. Targeting these correlated pathways (e.g., HIF1A inhibitors) may disrupt inferred causal mechanisms, though clinical trials should validate causality, as spatial data primarily show associations.

**Microvascular Proliferation**: Vascular niches cluster mo-TAMs for angiogenesis via VEGF/ANGPT-TIE2/CSF1R. Insights from spatial profiling enable therapies by revealing vascular-specific myeloid hubs, supporting combined blockade of VEGF/CSF1R to inhibit angiogenesis and infiltration, with nanoparticle delivery exploiting these architectural features for enhanced specificity. Block these to inhibit proangiogenic functions and MDSC infiltration, addressing exosome-mediated resistance; nanoparticle CDK inhibitors enhance delivery, balancing normalization to avoid hypoxia escalation [5, 12, 45, 61, 62, 67, 117].

#### Emerging therapeutic modalities

Therapeutic modalities extend these niche-directed approaches, with small-molecule inhibitors such as STAT3 or TGF-β blockers facilitating the repolarization of immunosuppressive TAMs and MDSCs toward anti-tumor states [43, 98]. Building on spatial insights, these modalities translate to precision by enabling compartment-selective repolarization, as informed by niche-specific expression profiles. Such interventions could feasibly disrupt spatial organization by altering myeloid migration and polarization, potentially leading to reduced immunosuppression and enhanced anti-tumor immunity, though challenges like off-target effects on non-hypoxic regions must be addressed [63]. For instance, HIF-1α in TAMs drives immunosuppressive polarization via LGMN; targeting this axis reprograms TAMs (e.g., microglia-derived and monocyte-derived) to activate NF-κB/STAT1, reducing IL-10/TGF-β secretion and enhancing T-cell activation [121]. Receptor antagonists targeting CSF1R, CCR2, or CXCR2 provide complementary mechanisms to deplete or reprogram myeloid cells,

leveraging their spatial dependencies for selective efficacy [5, 79, 81]. More advanced interventions, including oncolytic viruses for in situ dendritic cell priming, chimeric antigen receptor (CAR)-macrophage therapies for TAM reprogramming, and nanoparticle-based delivery systems, enable precise niche modulation, overcoming barriers like the blood-brain interface [46, 47, 58]. Combinations with checkpoint inhibitors, such as anti-PD-1, amplify these effects by synergizing with reprogrammed myeloid cells to reinvigorate T-cell responses [39, 62, 122]. Ongoing trials underscore the value of rational combinations, though interpatient heterogeneity necessitates biomarkers for optimal sequencing [47].

### Clinical trial design considerations

For trial design, incorporating spatial biomarkers—such as imaging mass cytometry or transcriptomic signatures—allows real-time monitoring of niche-specific responses, exemplified by TAM reprogramming in hypoxic zones, to refine predictive models and outcomes [9, 42, 49]. These designs directly stem from spatial insights, translating heterogeneous maps into stratified protocols that evaluate compartment-targeted efficacy. Endpoints should encompass compartment-specific metrics, including myeloid infiltration shifts assessed via apparent diffusion coefficient imaging or single-cell profiling, to rigorously evaluate targeted therapies [47, 54]. Patient stratification based on IDH status or sex-linked MDSC patterns further tailors interventions, ensuring alignment with individual TME architectures [67, 79, 81]. Emerging strategies, such as RNA-based therapies and exosome modulation, warrant inclusion in adaptive trials to address therapeutic resistance [59]. Critically, integrating patient-derived models will bridge preclinical insights to clinical efficacy, accelerating the path to durable responses [46].

**Key Takeaways:** Spatial omics unveils myeloid heterogeneity as a blueprint for niche-targeted GBM therapies, with compartment-specific interventions—such as CCL2–CCR2 blockade at edges, HIF1A/STAT3 inhibition in hypoxic rims, and VEGF/CSF1R antagonists in vascular zones—disrupting immunosuppressive networks and resistance mechanisms. Emerging modalities like oncolytic priming and nanoparticle delivery, combined with spatial biomarkers in adaptive trials, promise to reprogram the TME, stratify patients by genetics/sex, and enhance checkpoint synergy for improved clinical outcomes.

## Conclusion

In this review, we synthesize spatial transcriptomics to elucidate roles of myeloid cells—TAMs, MDSCs, DCs—within heterogeneous GBM landscape. Review illuminates them as dynamic TME orchestrators, functions tied spatial distribution. Invasive front, TAMs promote expansion; hypoxic core, synergize MDSCs for immunosuppressive/stemness niche. DCs display graded competence, diminishing periphery inward, reframing potential. Spatially resolved perspective redefines heterogeneity as navigable map for intervention. Findings inspire avenues: disrupting TAM-MDSC axis hypoxic zones, amplifying DC immunogenicity periphery, leveraging myeloid signatures biomarkers tailored treatments. Critically, these spatial insights translate into targeted therapies by providing a blueprint for niche-specific modulation, where compartment-resolved data guides the selection of inhibitors, delivery systems, and biomarkers to overcome GBM resilience in a precision manner. By clarifying that spatial data supports molecular conclusions through integrated gene expression and proximity analyses, this review underscores that these are primarily correlations, with the need for functional validation to transition to causal therapies. Revelations shift paradigm uniform targeting to spatially informed strategies, heralding personalized oncology. Challenges remain: myeloid adaptability, TME complexity necessitating advanced tools precise intervention, including the current limitations of spatial and molecular technologies—such as low subcellular resolution, difficulties in data deconvolution, and inability to capture real-time cellular dynamics—which underscore the need for next-generation platforms to fully unravel GBM heterogeneity. We urge embracing spatial paradigm, integrating disciplines pioneer technologies like niche-targeted delivery/in situ reprogramming. Longitudinal studies tracking evolution ensure durability. Through this, deepened GBM immunological architecture, laid foundation conquest, converting complexity strategic advantage. Journey concludes empowered vision, transforming complexity conquerable terrain spatial wisdom, emphasizing clinical trials validating targets.

**Abbreviation**

| | |
|---|---|
| ADM | Adrenomedullin |
| APOE | Apolipoprotein E |
| ARG1 | Arginase 1 |
| BBB | Blood-Brain Barrier |
| BNIP3 | BCL2/Adenovirus E1B 19kDa Interacting Protein 3 |
| CCL | C-C Motif Chemokine Ligand (e.g., CCL2, CCL8) |
| CCR | C-C Motif Chemokine Receptor (e.g., CCR2) |
| cDC | Conventional Dendritic Cell (e.g., cDC1, cDC2) |
| CD | Cluster of Differentiation (e.g., CD11b, CD14, CD39, CD73, CD206) |
| CT | Cellular Tumor |
| CTL | Cytotoxic T Lymphocyte |
| CXCL | C-X-C Motif Chemokine Ligand (e.g., CXCL1, CXCL2, CXCL8) |
| CXCR | C-X-C Motif Chemokine Receptor (e.g., CXCR2, CXCR4) |
| DC | Dendritic Cell |
| e-MDSC | Early-Stage Myeloid-Derived Suppressor Cell |
| EGFR | Epidermal Growth Factor Receptor |
| EMT | Epithelial-Mesenchymal Transition |
| FTL | Ferritin Light Chain |
| GBM | Glioblastoma |

| | |
|---|---|
| GPNMB | Glycoprotein Non-Metastatic Melanoma Protein B |
| GSC | Glioma Stem Cell |
| HIF1A/HIF-1α | Hypoxia-Inducible Factor 1 Alpha |
| HLA-DR | Human Leukocyte Antigen-DR |
| HMOX1 | Heme Oxygenase 1 |
| IDH | Isocitrate Dehydrogenase |
| IDO1 | Indoleamine 2,3-Dioxygenase 1 |
| IFN | Interferon (e.g., IFN-α, IFN-γ) |
| IHC | Immunohistochemistry |
| IL | Interleukin (e.g., IL-1β, IL-6, IL-10) |
| iNOS | Inducible Nitric Oxide Synthase |
| IRF | Interferon Regulatory Factor (e.g., IRF7, IRF8) |
| JAK | Janus Kinase |
| LE | Leading Edge |
| LLM | Lipid-Laden Macrophage/Microglia |
| LOX-1 | Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 |
| M-MDSC | Monocytic Myeloid-Derived Suppressor Cell |
| MDSC | Myeloid-Derived Suppressor Cell |
| MES | Mesenchymal |
| MHC | Major Histocompatibility Complex (e.g., MHC-I, MHC-II) |
| MIF | Macrophage Migration Inhibitory Factor |
| moDC | Monocyte-Derived Dendritic Cell |
| Mo-TAM | Monocyte-Derived Tumor-Associated Macrophage |
| Mg-TAM | Microglia-Derived Tumor-Associated Macrophage |
| MVP | Microvascular Proliferation |
| NF-κB | Nuclear Factor Kappa B |
| NK | Natural Killer (Cell) |
| NO | Nitric Oxide |
| OPC | Oligodendrocyte Precursor Cell |
| PAN | Pseudopalisades |
| PD-L1 | Programmed Death-Ligand 1 |
| pDC | Plasmacytoid Dendritic Cell |
| PGE2 | Prostaglandin E2 |
| PI3K | Phosphoinositide 3-Kinase |
| PMN-MDSC | Polymorphonuclear Myeloid-Derived Suppressor Cell |
| PVM | Perivascular Macrophage |
| ROS | Reactive Oxygen Species |
| S100A8/A9 | S100 Calcium-Binding Protein A8/A9 |
| scRNA-seq | Single-Cell RNA Sequencing |
| SIGLEC9 | Sialic Acid-Binding Ig-Like Lectin 9 |
| SPP1 | Secreted Phosphoprotein 1 (Osteopontin) |
| STAT | Signal Transducer and Activator of Transcription (e.g., STAT1, STAT3) |
| TAM | Tumor-Associated Macrophage |
| TGF-β | Transforming Growth Factor Beta |
| TLR | Toll-Like Receptor (e.g., TLR7/9) |
| TME | Tumor Microenvironment |
| TNF-α | Tumor Necrosis Factor Alpha |
| Treg | Regulatory T Cell |
| VEGF | Vascular Endothelial Growth Factor |
| VSIG4 | V-Set and Immunoglobulin Domain-Containing 4 |

**Acknowledgements**
Not applicable.

**Author contributions**
YC, WZ, and MX performed the literature review, data interpretation, and figure preparation, drafted the manuscript, and contributed equally to the conceptualization and writing. XRZ, FD, and JD supervised the project, provided critical revisions, and finalized the manuscript. All authors read and approved the final manuscript.

**Funding**
This work was funded by the National Natural Science Foundation of China (No. 82203472, 82503692), Natural Science Foundation of Shandong Province (No. ZR2023MH202, ZR2024QH042, ZR2025MS1404, ZR2025MS1307, ZR2022QH231), Key Scientific and Technological Projects in Henan Province (No.252102311181), and 2023 Youth Talent Support Project of Shandong Medical Association (2023_LC_0021).

**Data availability**
Not applicable. This review article does not involve the generation or analysis of new datasets. All data discussed are derived from previously published studies cited in the reference list.

## Declarations

**Ethics approval and consent to participate**
Not applicable. This manuscript is a review article and does not report on or involve the use of any animal or human data or tissue.

**Consent for publication**
Not applicable. This manuscript does not contain data from any individual person.

**Competing interests**
All authors declare no financial or non-financial competing interests.

**Author details**
[1]Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China

Received: 29 November 2025 / Accepted: 8 February 2026
Published online: 21 February 2026

**References**

1. Müller S, et al. Single-cell profiling of human gliomas reveals macrophage ontogeny as a basis for regional differences in macrophage activation in the tumor microenvironment. Genome Biol. 2017;18:234. https://doi.org/10.1186/s13059-017-1362-4.
2. D B, Jd L. Cancer stem cell-immune cell crosstalk in tumour progression - PubMed. Nat Rev Cancer. 2021, Aug;21. https://doi.org/10.1038/s41568-021-00366-w.
3. S L, J C-C, E H, Ap C, Ss M. New insights into the multifaceted Role of myeloid-derived suppressor cells (MDSCs) in high-grade gliomas: from metabolic reprograming, immunosuppression, and therapeutic resistance to current strategies for targeting MDSCs - PubMed. Cells. 10. 04/14/2021https://doi.org/10.3390/cells10040893.
4. J V, C S-F, Cm S. Dendritic cells in the tumor microenvironment: prognostic and theranostic impact - PubMed. Semin Immunol. 2020 Apr;48. https://doi.org/10.1016/j.smim.2020.101410.
5. Pombo Antunes AR, et al. Single-cell profiling of myeloid cells in glioblastoma across species and disease stage reveals macrophage competition and specialization. Nat Neurosci. 2021;24:595–610. https://doi.org/10.1038/s41593-020-00789-y.
6. Ye Z, et al. Phenotypic plasticity of myeloid cells in glioblastoma development, progression, and therapeutics. Oncogene. 2021;40:6059–70. https://doi.org/10.1038/s41388-021-02010-1.
7. Bl M, et al. Impact of epigenetic reprogramming on antitumor immune responses in glioma - PubMed. J Clin Investigation. 133. 01/17/2023. https://doi.org/10.1172/JCI163450.
8. M SP, et al. Myeloid-derived suppressor cells (MDSCs) in brain cancer: challenges and therapeutic strategies - PubMed. Inflammopharmacology. 2021 Dec;29. https://doi.org/10.1007/s10787-021-00878-9.
9. Haley MJ, et al. Hypoxia coordinates the spatial landscape of myeloid cells within glioblastoma to affect survival. Sci Adv. 2024;10:eadj3301. https://doi.org/10.1126/sciadv.adj3301.
10. A S, et al. Hypoxic niches attract and sequester tumor-associated macrophages and cytotoxic T cells and reprogram them for immunosuppression - PubMed. Immunity. 56. 08/8/2023. https://doi.org/10.1016/j.immuni.2023.06.017.
11. Cao L, Lu X, Wang X, Wu H, Miao X. From single-cell to spatial transcriptomics: decoding the glioma stem cell niche and its clinical implications. Front Immunol. 2024;15:1475235. https://doi.org/10.3389/fimmu.2024.1475235.
12. Motevasseli M, et al. Distinct tumor-TAM interactions in IDH-stratified glioma microenvironments unveiled by single-cell and spatial transcriptomics. Acta Neuropathol Commun. 2024;12:133. https://doi.org/10.1186/s40478-024-01837-5.

13. Vm R, et al. Spatially resolved multi-omics deciphers bidirectional tumor-host interdependence in glioblastoma - PubMed. Cancer Cell. 40. 06/13/2022. https://doi.org/10.1016/j.ccell.2022.05.009.
14. S K, J Y, B L, X F. Causal Association between immune cell traits and risk of multiple malignant and nonmalignant CNS Diseases: a Mendelian randomization and single-cell transcriptomic analysis - PubMed. Brain Behav. 2025, Aug;15. https://doi.org/10.1002/brb3.70632.
15. Db B, et al. Quantifying the effect of experimental perturbations at single-cell resolution - PubMed. Nat Biotechnol. 2021 May;39. https://doi.org/10.1038/s41587-020-00803-5.
16. Ma IG, Á L-J, A LA, I A-I, F G-G. A quantitative digital analysis of tissue immune components reveals an immunosuppressive and anergic immune response with relevant prognostic significance in glioblastoma - PubMed. Biomedicines. 10. 07/21/2022. https://doi.org/10.3390/biomedicines10071753.
17. M T, et al. A review of emerging immunotherapeutic strategies for IDH-Mutant glioma - PubMed. Cancers. 17. 06/27/2025. https://doi.org/10.3390/cancers17132178.
18. Ep G, et al. Mutant IDH Modulates Suppressive Myeloid Populations in Malignant Glioma - PubMed. Clin Cancer Res: Off J Am Assoc Cancer Res. 30. 09/13/2024. https://doi.org/10.1158/1078-0432.CCR-24-1056.
19. S P, et al. Diverse facets of MDSC in different phases of chronic HBV infection: impact on HBV-specific T-cell response and homing - PubMed. Hepatol (Baltim, Md.). 2022 Sep;76. https://doi.org/10.1002/hep.32331.
20. L K, et al. A structured tumor-immune microenvironment in triple negative breast cancer revealed by multiplexed ion beam imaging - PubMed. Cell. 174. 09/6/2018. https://doi.org/10.1016/j.cell.2018.08.039.
21. G M, V LC, M G, G G, S C. Artificial intelligence-driven multi-omics approaches in glioblastoma - PubMed. Int J Mol Sci. 26. 09/25/2025. https://doi.org/10.3390/ijms26199362.
22. Z C, et al. Cellular and molecular identity of tumor-associated macrophages in glioblastoma - PubMed. Cancer Res. 77. 05/1/2017. https://doi.org/10.1158/0008-5472.CAN-16-2310.
23. S B, Ka H, N R, Ss G, Aj T. Single-cell analysis reveals diversity of tumor-associated macrophages and their interactions with T lymphocytes in glioblastoma - PubMed. Sci Rep. 13. 11/27/2023. https://doi.org/10.1038/s41598-023-48116-2.
24. X L, W G, X L, M W. New insights into monocyte-derived macrophages in glioblastoma - PubMed. Res (Wash, D.C. (8). 08/12/2025. https://doi.org/10.34133/research.0836.
25. Me C, et al. Tumor progression is independent of tumor-associated macrophages in cell lineage-based mouse models of glioblastoma - PubMed. Proceedings of the National Academy of Sciences of the United States of America, 120. 04/18/2023. https://doi.org/10.1073/pnas.2222084120.
26. F K, et al. Interrogation of the microenvironmental landscape in brain tumors reveals disease-specific alterations of immune cells - PubMed. Cell. 2020;181. https://doi.org/10.1016/j.cell.2020.05.007.
27. N O, et al. Single-cell RNA sequencing reveals functional heterogeneity of glioma-associated brain macrophages - PubMed. Nat Commun. 2021;12. https://doi.org/10.1038/s41467-021-21407-w.
28. Y G, D C, Q J, H X, J Z. Mechanisms underlying the Role of myeloid-derived suppressor cells in clinical Diseases: good or bad - PubMed. Immune Network. 21. 05/26/2021. https://doi.org/10.4110/in.2021.21.e21.
29. X G, et al. Immunosuppressive effects of hypoxia-induced glioma exosomes through myeloid-derived suppressor cells via the miR-10a/Rora and miR-21/Pten pathways - PubMed. Oncogene. 2018, Aug;37. https://doi.org/10.1038/s41388-018-0261-9.
30. F K, et al. Macrophages and microglia in glioblastoma: heterogeneity, plasticity, and therapy - PubMed. J Clin Investigation. 133. 01/3/2023. https://doi.org/10.1172/JCI163446.
31. Hattermann K, et al. Chemokine expression profile of freshly isolated human glioblastoma-associated macrophages/microglia. Oncol Rep. 2014;32:270–76. https://doi.org/10.3892/or.2014.3214.
32. X G, R S, H P. Tumor-derived small extracellular vesicles: potential roles and mechanism in glioma - PubMed. J Nanobiotechnol. 20. 08/23/2022. https://doi.org/10.1186/s12951-022-01584-6.
33. R S, et al. Mapping microglia states in the human brain through the integration of high-dimensional techniques - PubMed. Nat Neurosci. 2019 Dec;22. https://doi.org/10.1038/s41593-019-0532-y.
34. S G, et al. Radiation-induced circulating myeloid-derived suppressor cells induce systemic lymphopenia after chemoradiotherapy in patients with glioblastoma - PubMed. Sci Transl Med. 15. 01/25/2023. https://doi.org/10.1126/scitranslmed.abn6758.
35. Mei Y, et al. Siglec-9 acts as an immune-checkpoint molecule on macrophages in glioblastoma, restricting T-cell priming and immunotherapy response. Nat Cancer. 2023;4:1273–91. https://doi.org/10.1038/s43018-023-00598-9.
36. L P, F Z, P C. Lipid-laden macrophages recycle myelin to feed glioblastoma - PubMed. Cancer Res. 2024;84. https://doi.org/10.1158/0008-5472.CAN-24-3362.
37. S R, et al. Single-cell RNA sequencing reveals immunosuppressive myeloid cell diversity during malignant progression in a murine model of glioma - PubMed. Cell Rep. 2023;42. https://doi.org/10.1016/j.celrep.2023.112197.
38. Ruiz-Moreno C, et al. Harmonized single-cell landscape, intercellular crosstalk and tumor architecture of glioblastoma. bioRxiv. 2022;2022:2008.2027.505439. https://doi.org/10.1101/2022.08.27.505439.
39. Coy S, et al. Single cell spatial analysis reveals the topology of immunomodulatory purinergic signaling in glioblastoma. Nat Commun. 2022;13:1(13):2022–08–16. https://doi.org/10.1038/s41467-022-32430-w.
40. K B, et al. Distinct spatiotemporal features of microglia and monocyte-derived macrophages in glioma - PubMed. Eur J Immunol. 2023 Apr;53. https://doi.org/10.1002/eji.202250161.
41. S M, Mhh S, U S. The glioma immune landscape: a Double-edged sword for treatment regimens - PubMed. Cancers. 15. 03/28/2023. https://doi.org/10.3390/cancers15072024.
42. Z L, et al. Single-cell and spatial analyses reveal the effect of VSIG4+S100A10+TAMs on the immunosuppression of glioblastoma and anti-PD-1 immunotherapy - PubMed. Int J Biol Macromolecules. 2025 May;308. https://doi.org/10.1016/j.ijbiomac.2025.142415.
43. Ravi VM, et al. T-cell dysfunction in the glioblastoma microenvironment is mediated by myeloid cells releasing interleukin-10. Nat Commun. 2022;13:925. https://doi.org/10.1038/s41467-022-28523-1.
44. Miller TE, et al. Programs, origins and immunomodulatory functions of myeloid cells in glioma. Nature. 2025;640(8060):640. 2025-02-26. https://doi.org/10.1038/s41586-025-08633-8.
45. Wang W, et al. Identification of hypoxic macrophages in glioblastoma with therapeutic potential for vasculature normalization. Cancer Cell. 2024;42:815–32.e812. https://doi.org/10.1016/j.ccell.2024.03.013.
46. Tang J, Karbhari N, Campian JL. Therapeutic targets in glioblastoma: molecular pathways, emerging strategies, and future directions. Cells. 2025 Mar, 26;14. https://doi.org/10.3390/cells14070494.
47. Jain KK. A critical overview of targeted therapies for glioblastoma. Front Oncol. 2018 Oct 15;8. https://doi.org/10.3389/fonc.2018.00419.
48. E A, et al. Tumor microenvironment and glioblastoma cell interplay as promoters of therapeutic resistance - PubMed. Biology. 12. 05/18/2023. https://doi.org/10.3390/biology12050736.
49. Dk T, Lp P, S B, K B. Insights into the glioblastoma tumor microenvironment: current and emerging therapeutic approaches - PubMed. Front Pharmacol. 15. 03/8/2024. https://doi.org/10.3389/fphar.2024.1355242.
50. Aj Y, S R. Molecular targets for combined therapeutic strategies to limit glioblastoma cell migration and invasion - PubMed. Front Pharmacol. 11. 03/27/2020. https://doi.org/10.3389/fphar.2020.00358.
51. G Y, et al. Glioblastoma exploits ATP from leading-edge astrocytes to fuel its infiltrative growth revealed by spatially resolved chimeric analysis - PubMed. Sci Adv. 11. 09/26/2025. https://doi.org/10.1126/sciadv.adv5673.
52. Ai CB, et al. Metabolic reprogramming in glioblastoma multiforme: a review of pathways and therapeutic targets - PubMed. Cells. 13. 09/19/2024. https://doi.org/10.3390/cells13181574.
53. Ayuso JM, et al. Glioblastoma on a microfluidic chip: generating pseudopalisades and enhancing aggressiveness through blood vessel obstruction events. Neuro-Oncology. 2017/04/01;19. https://doi.org/10.1093/neuonc/now230.
54. Kim Y, et al. Translational mRNA profiling analysis of pseudopalisading cells in bevacizumab resistance of GBM. Adv Ther. 2023/11/01;6. https://doi.org/10.1002/adtp.202300148.
55. M H, Y L, J P, Y C. Causal effects of immune cells in glioblastoma: a Bayesian Mendelian randomization study - PubMed. Front Neurol. 15. 04/29/2024. https://doi.org/10.3389/fneur.2024.1375723.
56. Tj A, et al. Glioblastoma myeloid-derived suppressor cell subsets express differential macrophage migration Inhibitory Factor receptor profiles that can Be targeted to reduce immune suppression - PubMed. Front Immunol. 11. 06/18/2020. https://doi.org/10.3389/fimmu.2020.01191.
57. A R, et al. Myeloid cell-derived creatine in the hypoxic niche promotes glioblastoma growth - PubMed. Cell Metab. 36. 01/2/2024. https://doi.org/10.1016/j.cmet.2023.11.013.

58. Schupper AJ, Hadjipanayis CG. Novel approaches to targeting gliomas at the leading/cutting edge. J Neurosurg. 2023 Feb 24;139. https://doi.org/10.3171/2023.1.JNS221798.
59. R S, M D, H Z, X L, B H. Tumor niches: perspectives for targeted therapies in glioblastoma - PubMed. Antioxid Redox Signaling. 2023 Nov;39. https://doi.org/10.1089/ars.2022.0187.
60. H L, et al. Therapeutic strategies of glioblastoma (GBM): the current advances in the molecular targets and bioactive small molecule compounds - PubMed. Acta Pharmaceutica Sin. B. 2022 Apr;12. https://doi.org/10.1016/j.apsb.2021.12.019.
61. A T, et al. Glioblastoma: current status, emerging targets, and Recent advances - PubMed. J Med Chem. 65. 07/14/2022. https://doi.org/10.1021/acs.jmedchem.1c01946.
62. Yy X, P G, Y S, Yr D. Development of targeted therapies in treatment of glioblastoma - PubMed. Cancer Biol Med. 2015 Sep;12. https://doi.org/10.7497/j.issn.2095-3941.2015.0020.
63. W G, et al. Targeting mesenchymal monocyte-derived macrophages to enhance the sensitivity of glioblastoma to temozolomide by inhibiting TNF/CELSR2/p65/Kla-HDAC1/EPAS1 axis - PubMed. J Adv Res. 05/13/2025. https://doi.org/10.1016/j.jare.2025.05.032.
64. Sk W, et al. Dendritic cells in cancer immunology and immunotherapy - PubMed. Nat Rev. Immunol. 2020, Jan;20. https://doi.org/10.1038/s41577-019-0210-z.
65. J Z, et al. Immunostimulant hydrogel for the inhibition of malignant glioma relapse post-resection - PubMed. Nat Nanotechnol. 2021 May;16. https://doi.org/10.1038/s41565-020-00843-7.
66. Ki L, et al. Bavituximab decreases immunosuppressive myeloid-derived suppressor cells in newly diagnosed glioblastoma patients - PubMed. Clin Cancer Res: Off J Am Assoc Cancer Res. 2023;29. https://doi.org/10.1158/1078-0432.CCR-23-0203.
67. Pandey S, et al. Frontiers in glioblastoma therapy: novel therapeutics, molecular pathways, and future clinical perspectives. Hum Gene. 2026/02/01;47. https://doi.org/10.1016/j.humgen.2025.201507.
68. N DI, S M, S P. Altered metabolism in glioblastoma: myeloid-derived suppressor cell (MDSC) fitness and tumor-infiltrating Lymphocyte (TIL) dysfunction - PubMed. Int J Mol Sci. 22. 04/24/2021. https://doi.org/10.3390/ijms22094460.
69. Al C, et al. CCL2 produced by the glioma microenvironment is essential for the recruitment of regulatory T cells and myeloid-derived suppressor cells - PubMed. Cancer Res. 2016;76. https://doi.org/10.1158/0008-5472.CAN-16-0144.
70. D G, O R, MC A-G, F P, C P-G-S. Like cells, metabolic strategy to kill a challenging target - PubMed. Front Oncol. 9. 03/6/2019. https://doi.org/10.3389/fonc.2019.00118.
71. S K, et al. Role of neutrophils and myeloid-derived suppressor cells in glioma progression and treatment resistance - PubMed. Int J Mol Sci. 21. 03/13/2020. https://doi.org/10.3390/ijms21061954.
72. A DL, A U, F V. Myeloid cells in glioblastoma microenvironment - PubMed. Cells. 10. 12/24/2020. https://doi.org/10.3390/cells10010018.
73. M P, et al. Mechanisms regulating transitory suppressive activity of neutrophils in newborns: PMNs-MDSCs in newborns - PubMed. J Leukocyte Biol. 2022 Nov;112. https://doi.org/10.1002/JLB.4HI0921-514RR.
74. Y W, M Y, M N, Q M, K W. Myeloid-derived suppressor cells: an emerging target for anticancer immunotherapy - PubMed. Mol Cancer. 21. 09/26/2022. https://doi.org/10.1186/s12943-022-01657-y.
75. Kcm S, et al. Expression profiling of immune inhibitory siglecs and their ligands in patients with glioma - PubMed. Cancer Immunol, Immunother: CII. 2019, Jun;68. https://doi.org/10.1007/s00262-019-02332-w.
76. Y Z, L G, M S, X L. Targeting and exploitation of tumor-associated neutrophils to enhance immunotherapy and drug delivery for cancer treatment - PubMed. Cancer Biol Med. 17. 02/15/2020. https://doi.org/10.20892/j.issn.2095-3941.2019.0372.
77. D G, et al. Neutrophils as potential therapeutic targets in hepatocellular carcinoma - PubMed. Nat Rev. Gastroenterol Hepatol. 2022 Apr;19. https://doi.org/10.1038/s41575-021-00568-5.
78. Ca L, et al. Hallmarks of the tumour microenvironment of gliomas and its interaction with emerging immunotherapy modalities - PubMed. Int J Mol Sci. 24. 08/25/2023. https://doi.org/10.3390/ijms241713215.
79. Jackson C, et al. Distinct myeloid-derived suppressor cell populations in human glioblastoma. Science. 2025;387:eabm5214. https://doi.org/10.1126/science.abm5214.
80. B O, et al. Cancer stem cell-Secreted macrophage migration Inhibitory Factor stimulates myeloid derived suppressor cell function and facilitates glioblastoma immune evasion - PubMed. STEM Cells (Dayt, Ohio). 2016 Aug;34. https://doi.org/10.1002/stem.2393.
81. D B, et al. Myeloid-derived suppressor cell subsets drive glioblastoma growth in a sex-specific manner - PubMed. Cancer Discov. 2020 Aug;10. https://doi.org/10.1158/2159-8290.CD-19-1355.
82. At Y, et al. Single-cell RNA sequencing reveals evolution of immune landscape during glioblastoma progression - PubMed. Nat Immunol. 2022 Jun;23. https://doi.org/10.1038/s41590-022-01215-0.
83. P DB, et al. Myeloid diagnostic and prognostic markers of immune suppression in the blood of glioma patients - PubMed. Front Immunol. 2022;12. https://doi.org/10.3389/fimmu.2021.809826.
84. Qt O, et al. CBTRUS statistical report: primary brain and other central nervous System tumors Diagnosed in the United States in 2015–2019 - PubMed. Neuro-Oncology. 24. 10/5/2022. https://doi.org/10.1093/neuonc/noac202.
85. W Y, et al. Sex differences in GBM revealed by analysis of patient imaging, transcriptome, and survival data - PubMed. Sci Transl Med. 11. 01/2/2019. https://doi.org/10.1126/scitranslmed.aao5253.
86. Pr G, et al. Elevated levels of polymorphonuclear myeloid-derived suppressor cells in patients with glioblastoma highly express S100A8/9 and arginase and suppress T cell function - PubMed. Neuro-Oncology. 2016 Sep;18. https://doi.org/10.1093/neuonc/now034.
87. E C, L Z, C L. LOX-1+ PMN-MDSC enhances immune suppression which promotes glioblastoma multiforme progression - PubMed. Cancer Manag Res. 2019;11. https://doi.org/10.2147/CMAR.S210545.
88. H L, et al. Host STING-dependent MDSC mobilization drives extrinsic radiation resistance - PubMed. Nat Commun. 2017;8. https://doi.org/10.1038/s41467-017-01566-5.
89. V B, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards - PubMed. Nat Commun. 7. 07/6/2016. https://doi.org/10.1038/ncomms12150.
90. V K, S P, E T, DI G. The Nature of myeloid-derived suppressor cells in the tumor microenvironment - PubMed. Trends Immunol. 2016 Mar;37. https://doi.org/10.1016/j.it.2016.01.004.
91. F V, DI G. Dendritic cells in cancer: the role revisited - PubMed. Curr Opin Immunol. 2017 Apr;45. https://doi.org/10.1016/j.coi.2017.01.002.
92. Cs N, et al. The granulocyte progenitor stage is a Key target of IRF8-mediated regulation of myeloid-derived suppressor cell production - PubMed. In: Journal of immunology. Vol. 198. (*Baltimore, Md; 1950*). 05/15/2017). https://doi.org/10.4049/jimmunol.1601722.
93. D E, Ya W. Glioblastoma heterogeneity at single cell resolution - PubMed. Oncogene. 2023 Jun;42. https://doi.org/10.1038/s41388-023-02738-y.
94. Kmb B, et al. Radiation therapy and myeloid-derived suppressor cells: breaking down their cancerous partnership - PubMed. Int J Radiat Oncol, Biol, Phys. 119. 05/1/2024. https://doi.org/10.1016/j.ijrobp.2023.11.050.
95. E K, et al. Single-cell spatial immune landscapes of primary and metastatic brain tumours - PubMed. Nature. 2023 Feb;614. https://doi.org/10.1038/s41586-022-05680-3.
96. K A, et al. Dendritic cells trigger IFN-γ secretion by NK cells independent of IL-12 and IL-18 - PubMed. Eur J Immunol. 2022 Sep;52. https://doi.org/10.1002/eji.202149733.
97. X H, C J, Y G, X X. Human dendritic cell subsets in the glioblastoma-associated microenvironment - PubMed. J Neuroimmunol. 383. 10/15/2023. https://doi.org/10.1016/j.jneuroim.2023.578147.
98. L Z, et al. CCL21 Induces Plasmacytoid Dendritic cell migration and activation in a mouse model of glioblastoma - PubMed. Cancers. 2024;16. https://doi.org/10.3390/cancers16203459.
99. D O, et al. Tumor-mediated inhibition of human dendritic cell differentiation and function is consistently counteracted by combined p38 MAPK and STAT3 inhibition - PubMed. Oncoimmunology. 1. 08/1/2012. https://doi.org/10.4161/onci.20365.
100. Z W, et al. TSH-TSHR axis promotes tumor immune evasion - PubMed. J Immunother Cancer. 2022 Jan;10. https://doi.org/10.1136/jitc-2021-004049.
101. M H, et al. Suppressor of cytokine signaling 1 inhibits the maturation of dendritic cells involving the nuclear factor kappa B signaling pathway in the glioma microenvironment - PubMed. Clin Exp Immunol. 2020 Oct;202. https://doi.org/10.1111/cei.13476.
102. Ew R, et al. Critical Role for CD103(+)/CD141(+) Dendritic cells bearing CCR7 for tumor antigen trafficking and priming of T cell immunity in Melanoma - PubMed. Cancer Cell. 30. 08/8/2016. https://doi.org/10.1016/j.ccell.2016.06.003.

103. G W, J W, C N, Y Z, P W. Neutrophils: new critical regulators of glioma - PubMed. Front Immunol. 13. 07/4/2022. https://doi.org/10.3389/fimmu.2022.927233.
104. Sankowski R, et al. Multiomic spatial landscape of innate immune cells at human central nervous system borders. Nat Med. 2024;30:186–98. https://doi.org/10.1038/s41591-023-02673-1.
105. Friedrich M, et al. Dysfunctional dendritic cells limit antigen-specific T cell response in glioma. Neuro-Oncology. 2023/02/14;25. https://doi.org/10.1093/neuonc/noac138.
106. Gp T, et al. Glioma-derived CCL2 and CCL7 mediate migration of immune suppressive CCR2+/CX3CR1+ M-MDSCs into the tumor microenvironment in a redundant manner - PubMed. Front Immunol. 13. 01/4/2023. https://doi.org/10.3389/fimmu.2022.993444.
107. Ja B-K, et al. The Conventional Dendritic cell 1 Subset primes CD8+ T cells and traffics tumor antigen to drive antitumor immunity in the brain - PubMed. Cancer Immunol Res. 11. 01/3/2023. https://doi.org/10.1158/2326-6066.CIR-22-0098.
108. D K, et al. Direct oHSV infection Induces DC maturation and a tumor therapeutic response - PubMed. Viruses. 17. 08/19/2025. https://doi.org/10.3390/v17081134.
109. Z Z, X H, E W, Y H, R Y. Identification and characterization of B220+/B220- subpopulations in murine Gr1+CD11b+ cells during tumorigenesis - PubMed. Oncoimmunology. 10. 04/14/2021. https://doi.org/10.1080/2162402X.2021.1912472.
110. W F, X H, L D, W H. Roles of STAT3 in the pathogenesis and treatment of glioblastoma - PubMed. Front Cell Dev Biol. 11. 02/27/2023. https://doi.org/10.3389/fcell.2023.1098482.
111. M B, L C, M R, M S. A two-step human culture system replicates intestinal monocyte maturation cascade: conversion of tissue-like inflammatory monocytes into macrophages - PubMed. Eur J Immunol. 2020 Nov;50. https://doi.org/10.1002/eji.202048555.
112. Q F, et al. Hypoxia Inducible factors' signaling in pediatric high-grade gliomas: role, modelization and innovative targeted approaches - PubMed. Cancers. 12. 04/15/2020. https://doi.org/10.3390/cancers12040979.
113. A O, Wka Y, N M. Molecular mechanisms of treatment resistance in glioblastoma - PubMed. Int J Mol Sci. 22. 12/31/2020. https://doi.org/10.3390/ijms22010351.
114. Jm S, et al. Spatial transcriptomics in glioblastoma: is knowing the right zip code the key to the next therapeutic breakthrough? - PubMed. Front Oncol. 13. 10/17/2023. https://doi.org/10.3389/fonc.2023.1266397.
115. R R, et al. Hypoxia-induced complement component 3 promotes aggressive tumor growth in the glioblastoma microenvironment - PubMed. JCI Insight. 9. 08/22/2024. https://doi.org/10.1172/jci.insight.179854.
116. Ji E, et al. Glioblastoma microenvironment and invasiveness: new insights and therapeutic targets - PubMed. Int J Mol Sci. 24. 04/11/2023. https://doi.org/10.3390/ijms24087047.
117. S S, et al. Glioblastoma at the crossroads: current understanding and future therapeutic horizons - PubMed. Signal Transduct Targeted Ther. 10. 07/9/2025. https://doi.org/10.1038/s41392-025-02299-4.
118. J J, et al. Mitochondrial NIX promotes tumor survival in the hypoxic niche of glioblastoma - PubMed. Cancer Res. 79. 10/15/2019. https://doi.org/10.1158/0008-5472.CAN-19-0198.
119. W Z, et al. Exploring tumor-associated macrophages in glioblastoma: from diversity to therapy - PubMed. NPJ Precis Oncol. 9. 05/2/2025. https://doi.org/10.1038/s41698-025-00920-x.
120. Y L, et al. Interactions between glioblastoma and myeloid cells - PubMed. Front Cell Dev Biol. 13. 06/24/2025. https://doi.org/10.3389/fcell.2025.1632122.
121. V D, G J, S M, Sh C, Py P. Analyzing one cell at a TIME: analysis of myeloid cell contributions in the tumor immune microenvironment - PubMed. Front Immunol. 11. 09/2/2020. https://doi.org/10.3389/fimmu.2020.01842.
122. Shard C, et al. Novel GABAAR antagonists target networked gene hubs at the leading edge in high-grade gliomas. Neuro-Oncology. 2025. https://doi.org/10.1093/neuonc/noaf143.


## Publisher's Note