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REVIEW ARTICLE

Neuroinflammation and tumor microenvironment remodeling in brain tumors: Cellular interactions, immunometabolic adaptations, and therapeutic perspectives

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Abstract

Brain tumors remain among the most aggressive and therapeutically challenging malignancies due to their highly complex and immunosuppressive tumor microenvironment. Increasing evidence suggests that neuroinflammation plays a central role in tumor initiation, progression, angiogenesis, immune evasion, therapeutic resistance, and tumor recurrence. This review discusses the multifaceted role of neuroinflammatory signaling in primary and secondary brain tumors, with emphasis on the dynamic interactions between tumor cells, microglia, tumor-associated macrophages, neutrophils, dendritic cells, lymphocytes, and stromal components within the tumor microenvironment. Particular focus is placed on inflammatory cytokines and signaling pathways, including interleukin (IL)-6, tumor necrosis factor-alpha, transforming growth factor beta, programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1), nuclear factor kappa-light-chain-enhancer of activated B cells, signal transducer and activator of transcription 3, and hypoxia-associated hypoxia-inducible factor 1-alpha signaling, which collectively contribute to immunosuppression and tumor progression. The review further highlights the importance of metabolic adaptation, hypoxia-driven remodeling, oxidative stress, and immune exhaustion in shaping the inflammatory landscape of central nervous system tumors. Emerging evidence regarding nicotinamide adenine dinucleotide phosphate oxidases (NADPH oxidase 2 [NOX2], NOX4, and NOX5) and reactive oxygen species-mediated therapeutic resistance, particularly temozolomide resistance in glioblastoma, is also discussed. In addition, clinically relevant inflammatory biomarkers such as $CD163^+$ tumor-associated macrophages, neutrophil-to-lymphocyte ratio, PD-L1 expression, and isocitrate dehydrogenase-associated immune phenotypes are examined for their potential prognostic and therapeutic significance. Recent advances in therapeutic strategies targeting neuroinflammation, including colony-stimulating factor 1 receptor inhibitors, IL-6 pathway blockade, immune checkpoint modulation, anti-angiogenic therapy, and tumor microenvironment reprogramming approaches, are reviewed along with their current translational limitations. Overall, this review provides an integrative overview of the relationship between neuroinflammation and tumor microenvironment remodeling in brain tumors and highlights the growing potential of biomarker-guided and microenvironment-directed therapeutic strategies in neuro-oncology.

Keywords: Neuroinflammation; Central nervous system tumors; Tumor microenvironment; Immunotherapy; Anti-angiogenic therapy; Cytokine signaling

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1. Introduction

Primary brain tumors encompass a heterogeneous group of neoplasms arising from different intracranial tissues.[1] The 2021 World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5) categorizes meningiomas, pituitary neuroendocrine tumors, and schwannomas as typically benign, whereas glioblastoma multiforme (GBM), astrocytoma, oligodendrogliomas, and ependymomas are classified as malignant, with an emphasis on integrated histopathological and molecular diagnostics.[2,3] Globally, brain tumors accounted for approximately 308,102 new cases and 251,329 deaths in 2020, with a global age-standardized incidence rate (ASIR) of approximately 4.34 per 100,000 people, while the mortality-to-incidence ratio is around 0.7.[4,5] Asia bears a significant burden of such tumors, contributing substantially to global cases and deaths, with projections indicating a rising ASIR and a persistently high disease burden in the coming years.[5,6]

Neuroinflammation within the tumor microenvironment (TME) is a highly coordinated immune response in the brain that causes tumor progression, arising from complex interactions between resident glial cells, infiltrating immune cells, and pro-inflammatory mediators.[7] While initially protective, dysregulated chronic neuroinflammation can drive pathological processes, contributing to brain tumor progression through sustained immune activation, cytokine release, and microenvironmental remodeling.[7–9] The blood–brain barrier (BBB), a selective permeability barrier, regulates the infiltration of such immune cells into the brain.[10] Systemic infections such as bloodstream infections further illustrate this vulnerability, as circulating pathogens and inflammatory mediators can disrupt BBB integrity, activate neuroglial responses, and initiate neuroinflammatory cascades that contribute to neuronal injury and long-term neurological dysfunction.[11] Disruption of the neurovascular unit, including endothelial cells, pericytes, astrocytes, and microglia, has been shown to compromise BBB integrity, amplify inflammatory signaling, and facilitate immune cell infiltration, highlighting a critical link between vascular dysfunction and neuroinflammation.[12] In the context of tumors, the BBB's integrity may be compromised, facilitating the entry of peripheral immune cells and contributing to an inflammatory milieu.[10] This inflammation can act as a double-edged sword: on one hand, an effective immune response involving activated microglia, macrophages, and cytotoxic T cells can contribute to tumor suppression by targeting and eliminating malignant cells.[13,14] Chronic or dysregulated inflammation, on the other hand, can have the opposite effect, encouraging the growth of tumors by releasing angiogenic factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), pro-inflammatory cytokines such as interleukin (IL)-6, IL-1β, and tumor necrosis factor-alpha (TNF-α), and immunosuppressive signal mediators including transforming growth factor-beta (TGF-β) and IL-10 that promote tumor proliferation, aid immune evasion, and contribute to therapeutic resistance.[15,16]

The TME is a dynamic and intricate ecosystem enriched with diverse inflammatory cells, including resident microglia, infiltrating neutrophils, mast cells, macrophages, and dendritic cells (DCs).[17,18] It also harbors immunoregulatory players such as myeloid-derived suppressor cells (MDSCs), T and B lymphocytes, natural killer (NK) cells, eosinophils, and vascular endothelial (VE) cells that shape the tumor's immune landscape.[18,19] These cells, upon activation, release a plethora of cytokines, chemokines, and growth factors, orchestrating complex networks that can alter normal neurophysiology and influence tumor behavior.[20] Tumor-associated macrophages (TAMs), for instance, may polarize toward pro- or anti-tumor phenotypes, thereby influencing disease progression and therapeutic response.[18] Similarly, MDSCs play a crucial role in dampening T cell activity, creating an immunosuppressive shield that allows tumors to evade immune surveillance and thrive unchecked.[21,22] Targeting common markers on these cells unlocks a powerful therapeutic strategy, potentially transforming brain tumor treatment.

Several clinical trials have explored immunotherapies targeting the TME in high-grade gliomas and other brain tumors.[23] A randomized phase 3 trial evaluated nivolumab versus bevacizumab in recurrent GBM but did not demonstrate improved overall survival with nivolumab.[24] A phase 1 study investigated the oncolytic adenovirus DNX-2401 in recurrent malignant glioma, revealing that 20% of patients survived beyond three years post-treatment, with some experiencing significant tumor reduction.[25] Additionally, a phase 1/2 trial combined DNX-2401 with pembrolizumab in recurrent GBM, aiming to enhance anti-tumor immunity, though detailed efficacy outcomes are pending further analysis.[26] Another study demonstrated that DNX-2401 not only directly lysed tumor cells but also activated an immune-mediated anti-glioma response, leading to sustained tumor regression.[27] Early-stage clinical trials have explored chimeric antigen receptor (CAR) T-cell therapies targeting GBM, focusing on antigens such as human epidermal growth factor receptor 2, IL-13 receptor subunit alpha-2, and epidermal growth factor receptor variant III (EGFRvIII), exhibiting prolonged progression-free survival.[28] Despite

advancements in immunotherapy, there remains a paucity of literature elucidating the differential impact of inflammatory processes across various brain tumors. The decision to treat aggressively or adopt a more conservative approach remains complex, as inflammation can have both pro-tumor and anti-tumor effects depending on the tumor type and microenvironment. A comprehensive review is warranted to delineate these pathways, identify potential biomarkers as well as the common markers involved in multiple brain tumors, and explore the targeted therapeutic strategies tailored to the unique inflammatory landscapes of each tumor type, eventually improving patient outcomes.

2. Neuroinflammation

Inflammation is a fundamental protective response of the host against infection and tissue damage, aiming to eliminate harmful stimuli and initiate tissue repair processes.[16,29] This complex biological response involves the activation of various immune cells, the release of signaling molecules, and alterations in blood flow, all orchestrated to restore tissue homeostasis.[30] The inflammatory response is triggered when pathogen-associated molecular patterns or damage-associated molecular patterns are recognized by pattern recognition receptors on resident immune cells, such as macrophages and mast cells.[16,29,31] This recognition leads to the secretion of pro-inflammatory cytokines, chemokines, and vasoactive amines, which enhance the immune response by increasing vascular permeability and recruiting additional immune cells to the site of injury or infection.[16,32,33] The increased vascular permeability allows plasma proteins, including antibodies and complement components, to enter the affected tissue, aiding in pathogen neutralization and clearance.[33–35] Neutrophils serve as the first line of immune defense, rapidly migrating to sites of inflammation in response to chemotactic gradients, where they release cytokines and exert direct cytotoxic activity.[36,37] They phagocytose pathogens and release enzymes and reactive oxygen species (ROS) to combat infection.[38] As the response progresses, monocytes are recruited and differentiate into macrophages, which continue pathogen clearance and release factors that promote tissue repair.[39] The resolution of inflammation is orchestrated through neutrophil apoptosis, their efferocytic clearance by macrophages, and the release of specialized pro-resolving mediators that restore tissue homeostasis while preventing chronic immune activation.[40,41]

3. Tumor interaction with the immune-privileged brain

The brain has long been regarded as an immune-privileged site due to the presence of the BBB, which tightly regulates the entry of immune cells and molecules.[42] However, this notion has evolved with the discovery of brain-resident antigen-presenting cells, such as microglia and perivascular macrophages, which can process and present antigens to infiltrating T cells.[42,43] Additionally, the identification of a functional meningeal lymphatic system that drains into deep cervical lymph nodes suggests active immune surveillance within the brain.[44,45] In the context of tumors, BBB disruption allows peripheral immune cells—including $CD8^+$ cytotoxic T cells, regulatory T cells (Tregs), and MDSCs—to infiltrate the TME.[46,47] One study reported that some GBM regions retain an intact BBB, highlighting the need for treatment strategies that achieve adequate drug delivery to both BBB-disrupted and BBB-intact tumor regions.[48] While $CD8^+$ T cells may attempt to mount an anti-tumor response, gliomas and other brain malignancies exploit the brain's immunosuppressive milieu by recruiting Tregs and MDSCs, which suppress cytotoxic activity and promote tumor progression through the release of TGF-β and IL-10.[49–51] This dynamic interplay between tumor cells and immune components highlights the complexity of immune regulation within the brain and presents both challenges and opportunities for immunotherapeutic interventions.

4. The dual role of inflammation in neuro-oncology

Inflammation in neuro-oncology is a dynamic and bidirectional process, occurring as both acute and chronic responses that influence tumor progression and immune interactions.[16,18,52] Acute inflammation, typically triggered by tissue injury or tumor-associated stress signals, involves the rapid recruitment of neutrophils and activation of innate immune pathways.[15,29,53] This response can occur after surgical resection or radiation therapy, where inflammatory mediators such as TNF-α and IL-1β contribute to transient immune activation.[54–56] In some cases, acute inflammation can exert anti-tumor effects by activating cytotoxic T cells and NK cells, enhancing immune surveillance, and promoting tumor cell apoptosis.[16,57–59] However, unresolved acute inflammation can transition into chronic inflammation, which plays a central role in tumor progression and immune evasion.[60,61] Age-related gut microbiota dysbiosis further exemplifies how systemic factors can drive chronic neuroinflammation through the gut–brain axis, where microbial metabolites and endotoxins promote BBB disruption, microglial activation, and sustained inflammatory signaling, thereby extending the concept of inflammation beyond the TME to a broader systems-level regulatory network.[62] Within the TME, brain malignancies hijack inflammatory pathways by recruiting microglia, macrophages, and MDSCs, which secrete cytokines such as IL-6 and TGF-β to suppress anti-

tumor immunity and promote angiogenesis.[18,63,64] This persistent inflammation creates an immunosuppressive niche that sustains tumor growth and resistance to therapy.[65,66] Beyond the brain, systemic inflammatory responses driven by tumor-derived factors disrupt immune homeostasis, leading to lymphopenia, immune exhaustion, and paraneoplastic syndromes.[65,67] Additionally, treatment modalities such as surgery, radiation, and immunotherapy can further amplify both local and systemic inflammatory responses, sometimes exacerbating immune dysfunction.[68] While chronic inflammation often fosters tumor progression, certain pro-inflammatory signals, such as interferon gamma (IFN-γ)–driven T-cell responses, can sustain anti-tumor immunity by enhancing immune-mediated tumor clearance.[16,65,69] This intricate interplay between acute and chronic inflammation in neuro-oncology underscores the need for immunomodulatory strategies that mitigate tumor-promoting inflammation while preserving effective anti-tumor immune responses, providing potential avenues for improved therapeutic outcomes.

5. Roles of various inflammatory cells

5.1. Microglia

Microglia, the brain's resident immune cells, are key players in the inflammatory landscape of brain tumors.[70,71] In an acute response, they adopt a pro-inflammatory (M1) state, driven by IFN-γ and TNF-α, releasing IL-1β, IL-6, and TNF-α to attack abnormal cells.[72–75] While this can suppress tumor growth initially, prolonged activation leads to neurotoxicity.[73] In chronic inflammation, tumors such as GBM, medulloblastoma, and diffuse midline glioma reprogram microglia into an anti-inflammatory (M2) state using IL-4 and IL-13.[76–78] M2 microglia secrete IL-10 and TGF-β, suppressing immune attacks, enhancing blood vessel growth, and reshaping the TME to support progression.[73,79] In primary brain tumors, they create a tumor-supportive niche, whereas in metastatic brain tumors, they may facilitate immune evasion.[80–83] This balance among microglial activation states regulates tumor behavior, making them a viable target for future therapeutics.

5.2. Neutrophils

Neutrophils, the first responders of acute inflammation, rapidly infiltrate brain tumors in response to chemokines such as CXCL1 and CXCL8 (IL-8) released by tumor cells.[36,84] In their pro-inflammatory (N1) state, they unleash ROS, myeloperoxidase, and neutrophil elastase, inducing tumor cell apoptosis and restricting early tumor growth.[17,85,86] Nevertheless, in chronic neuroinflammation, brain metastases and tumors such as GBM induce neutrophils to adopt an immunosuppressive (N2) state.[87,88] These tumor-associated neutrophils secrete VEGF and matrix metalloproteinases (MMPs), fostering angiogenesis, invasion, and immune evasion.[89,90] In benign tumors such as meningioma, though less explored, studies suggest that raised levels of neutrophils in high-grade meningiomas are highly associated with their recurrence.[91] Their dual role—tumor-suppressive in acute inflammation and tumor-promoting in chronic settings—makes them a compelling target for therapeutic intervention in brain malignancies.

5.3. Mast cells

Mast cells, traditionally known for their role in allergic responses, are now recognized as key regulators of neuroinflammation and brain tumor progression, exhibiting both pro-inflammatory and immunosuppressive functions.[92–94] They accumulate at the periphery of brain tumors, including GBMs, meningiomas, hemangioblastomas, medulloblastomas, and metastatic brain tumors, where they actively modulate the TME.[95,96] By releasing histamine, tryptase, and chymase, mast cells degrade the extracellular matrix, facilitating tumor cell invasion and migration. Their pro-tumorigenic role extends to angiogenesis, as they secrete VEGF, FGF, and TNF-α to enhance vascular remodeling and tumor vascularization.[97,98] Additionally, mast cells contribute to immune suppression through the release of IL-10, TGF-β, and prostaglandin E2 (PGE2), which inhibit cytotoxic T-cell responses and create an immune-privileged tumor niche.[99] Their presence is strongly correlated with peritumoral edema and chronic neuroinflammation, further exacerbating disease progression.[92,100] Furthermore, mast cells interact with microglia and astrocytes, amplifying neuroinflammatory cascades that may accelerate neurodegenerative processes.[101] Given their dual role in tissue remodeling and immune suppression, targeting mast cell activation and their signaling pathways represents a promising therapeutic strategy for modulating tumor growth and the immune landscape in neuro-oncology.

5.4. Tumor-associated macrophages

Macrophages infiltrating brain tumors differentiate into TAMs, which play a pivotal role in shaping the TME.[18,102] While M1 TAMs exhibit anti-tumor activity by releasing TNF-α, IL-12, and nitric oxide, most brain tumors, including GBMs and brain metastases, drive TAMs toward an M2 phenotype via IL-4, IL-10, and colony-stimulating factor 1 (CSF-1).[103,104] M2 TAMs promote tumor progression by suppressing immune responses, remodeling the extracellular matrix, and enhancing angiogenesis through VEGF and hypoxia-inducible factor

1-alpha (HIF-1α).[105,106] Higher M2 macrophage infiltration in meningioma is correlated with higher tumor grade and recurrence.[107] Larger pituitary adenomas tend to exhibit increased macrophage infiltration, suggesting a potential role in tumor growth.[108] In vestibular schwannomas, higher levels of $CD163^+$ M2 macrophages are associated with tumor progression.[109] Their immunosuppressive and pro-angiogenic functions make them critical players in tumor immune evasion, positioning TAM-targeting strategies as a promising avenue in neuro-oncology.[102,110]

5.5. Dendritic cells

Dendritic cells are essential antigen-presenting cells that link innate and adaptive immunity by capturing tumor antigens and activating T cells.[111] However, in brain tumors such as GBMs, medulloblastomas, and metastatic brain tumors, tumor-derived factors such as TGF-β and IL-6 impair DC maturation, reducing their antigen-presenting ability and weakening anti-tumor immunity.[112–114] The accumulation of immature DCs in the TME promotes immune evasion by inducing T-cell anergy and expanding Tregs, further suppressing cytotoxic responses.[115,116] This dysfunction in DC-mediated immunity contributes to tumor persistence, making DC-targeting strategies a potential avenue for enhancing immune responses in neuro-oncology.[113,117]

5.6. Myeloid-derived suppressor cells

Myeloid-derived suppressor cells are a heterogeneous population of immature myeloid cells that accumulate in brain tumors such as GBMs and medulloblastomas, driven by C-C motif chemokine ligand 2 and C-X-C motif chemokine ligand 5 signaling.[21,118] They suppress anti-tumor immunity by inhibiting cytotoxic T-cell activity through arginase-1 and inducible nitric oxide synthase.[119,120] Additionally, MDSCs promote Treg expansion and secrete immunosuppressive cytokines such as IL-10 and TGF-β, fostering an immune-evading TME.[121,122] Their role in dampening immune responses makes them a key target for strategies aimed at restoring anti-tumor immunity and improving therapeutic outcomes in brain tumors.[22,120,123]

5.7. T cells

T cells are key players in brain tumor immunity, but often become dysfunctional. $CD8^+$ cytotoxic T cells, responsible for tumor cell destruction, often decrease in number due to the immunosuppressive TME, which promotes T-cell exhaustion through programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways.[124–126] Conversely, $CD4^+$ helper T cells can increase, but they are frequently skewed toward regulatory phenotypes that secrete IL-10 and TGF-β, further suppressing anti-tumor immunity.[18,127] Memory T cells, essential for long-term immune surveillance, also decline in these tumors, impairing sustained anti-tumor responses.[128,129] These shifts in T-cell subsets contribute to tumor progression and pose challenges for effective immunotherapy in neuro-oncology.[130,131]

5.8. B cells

B cells, integral to humoral immunity, produce antibodies and present antigens to T cells.[132] In GBM, their role is complex; while they can act as antigen-presenting cells to stimulate T cells, the TME often impairs their function.[133] Factors such as TGF-β suppress B cell activity, leading to reduced antibody production and antigen presentation, thereby facilitating tumor immune evasion.[134,135] In medulloblastoma, B cells are less prevalent, and their impact remains under investigation.[136] Understanding B-cell dynamics in these tumors could inform therapeutic strategies.

5.9. Natural killer cells

Natural killer cells are pivotal components of the innate immune system, recognized for their ability to identify and eliminate malignant cells, particularly those deficient in major histocompatibility complex (MHC) class I molecules.[137,138] However, in brain tumors such as GBMs and medulloblastomas, their function is suppressed through multiple mechanisms. TGF-β, IL-6, and IL-8 in the TME inhibit NK cell activation, while tumor cells evade detection by upregulating MHC class I.[77,139] Additionally, hypoxia-driven factors and prostaglandins (e.g., PGE2) reduce NK cell infiltration and cytotoxicity. These immunosuppressive signals collectively weaken NK cell-mediated tumor control, promoting tumor immune evasion.[140] Consequently, despite their inherent tumoricidal potential, NK cells are rendered less effective in targeting brain malignancies due to these multifaceted inhibitory mechanisms.[141,142]

5.10. Eosinophils

Eosinophils play a dual role in brain tumors, exhibiting both cytotoxic and tumor-promoting functions.[18,143] They release eosinophil-derived neurotoxin, major basic protein (MBP), and ROS, directly damaging tumor cells.[144–146] However, they also secrete IL-4 and IL-13, shifting macrophages to an immunosuppressive M2 phenotype and promoting Treg expansion.[147] By releasing VEGF and MMPs, eosinophils enhance angiogenesis and extracellular matrix remodeling, facilitating tumor invasion. Additionally, they recruit mast cells and suppress NK cell activity via prostaglandin release, further weakening anti-

tumor immunity.[115,148,149] Their impact depends on tumor type and microenvironmental signals, making them a potential target for immunotherapy.

5.11. Vascular endothelial cells

Vascular endothelial cells play a central role in brain tumor angiogenesis and progression. Brain tumors such as GBMs and hemangioblastomas secrete VEGF, FGF, and HIF-1α, driving endothelial cell proliferation and abnormal neovascularization.[150] These structurally defective vessels lead to increased permeability, facilitating tumor cell invasion and immune cell infiltration. Additionally, pro-inflammatory cytokines such as IL-6 and TNF-α exacerbate endothelial dysfunction, promoting a hypoxic and immunosuppressive microenvironment that sustains tumor growth.[150,151] Targeting tumor-associated endothelial signaling pathways is a key therapeutic strategy to disrupt brain tumor vascularization and limit disease progression. These mechanisms highlight how neuroinflammation can both suppress and promote brain tumor growth through intricate immune interactions and are summarized in Table 1 and 2. Advancing targeted immunotherapies is crucial to enhancing anti-tumor immunity while counteracting tumor-promoting inflammation.

6. Metabolic and hypoxia-driven remodeling of the tumor microenvironment

Hypoxia and metabolic adaptation are major contributors to TME remodeling in central nervous system (CNS) tumors.[152] Rapid tumor growth often exceeds the available blood supply, resulting in hypoxic regions within GBM and other aggressive brain tumors. In response to low oxygen levels, tumor cells activate HIF-1α, which promotes angiogenesis, metabolic reprogramming, tumor survival, and inflammatory signaling.[153] Hypoxia also increases the production of immunosuppressive cytokines and growth factors such as VEGF, TGF-β, and IL-10, which contribute to an immunosuppressive TME.

These hypoxia-driven changes influence the behavior of several immune cell populations within the TME. Macrophages and microglia are often polarized toward an M2-like phenotype that supports tumor growth, angiogenesis, and immune evasion.[154,155] At the same time, cytotoxic $CD8^+$ T-cell activity becomes impaired, while Treg expansion and immune exhaustion become more prominent. Metabolic alterations within tumor cells, including increased glycolysis and lactate accumulation, further suppress anti-tumor immune responses by reducing T-cell and NK-cell function.[156,157] In addition, stromal and endothelial interactions contribute to extracellular matrix remodeling, abnormal vascular permeability, hypoxia persistence, and therapy resistance.

Recent studies suggest that targeting hypoxia-associated signaling, tumor metabolism, and inflammatory pathways may help therapeutically reprogram the TME.[158–164] Approaches aimed at reducing immunosuppression, improving immune-cell infiltration, and normalizing tumor vasculature may enhance the effectiveness of immunotherapy and targeted treatment strategies in brain tumors. However, the complexity and heterogeneity of TME interactions continue to present major challenges for successful clinical translation.

7. Neuroinflammation in brain tumors and its clinical implications

The WHO 2021 classification of brain tumors introduced a molecularly driven framework, moving beyond histopathological grading to integrate genetic and epigenetic alterations.[3] Tumors are now categorized based on isocitrate dehydrogenase (*IDH*) mutation status, chromosomal co-deletions, epigenetic profiles, and molecular subtypes. This has improved prognostication and therapeutic stratification. Brain tumors are broadly classified into gliomas, neuronal-glial tumors, ependymal tumors, embryonal tumors, meningeal tumors, and peripheral nerve sheath tumors.[3] Below, we discuss key brain tumors, emphasizing their inflammatory pathways, interactions with immune cells, and their clinical implications.

7.1. Glioblastoma multiforme

Glioblastoma multiforme, *IDH*-wildtype, is the most aggressive adult-type diffuse astrocytic glioma, classified as CNS WHO grade 4 and characterized by significant necrosis and microvascular proliferation.[165,166] Key genetic mutations play a critical role in shaping its inflammatory microenvironment. Epidermal growth factor receptor (EGFR) amplification activates NF-κB, leading to a pro-inflammatory milieu rich in IL-6, IL-8, and TNF-α, while *PTEN* loss suppresses immune activation by increasing TGF-β levels and promoting immune evasion.[167–170] *TERT* promoter mutations further sustain chronic inflammation by facilitating macrophage infiltration.[171] The tumor-inflammation crosstalk involves TAMs and microglia, which secrete IL-10 and TGF-β, fostering an immunosuppressive environment, while neutrophils contribute to tumor invasion through neutrophil extracellular trap formation (NETosis) and MMP-9 secretion.[105,172,173] T-cell exhaustion, mediated by PD-L1 expression, impairs anti-tumor responses, and cytokines such as VEGF and CSF-1 drive angiogenesis and myeloid

Table 1. Innate immune and myeloid components in brain tumor neuroinflammation

Cell type	Inflammatory role	Acute vs. chronic role	Primary or secondary in tumor development	Effect on benign vs. malignant tumors	Mechanisms of action	Key cytokines & molecules released
Microglia	Both (M1: pro-inflammatory; M2: anti-inflammatory)	Acute: M1 microglia activated by IFN-γ and TNF-α produce pro-inflammatory cytokines and ROS, exhibiting anti-tumor activity	Primary: Resident immune cells in the CNS; directly interact with tumor cells	Benign: Role less defined; potential to maintain tissue homeostasis	M1: Antigen presentation, cytotoxicity	M1: IL-1β, TNF-α, IL-12, ROS
		Chronic: Tumor environment induces M2 polarization via IL-4, IL-10, IL-13, and TGF-β, leading to immunosuppression and tumor progression	Secondary: Recruited to metastatic sites, aiding tumor cell colonization	Malignant: In gliomas, M2 microglia promote tumor growth and invasion	M2: Immunosuppression, angiogenesis, extracellular matrix remodeling	M2: IL-10, TGF-β, VEGF, MMPs
Neutrophils	Both (N1: Pro-inflammatory; N2: Anti-inflammatory)	Acute: N1 neutrophils release ROS and proteases, exhibiting anti-tumor activity	Secondary: Recruited to tumor sites in response to chemokines	Benign: Studies suggest that neutrophilia causes a high recurrence of high-grade meningiomas more than lower-grade ones	N1: Cytotoxicity towards tumor cells	N1: ROS, proteases
		Chronic: Tumor microenvironment induces N2 polarization, promoting tumor progression		Malignant: In gliomas, N2 neutrophils promote tumor growth and invasion	N2: Immunosuppression, angiogenesis, and extracellular matrix remodeling	N2: VEGF, MMPs
Mast cells	Both (Pro-inflammatory and Immunosuppressive)	Chronic: accumulates in the tumor periphery, modulating the tumor microenvironment	Primary: Resident in CNS tissues; interacts with tumor cells. No profound secondary role known	Malignant: Promote tumor growth and invasion	Degradation of the extracellular matrix, facilitation of tumor invasion, promotion of angiogenesis, and immune suppression	Histamine, tryptase, chymase, VEGF, FGF, TNF-α, IL-10, TGF-β, PGE2
TAMs	Both (M1: pro-inflammatory, M2: anti-inflammatory)	Acute: Induces tumor cell apoptosis, activates cytotoxic immune responses	Primary: Regulate tumor immunity & inflammation	Benign: M1 is suppressive in nature. M2 promotes meningiomas, schwannomas, and pituitary adenomas	M1: Enhances cytotoxic responses, induces tumor cell apoptosis	M1: TNF-α, IL-12, NO
		Chronic: Suppresses immune response, enhances angiogenesis, supports tumor growth	Secondary: Modify microenvironment, aid angiogenesis, and immune evasion	Malignant: M1 is suppressive in nature for glioblastoma and malignant tumors. M2 promotes malignant tumor progression	M2: Suppresses immune response, enhances angiogenesis, remodels extracellular matrix	M2: IL-4, IL-10, CSF-1, VEGF, HIF-1α

(*Cont'd...*)

Table 1. (*Continued*)

Cell type	Inflammatory role	Acute vs. chronic role	Primary or secondary in tumor development	Effect on benign vs. malignant tumors	Mechanisms of action	Key cytokines & molecules released
DCs	Both (Pro-inflammatory when mature, Immunosuppressive when immature)	Acute: Capture tumor antigens, activate T cells, stimulate anti-tumor immunity	Primary: Bridge innate and adaptive immunity, regulate tumor-specific immune responses	Benign: Role unclear, but impaired antigen presentation may allow immune evasion	Mature DCs: Promote T-cell activation, enhance anti-tumor immune responses	Mature DCs: IL-12, IFN-γ
		Chronic: Tumor-derived factors suppress maturation, impair antigen presentation, and induce T-cell anergy	Secondary: Modify immune landscape, promote immune evasion through Treg expansion	Malignant: Dysfunctional DCs weaken immune surveillance, allowing tumor progression	Immature DCs: Promote T-cell anergy, expand regulatory T cells, suppress cytotoxic responses	Immature DCs: IL-10, TGF-β, IL-6
Myeloid-derived suppressor cells	Anti-inflammatory, Immunosuppressive	Acute: suppresses cytotoxic T-cell activity, dampens early immune response	Primary: Regulates immune suppression, inhibits T-cell activation	Benign: Limited evidence, potential role in immune evasion	Suppresses cytotoxic T cells via arginase-1 and iNOS; expands regulatory T cells (Tregs)	IL-10, TGF-β, arginase-1, iNOS
		Chronic: Maintains immunosuppressive tumor microenvironment, promotes Treg expansion	Secondary: Enhances tumor progression through immune evasion	Malignant: Promotes immune evasion and tumor persistence	Enhances immune evasion, fosters tumor-promoting inflammation	CCL2, CXCL5

Abbreviations: CCL2: C-C motif chemokine ligand 2; CNS: Central nervous system; CSF-1: Colony-stimulating factor 1; CXCL5: C-X-C motif chemokine ligand 5; DCs: Dendritic cells; FGF: Fibroblast growth factor; HIF-1α: Hypoxia-inducible factor 1-alpha; IFN-γ: Interferon-gamma; IL: Interleukin; iNOS: Inducible nitric oxide synthase; MMPs: Matrix metalloproteinases; NO: Nitric oxide; PGE2: Prostaglandin E2; ROS: Reactive oxygen species; TAMs: Tumor-associated macrophages; TGF-β: Transforming growth factor-beta; TNF-α: Tumor necrosis factor-alpha; Tregs: Regulatory T cells; VEGF: Vascular endothelial growth factor.

Table 2. Adaptive immune and stromal components in brain tumor neuroinflammation

Cell type	Inflammatory role	Acute vs. chronic role	Primary or secondary in tumor development	Effect on benign vs. malignant tumors	Mechanisms of action	Key cytokines & molecules released
T cells ($CD8^+$, $CD4^+$, Tregs, Memory)	Both (Cytotoxic: anti-tumor, Tregs: immunosuppressive)	Acute: $CD8^+$ T cells attack tumor cells (Granzyme B, Perforin), $CD4^+$ (Th1) enhances immunity, Memory T cells sustain the response	Primary: $CD8^+$ cells directly lyse tumor cells, Th1 activates immune response	Benign: Limited data, but Th1/$CD8^+$ may suppress tumor growth, and Tregs may promote immune privilege.	$CD8^+$ induces apoptosis, Th1 enhances immunity, and Tregs suppress response.	$CD8^+$: IFN-γ, Granzyme B; Th1: IL-2, IFN-γ; Tregs: IL-10, TGF-β
		Chronic: $CD8^+$ T cells undergo exhaustion (PD-1/PD-L1, CTLA-4), Th2 skews immunity, Tregs suppress $CD8^+$ response, Memory T cells decline	Secondary: Tregs enhance immune suppression, the TME favors Th2 over Th1, and suppresses $CD8^+$	Malignant: $CD8^+$ suppressed, Tregs expanded, favoring tumor growth and immune evasion	T-cell exhaustion, immune suppression, reduced memory response	PD-1, CTLA-4, IL-10, TGF-β

(*Cont'd...*)

Table 2. (*Continued*)

Cell type	Inflammatory role	Acute vs. chronic role	Primary or secondary in tumor development	Effect on benign vs. malignant tumors	Mechanisms of action	Key cytokines & molecules released
B cells	Both (pro-inflammatory via antigen presentation and antibody production; anti-inflammatory via Bregs)	Acute: Act as APCs, activating T-cell responses against tumor antigens	Primary: Regulate humoral immunity via antibody production and antigen presentation	Benign: Limited data, but may contribute to immune regulation in meningioma, pituitary adenoma	Stimulate or suppress immune response depending on subset (APC vs. Bregs)	Antibodies, IL-10, TGF-β, PD-L1
		Chronic: Suppressed B-cell activity due to tumor-derived factors (e.g., TGF-β), leading to immune evasion	Secondary: Influence tumor progression through immunosuppression (Bregs) or failed immune activation		Bregs suppress $CD8^+$ T cells, interact with MDSCs to enhance immunosuppression	
NK cells	Pro-inflammatory (cytotoxic activity against tumor cells)	Acute: Rapid identification and destruction of malignant cells, particularly those with low MHC class I expression	Primary: Direct cytotoxicity against tumor cells	Benign: Limited data on NK cell involvement; potential surveillance role Malignant: Suppressed NK cell activity due to TME factors, aiding tumor progression	Tumor-derived factors (e.g., TGF-β) inhibit NK cell activation; upregulation of MHC class I on tumor cells prevents NK cell recognition; hypoxia and prostaglandins reduce NK cell infiltration and function	TGF-β, IL-6, IL-8, PGE2, MHC class I molecules
Eosinophils	Both (cytotoxic and tumor-promoting)	Acute: Release of cytotoxic proteins (EDN, MBP) and ROS, directly damaging tumor cells.	Primary: Direct cytotoxicity against tumor cells through the release of toxic granules	Benign: Limited data, but may contribute to inflammation in pituitary adenomas and meningiomas	Cytotoxicity via EDN, MBP, ROS; promotes angiogenesis (VEGF, MMPs); shifts macrophages to M2 phenotype (IL-4, IL-13); suppresses NK cells and recruits mast cells (prostaglandins)	EDN, MBP, ROS, IL-4, IL-13, VEGF, MMPs, Prostaglandins
		Chronic: Enhances angiogenesis, suppresses immune responses, remodels ECM, promotes tumor progression	Secondary: Indirectly aids tumor progression by modifying the microenvironment (Treg expansion, macrophage polarization, angiogenesis)	Malignant: Promotes tumor growth by enhancing angiogenesis, ECM remodeling, and immune evasion		

(*Cont'd...*)

Table 2. (*Continued*)

Cell type	Inflammatory role	Acute vs. chronic role	Primary or secondary in tumor development	Effect on benign vs. malignant tumors	Mechanisms of action	Key cytokines & molecules released
VE cells	Pro-angiogenic and pro-inflammatory	Acute: rapidly respond to hypoxia by inducing neovascularization, enhancing immune cell infiltration	Primary: Regulate tumor vascularization, immune cell trafficking	Benign: Promote vascularization in hemangioblastomas, meningiomas, and pituitary adenomas, supporting slow-growing but persistent tumor progression	Enhances angiogenesis, increases vascular permeability, and sustains immune suppression through endothelial dysfunction.	VEGF, FGF, HIF-1α, IL-6, TNF-α
		Chronic: Persistent angiogenesis leads to structurally defective vessels, hypoxia, and immune evasion	Secondary: Modulate immune responses, contribute to tumor immune escape	Malignant: Drive aggressive neovascularization in glioblastomas, leading to hypoxia, therapy resistance, and rapid tumor expansion		

Abbreviations: APCs: Antigen-presenting cells; Bregs: Regulatory B cells; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; ECM: Extracellular matrix; EDN: Eosinophil-derived neurotoxin; FGF: Fibroblast growth factor; HIF-1α: Hypoxia-inducible factor 1-alpha; IFN-γ: Interferon-gamma; IL: Interleukin; MBP: Major basic protein; MDSCs: Myeloid-derived suppressor cells; MHC: Major histocompatibility complex; MMPs: Matrix metalloproteinases; NK: Natural killer; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PGE2: Prostaglandin E2; ROS: Reactive oxygen species; TGF-β: Transforming growth factor-beta; Th1: T helper 1; Th2: T helper 2; TNF-α: Tumor necrosis factor-alpha; Tregs: Regulatory T cells; VE: Vascular endothelial; VEGF: Vascular endothelial growth factor.

infiltration, respectively.[174] GBM's immunosuppressive microenvironment limits immunotherapy effectiveness, necessitating novel strategies.[175] colony-stimulating factor 1 receptor (CSF-1R) inhibitors reprogram macrophages, while anti-IL-6 therapies mitigate inflammation-driven progression.[77,176–178] VEGF inhibitors such as bevacizumab reduce edema but do not extend survival, whereas PD-1/PD-L1 checkpoint inhibitors are under investigation to enhance T-cell activity.[179,180] Given GBM's invasiveness and treatment resistance, an integrated approach with maximal safe resection, radiotherapy, temozolomide, and experimental immunotherapies remains crucial for improving outcomes.

7.2. Oligodendroglioma

Oligodendrogliomas, WHO grade 2 or 3 tumors, arise from oligodendrocytes and are defined by *IDH* mutations and 1p/19q co-deletion.[181,182] Their genetic landscape shapes a distinct inflammatory microenvironment. *IDH1/2* mutations produce D-2-hydroxyglutarate, which suppresses T-cell infiltration and immune activation, while 1p/19q co-deletion reduces macrophage recruitment and lowers immune cell density.[183,184] Tumor-inflammation crosstalk involves microglia producing IL-1β and IL-6, driving low-grade inflammation, while lower PD-L1 expression allows T cells to remain more active.[185] Clinically, oligodendrogliomas exhibit better immunogenicity than GBM, making them promising candidates for immune-modulating therapies.[186] Standard treatment includes maximal safe resection followed by radiotherapy and chemotherapy with PCV (procarbazine, lomustine, and vincristine) or temozolomide, with emerging immunotherapies being explored for potential benefit.[187,188]

7.3. Ependymoma

Ependymomas arise from ependymal cells lining the ventricles and spinal cord and are classified by molecular subgroups, with RELA fusion-positive ependymomas being the most aggressive.[189] Key genetic alterations influence their inflammatory microenvironment, with RELA fusion activating NF-κB, leading to sustained TNF-α and IL-6 production, while 1q gain enhances pro-inflammatory cytokines, contributing to tumor aggressiveness.[190–192] Tumor-inflammation crosstalk involves various immune and stromal cells. TAMs contribute to an immunosuppressive milieu by secreting IL-10 and TGF-β, further dampening anti-tumor responses.[193] Additionally, VE cells play a role in promoting angiogenesis, sustaining tumor growth, and creating a hypoxic environment that supports immune evasion.[194] Clinically, ependymomas require aggressive treatment, with maximal safe resection followed by radiotherapy, as emphasized by the European Association of Neuro-Oncology.[195] A 50-year multi-institutional study of 122 adults with intracranial ependymomas found that gross-total or near-total resection with adjuvant radiotherapy significantly improved PFS and OS, while subtotal resection or biopsy without radiotherapy led to poorer outcomes.[196] With chemotherapy showing limited efficacy, alternative strategies targeting NF-κB-driven inflammation, enhancing DC function, and restoring NK cell cytotoxicity are being explored.

7.4. Astrocytoma

Astrocytomas (WHO grade 2–4) exhibit distinct immune and inflammatory profiles, with *IDH*-mutant tumors showing better prognosis due to their altered metabolic and immune landscape.[197] *IDH* mutations suppress T-cell infiltration through D-2-hydroxyglutarate production, dampening immune activation, while *TP53* mutations drive chronic inflammation via IL-6 and IL-8 secretion.[184,198] TAMs secrete TGF-β, promoting an immunosuppressive microenvironment, whereas MDSCs further inhibit T-cell responses.[47,199] Eosinophils contribute to peritumoral edema, potentially exacerbating neurological symptoms, while DCs exhibit impaired antigen presentation, weakening adaptive immunity.[200–203] Tregs suppress cytotoxic $CD8^+$ T-cell activity, limiting effective anti-tumor responses, and VE cells drive angiogenesis, sustaining tumor progression.[204,205] Clinically, *IDH*-mutant astrocytomas respond well to standard therapies like temozolomide and radiotherapy but exhibit immunosuppressive features that limit immunotherapy efficacy.[206] Despite a hypermutated phenotype post-temozolomide, immune checkpoint blockade has shown limited success.[207] Emerging strategies, including TAM polarization, Treg depletion, and PD-1/PD-L1 blockade, aim to enhance immune activation and improve therapeutic outcomes.

7.5. Meningioma

Meningiomas, arising from arachnoid cap cells, exhibit distinct immune microenvironments across WHO grades 1–3, influencing tumor behavior and therapeutic responses.[208] They generally arise from the dura, but rarely, they may arise in the neck, skin, paranasal sinus, oral cavity, skull, and orbit.[209] Grade 1 meningiomas show moderate immune cell infiltration, with $CD8^+$ T cells being predominant and Tregs ($FOXP3^+$) less frequent.[210] Mast cells are present in ~32–40% of cases and are linked to peritumoral edema, while TAMs, mostly M2-like, make up ~18% of the tumor mass.[211,212] In grade 2 meningiomas, there is an increased infiltration of Tregs, fostering an immunosuppressive environment, and mast cells are

observed in up to 90% of cases.[95,210,211] Grade 3 meningiomas show a significant rise in Tregs, correlating with tumor aggressiveness, along with a marked M2-TAM enrichment, driving tumor progression.[210,212] Mast cells further increase, potentially exacerbating peritumoral edema. Given the shift toward an immunosuppressive microenvironment in higher grades, targeting Tregs, reprogramming TAMs, and utilizing anti-angiogenic therapies for VEGF-driven tumors (linked to *NF2* mutations) may offer novel therapeutic avenues.[208] Understanding these stage-specific immune dynamics could enhance immunotherapy strategies and improve patient outcomes.

7.6. Hemangioblastoma

Hemangioblastomas, highly vascular tumors linked to *VHL* mutations, exhibit a distinct inflammatory microenvironment that evolves with tumor progression.[213] TAMs, particularly M2-polarized, secrete VEGF and PDGF, promoting angiogenesis and immune suppression.[105] In early-stage tumors, B cells form aggregates resembling tertiary lymphoid structures, suggesting chronic inflammation, but their role in tumor immunity remains unclear.[214] $CD8^+$ T cells are present but often dysfunctional due to the hypoxic and immunosuppressive microenvironment.[215] Given these dynamics, VEGF inhibitors (e.g., bevacizumab) and HIF-1α-targeting strategies are promising approaches to counteract tumor-induced angiogenesis and inflammation.[216,217] Understanding the immune landscape of hemangioblastomas could refine immunotherapeutic strategies and improve clinical outcomes.

7.7. Pituitary adenoma

Pituitary adenomas, originating from anterior pituitary cells, exhibit diverse hormonal activities and are influenced by specific genetic mutations that modulate their inflammatory microenvironment.[218] *GNAS* mutations, frequently observed in somatotroph adenomas, lead to constitutive activation of the cyclic adenosine monophosphate signaling pathway, promoting tumorigenesis and potentially enhancing inflammatory responses.[219–221] *USP8* mutations, particularly prevalent in corticotroph adenomas associated with Cushing's disease, result in increased deubiquitination and stabilization of the EGFR, thereby amplifying EGFR signaling and promoting IL-6 production.[222,223] The TME is further shaped by immune cell interactions; for instance, TAMs secrete IL-6, fostering tumor growth, while T cells are present in non-functional adenomas, potentially modulating tumor progression.[224,225] Given these insights, therapeutic strategies targeting the IL-6 signaling pathway may offer benefits for managing aggressive pituitary adenomas characterized by heightened inflammatory activity.

7.8. Schwannoma

Schwannomas are benign tumors originating from Schwann cells, frequently associated with *NF2* gene mutations.[226] Loss of NF2 function leads to dysregulation of the Hippo signaling pathway, resulting in unchecked cellular proliferation and tumor growth.[227] Within the TME, mast cells play a significant role by secreting histamine and TNF-α, which facilitate tumor progression.[228] This crosstalk between genetic mutations and inflammatory mediators suggests that targeting these pathways may offer therapeutic benefits for individuals with schwannomas. Emerging evidence indicates that Schwann cells themselves are active participants in the TME, influencing tumor behavior and immune responses.[229] Additionally, the NF-κB signaling pathway has been implicated in schwannoma progression, with its activation leading to increased expression of pro-inflammatory cytokines such as IL-6.[227] These insights highlight potential therapeutic targets, including NF-κB inhibitors and modulators of Schwann cell activity, to manage schwannoma growth and associated inflammation. Table 3 summarizes all the tumors, their interactions with inflammatory cells, and their potential therapeutic targets.

8. Balancing neuroinflammation: Therapeutic approaches for brain tumor

Managing neuroinflammation in brain tumors is a delicate balance, as not all inflammatory responses are harmful.[230] While some aspects of inflammation aid in immune surveillance and tumor suppression, others promote tumor growth, immune evasion, and resistance to therapy.[16] Thus, targeted modulation of inflammation is essential for optimizing patient outcomes. Emerging evidence from other malignancies, such as breast cancer, highlights how systemic metabolic dysfunction, particularly insulin resistance assessed by markers such as the TyG index, is associated with pro-inflammatory states and tumor progression, suggesting a broader link between metabolic dysregulation and inflammation-driven oncogenic pathways.[231] Given the complexity of brain tumors, a multi-modal therapeutic strategy integrating immunotherapy, anti-angiogenic agents, anti-inflammatory drugs, and combination therapies is crucial.[232,233] Targeting neurovascular unit dysfunction, particularly BBB instability, endothelial injury, and perivascular inflammation, represents an emerging strategy to modulate neuroinflammation while preserving tissue homeostasis.[12] Furthermore, identifying common inflammatory markers across brain tumors could pave the way for broad-spectrum therapeutic strategies, offering

Table 3. Summary of central nervous system tumors, inflammatory cell interactions, and potential therapeutic targets

Tumor type	WHO grade	Key genetic mutations	Inflammatory cells & cytokines (progression-associated)	Stage-specific mechanisms of tumor growth	Clinical impact & immune response	Potential therapeutic strategies
Glioblastoma	WHO Grade 4 (high-grade astrocytoma)	*EGFR* amplification, *PTEN* loss, *TERT* promoter mutation	Early (pre-invasive/low inflammation): microglia (IL-6, TGF-β), low $CD8^+$ T cells, low TAMs Progressive (highly inflamed tumor microenvironment): TAMs (IL-10, VEGF, CCL2), neutrophils (MMP-9, IL-8), Tregs (IL-10), exhausted $CD8^+$ T cells, MDSCs (TGF-β), suppressed DCs (low IL-12)	Early: local immune evasion, peritumoral edema. Advanced: angiogenesis, GAMs suppress immune surveillance, and ECM remodeling	Highly immunosuppressive, PD-L1 overexpression, T-cell exhaustion, and ineffective NK cell response. Immune evasion worsens with grade progression	Anti-PD-1, CXCR2 inhibitors (neutrophil-targeted therapy), TAM reprogramming (CSF-1R inhibitors), VEGF inhibition
Oligodendroglioma	WHO Grade 2 (low-grade) & Grade 3 (anaplastic)	*IDH1/2* mutations, 1p/19q co-deletion	Grade 2 (low-inflammation, slow-growing): T-cell infiltration ($CD8^+$, $CD4^+$), microglia (IL-1β, IL-6) Grade 3 (more immunogenic, increased inflammation): TAMs (IL-12, IL-10), low MDSCs, increased $CD8^+$ T-cell cytotoxicity, B-cell infiltration (IL-6)	Grade 2: metabolic adaptation via *IDH* mutation (low immune activation) Grade 3: increased pro-inflammatory signaling, increased vascularization	More immunogenic than GBM, lower PD-L1 expression, T-cell infiltration improves prognosis	IDH inhibitors, anti-PD-1, DC-based vaccines
Ependymoma	WHO Grade 1 (subependymoma), Grade 2, Grade 3 (anaplastic ependymoma)	RELA fusion (supratentorial), 1q gain	Grade 2 (immune cold, minimal inflammation): microglia (TGF-β, IL-10), few neutrophils Grade 3 (more pro-inflammatory, higher infiltration): TAMs (CCL2, IL-10), neutrophils (IL-8, MMP-9), DC suppression, $CD8^+$ T-cell exhaustion	Grade 2: minimal immune interactions, local tumor growth Grade 3: chronic inflammation, immune evasion via IL-10, enhanced vascularization via VEGF	High TGF-β, weak immune activation, poor $CD8^+$ T-cell response	NF-κB inhibitors, TGF-β blockade, DC-targeted therapy

(*Cont'd...*)

Table 3. (*Continued*)

Tumor type	WHO grade	Key genetic mutations	Inflammatory cells & cytokines (progression-associated)	Stage-specific mechanisms of tumor growth	Clinical impact & immune response	Potential therapeutic strategies
Astrocytoma	WHO Grade 2 (low-grade), Grade 3 (anaplastic), Grade 4 (IDH-wildtype = GBM equivalent)	*IDH1* mutations (Grade 2–3), *TP53* mutations (Grade 4, GBM-like progression)	Grade 2 (low inflammatory, *IDH*-mutation-associated immunosuppressive microenvironment): Tregs (IL-10), microglia (IL-6, TGF-β) Grade 3 (more aggressive, pro-inflammatory shift): TAMs (CCL2, IL-10, VEGF), neutrophils (IL-8, VEGF), $CD8^+$ T cells (reduced IFN-γ response). Grade 4 (GBM-like immunosuppression): PD-L1 overexpression, MDSCs (TGF-β), microglia-driven tumor support	Grade 2: IDH mutation creates an immunosuppressive environment Grade 3–4: angiogenesis, tumor immune evasion, chronic inflammation driving proliferation	IDH-mut tumors have better immune response, while *IDH*-wildtype (Grade 4) is highly immune evasive	IDH-targeted therapy, TGF-β inhibitors, anti-VEGF therapy, $CD8^+$ T-cell activation
Meningioma	WHO Grade 1 (benign), Grade 2 (atypical), Grade 3 (anaplastic)	*NF2* loss, *TRAF7* mutation	Grade 1 (low inflammatory, favorable outcome): microglia (IL-1β, IL-6), $CD8^+$ T cells (functional) Grade 2–3 (increased inflammation & aggression): TAMs (IL-6, TNF-α), neutrophils (IL-8), mast cells (Histamine, TNF-α), Tregs (IL-10)	Grade 1: slow-growing, limited immune involvement Grade 2–3: chronic inflammation promoting proliferation, ECM remodeling, angiogenesis	Immune infiltration increases with grade progression, inflammation-driven tumor aggression in high-grade meningiomas	VEGF inhibitors, Anti-histamine therapy, TNF-α inhibitors, Treg depletion strategies
Hemangioblastoma	WHO Grade 1	*VHL* mutation (HIF-1α activation)	Early stage (hypoxia-driven proliferation): TAMs (VEGF, IL-6, PDGF), mast cells (histamine, TNF-α), neutrophils (IL-8, VEGF) Later stage (highly vascularized, inflammatory environment): increased TAMs, $CD8^+$ T-cell exhaustion, VEGF-driven endothelial activation	Hypoxia-driven angiogenesis, immune evasion, and chronic inflammation promoting tumor progression	Tumor relies on VEGF-driven vascularization, with minimal immune response until late stages	HIF-1α inhibitors, VEGF-targeted therapy

(*Cont'd...*)

Table 3. (*Continued*)

Tumor type	WHO grade	Key genetic mutations	Inflammatory cells & cytokines (progression-associated)	Stage-specific mechanisms of tumor growth	Clinical impact & immune response	Potential therapeutic strategies
Pituitary adenoma	WHO Grade 1 (benign) & Grade 2 (atypical adenoma)	*GNAS* mutation (cAMP pathway activation), *USP8* mutations	Early (low-grade, minimal inflammation): microglia (IL-1β, IL-6), low neutrophils, Tregs (IL-10). Later stages (inflammatory shift, tumor growth): increased TAMs (IL-6, TNF-α), neutrophils (IL-8, VEGF), Mast Cells (histamine, TNF-α)	Inflammation-driven hormonal dysregulation and tumor growth, microglial activation sustaining pituitary proliferation	Immunosuppressive environment, but less aggressive than gliomas	IL-6 blockers, EGFR inhibitors, TNF-α inhibitors
Schwannoma	WHO Grade 1 (benign, slow-growing)	*NF2* (Merlin loss), *SMARCB1* (rare forms like Schwannomatosis)	Early: Microglia (IL-1β, IL-6, TGF-β), Low neutrophil infiltration Later: TAMs (VEGF, TGF-β), Mast Cells (Histamine, TNF-α), increased $CD8^+$ T cells	Merlin loss → Dysregulated PI3K/Akt signaling → Increased inflammatory signaling (IL-6, VEGF) → Promotes Schwann cell proliferation and ECM remodeling	Minimal immune evasion, but chronic inflammation sustains tumor survival. Mast cell activation drives peritumoral fibrosis and vascular changes	VEGF inhibitors, PI3K/Akt pathway blockers, IL-6 inhibitors, mast cell stabilizers (e.g., cromolyn sodium)

Abbreviations: Akt: Protein kinase B; cAMP: Cyclic adenosine monophosphate; CCL2: C-C motif chemokine ligand 2; CNS: Central nervous system; CSF-1R: Colony-stimulating factor 1 receptor; CXCR2: C-X-C motif chemokine receptor 2; DCs: Dendritic cells; ECM: Extracellular matrix; EGFR: Epidermal growth factor receptor; GAMs: Glioma-associated microglia/macrophages; GBM: Glioblastoma; HIF-1α: Hypoxia-inducible factor 1-alpha; IDH: Isocitrate dehydrogenase; IFN-γ: Interferon-gamma; IL: Interleukin; MDSCs: Myeloid-derived suppressor cells; MMP-9: Matrix metalloproteinase 9; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NK: Natural killer; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PDGF: Platelet-derived growth factor; PI3K: Phosphoinositide 3-kinase; PTEN: Phosphatase and tensin homolog; TAMs: Tumor-associated macrophages; TERT: Telomerase reverse transcriptase; TGF-β: Transforming growth factor-beta; TME: Tumor microenvironment; TNF-α: Tumor necrosis factor-alpha; Tregs: Regulatory T cells; VEGF: Vascular endothelial growth factor.

a universal inflammation-targeted approach in neuro-oncology.

Immunotherapy-based approaches have transformed cancer treatment, but their efficacy in brain tumors remains limited due to the immunosuppressive TME.[234] Immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 have shown promise in systemic cancers but have had only modest success in GBMs, possibly due to poor T-cell infiltration and a highly immunosuppressive milieu.[130,235–237] Combining checkpoint inhibitors with radiation or chemotherapy is being explored to enhance immune activation. Another promising avenue is the use of CSF-1R inhibitors, which reprogram TAMs from an immunosuppressive M2 phenotype to an immunostimulatory M1 state, potentially improving anti-tumor immunity.[176,238,239] However, clinical trials have not yet demonstrated significant survival benefits with these therapies. CAR-T cell therapy targeting tumor-specific antigens such as EGFRvIII in GBM and GPR20 in ependymomas has shown early success but is limited by poor T-cell trafficking into brain tumors and antigen heterogeneity, leading to immune escape.[240,241] Most prevalent adverse effects found with this therapy in glioma are cytokine release syndrome and CAR T-cell-related encephalopathy syndrome.[242]

8.1. NADPH oxidases and oxidative stress in brain tumor neuroinflammation

NADPH oxidases (NOX), particularly NOX2, NOX4, and NOX5, are increasingly recognized as important contributors to neuroinflammation and tumor progression in CNS tumors.[243,244] These enzymes are overexpressed in glioma cells, microglia, macrophages, and other components of the TME, where they promote the production of ROS and pro-inflammatory cytokines such as IL-6 and TNF-α.[245,246] Persistent NOX-associated oxidative stress contributes to chronic inflammation, extracellular matrix remodeling, angiogenesis, and tumor cell survival.[247] In addition, NOX-derived ROS have been implicated in resistance to chemotherapy and radiotherapy through activation of cellular survival pathways that protect tumor cells from oxidative damage.[248] Notably, NOX4 has been associated with temozolomide resistance in GBM.[249] Emerging evidence also suggests that pharmacological NOX inhibition may provide therapeutic benefit in brain tumors. In preclinical GBM models, NOX inhibitors such as GKT137831 (NOX1/NOX4 inhibitor) and VAS2870 (NOX1/NOX2/NOX4 inhibitor) have demonstrated reduced tumor growth, angiogenesis, invasion, and inflammatory signaling.[249] These findings highlight the potential role of NOX-targeted therapies as an emerging strategy for modulating tumor-associated neuroinflammation and therapeutic resistance.

8.2. Translational biomarkers and emerging therapeutic targets

Emerging evidence suggests that inflammatory biomarkers possess both prognostic and therapeutic significance in neuro-oncology. Elevated expression of IL-6, TGF-β, and PD-L1, increased infiltration of $CD163^+$ TAMs, and higher neutrophil-to-lymphocyte ratios have been associated with aggressive tumor phenotypes, immune evasion, and poorer clinical outcomes in GBM and other CNS tumors.[154] These inflammatory signatures may aid in patient stratification for immunomodulatory therapies and potentially predict therapeutic responsiveness. In addition, *IDH* mutation status has emerged as an important determinant of the tumor immune landscape, as *IDH*-mutant gliomas generally exhibit reduced immune-cell infiltration, lower inflammatory signaling, and a comparatively immunologically "cold" microenvironment.[197,250]

Several early-phase clinical studies have explored therapeutic targeting of inflammatory pathways in brain tumors.[251–254] CSF-1R inhibitors, including pexidartinib and related agents, have demonstrated the ability to modulate macrophage polarization and reduce immunosuppressive signaling in preclinical and early clinical investigations; however, durable survival benefits remain limited due to adaptive resistance mechanisms and compensatory pathway activation.[176,255,256] Similarly, IL-6 pathway inhibition using tocilizumab has shown potential in reducing inflammation-associated tumor progression and peritumoral edema, particularly in recurrent GBM and selected inflammatory pituitary adenomas and craniopharyngiomas.[257–263] Despite these advances, major challenges, including BBB penetration, intratumoral heterogeneity, and redundant cytokine signaling networks, continue to limit therapeutic efficacy. Collectively, these findings underscore the importance of biomarker-guided and combination-based immunotherapeutic strategies for improving clinical outcomes in neuro-oncology.

Since tumor vasculature is inherently abnormal and promotes hypoxia, immune exclusion, and therapy resistance, anti-angiogenic strategies have been explored to normalize blood vessels, enhance immune infiltration, and improve drug delivery.[264–266] Bevacizumab, an anti-VEGF monoclonal antibody, has been approved for recurrent GBM, where it reduces peritumoral edema and steroid dependence.[267,268] However, while it improves quality of life, it does not significantly prolong survival, as tumors adapt by activating alternative angiogenic pathways.[269,270] Multi-targeted tyrosine kinase inhibitors such as cabozantinib and lenvatinib inhibit VEGF signaling along with additional

pathways such as MET and AXL, potentially overcoming resistance to bevacizumab and offering a broader anti-angiogenic approach.[271,272]

As chronic inflammation sustains tumor growth, anti-inflammatory agents are a rational approach to modulating the immune response in brain tumors.[273,274] COX-2 inhibitors, such as celecoxib, have been explored in GBMs and meningiomas due to their ability to inhibit prostaglandin-mediated inflammation and immunosuppression.[273,275] However, despite preclinical promise, clinical trials have yielded mixed results. Corticosteroids such as dexamethasone are widely used to control peritumoral edema, but their immunosuppressive effects can diminish the efficacy of immunotherapies, making their judicious use essential.[276,277] Targeting specific cytokines involved in tumor inflammation, such as IL-6 and TGF-β, has also been investigated.[278–280] Tocilizumab, an anti-IL-6 receptor antibody, may be beneficial in GBMs and pituitary adenomas, where IL-6 plays a role in tumor progression.[281,282] Similarly, TGF-β inhibitors, which counteract the immunosuppressive and pro-tumorigenic effects of TGF-β in gliomas and ependymomas, have shown potential in trials, though challenges remain in achieving adequate brain penetration.[278,279,283,284]

In this review, we highlighted the critical role of TAMs, mast cells, and microglia in brain tumors, emphasizing their dual nature in both tumor progression and immune regulation. Inflammatory profiles differ substantially between low-grade and high-grade tumors, suggesting that stage-specific immunomodulatory approaches may be beneficial. In low-grade malignancies, microglia (IL-6, TGF-β) and early $CD8^+$ T-cell infiltration play a crucial role. Targeting IL-6 and TGF-β with specific inhibitors can help prevent progression while maintaining immune surveillance. In high-grade malignancies, there is a dominant shift toward immunosuppression and pro-tumor inflammation, primarily driven by TAMs and neutrophils (VEGF, IL-8, IL-10, MMP-9). In these cases, VEGF inhibitors, CXCR2 inhibitors (targeting neutrophils), and CSF-1R inhibitors (reprogramming TAMs) are key therapeutic strategies to counteract immune evasion and angiogenesis.

For such brain tumors, determining whether they are in an early stage (low inflammation) or a late progressive stage (chronic inflammation) is essential. In early-stage tumors, microglia (IL-1β, IL-6) and low neutrophil involvement suggest minimal immune modulation is needed. However, in progressive tumors, mast cells and TAMs (histamine, TNF-α, VEGF, IL-6) drive inflammation and vascular remodeling, promoting growth. Mast cell stabilizers (cromolyn sodium), IL-6 blockade, and VEGF-targeted therapy can help control tumor-associated inflammation while preserving function. By adopting this progression-associated, inflammation-guided strategy, clinicians can personalize treatment, balancing immune suppression and tumor control for optimal patient outcomes (Figure 1).

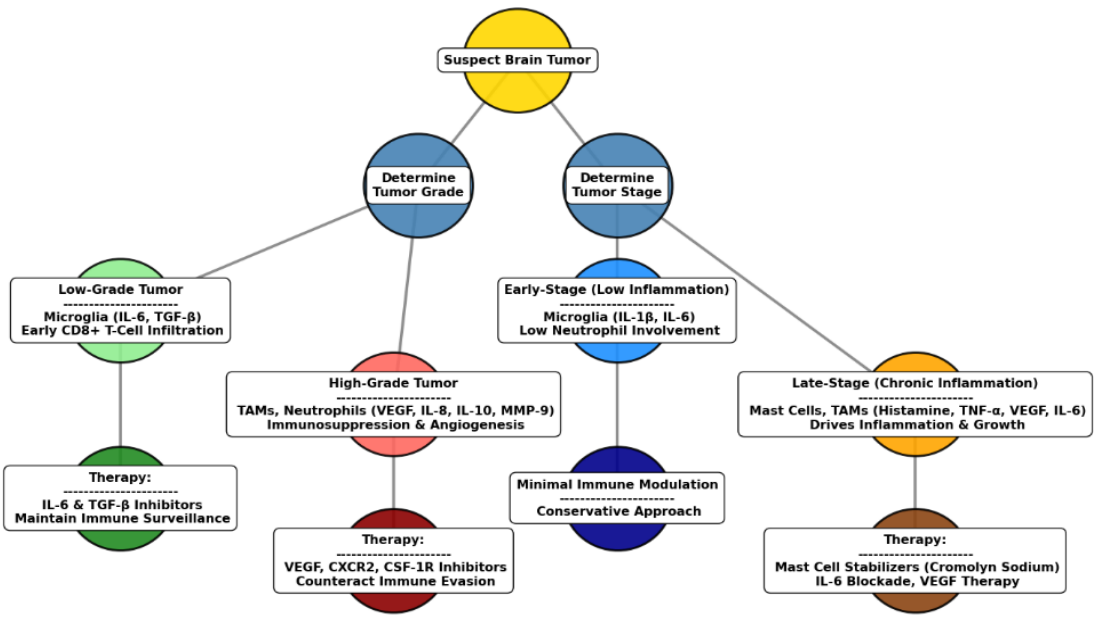

Figure 1. Schematic diagram of an inflammation-guided clinical approach to brain tumors

Early detection of these cells may guide therapy selection, helping prevent progression to more aggressive forms and to maximize anti-tumor immunity while preserving surrounding neural function.

9. Current limitations and future directions

This review has several limitations. Much of the currently available literature remains dependent on preclinical investigations, in vitro studies, and heterogeneous experimental models. The dynamic and highly variable nature of TME interactions across different CNS tumor types also limits direct comparison between studies. In addition, longitudinal clinical validation and large patient-derived investigations remain limited in several areas of neuroinflammatory research. Future studies integrating molecular, immunological, metabolic, and clinical datasets may improve understanding of TME dynamics and support the development of more personalized therapeutic strategies. Further mechanistic and longitudinal studies are required to better clarify the direct contribution of specific inflammatory pathways to tumor progression and therapeutic resistance.

10. Conclusion

Neuroinflammation in brain tumors serves as both a driver of tumor progression and a potential therapeutic target. The complex interplay between immune cells and the TME influences treatment response and disease outcomes. While immunotherapies have shown promise, their efficacy remains inconsistent, highlighting the need for a deeper understanding of inflammatory pathways. Identifying common inflammatory markers across brain malignancies could facilitate the development of more precise and effective therapeutic strategies. Acute inflammation may initially suppress tumor growth through immune activation; chronic inflammation fosters an immunosuppressive microenvironment that supports tumor survival and therapy resistance. Various immune cells, including microglia, neutrophils, mast cells, and TAMs, contribute to this dynamic interplay. Persistent inflammation can also drive angiogenesis, tissue remodeling, and tumor recurrence in brain malignancies. Both malignant and benign tumors exhibit diverse inflammatory microenvironments that influence their growth, progression, and treatment response. Genetic and immune interactions shape cytokine profiles, immune cell activity, and inflammatory pathways, impacting therapy effectiveness. Effective management of brain tumors requires balancing pro- and anti-inflammatory responses to optimize immune surveillance while minimizing tumor-promoting inflammation. A multi-modal approach integrating immunotherapy, anti-angiogenic agents, and targeted anti-inflammatory treatments can improve outcomes. Understanding stage-specific inflammatory patterns helps personalize therapy, guiding the use of immune modulators, cytokine inhibitors, and vascular-targeted strategies.

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