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Review Articles

Tumor microenvironment in glioblastoma: The central role of the hypoxic–necrotic core

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ABSTRACT

Glioblastoma (GBM), the most aggressive and lethal primary brain tumor, is characterized by profound intratumoral heterogeneity and a hostile tumor microenvironment (TME) that drives immune evasion, therapeutic resistance, and relentless progression. Among its defining pathological features is the development of a hypoxic–necrotic core, long recognized as a hallmark of poor clinical outcome. This review synthesizes current insights into how hypoxia and necrosis act not merely as pathological markers, but as a spatiotemporal evolution engine of the GBM TME, driving metabolic adaptation, extracellular matrix (ECM) remodeling, and immune evasion. We examine how oxygen and nutrient deprivation activate hypoxia-inducible factors (HIFs), triggering cascades that promote angiogenesis, altered metabolism, and accumulation of immunosuppressive metabolites. These stressors also contribute to the recruitment and polarization of tumor-associated macrophages (TAMs) and neutrophils (TANs), expansion of myeloid-derived suppressor cells (MDSCs), and infiltration of regulatory T cells (Tregs), collectively creating an immune-excluded niche. Furthermore, hypoxia-induced ECM stiffening and degradation enhance tumor invasiveness while limiting immune cell access. By exploring the dynamic interplay between physicochemical stressors and immune modulation within the necrotic core, this review highlights the need for targeting the hypoxia-necrosis axis to overcome current therapeutic limitations. A deeper understanding of these processes will be crucial for the development of precision-targeted therapies in this highly refractory malignancy.

1. Introduction

Gliomas are the most common primary brain tumors, originating from glial or neuroglial progenitor cells in the central nervous system (CNS). Representing a heterogeneous group, gliomas are classified histologically and molecularly into astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas [1,2]. The malignancy of gliomas is graded from 1 to 4 according to the World Health Organization (WHO) classification system [3]. Low-grade gliomas (grades 1 and 2) are characterized by low proliferative potential, with grade 1 lesions often being curable through surgical resection. In contrast, high-grade gliomas (grades 3 and 4) exhibit aggressive proliferation, greater malignancy, and worse prognoses [3,4].

Among gliomas, glioblastoma, classified as a grade 4 astrocytoma, is the most malignant and prevalent subtype, accounting for 60 % of all astrocytic tumors and nearly 50 % of malignant brain tumors across all age groups [1,5,6]. GBM's biological complexity is matched by its clinical challenges. Despite significant advances in neuro-oncology, the standard treatment, known as the Stupp protocol, has remained unchanged for two decades. This regimen consists of maximal surgical resection followed by radiotherapy with concomitant and adjuvant temozolomide chemotherapy. However, patient outcomes remain bleak. Even after treatment, the median survival for GBM patients ranges from 10 to 15 months, with most experiencing tumor recurrence within one year of diagnosis. Long-term survival is exceptionally rare, with only 7 % of patients surviving five years post-diagnosis, a percentage that drops to 2 % for individuals aged 65 years or older [6,7].

Traditionally, CNS tumor grading was based exclusively on the

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analysis of histological features. Its hallmark histological features include microvascular proliferation, necrosis surrounded by hypercellular pseudopalisading regions, and marked heterogeneity in cell morphology and molecular profiles [8]. However, "The 2021 WHO Classification of CNS Tumors" has added molecular markers as a powerful diagnostic information technique [3]. Thus, telomerase reverse transcriptase (*TERT*) promoter mutation, epidermal growth factor receptor (*EGFR*) amplification, and +7/-10 copy number changes in isocitrate dehydrogenase (*IDH*)-wildtype diffuse astrocytoma allow the designation of a tumor as glioblastoma even in cases where, histologically, it appears as a lower-grade tumor [9].

A defining characteristic of glioblastoma is its profound intratumoral and microenvironmental heterogeneity, as recognized by the now outdated term 'multiforme'. This heterogeneity is not confined to tumor cells alone but extends to the tumor microenvironment, which constitutes a highly dynamic and interactive network that promotes tumor progression, immune evasion, and therapy resistance. In fact, while distinct GBM subtypes exist, patients not only display different subtypes within the same tumor but also show heterogeneity in the stromal cells of the TME [10]. This TME comprises both cellular and noncellular components that interact synergistically to sustain tumor growth. The cellular component includes not only tumor cells but also immune and stromal cells that contribute to an immunosuppressive and tumor-promoting niche. The noncellular component can be further categorized into physicochemical factors and structural elements. The physicochemical factors include oxygen and nutrient gradients, metabolic byproducts, and soluble signaling molecules, that promote the formation of hypoxic and necrotic regions. The structural elements are mainly represented by the extracellular matrix, which provides mechanical support and modulates cell signaling (Table 1).

Table 1
Hallmarks of the glioblastoma tumor microenvironment centered on the hypoxic–necrotic core. This table summarizes key physicochemical, structural, and cellular features of the glioblastoma microenvironment, highlighting how the hypoxic–necrotic core orchestrates metabolic reprogramming, extracellular matrix remodeling, and immune suppression to promote tumor progression.

Component	Key Features	Effects of the Hypoxic–Necrotic Core
Physicochemical	- Gradients of oxygen, glucose, pH, and interstitial fluid pressure - Accumulation of metabolites and soluble factors (e.g., adenosine, lactate)	- Stabilizes HIF-1/2/3α, reprogramming metabolism toward glycolysis and glutaminolysis (Warburg effect) - Promotes VEGF and other pro-angiogenic factors - Acidifies the TME, impairs immune cell function - Drives production of immunosuppressive metabolites (adenosine, kynurenine, ROS)
Structural	- ECM enriched in collagen, HA, fibronectin - Elevated stiffness (up to 26 kPa) vs normal brain (100–1000Pa)	- Promotes ECM remodeling via MMPs, LOX, TIMPs - Impairs immune infiltration - Enhances tumor cell invasion along rigid ECM tracks
Cellular	- Dominated by immunosuppressive populations (TAMs, TANs, MDSCs, Tregs) - Reduced infiltration and exhaustion of $CD8^+$ T cells	- Recruits TAMs/TANs and drives M2/N2-like polarization - Increases BMDM-derived TAMs (>80 %) in core, reinforces immunosuppression - Induces checkpoint molecules (PD-L1, TIM-3, LAG-3, VISTA) - Attracts Tregs via CCL20, IL-10, IL-23 - Suppresses NK via IL-2, IFN-γ, GM-CSF, CCL3, CCL5

Among these factors, central necrosis emerges as a central force in shaping GBM evolution (Fig. 1). Despite transcriptional class differences, all glioblastoma subsets share a common feature; the development of a necrotic core, suggesting that this may be a common final pathway that represents an abrupt turning point to rapid expansion [11]. Hypoxia plays a central role in this process [12–14], giving rise to central necrotic regions that induce cellular migration toward vascularized, nutrient-rich areas, forming pseudopalisades [15–17]. This cycle of necrosis, angiogenesis, and cellular invasion contributes to GBM's extensive infiltration into healthy brain parenchyma, rendering complete surgical resection impossible and fueling resistance to adjuvant therapies [18–20]. Besides, the emergence of the necrotic core further exacerbates tumor progression by driving metabolic reprogramming, altering immune cell recruitment, and enhancing invasive potential. In fact, patients with poorer prognosis consistently exhibit higher proportions of tumor cells enriched in hypoxia-associated transcriptional programs, both within malignant and immune compartments [21].

Collectively, these features emphasize the critical role of the TME in driving glioblastoma progression and underscore the hypoxic–necrotic niche as a central, unifying feature across diverse GBM subtypes. In this review, we provide a comprehensive analysis of the distinct components of the glioblastoma microenvironment, focusing on how the necrotic core shapes metabolic reprogramming, extracellular matrix remodeling, and immune modulation. By dissecting the reciprocal interactions between hypoxia-induced necrosis and each TME compartment, we aim to clarify the mechanisms of this hallmark process and highlight its potential as a therapeutic vulnerability. A deeper understanding of how the hypoxic–necrotic core orchestrates tumor-stroma crosstalk may contribute to the development of more precise and effective strategies targeting the most treatment-resistant niches within glioblastoma.

2. The physicochemical component: a focus on the hypoxic–necrotic core

The physicochemical component represents one of the most significant determinants of glioblastoma, contributing to the tumor's resistance and aggressiveness. It includes molecules such as growth factors, cytokines, chemokines, and gradients of oxygen and nutrients, which create regions of hypoxia, low pH, and elevated interstitial fluid pressure within the tumor mass [22]. This unique composition gives rise to one of the most distinct anatomical features, the hypoxic–necrotic core. The development of central necrosis is a turning point at which the tumor foreshadows an aggressive expansion. The presence of necrosis was the first feature associated with poor prognosis among diffuse gliomas and the sole criterion for naming glioblastoma as grade 4 for decades, and even today it remains a characteristic feature of this tumor. This necrotic core is characterized by severe oxygen and nutrient deprivation. It arises from the tumor's rapid growth and structurally abnormal vasculature, which often leads to intratumoral thrombosis [23]. As the tumor expands, the growing distance from functional blood vessels leads to hypoxia and subsequent necrosis at the tumor core [24]. In fact, oxygen concentration in the human brain ranges between approximately 4.6 % O_2 in the healthy brain to 1.7 % O_2 in a brain tumor [25].

2.1. Metabolic rewiring in the hypoxic–necrotic core

Tumor cells in the hypoxic regions of GBM adapt to these harsh conditions by activating survival pathways, increasing glycolysis (Warburg effect), and promoting the secretion of pro-angiogenic factors like vascular endothelial growth factor (VEGF) to stimulate the formation of new, often defective, blood vessels [26,27]. The Warburg effect enables cancer cells to prioritize glycolysis for energy and biosynthesis, even under aerobic conditions, producing lactate that acidifies the tumor microenvironment. In glucose-deprived conditions, lactate

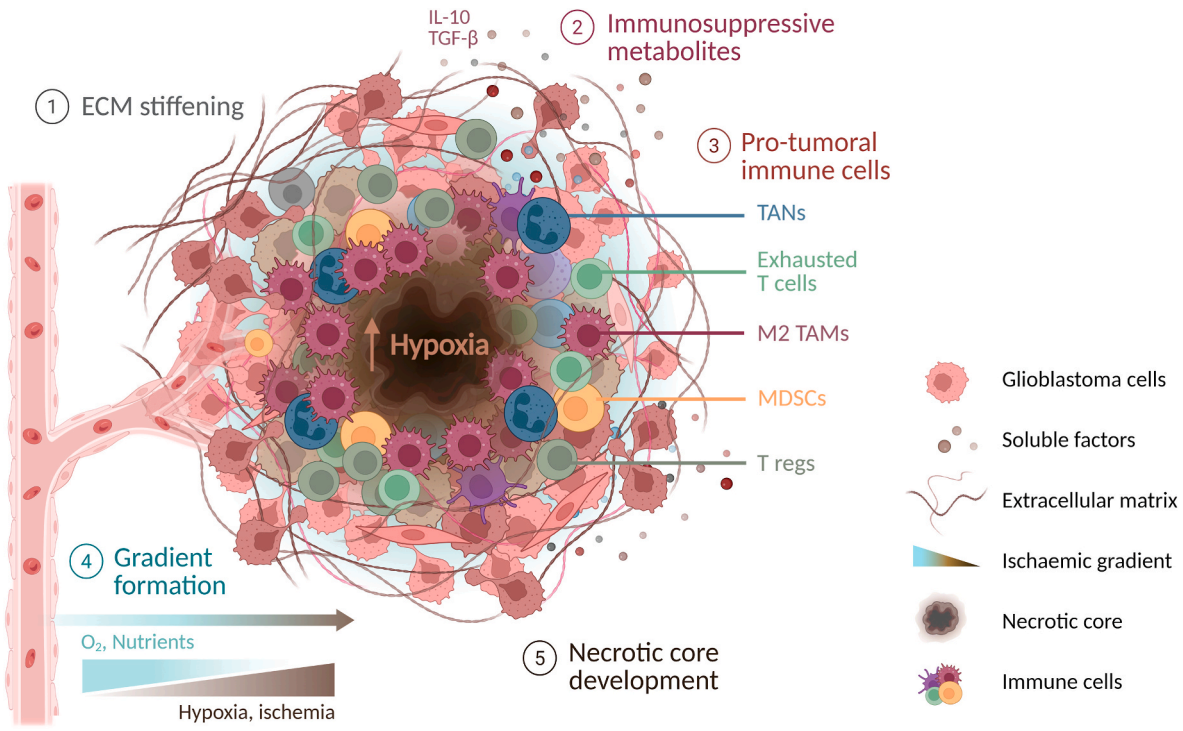

Fig. 1. The necrotic core as a central hub of tumor evolution: cellular and molecular landscape. Schematic representation of the glioblastoma microenvironment, highlighting the core where nutrient and oxygen gradients decline radially from nearby vasculature. The region exhibits increased extracellular matrix stiffness and is enriched in immunosuppressive cell types, including tumor-associated macrophages, regulatory T cells, myeloid-derived suppressor cells, tumor-associated neutrophils, and exhausted T cells. Soluble immunosuppressive factors such as IL-10 and TGF-β are also elevated, contributing to immune evasion. Rather than a static hostile niche, these hypoxic and ischemic conditions function as a dynamic driver of spatiotemporal adaptation, forcing tumor progression and limiting therapeutic efficacy.

signals oxidative tumor cells to rely on glutaminolysis, a key metabolic pathway fueled by glutamine to sustain rapid proliferation. Additionally, HIFs reshape the metabolic profile of tumors to generate immunosuppressive metabolites such as adenosine, kynurenine, and reactive oxygen species (ROS), which impair immune cell function within the tumor microenvironment [28,29]. Under ischemic stress, activation of the p38–MAPK/MK2 signaling axis further amplifies ROS-dependent cell death and inflammatory gene expression, linking metabolic stress to necrosis-driven inflammation and tumor progression in GBM [30].

Besides altering metabolism, the transcription factors HIF 1α, 2α, and 3α regulate the expression of genes involved in aggressive, pro-invasive, and highly immunosuppressive phenotypes [31]. Under normoxic conditions, HIF-α subunits are hydroxylated by prolyl hydroxylase domain proteins (PHDs) and factor-inhibiting HIF-1 (FIH), marking them for ubiquitination and proteasomal degradation via the Von Hippel-Lindau (VHL) protein. In hypoxic conditions, reduced oxygen availability inhibits PHD activity, allowing HIF-α to stabilize and translocate to the nucleus. Once there, HIF-α forms complexes with HIF-β and coactivators, binding to hypoxia response elements (HREs) to regulate the expression of genes involved in glycolysis (e.g., glucose transporter type 1, *GLUT1*), erythropoiesis (e.g., erythropoietin, *EPO*), and angiogenesis (e.g., *VEGF*). Additionally, HIF drives the production of other proangiogenic factors, including nitric oxide synthase (NOS), platelet-derived growth factor (PDGF), adrenomedullin, and interleukin 8 (IL-8), collectively promoting angiogenesis and supporting tumor adaptation to hypoxia within the microenvironment [32,33].

3. The structural component: stiffness-mediated modulation by extracellular matrix

Structurally, the tumor is surrounded by an extracellular matrix, a dense and intricate web of macromolecules such as collagen, laminin, fibronectin, and hyaluronan. It not only provides physical scaffolding, but also modulates cell signaling pathways central to cellular invasion, proliferation, differentiation, survival, and brain tissue homeostasis [34]. The ECM of GBM is characterized by an abnormal overexpression of collagens, hyaluronic acid (HA), and other fibrous components, which leads to increased tissue stiffness and reduced tissue flexibility [35,36]. It has been observed that the stiffness of normal brain tissue ranges from 100 to 1000 Pa. In the GBM tumor niche, increased secretion and remodeling of ECM fibrous proteins can lead to an increase in tissue stiffness, up to 26 kPa [37]. This dense ECM structure impairs the diffusion of molecules and limits the ability of immune cells to infiltrate the tumor, further promoting tumor cell survival and resistance to therapy [34,38]. The abnormal ECM composition is one of the factors that contributes to ECM's role in enhancing tumor migration and invasiveness, as tumor cells can exploit the rigid matrix to facilitate their spread to surrounding tissues [39–41]. Therefore, targeting ECM with anti-fibrotic agents or ECM-remodeling inhibitors may enhance the delivery of therapeutic agents and improve immune cell infiltration into the tumor.sla

3.1. *Matrix remodeling in the hypoxic–necrotic core*

The presence of the hypoxic–necrotic core is related to the modification of ECM properties in glioblastoma. Importantly, recent single-cell and spatial transcriptomic studies have revealed that hypoxia is not only a metabolic stressor but also a major driver of spatial organization in GBM, establishing concentric cellular layers that define its distinctive tumor microenvironment [42]. In fact, another single-cell study also highlights that hypoxia drives transcriptional and phenotypic shifts in GBM. For example, in glioblastoma, hypoxic cells preferentially adopt a mesenchymal (MES)-like state [43], aligning with prior characterizations of MES states as hypoxia-dependent [44]. Interestingly,

biomechanical factors such as ECM stiffness and integrin mechanosignaling further reinforce this mesenchymal, stem-like program. As demonstrated by Weaver's group, recurrent GBMs exhibit increased tissue tension and expansion of a glycoprotein-rich glycocalyx that amplifies integrin signaling and sustains a self-reinforcing circuit of mesenchymal reprogramming, invasion, and therapeutic resistance [45]. By contrast, in IDH-mutant gliomas, hypoxic cells tend to shift toward an astrocytic (AC)-like state, which may partly explain the more favorable prognosis in this subtype.

Hypoxia-driven HIF activation enhances the transcription of genes involved in ECM remodeling, facilitating tumor invasion and metastasis. HIFs upregulate matrix metalloproteinase 2 (MMP2), MMP9, MMP14, and MMP15, promoting basement membrane degradation, while also inducing ECM protein synthesis (e.g., collagen and fibronectin) to support ECM deposition and remodeling [46]. Notably, fibronectin accumulates in perinecrotic regions of GBM tumors and contributes to tumor progression by enhancing invasiveness, angiogenesis, and immunosuppression, partly through the recruitment of regulatory T cells [47–49]. In contrast, decorin, which is also markedly upregulated within the necrotic core, has been associated with reduced ECM stiffness and increased immune activation, suggesting that distinct ECM components enriched in hypoxic regions can have opposing roles in tumor behavior [47,50,51]. Additionally, HIFs regulate lysyl oxidases (LOX), increasing ECM stiffness, and modulate tissue inhibitors of metalloproteinases (TIMPs) to fine-tune MMP activity, ensuring a dynamic balance in ECM remodeling that supports tumor progression [52].

4. The cellular component: immune system and its modulation by the TME

Beyond physicochemical and structural factors, the cellular component of the TME contains a heterogeneous mix of non-neoplastic cells, including infiltrating and resident immune cells, vascular endothelial cells, and glial cells, which interact with glioblastoma cells to create a tumor-supportive and immunosuppressive niche [53–55].

Among immune components, TAMs have emerged as critical players in glioblastoma progression, with a strong immunosuppressive phenotype as shown in a recent pan-cancer study by The Cancer Genome Atlas (TCGA) [56–58]. This category includes ontogenetically distinct populations, such as resident brain microglia and bone-marrow-derived monocytes (BMDMs), which differentiate into macrophages upon extravasation into the brain parenchyma. Some studies suggest that BMDMs, but not microglia, are responsible for mediating the intratumoral immune response [59]. TAMs reciprocally interact with glioblastoma cells, promoting tumor growth, progression, and therapeutic resistance through mechanisms that include the secretion of immunosuppressive cytokines (e.g., transforming growth factor β (TGF-β), prostaglandin E−2 (PGE2) and IL-10) [60], recruitment of pro-tumoral MDSCs, facilitation of Tregs expansion and inhibition of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells [22,55].

MDSCs share functional similarities with TAMs, which complicates their phenotypic classification. In humans, MDSCs are commonly described based on a combination of myeloid surface markers, including CD33, CD14, and CD15, while in murine models, markers such as CD11b and Gr1 are used [61]. TAMs contribute to the recruitment of MDSCs by secreting C-C Motif Chemokine Ligand 2 (CCL2), promoting their mobilization from the bloodstream, while glioma stem cells (GSCs) secrete macrophage migration inhibitory factor (MIF), further amplifying the immunosuppressive capabilities of MDSCs [62]. The effects of MDSCs are largely associated with the inhibition of innate and adaptative responses, dampening the activity of CTLs and NKs. They have a crucial role in the upregulation of programmed death ligand 1 (PD-L1), which suppresses the activity of $CD4^+$ T cells within the glioblastoma TME [63].

Recent evidence expands this view of the myeloid compartment to include tumor-associated neutrophils as emerging modulators of the glioblastoma immune landscape. Traditionally viewed as short-lived and functionally limited, TANs are now recognized as versatile modulators of glioblastoma biology. They are recruited to the tumor site through chemotactic signals such as CXCL8/IL-8 and granulocyte colony-stimulating factor (G-CSF), where they adopt distinct polarization states ranging from pro-inflammatory and cytotoxic to immunosuppressive and pro-angiogenic phenotypes [64,65]. Comprehensive analyses of human IDH wild-type gliomas and brain metastases have shown that TANs infiltrate brain tumors in substantial numbers and exhibit prolonged survival within the TME. In a study by Joyce and colleagues, TANs were found to acquire an immunosuppressive and pro-angiogenic phenotype driven by tumor-derived TNF-α and ceruloplasmin secreted by surrounding myeloid cells, establishing a myeloid-centered regulatory niche that sustains immune evasion and vascular remodeling [66]. Concurrently, recent single-cell analyses in glioblastoma models identified a distinct subset of "hybrid" dendritic-like TANs, characterized by morphological complexity, antigen-processing capacity, and MHC class II-dependent T-cell activation [67]. These cells originate from immature precursors within the skull bone marrow, rather than from circulating neutrophils, and appear capable of exerting antitumoral effects when functional T-cell populations are present. Their discovery redefines the role of TANs as part of a broader continuum of myeloid plasticity, in which neutrophils can polarize toward either tumor-promoting or antigen-presenting phenotypes depending on local cues such as hypoxia, cytokine milieu, and T-cell infiltration.

In GBM, the number of infiltrating lymphocytes is markedly reduced compared to other solid tumors, accompanied by a pronounced suppression of Th1 lymphocytes [58]. The most commonly observed populations in the TME include Tregs, as well as $CD3^+$ T helper cells, $CD4^+$ and $CD8^+$ T cells. Tregs represent a specialized group of T lymphocytes essential for maintaining immune tolerance and homeostasis. Their interaction with myeloid cells forms a mutually reinforcing cycle of immunosuppression, as Tregs enhance the persistence and functionality of MDSCs [61]. This partnership plays a pivotal role in creating an immunosuppressive environment that protects GBM from effective immune detection and elimination. Tregs are recruited to the tumor site in response to CCL2 and indoleamine 2,3-dioxygenase (IDO) produced by GSCs and dendritic cells, worsening patient survival [68–70]. Additionally, GBM and pro-tumoral immune cells upregulate the expression of immune checkpoint molecules on infiltrating T cells, such as T-cell immunoglobulin and mucin containing protein-3 (TIM-3), programmed cell death-1 (PD-1)/PD-L1, cytotoxic T-lymphocyte associated protein 4 (CTLA-4), leading to T cell exhaustion [71]. Simultaneously, TAMs contribute to the depletion of hypoxia-induced phosphatidylserine (PS)-expressing $CD8^+$ T cells, further shaping the immunosuppressive TME [72,73].

4.1. Immunosuppressive niche in the hypoxic–necrotic core

Hypoxia and central necrosis greatly influence the immune compartment (Fig. 2). Following necrosis, TAMs represent the most abundant non-neoplastic cells within GBM, constituting up to 30–50 % of the GBM cellular mass and serving as a poor prognostic factor [53]. Functional diversity within this compartment reflects distinct ontogenies: resident microglia are more abundant in peripheral and hypercellular tumor regions, where they appear to facilitate diffuse infiltration, whereas BMDMs accumulate preferentially in necrotic and perivascular areas [74]. In fact, in advanced lesions characterized by extensive hypoxia and necrosis, over 80 % of TAMs are derived from BMDMs rather than microglia [75–77]. In addition, the density of TAMs is increased up to tenfold in hypoxic, perinecrotic areas [74,78]. Recent single-cell and spatial transcriptomic studies have confirmed these observations, showing a strong enrichment of immunosuppressive myeloid populations and a relative paucity of microglia in perinecrotic niches [79,80]. While some BMDMs remain within the perivascular niche,

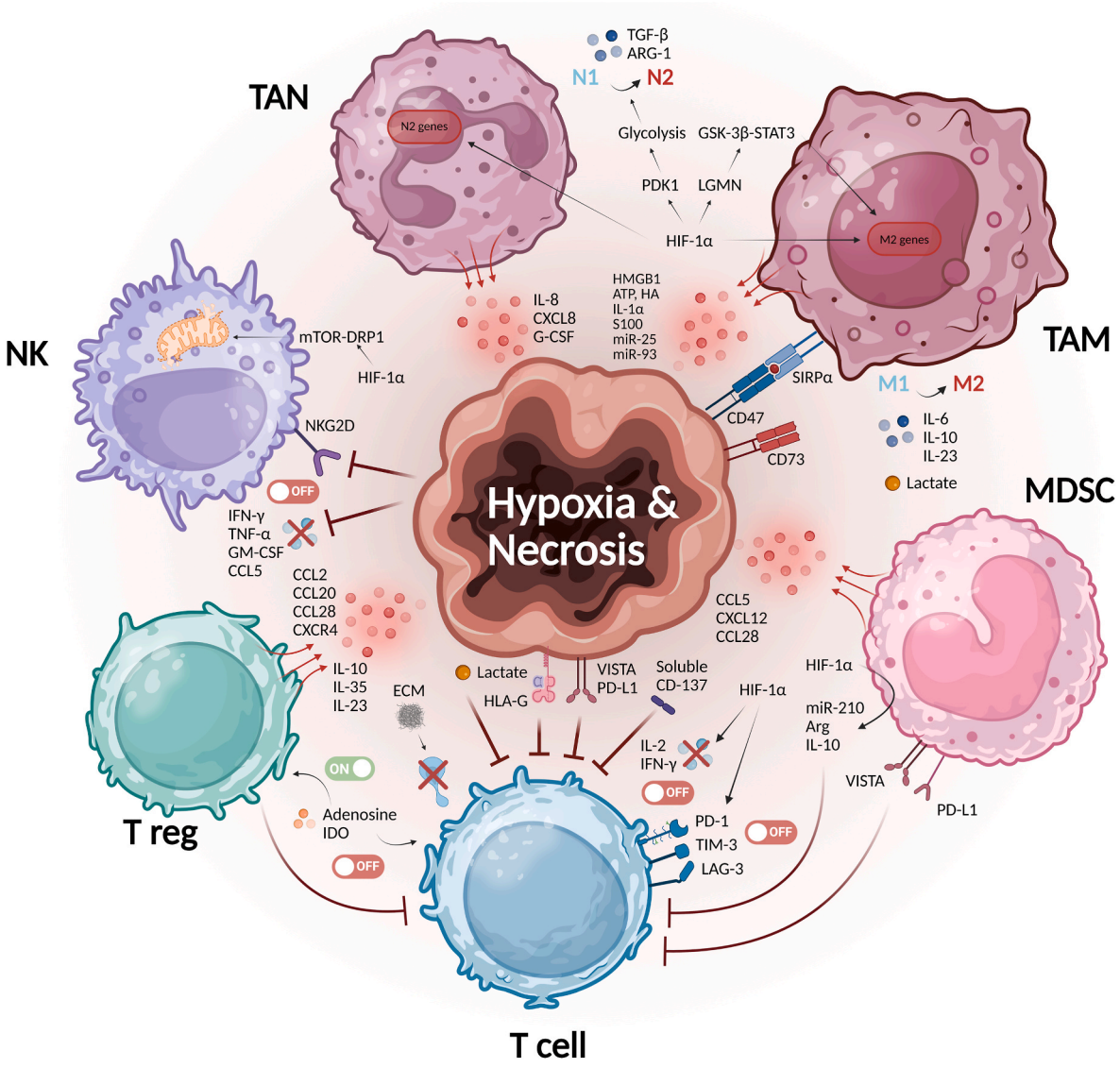

Fig. 2. Hypoxia and necrosis drive immunosuppressive remodeling in the GBM microenvironment. Central necrosis and hypoxia orchestrate a profound immunosuppressive shift within the GBM TME. Hypoxia promotes recruitment and M2/N2-like polarization of TAMs and TANs via HIF-1α signaling, DAMPs release, lactate accumulation, and immunosuppressive cytokines. T cell effector functions are inhibited through metabolic stress, immune checkpoint upregulation (PD-1, TIM-3, LAG-3), and reduced IL-2/IFN-γ signaling. Regulatory T cells and MDSCs are enriched and activated by hypoxia-induced chemokines, adenosine, and checkpoint molecules (PD-L1, VISTA). NK cell cytotoxicity is diminished via HIF-1α–mediated downregulation of activating receptors. Together, these mechanisms establish an immune-evading niche that supports tumor progression.

others migrate through the parenchymal space, guided by the hypoxic gradient, toward the necrotic core. Upon reaching this region, they encounter GSCs within the perinecrotic niche, forming a mutually advantageous relationship that supports their survival in an otherwise hostile environment [81]. A recent single-cell spatial analysis by Coy et al. demonstrated that perinecrotic hypoxic regions are also enriched for tumor cells with elevated CD73 expression, a key mediator of adenosine metabolism linked to the recruitment of protumoral myeloid cells and enhanced immunosuppression [82]. Interestingly, GSCs within these perinecrotic niches also appear intrinsically adapted to evade immune surveillance. It has been shown that GSCs exhibit reduced Toll-like receptor 4 (TLR4) expression compared with non-stem tumor cells, rendering them unresponsive to inflammatory stimuli present in the necrotic microenvironment and allowing their persistence despite local activation of innate immune pathways [83].

Importantly, hypoxia not only drives TAM recruitment but also regulates their immunosuppressive polarization through specific molecular mediators. Hypoxia promotes M2-like polarization of TAMs through direct induction of M2-specific genes and cytokine signaling (e.g., IL-6, IL-10 and IL-23) [84]. Necrotic cells additionally release endogenous damage-associated molecular patterns (DAMPs), including adenosine triphosphate (ATP), HA, high mobility group box 1 (HMGB1), IL-1α and S100 proteins, which are capable of modulating TAMs or damage-associated microglia in the TME [85]. A number of these molecules act by mediating inflammatory responses that initially attract anti-tumor (M1-like) populations and then switch these cells into immunosuppressive (M2-like) macrophages, thereby enriching TME in a pro-tumor landscape. Moreover, the HIF1α- 3-phosphoinositide-dependent protein kinase 1 (PDK1) axis drives glycolytic reprogramming in macrophages, enhancing their migratory capacity under hypoxia [86]. Recent work has identified the cysteine protease legumain (LGMN), transcriptionally induced by HIF-1α, as a key regulator of this process. LGMN enhances the GSK-3β–STAT3 signaling cascade, reinforcing TAM M2-like polarization and immune evasion, while its inhibition restores $CD8^+$ T-cell activity and sensitizes tumors to anti-PD-1 therapy, positioning it as a pivotal molecular link between hypoxia and

immunosuppression in GBM [87]. Notably, recent evidence indicates that TAMs residing in hypoxia-induced perinecrotic zones not only exert immunosuppressive effects but also destabilize endothelial adherens junctions, thereby restricting immune cell infiltration into the tumor [88].

Hypoxic glioma cells contribute further to this immunosuppressive microenvironment through the release of extracellular vesicles carrying microRNAs. For instance, miR-25 and miR-93 produced under hypoxia can be shuttled to normoxic macrophages, suppressing cGAS expression, impairing type I IFN release, reducing M1 gene expression, and decreasing chemoattraction of T cells via diminished CXCL9/10 levels [89]. Similarly, hypoxia-induced exosomal miR-25-3p promotes M2 polarization of macrophages by activating the PHLPP2/PI3K-AKT-mTOR signaling pathway, suggesting that interventions targeting miR-25-3p transmission or PI3K-AKT activation could disrupt immune suppression [90]. Beyond miRNAs, hypoxia-driven lactate accumulation in glioma cells is taken up by macrophages, where it drives M2 polarization through TNFSF9 regulation via MCT-1/H3K18La signaling, thereby supporting tumor progression [91].

Recent studies have revealed that TANs also localize preferentially within hypoxic and perinecrotic regions, where they actively contribute to the immunosuppressive and proangiogenic features of the niche [92]. Hypoxia-induced glioma cells secrete chemotactic factors such as IL-8/CXCL8 and G-CSF, promoting TAN recruitment and retention in oxygen-deprived areas [93]. Within these acidic and nutrient-poor environments, glycolytic adaptation enhances neutrophil survival, favoring their accumulation near necrotic cores [94,95]. Hypoxia further drives the acquisition of an N2-like phenotype through mediators such as acrolein and TGF-β, which suppress myeloperoxidase activity, reduce ROS production, and induce the expression of arginase-1, thereby attenuating their cytotoxic potential [96]. In parallel, a subset of TANs upregulates VEGFA in response to low oxygen tension, supporting angiogenesis and tumor expansion [97].

Hypoxia-induced signaling not only reshapes myeloid behavior but also favors immune evasion by suppressing cytotoxic responses. Recent studies have associated hypoxic niches with T cells displaying naïve or memory-like transcriptional states, rather than activated effector signatures [80]. Hypoxic zones inhibit $CD8^+$ T cell infiltration due to physical barriers like abnormal vasculature and enriched collagen, as well as the suppression of key immune signaling pathways mediated by HIF-1α and HIF-2α. Hypoxia-induced chemokines (e.g., IL-10, IL-35, CCL22, CCL28 and C-X-C chemokine receptor type 4 (CXCR4)) attract immunosuppressive Tregs, further impairing cytotoxic T cell responses [98]. Additionally, HIF-1α downregulates cytokines like IL-2 and interferon-gamma (IFN-γ), which are essential for T cell activation and proliferation [99]. Hypoxia also alters the expression of immune checkpoints. HIF-1α induces TIM-3 and lymphocyte activation gene-3 (LAG-3), which function as co-inhibitory molecules [100]. Other checkpoints, such as PD-L1 and V-type immunoglobulin domain-containing suppressor of T cell activation (VISTA), are upregulated under hypoxia, with VISTA suppressing T-cell activity in acidic environments [101]. Similarly, HIF-1α upregulates human leukocyte antigen-G (HLA-G) and downregulates the type I IFN, which inhibit T cell recognition and NK cell function by reducing tumor necrosis factor-alpha (TNF-α) and IFN-γ secretion [102]. While hypoxia upregulates CD137 on T cells to enhance immune responses, it simultaneously promotes soluble CD137 production, undermining antitumor immunity [53,103–105]. In addition to their direct effects on T cells, hypoxia also drives metabolic reprograming, which exacerbates T-cell dysfunction. HIF-1α-mediated upregulation of glycolysis enzymes, such as lactate dehydrogenase A (LDHA), depletes glucose in the TME and elevates lactate levels, creating an acidic environment that suppresses $CD8^+$ T cell activity and IFN-γ production [106]. Lactate also supports immunosuppressive functions, while HIF-1α-induced expression of adenosine-generating enzymes like CD39 and CD73, and the adenosine A2A receptor, further diminishes effector T cell responses [107].

Regarding other immune cell types, hypoxia significantly attracts MDSCs and Tregs, while impairing the tumor surveillance capabilities of NK cells. MDSCs and Tregs are recruited by the hypoxic TME through the secretion of chemokines like C-X-C chemokine ligand 12 (CXCL12), CCL5, and CCL28 by tumor cells [108,109]. IL-23 amplifies this effect by supporting Treg proliferation and enhancing TGF-β production. HIF-1α increases CCL20 and IDO expression, leading to Treg accumulation and impaired T-cell responses, while upregulating CD47 to inhibit TAM phagocytosis [110–112]. It also governs MDSC differentiation and function and enhances PD-L1 expression on their surface, suppressing T-cell activation and promoting Treg differentiation [113,114]. HIF-regulated factors like miR-210, Arginase 1, and IL-10, reinforce the immunosuppressive roles of MDSCs, contributing to immune evasion within the TME [115]. Regarding NK cells, HIF-1α suppresses the expression of NKG2D, a critical activating receptor, and its ligand MIC-A, leading to reduced NK cell cytotoxicity [116,117]. Hypoxia also alters the transcriptomic profile of NK cells, inhibiting the secretion of key cytokines and chemokines, including IFN-γ, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), CCL3, and CCL5 [118]. Additionally, hypoxia induces mitochondrial fragmentation via the mechanistic target of rapamycin-dynamin-related protein 1 (mTOR-DRP1) pathway, further diminishing NK cell function and survival [119].

5. Therapeutic opportunities targeting the hypoxic–necrotic core

5.1. HIF-1α inhibition

Hypoxia-inducible factors, particularly HIF-1α, are central mediators of GBM adaptation to the hostile conditions of the necrotic core. Oxygen deprivation stabilizes HIF-1α, leading to transcriptional activation of multiple pro-tumorigenic pathways, including angiogenesis, metabolic reprogramming, immune suppression, and extracellular matrix remodeling [120].

Despite numerous attempts to pharmacologically inhibit HIF-1α, clinical success remains limited (Table 2). Various agents have been developed to downregulate HIF-1α mRNA (e.g., Aminoflavone, OKN-007, NNC-55-0396) [121–124], inhibit its protein stability (e.g., KC7F2, 103D5R, topotecan, cardiac glycosides) [125–129], promote its degradation (e.g., vorinostat, IDF-11774, LBH589, PX-478) [130–135], or block its binding to HREs (e.g., KCN1, echinomycin) [136,137]. Nevertheless, none have yet demonstrated meaningful improvement in overall survival in clinical trials, although many remain under investigation in preclinical or early-phase clinical studies.

5.2. VEGF blockade

VEGF is a key effector of the hypoxic signaling cascade and is robustly upregulated in GBM via HIF-1α (Table 2). VEGF drives aberrant neovascularization, contributing to the formation of structurally and functionally abnormal blood vessels within the tumor core [138]. Bevacizumab, a monoclonal antibody against VEGF, gained FDA approval for recurrent GBM, either as monotherapy or in combination with irinotecan [139]. Although bevacizumab has shown improvement in progression-free survival, it has failed to demonstrate a significant benefit in overall survival [140].

Beyond these general outcomes, recent evidence suggests that the response to VEGF blockade may be influenced by sex-specific vascular and immune phenotypes in GBM [141]. Transcriptomic and immunohistochemical analyses have revealed that, under hypoxic conditions, two distinct immuno-angiogenic ecosystems emerge according to sex. Male patients with low ESR1 expression exhibit a “necroinflamed” GBM subtype characterized by vascular fragility, extensive necrosis, and high infiltration of myeloid-derived suppressor cells. This subgroup appears

Table 2
Therapeutic strategies targeting the hypoxic–necrotic core microenvironment in glioblastoma. This table summarizes current and emerging pharmacological interventions aimed at disrupting key pathological mechanisms within the necrotic core, including HIF-1α signaling, VEGF-driven angiogenesis, tumor acidosis, extracellular matrix remodeling by MMPs, and immunosuppressive modulation, highlighting their modes of action and clinical development status.

Therapeutic target	Mechanism	Agents	Clinical status in GBM
HIF-1α Inhibition	mRNA downregulation	Aminoflavone, OKN-007, NNC-55-0396	Preclinical/early-phase trials; no clear survival benefit [120–123]
	Protein stability inhibition	KC7F2, 103D5R, Topotecan, Cardiac glycosides	Early-phase studies, limited clinical data [124–128]
	Protein degradation	Vorinostat, IDF-11774, LBH589, PX-478	No meaningful OS improvement yet [129–134]
	Blockade of DNA binding (HREs)	KCN1, Echinomycin	Preclinical and early clinical studies [135,136]
VEGF Blockade	Anti-VEGF antibodies	Bevacizumab	FDA-approved for rGBM; improved PFS, no OS benefit [138,139] Improved response in male "necroinflamed" GBM subtype [141]
	VEGF/PlGF Trap	Aflibercept	Phase II trials failed to improve survival [141,142]
	Anti-VEGFR-2 antibodies	Ramucirumab	Currently in clinical trials (NCT00895180)
	bFGF inhibitor	Dovitinib	No clinical benefit [144]
	Tyrosine kinase inhibitors	Sunitinib, Sorafenib, Cediranib, Imatinib, Pazopanib	Preclinical promise; clinical failure due to toxicity/resistance [145–150]
	Other antiangiogenic agents	Cilengitide, Marizomib	Failed to demonstrate clinical benefit in phase III trials [151,152]
Tumor Acidosis Modulation	pH buffering agents	Sodium bicarbonate	Preclinical efficacy; dosing challenges in humans [155,156]
	Extracellular pH modulators	L-DOS47, TRC101	Under clinical evaluation [157,158]
	Proton pump inhibitors	Omeprazole and related PPIs	Potential to impair invasiveness and chemoresistance [159]
MMPs and TIMPs	Isoform-selective MMP inhibitors	Targeting MMP-2, MMP-9, MMP-14	Promising preclinical results with reduced toxicity [161–163]
	Tissue inhibitors of metalloproteinases	Engineered TIMP-3	Promising preclinical data [164,165]
Immunosuppression Modulation	TAM reprogramming	Nanodelivery of IRF5, CD40 agonistic antibodies	Preclinical data [166,167]
	Enhancement of TAM phagocytosis	PI3Kγ inhibitors, CD47-SIRPα axis blockade	Early preclinical data [168]
	Inhibition of TAM infiltration	CCR2 inhibitors (synergistic with anti–PD-1)	Preclinical evidence of efficacy [169]
	Immune checkpoint blockade	CA-170 (VISTA and PD-1 antagonist)	Under clinical evaluation [170]
	DAMP (HMGB1) inhibition	Lf-GL	Promising preclinical data [173]
	Metabolically conditioned CAR-T cells	Met + Rap preconditioned CAR constructs	Preclinical murine GBM models [174]
	Hypoxia-responsive CAR therapy	TME-iCAR-T, 5H1P-CEA CAR	Xenograft models; translational potential for human GBM [175,176]

to derive greater clinical benefit from bevacizumab, suggesting that sex-linked molecular stratification could refine patient selection for anti-angiogenic therapy.

Among alternative agents, aflibercept, a VEGF and PlGF trap, and ramucirumab, targeting VEGFR-2, have shown limited efficacy in clinical trials (ramucirumab: Clinical Trials.gov Identifier number NCT00895180) [142–144]. Dovitinib, which also inhibits bFGF, failed to improve outcomes [145]. Similarly, small-molecule tyrosine kinase inhibitors (TKIs) (e.g., sunitinib, sorafenib, cediranib, imatinib, pazopanib) and agents like cilengitide and marizomib have not translated preclinical promise into survival benefit, primarily due to resistance mechanisms and toxicity [146–153]. These setbacks highlight the need for novel anti-angiogenic strategies. Emerging targets such as epithelial membrane protein-2 (EMP2), which regulates VEGF via HIF1α and is upregulated post-bevacizumab, may offer future therapeutic avenues [154].

5.3. Targeting tumor acidosis

Aerobic glycolysis (the Warburg effect), predominant in hypoxic GBM regions, leads to lactic acid accumulation and acidification of the tumor microenvironment. This acidic milieu fosters immune evasion, supports glioma stem cell survival, and enhances invasiveness [155]. Attempts to buffer tumor pH using oral agents such as sodium bicarbonate have shown some efficacy in preclinical metastasis models [156], but effective dosing in humans remains a challenge (Table 2) [157]. Alternative strategies under clinical evaluation include agents such as L-DOS47 and TRC101, which increase extracellular pH to counteract tumor acidosis [158,159]. Additionally, repurposing proton pump inhibitors such as omeoprazole, initially developed for gastric acid suppression, has shown promise in neutralizing lysosomal acidity in tumor cells, potentially impairing invasive capacity and chemoresistance [160].

5.4. MMPs and TIMPs

The necrotic core is a site of active extracellular matrix remodeling, driven in part by upregulated MMPs. However, early clinical trials using broad-spectrum MMP inhibitors were hindered by toxicity and off-target effects, particularly musculoskeletal complications (Table 2) [161]. Current efforts focus on the development of isoform-selective MMP inhibitors such as ALS 1–0635 [162], especially targeting MMP-2, MMP-9, and MMP-13, which are strongly implicated in GBM invasion and angiogenesis and are not associated with musculoskeletal side effects [163,164]. Additionally, engineered TIMPs, particularly TIMP-3, have demonstrated promising results in selectively inhibiting pathological MMP isoforms such as MMP-2, thereby reducing glioma invasiveness while avoiding systemic toxicity [165,166].

5.5. Immunosuppression modulation

The hypoxic–necrotic niche profoundly alters immune cell infiltration and phenotype. As previously mentioned, TAMs accumulate in perinecrotic zones and acquire an M2-like immunosuppressive phenotype under the influence of HIF-1α, lactate, and cytokines such as IL-6, IL-10, and IL-23. Therapeutic strategies aiming to reverse this polarization are gaining attention (Table 2). Nanodelivery systems carrying the IRF5 transcription factor and CD40 agonistic antibodies have been

shown to effectively reprogram TAMs toward a pro-inflammatory, anti-tumor phenotype [167,168]. Moreover, pharmacologic inhibition of PI3Kγ or blockade of the CD47–SIRPα axis has been demonstrated to enhance TAM phagocytic capacity and support anti-tumor immunity [169]. CCR2 inhibitors also reduce TAM infiltration and exhibit synergistic efficacy when combined with anti–PD-1 checkpoint inhibitors [170].

In parallel, hypoxia-driven expression of immune checkpoints such as VISTA, TIM-3, and LAG-3 dampens cytotoxic T cell responses. Targeting these molecules with agents like CA-170, which antagonizes both VISTA and PD-1, is under active clinical evaluation and may help restore T cell functionality within the necrotic core [171].

Recent efforts have also focused on modulating the necrotic core's immune landscape by targeting DAMPs released from dying tumor cells. HMGB1, a prototypical DAMP enriched in necrotic GBM zones, has been implicated in the recruitment of immunosuppressive MDSCs and the promotion of chronic inflammation [172,173]. In this context, a novel conjugate of glycyrrhizin and lactoferrin, Lf-GL, has demonstrated promising results in preclinical glioblastoma models. Lf-GL targets lactoferrin receptors on the BBB and glioma cells, showing improved delivery and efficacy in blocking HMGB1 activity. In preclinical models, Lf-GL reduced tumor angiogenesis and growth while enhancing glycyrrhizin's pharmacokinetics, highlighting its potential in modulating the necrotic tumor microenvironment [174].

Chimeric antigen receptor (CAR) T cell therapies have emerged as a promising strategy to overcome immunosuppression in GBM, though their efficacy against solid tumors remains limited compared with hematologic malignancies. The hypoxic and metabolically hostile microenvironment of glioblastoma rapidly diminishes T cell mitochondrial function, leading to exhaustion and reduced cytotoxicity. Recent preclinical studies show that metabolic preconditioning of CAR-T cells with AMPK activators (e.g., metformin) and mTOR inhibitors (e.g., rapamycin) enhances mitochondrial spare respiratory capacity, sustains effector function under hypoxia, and increases intratumoral persistence, resulting in improved antiglioma activity and extended survival in murine models [175]. Another major challenge for CAR-T therapies is off-tumor toxicity. To address this, several groups are now using the unique features of the hypoxic tumor microenvironment to control CAR activity and restrict it to tumor sites. Synthetic "logic-gated" CARs that integrate Boolean AND/OR/NOT functions or small-molecule–controlled switches have been developed to enhance tumor specificity. In this context, Nguyen et al. recently reported a split-CAR system activated by the plant hormone abscisic acid, in which a hypoxia-sensitive "caged" version of the molecule enabled CAR activation only in low-oxygen environments, achieving effective tumor clearance in vivo while limiting off-tumor activity [176]. Similarly, another study engineered hypoxia-responsive CAR-T cells by placing the CAR under the control of hypoxia-responsive elements. These CARs remained in a resting state under normoxia but were robustly activated in hypoxic tumor niches, showing improved oxidative metabolism, reduced exhaustion, and superior antitumor activity in xenograft models [177].

6. Concluding remarks: remaining challenges and potential opportunities

The complex and dynamic interactions within the tumor microenvironment are central to glioblastoma pathogenesis, driving its aggressive behavior, therapeutic resistance, and poor clinical outcomes. The late-stage diagnosis of GBM often coincides with the full establishment of a hostile and immunosuppressive microenvironment, further diminishing the efficacy of current treatments. Far from being a static feature, this review highlights that the hypoxic-necrotic core functions as a dynamic engine of spatiotemporal evolution, actively generating a protumorigenic niche through metabolic reprogramming, ECM remodeling, and immune evasion.

Targeting this niche represents a compelling strategy, yet translating this concept into clinical practice presents distinct challenges. While the core's expansion rate could serve as a predictive biomarker via advanced radiomics or metabolic imaging, effective drug delivery remains an obstacle. The features that define this niche create biophysical barriers that limit the penetration of systemic therapies. Moreover, the heterogeneity of the core implies that a single approach may fail; factors such as sex-specific vascular phenotypes suggest that patient stratification based on the core's metabolic-immune status will be crucial for precision medicine.

In parallel to these clinical hurdles, replicating the complexity of these spatially and biochemically distinct microenvironments remains a major obstacle in preclinical research. Conventional two-dimensional culture systems lack the structural, mechanical, and oxygen gradients of native tissues, failing to recreate key aspects of GBM pathophysiology [178]. Similarly, animal models, although indispensable in many areas, often do not exhibit hallmark pathological features such as necrosis and present significant immunological discrepancies that compromise their translational value [179,180]. These limitations contribute to the low success rate of oncology drugs in clinical trials, emphasizing the need for more predictive and human-relevant preclinical models.

Recent advances in three-dimensional culture technologies offer new opportunities to recapitulate the intricate TME features of GBM, including the emergence of hypoxic gradients and necrotic regions. These systems enable spatial and temporal resolution of tumor-immune dynamics and the evaluation of immunosuppressive programs in response to microenvironmental stressors. Several studies have already demonstrated the potential of three-dimensional organoids to mimic GBM-specific hypoxic gradients and necrosis [181,182]. Beyond organoids, microfluidic "tumor-on-a-chip" systems now allow precise regulation of oxygen delivery, perfusion, and nutrient gradients, enabling real-time study of hypoxia-driven processes [124,183].

Future research will benefit from the development of hybrid platforms that combine organoids, microfluidics, and immune co-culture, ideally in humanized systems that capture the full spectrum of metabolic, biomechanical, and immunological cues of the GBM microenvironment. A deeper understanding of these interactions is crucial not only for identifying actionable therapeutic targets but also for improving the predictive power of preclinical models and bridging the long-standing gap with clinical efficacy. Ultimately, acknowledging the hypoxic–necrotic core as the central spatiotemporal evolution engine of glioblastoma will be key to shifting from reactive treatments to proactive strategies that anticipate and halt the tumor's deadly progression.

CRediT authorship contribution statement

Clara Bayona: Writing – original draft, Methodology, Investigation, Conceptualization. **Teodora Ranđelović:** Writing – review & editing. **Ignacio Ochoa:** Writing – review & editing, Supervision.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Glossary

ATP Adenosine Triphosphate
BMDM Bone Marrow-Derived Monocyte
CAR Chimeric Antigen Receptor
CCL C-C Motif Chemokine Ligand
CNS Central Nervous System
CTL Cytotoxic T Lymphocyte
CTLA-4 Cytotoxic T-Lymphocyte Associated Protein 4
CXCR C-X-C Chemokine Receptor
DAMP Damage-Associated Molecular Pattern
ECM Extracellular Matrix
EGFR Epidermal Growth Factor Receptor
EMP2 Epithelial Membrane Protein-2
EPO Erythropoietin
FIH Factor-Inhibiting HIF-1
GBM Glioblastoma
GLUT1 Glucose Transporter Type 1
G-CSF Granulocyte Colony-Stimulating Factor
GM-CSF Granulocyte-Macrophage Colony-Stimulating Factor
GSC Glioma Stem Cell
HA Hyaluronic Acid
HIF Hypoxia-Inducible Factor
HLA Human Leukocyte Antigen
HMGB1 High Mobility Group Box 1
HRE Hypoxia Response Element
IDH Isocitrate Dehydrogenase
IDO Indoleamine 2,3-Dioxygenase
IFN-γ Interferon-Gamma
IL Interleukin
LAG-3 Lymphocyte Activation Gene-3
LDHA Lactate Dehydrogenase A
LGMN Legumain
LOX Lysyl Oxidase
MDSC Myeloid-Derived Suppressor Cell
MES Mesenchymal
MIF Macrophage Migration Inhibitory Factor
MMP Matrix Metalloproteinase
mTOR-DRP1 Mechanistic Target Of Rapamycin-Dynamin-Related Protein 1
NK Natural Killer
NOS Nitric Oxide Synthase
PD-1 Programmed Cell Death-1
PD-L1 Programmed Death Ligand 1
PDGF Platelet-Derived Growth Factor
PDK1 3-Phosphoinositide-Dependent Protein Kinase 1
PGE2 Prostaglandin E−2
PHD Prolyl Hydroxylase Domain Protein
PS Phosphatidylserine
ROS Reactive Oxygen Species
TAM Tumor-Associated Macrophage
TAN Tumor-Associated Neutrophil
TCGA The Cancer Genome Atlas
TERT Telomerase Reverse Transcriptase
TGF- β Transforming Growth Factor Beta
TIM-3 T-Cell Immunoglobulin and Mucin Containing Protein-3
TIMP Tissue Inhibitors of Metalloproteinases
TKI Tyrosine Kinase Inhibitors
TLR Toll-Like Receptor
TME Tissue Microenvironment
TNF-α Tumor Necrosis Factor Alpha
Treg Regulatory T Cell
VEGF Vascular Endothelial Growth Factor
VHL Von Hippel-Lindau
VISTA V-Type Immunoglobulin Domain-Containing Suppressor Of T Cell Activation
WHO World Health Organization

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