BBA - Reviews on Cancer 1881 (2026) 189691

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review Article

Decoding the spatiotemporal dynamics of T cell immune landscapes in glioblastoma: remodeling precision combination therapies

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ARTICLE INFO

Keywords:
Glioblastoma
T cells
Spatiotemporal heterogeneity
Tumor immune microenvironment
Immunotherapy

ABSTRACT

The profound intratumoral heterogeneity and the highly dynamic spatiotemporal evolution of its immunosuppressive microenvironment in glioblastoma (GBM) are major factors underlying the limited efficacy of the standard-of-care treatment (SOC). Although immunotherapy has revolutionized the treatment of many solid tumors, it has produced limited clinical benefit in patients with GBM. This limited efficacy is closely associated with the abundance, distribution, and functional state of T cells, which constitute the core effector population mediating antitumor immune responses. However, previous studies have largely focused on the static characteristics of T cells in GBM, whereas the mechanisms governing their spatiotemporal dynamics remain poorly defined, thereby impeding clinical translation. In this review, we delineate the spatiotemporal dynamics of T cells in GBM and re-evaluate the mechanisms underlying immunotherapy failure, thereby identifying potential therapeutic opportunities. Furthermore, we aim to provide new insights into patient stratification, the development of precise targets that modulate T-cell spatiotemporal dynamics, and personalized combination strategies for patients with GBM.

1. Introduction

Glioblastoma (GBM), distinguished by its highly invasive growth, profound therapeutic resistance, and dismal prognosis, remains one of the most formidable clinical challenges in neuro-oncology [1,2]. Even with SOC involving surgery combined with radiotherapy and temozolomide chemotherapy, the median overall survival of patients with GBM remains approximately 15 months, and tumor recurrence is almost inevitable [3,4]. This persistent clinical impasse underscores the urgent need to develop more effective therapeutic strategies for patients with GBM. In recent years, immunotherapy has produced substantial clinical benefit not only in hematological malignancies but also across a range of solid tumors [5–7]. However, owing to the immunosuppressive microenvironment of GBM, the clinical translation of immunotherapeutic approaches has been largely disappointing [8–12].

As the direct cellular effectors of antitumor immunity, T cells have become a central focus. Accumulating evidence indicates that functionally distinct T-cell subsets ($CD4^+$ and $CD8^+$), together with their interactions with myeloid populations and tumor cells within the tumor microenvironment (TME), collectively shape the magnitude and orientation of local immune responses. [13]. Among $CD4^+$ T cells, T helper 1 (Th1) cells contribute to antitumor immunity by providing helper signals and modulating the balance of the TME, whereas T helper 2 (Th2) cells, regulatory T cells (Tregs), and other suppressive subsets restrain effector immune responses and reinforce immune tolerance [14–16]. In contrast, $CD8^+$ T cells, which differentiate into cytotoxic T lymphocytes (CTLs) upon activation, constitute the principal effector population responsible for tumor cell killing, and increased CTL infiltration has been associated with prolonged survival in patients with GBM [17–19]. Although effector T cell infiltration is markedly higher in GBM than in normal brain tissue, it still represents only approximately 10–15% of the immune compartment. Their abundance remains far below that observed in prototypical “immune-hot” tumors. By comparison, tumor-associated macrophages (TAMs), the overwhelmingly dominant immune population in the GBM microenvironment, account for more than 80% of intratumoral immune cells [20]. Through intricate cellular interaction networks, TAMs spatially restrict T-cell infiltration and functionally promote T-cell exhaustion. GBM is therefore widely

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https://doi.org/10.1016/j.bbcan.2026.189691
Received 26 May 2026; Received in revised form 19 August 2026; Accepted 20 August 2026
Available online 21 August 2026
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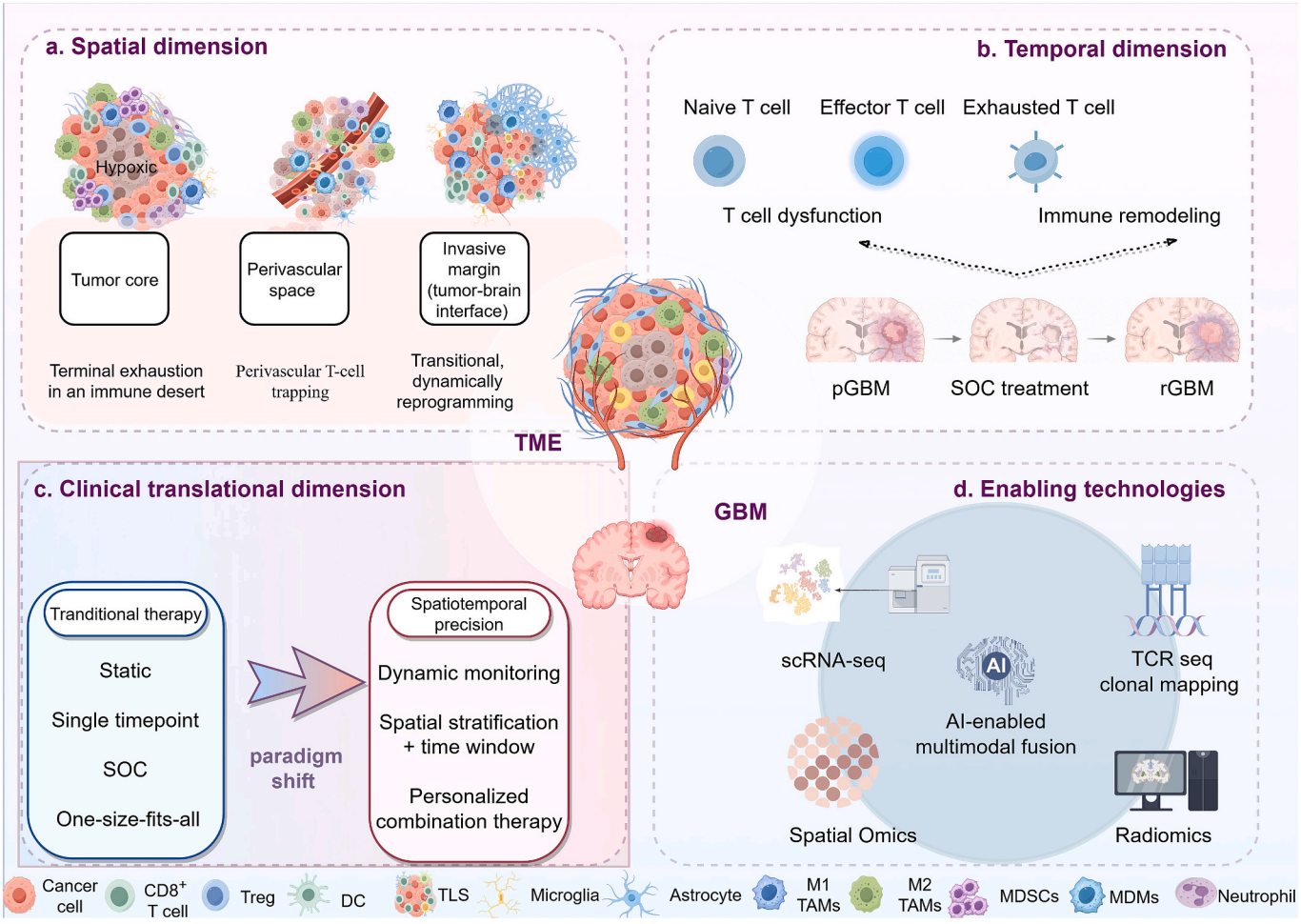

Fig. 1. Spatiotemporal dynamics of T cells in glioblastoma: a conceptual framework. The framework integrates T-cell functional states across spatial and temporal dimensions, with translational implications for therapeutic optimization and emerging detection technologies outlined. Abbreviations: GBM, glioblastoma; TME, tumor microenvironment; SOC, standard of care; scRNA-seq, single-cell RNA sequencing; TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell; MDMs, monocyte-derived macrophages; Treg, regulatory T cell; DC, dendritic cell; TLS, tertiary lymphoid structure; pGBM, primary glioblastoma; rGBM, recurrent glioblastoma.

regarded as an immunologically "cold" tumor [21,22]. Importantly, this state is not a static pathological attribute. The concept of T cell spatiotemporal dynamics has increasingly been used to interpret immune evolution during the progression of hematological malignancies, melanoma, lung cancer, and other tumor types [23,24]. T cells display compartmentalized spatial distributions and, over time, undergo a trajectory from initial activation to progressive functional attrition during the evolution of GBM. Therapeutic interventions may further reshape this dynamic process [25]. Thus, the spatiotemporal fate trajectory of T cells may serve as an ideal lens through which to decode intratumoral heterogeneity and mechanisms of immune escape in GBM. Nevertheless, how T-cell fate is dynamically remodeled across spatial and temporal dimensions in GBM remains incompletely understood.

Against this background, conventional immune phenotyping is no longer sufficient to resolve the complex spatiotemporal heterogeneity of T cells in GBM. Recent advances in single-cell sequencing, spatial transcriptomics, and highly sensitive spatially resolved T-cell receptor sequencing [26] have provided powerful technical platforms for mapping T-cell interaction networks within defined spatial niches and for tracing stage-specific functional responses throughout disease progression [27]. In this review, we integrate single-cell and spatial omics to map T-cell fate along coupled spatial and temporal axes, constructing a four-dimensional spatiotemporal atlas of T-cell fate. We emphasize that identical therapeutic interventions elicit markedly divergent T-cell dynamics across distinct spatial niches. Temporal evolution, likewise, does not occur in isolation from its spatial context but is constrained by local spatial niches and subject to continuous feedback. Together, they constitute an inseparable unified framework for understanding immunotherapy response in GBM. Ultimately, this framework may provide a translational roadmap for overcoming the current barriers to effective immunotherapy in GBM (Fig. 1).

2. Dissecting spatial heterogeneity: The distribution and fate of T cells within the GBM

The emergence of spatial omics technologies consistently indicates that GBM comprises multiple interrelated yet biologically distinct spatial niches, including the hypoxic necrotic tumor core, the perivascular zone, the invasive margin, and the peritumoral brain tissue [28]. These regions exhibit marked heterogeneity in tumor cell state, immune cell state, vascular function, and metabolic stress [29]. Existing research indicates that the distribution and functional states of T cells within GBM are embedded within a highly compartmentalized spatial structure, undergoing differential activation, clonal expansion, and exhaustion shaped by the local microenvironment [30].

2.1. Tumor core: A spatial niche characterized by hypoxia, myeloid enrichment, and T cell exhaustion

The tumor core of GBM is one of the regions where its unique malignant biological characteristics are most concentrated, exhibiting significant hypoxia and necrosis, metabolic imbalance, and vascular dysfunction; these features collectively shape a highly immunosuppressive microenvironment [31]. This region exhibits high levels of mesenchymal-like (MES-like) tumor cells and immunosuppressive cells such as monocyte-derived macrophages (MDMs), myeloid-derived suppressor cells (MDSCs), Tregs, and tumor-associated neutrophils (TANs). In contrast, effector T cells are relatively scarce and do not exist in an initial or immature state; rather, they are predominantly in late-stage differentiation, consisting mainly of effector memory T cells (TEMs) and tissue-resident memory T cells (TRMs). This implies that they have previously encountered antigens and are characterized by functional exhaustion, marked by a shift from cytotoxic to suppressive states and by the upregulation of inhibitory markers such as PD-1, TIM-3, LAG-3, TIGIT, CD161, and VISTA, among others. Moreover, this is accompanied by decreased expression of key cytotoxic factors such as IFN-γ, TNF-α, and granzyme B, as well as reduced proliferative capacity and diminished antitumor activity [32]. Notably, this core-exclusion phenotype is not static; rather, it evolves dynamically with disease progression and therapeutic intervention.

The hypoxic-necrotic microenvironment in the tumor core, which is one of the hallmark pathological features of GBM, serves not only as a driver of metabolic reprogramming in tumor cells but also as a key regulatory hub for the spatial evolution of T cells. The hypoxia-inducible factor (HIF) activation initiates a series of cascading reactions, leading to the accumulation of immunosuppressive metabolic byproducts such as lactate driven by glycolysis, adenosine, kynurenine, and reactive oxygen species (ROS) [33]. These metabolic changes not only upregulate the expression of immune checkpoint molecules and chemokines such as CCL20, IL-10, and IL-23, thereby recruiting Tregs and enhancing the suppression of T cell effector responses, but also promote the accumulation of MDSCs and TANs in the periphery of the necrotic region. These cells, together with hypoxic tumor cells in this area, form a pseudopalisade-like physical barrier. Meanwhile, the local vasculature fails due to hypoxia and necrosis, further hindering the effective delivery of immune cells to the tumor core [34]. Moreover, this barrier is temporally plastic, as therapy acutely intensifies core hypoxia and restricts T-cell access, yet prolonged anti-VEGF treatment paradoxically promotes adaptive hypoxia escape and increased parenchymal invasion [35]. Furthermore, HIFs upregulate lysyl oxidase (LOX) and matrix metalloproteinases (MMPs), leading to abnormal overexpression of extracellular matrix (ECM) components such as collagen and hyaluronic acid in the core region. This increases matrix stiffness, blocking the invasion of immune cells into the tumor core where they would otherwise exert their effects [36]. Therefore, ECM remodeling inhibitors may enhance the delivery of therapeutic drugs and improve the infiltration of immune cells into the tumor. Beyond serving as a passive physical barrier, ECM remodeling actively organizes glioma architecture into structured patterns. Comba et al. described “oncostreams” as dynamic multicellular fascicles of spindle-like mesenchymal cells characterized by COL1A1 overexpression. These structures promote mesenchymal-associated ECM protein expression and may facilitate tumor invasion and correlate with immune exclusion phenotypes [37,38].

Myeloid cells constitute the vast majority of immune cells in GBM and are a key determinant of T cell dysfunction. Spatial co-localization analysis revealed that the hypoxic core region collectively recruits large numbers of Tregs and MDSCs via IL-10, TGF-β, ARG1, IDO1, and PGE2. TAMs in this region polarize toward the immunosuppressive phenotype, inducing $CD8^+$ T cell exhaustion [39,40]. $CD8^+$ T cells, $FOXP3^+$ Tregs, and $IBA1^+$ TAMs were found to be most highly enriched in the hypoxic core of IDHwt glioblastomas; however, the ratios of $CD8^+$, $FOXP3^+$, and $IBA1^+$ cells to tumor cells all increased gradually from the core through the transition zone to the periphery. The ratio of $FOXP3^+$ Tregs to $CD8^+$ T cells and their spatial proximity are both highest in the core region. Importantly, this myeloid-dominated suppressive architecture is progressively reinforced, with core Treg–TAM clusters becoming increasingly entrenched in recurrent versus primary tumors [41,42].

In addition to TAM-mediated myeloid suppression, other immune populations in GBM also contribute to the remodeling of the spatial T-cell ecosystem. Recent evidence indicates that TANs, particularly the $dcTRAIL\text{-}R1^+$ subtype, preferentially localize to the core region. By releasing proteases, ROS, and chemokines, they promote matrix remodeling and actively participate in the immunosuppression of this niche [43]. Spatial analysis of GBM tissue reveals that $PD\text{-}L1^+$ TANs colocalize with PD-1-expressing $CD8^+$ T cells [44]. Furthermore, in the context of a compromised blood-brain barrier in GBM, TAMs can promote N2-type TAN polarization by secreting inhibitory factors such as TGF-β, thereby forming neutrophil extracellular traps (NETs) and preventing effector T cells from reaching the site of action [45]. Moreover, although MAITs are outnumbered by TAMs overall, their spatial clustering and local effects may have an amplifying impact on T cell status within specific regions. They can activate TANs by producing IL-17, and their reduced IFN-γ production further limits the T cell response [46].

2.2. Infiltration margin: A dynamic transition zone for T cells

As the interface between the tumor and normal brain tissue, the infiltration margin and peritumoral regions constitute the areas that are difficult to completely resect surgically; approximately 90% of recurrences occur here [47]. This region is relatively well-oxygenated, with largely intact blood-brain barrier components. Tumor cells accumulate at the invasion margin, where they integrate into neural circuits through synaptic connections with normal brain parenchyma and neurons. This integration allows them to compete for nutrients and comprehensively reshape the TME [48]. Using multimodal MRI-guided multi-region sampling and single-cell sequencing, Wang et al. further subdivided the peritumoral brain zone into the high cerebral blood flow interface (HBI) and the low cerebral blood flow interface (LBI) based on cerebral blood flow heterogeneity. The LBI is characterized by sparse vascular and immune infiltration. In contrast, the HBI region is characterized by high expression of VEGFA and EGFR, featuring abundant neovascularization, actively proliferating tumor cells, and significant immune cell infiltration. From the LBI to the HBI and then to the tumor core, macrophages exhibit progressive differentiation toward a pro-tumor phenotype, limiting T cell effector function [49]. Single-cell studies across multiple regions suggest that the activation status of tumor infiltrating lymphocytes (TILs) varies across different anatomical regions, with T cell functional states exhibiting a spatial gradient. T cells gradually exhibit exhaustion characteristics adjacent to the deep tumor parenchyma, whereas on the side adjacent to normal brain parenchyma, they retain relatively intact effector functions. Compared to the core region, T cells in the margin may retain relatively higher activation potential and clonal diversity but are simultaneously constrained by local inhibitory signals, exhibiting an intermediate state characterized by coexisting underactivation and suppression [41,50].

In recent years, tertiary lymphoid structures (TLS), a type of ectopic lymphoid aggregate formed in non-lymphoid tissues, hold great promise across diverse malignancies [51]. Using spatial transcriptomic and proteomic analyses, Cakmak et al. found that these structures are often located close to the tumor margin, the pia mater, or highly vascularized regions. However, the biological significance of TLS in GBM remains equivocal. On the one hand, the presence of TLS is associated with features such as enhanced antigen presentation, spatial compartmentalization of lymphocytes, and proliferation of $CD20^+Ki67^+$ B cells and $CD4^+Ki67^+$ T cells, suggesting that local T cell clonal expansion and immune activation may occur [52]. On the other hand, induced TLS does not necessarily translate into effective antitumor immunity,

preclinical studies have shown that while CD40 agonists can induce TLS formation, they may lead to reduced $CD8^+$ T-cell cytotoxicity and weakened checkpoint blockade responses, thereby inhibiting therapeutic efficacy [53].

Bidirectional communication between astrocytes and GBM cells constitutes another dimension of immune suppression. Astrocytes, the most abundant glial cells in the central nervous system, also play a crucial immunoregulatory role in the peritumoral zone of GBM. Faust et al. identified $pSTAT3^+TRAIL^+$ astrocytes enriched at the tumor–host interface that are activated by GBM cells via the IL-11-STAT3 signaling axis and directly promote apoptosis of tumor-specific $CD8^+$ T cells. Their spatial abundance correlates with shorter time to recurrence and reduced survival, highlighting the peritumoral astrocytic checkpoint as a spatial determinant of T-cell fate during tumor progression. Based on these findings, the researchers engineered an oncolytic HSV-1 virus capable of locally blocking TRAIL signaling within the tumor. Preclinical models demonstrated that this strategy optimizes the interaction between T cells and TAMs, reduces T cell apoptosis, and significantly prolongs survival [54]. Furthermore, Andersen et al. confirm that bidirectional immunosuppressive interactions occur between astrocytes and tumor cells. This interaction directly limits $CD8^+$ T cell infiltration and promotes the activation of T cell exhaustion transcriptional modules. Blocking ANXA1-FPR1 signaling enhances tumor-specific $CD8^+$ T cell infiltration and limits exhaustion, suggesting that the astrocyte-tumor interaction interface may serve as a new target for immunotherapy [55]. Consequently, precision interventions targeting the spatial heterogeneity of GBM must go beyond T cell targeting and shift toward reshaping the T cell niche.

2.3. Perivascular niche: The spatial gateway for T cell entry into tumor parenchyma

The perivascular region serves as the gateway through which T cells enter the central tumor tissue from the peripheral circulation, and it is also one of the most active niches for local immune regulation. In this region, tumor cells utilize blood vessels to support their metabolic and invasive needs, while immune cells establish networks that promote immune remodeling, collectively influencing antigen presentation, chemokine release, and immune checkpoint-mediated inhibitory effects. Additionally, these vessels often exhibit uneven perfusion, endothelial dysfunction, and local barrier remodeling, leading to altered adhesion molecule expression, which in turn restricts T cell migration and penetration into the deep parenchyma. Previous studies have suggested that, unlike the tumor core and the infiltration margin, the perivascular region of GBM often exhibits a unique phenomenon of T cell retention, with Tregs tending to linger in the perivascular region. In contrast, $CD8^+$ T cells are more likely to further infiltrate the tumor interior, though to a very limited extent [56,57]. More importantly, the perivascular zone is often enriched with TAMs and MDSCs, which release inhibitory factors such as TGFβ, downregulate the expression of vascular endothelial adhesion molecules such as ICAM-1 and VCAM-1, and impede T cell infiltration [17]. Moreover, T cells that have already entered the tissue rapidly undergo apoptosis upon binding to Fas ligands expressed by immunosuppressive cells [58]. Simultaneously, impaired dendritic cell (DC) function and reduced antigen-presentation efficiency further weaken local T cell activity [59]. Wang et al. employed spatial transcriptomics combined with T cell receptor (TCR) clonality data to reveal that $CD8^+$ TILs, with $GZMK^+$ T cells constituting the largest proportion, form tight spatial colocalization with $CD163^+$ major histocompatibility complex (MHC) II^+ myeloid cells in perivascular niches [60]. Notably, some single-cell spatial immunomapping studies suggest that, in the presence of a vascular microenvironment, macrophages may provide beneficial signals to T cells; perivascular pro-inflammatory MDMs may exhibit higher levels of CD40 expression than those further away from blood vessels, while immunosuppressive MDMs express costimulatory molecules such as OX40L, suggesting that the perivascular region retains the potential for local immune regulation [61].

Furthermore, the perivascular region is linked to cerebrospinal fluid (CSF) immune surveillance and the cranial functional lymphoid unit. Integrated immunological analysis of CSF sequencing revealed that, GBM patients exhibit lower levels of immune infiltration than healthy controls, with CSF predominantly dominated by myeloid cells. Specifically, $CD4^+$ and $CD8^+$ T cells numbers are significantly reduced, TCR diversity is markedly decreased, and functionally exhausted $CD8^+$ T cells and Tregs are relatively enriched [62]. Concurrently, studies of cranial functional lymphoid units suggest that $CD8^+$ T cells with an effector memory phenotype can accumulate in the cranial bone marrow and adjacent structures, indicating that the brain's peripheral immune system may serve as a critical reservoir for local tumor immune responses [63]. These findings collectively support a broader anatomical framework: insufficient T cell recruitment and limited local activation in GBM are not solely attributable to the tumor itself but are also closely related to the brain immune pathway and the perivascular environment.

T cell clones in GBM are highly localized, with different dominant TCR clones present in different tumor regions, forming relatively isolated “immune hotspots.” Using CODEX-based spatial transcriptomics and spatial proteomics, Greenwald et al. established, for the first time, a five-layer concentric-circle organizational model of the unique TME centered on hypoxia gradients, revealing that the spatial distribution of T cell infiltration and status is highly localized. The first layer is the tumor core, characterized by hypoxia, necrosis, and myeloid-mediated immunosuppression with severe T cell depletion and functional exhaustion, where MES-like cells are enriched. The second layer is the hypoxia-associated layer, comprising MES-like and inflammatory-mac cells that mediate immunosuppression. The third layer is highly vascularized and serves as an immune hub, where vascular endothelial cells co-localize with cells in a proliferative-metabolic state, and T cells gradually accumulate. The fourth layer, the malignant neurodevelopmental state layer at the tumor margin, represents the relatively oxygenated periphery. The fifth layer is the brain parenchyma layer, the infiltration margin and peritumoral interface serve as transition zones where tumor cells come into direct contact with normal brain tissue, and T cell recruitment and early immune recognition predominantly occur here. These findings are highly consistent with traditional histopathological features but offer a more integrated perspective, providing a mechanistic framework for hypoxia-associated spatial niche heterogeneity of T cells, Notably, the perivascular niche exemplifies spatiotemporal coupling in GBM: rather than a static anatomical gateway, this interface undergoes progressive immunological remodeling over the disease course, with its T-cell accessibility and local suppressive tone shifting dynamically across treatment stages [64,65].

Therefore, future studies should combine spatial transcriptomics, spatial TCR sequencing, and multi-modal imaging technologies to map T cell clonal expansion, lineage states, and cell-cell interactions across spatial domains and time points. Furthermore, targeted interventions focused against the hypoxia-myeloid suppression axis in the core region, the residual tumor immune window in the periphery, and perivascular migration barriers are expected to yield more actionable spatial biological evidence for precision immunotherapy in GBM.

3. Temporal dimension: The evolutionary journey of T cells in therapeutic interventions and disease progression of GBM

Whereas the spatial dimension reveals T cell functional heterogeneity across different compartments, the temporal dimension further captures the dynamic evolution of T cell states during the disease progression and therapeutic intervention. Integrating these two dimensions not only accounts for variable treatment efficacy across different patients and disease stages but also informs the prediction of combination therapy outcomes and the optimization of treatment sequencing. To this end, this section will integrate the latest evidence from multi-omics and longitudinal cohort studies to systematically elucidate the dynamic

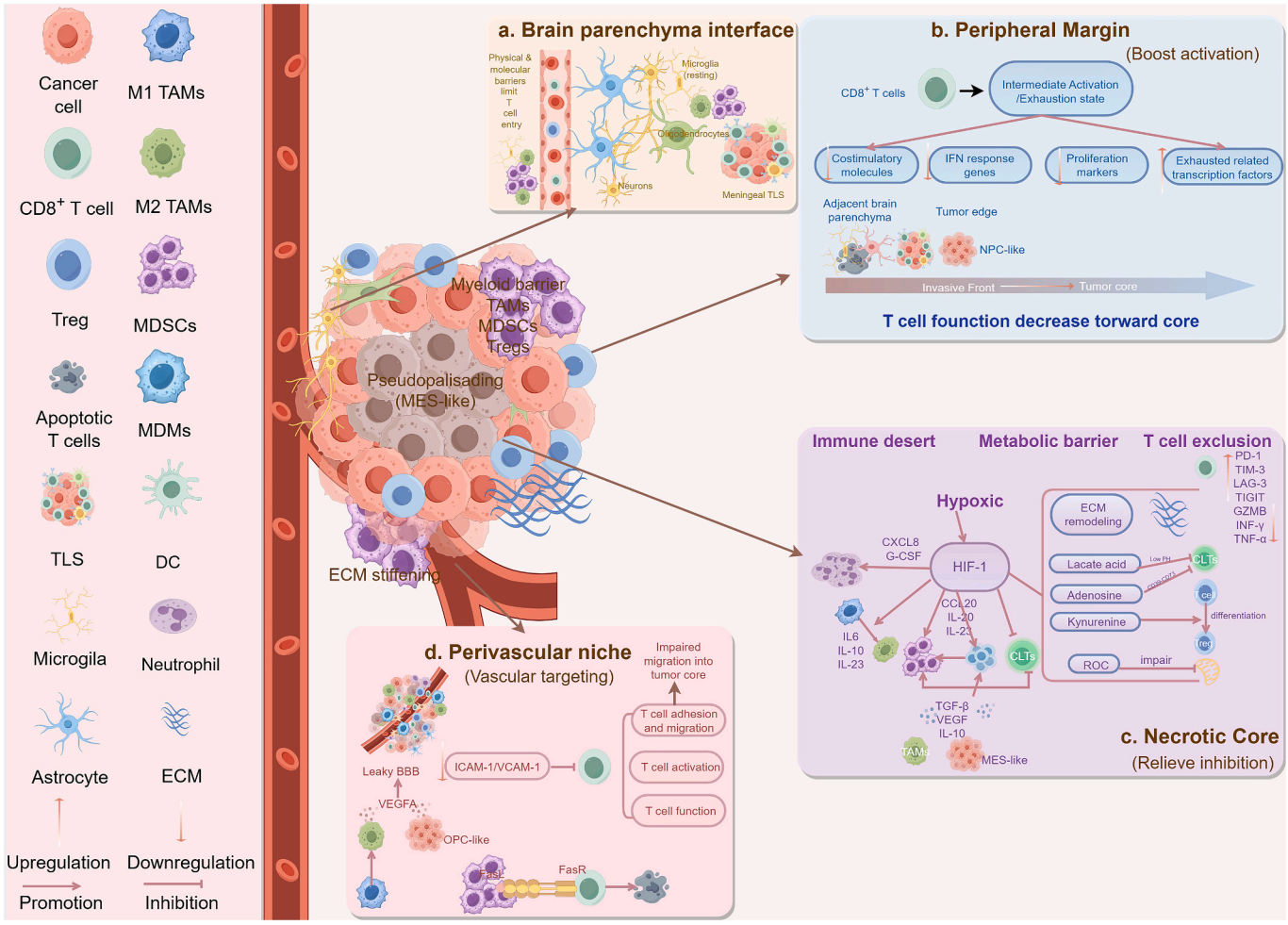

Fig. 2. Spatial zoning of the GBM microenvironment and T cell compartmentalization. (a) At the brain–tumor interface, physical and molecular barriers restrict T cell infiltration into the tumor core. (b) At the invasive front, microglial and astrocytic aggregates dominate the peritumoral brain zone adjacent to normal brain tissue, whereas NPC-like tumor cells are enriched in regions proximal to the tumor mass. T cells in this zone exhibit partial activation, characterized by downregulation of costimulatory molecules, interferon response genes, and proliferation-associated markers, along with upregulation of exhaustion-associated transcription factors, indicating progressive T cell dysfunction toward exhaustion. (c) Within the necrotic and hypoxic core, HIF-1 activation drives metabolic reprogramming and stimulates secretion of multiple cytokines, collectively suppressing T cell function within the necrotic core. (d) In the perivascular niche, endothelial cells secrete reduced levels of ICAM-1/VCAM-1 in response to VEGFA derived from TAMs and GBM cells, impairing T cell adhesion, migration, and activation toward the tumor core. Abbreviations: HIF-1α, hypoxia-inducible factor 1 alpha; ECM, extracellular matrix; NPC-like, neural progenitor cell-like; OPC-like, oligodendrocyte progenitor cell-like; MES-like, mesenchymal-like; BBB, blood-brain barrier; ROS, reactive oxygen species.

evolution of T cells across the GBM disease course, with emphasis on disease progression, standard therapy, and immunotherapy (Fig. 2).

3.1. *Treatment-induced remodeling of T cells*

3.1.1. *Dynamic remodeling of T cells during standard therapy*

Maximal safe resection, followed by concurrent radiotherapy and temozolomide (TMZ) treatment, remains the SOC strategy for newly diagnosed GBM. However, the standard treatment phase represents not merely a cytotoxic process but a critical window during which the tumor immune system undergoes substantial remodeling. Surgical resection reduces tumor burden and eliminates some sources of immunosuppression. Notably, the density and functional state of T cells at the invasive margin correlate with post-recurrence immune control, establishing this niche as a critical target for immunotherapy. Choi SH et al. demonstrated that resection of GBM tumors significantly reduces MDSCs and increases the recruitment of $CD8^+$ T cells [66].

3.1.2. *A dual-pronged therapeutic approach: Bidirectional regulation of T cell spatiotemporal dynamics by radiotherapy, chemotherapy, and glucocorticoids*

Radiotherapy can induce immunogenic cell death (ICD) by exerting a cytotoxic effect on tumor cells; it promotes antigen release within a specific time window, enhances MHC-I expression, and activates the type I interferon pathway, thereby creating conditions for the activation and recruitment of T cells, which offers survival benefits. However, radiation from radiotherapy carries a certain degree of lymphotoxicity. Even when the radiation does not directly irradiate hematopoietic organs, the relatively high volume of circulating blood exposed to radiation leads to cumulative radiation damage as the radiation repeatedly passes through the treatment field. This is associated with persistent peripheral lymphocyte depletion by directly killing circulating lymphocytes and damaging the structure of lymphoid organs, accompanied by MHC downregulation and overexpression of checkpoint inhibitory molecules [67]. More importantly, lymphocyte subsets exhibit differential radiosensitivity. Tregs exhibit greater radiation tolerance than other T cells or B cells, while naive T cells are more sensitive than memory T cells. This selective damage leads to insufficient infiltration of

$CD4^+$ and $CD8^+$ T cells in the TME following radiotherapy, with a relative enrichment of Tregs, thereby weakening the immune surveillance against neoantigens [68,69].

The efficacy of radiotherapy is fundamentally dependent on T cells. Relevant studies indicate that radiation regimens—such as the irradiated volume, fractionation scheme, dose distribution, and total treatment duration—as well as tumor type and location are all closely associated with T-cell damage [70,71]. Low-dose radiotherapy or specific fractionation schemes may induce ICD, leading to neoantigen expression, cGAS-STING pathway activation, and an immunostimulatory effect. This cascade upregulates inflammatory chemokines, recruits immune cells to the tumor bed, promotes pro-inflammatory macrophage polarization, suppresses Treg function, and enhances CTL infiltration, thereby activating a new round of T cell responses [72–74]. Crucially, the effects of radiotherapy on T cells depend not only on dose but are also closely related to its spatial dose distribution. Microbeam radiotherapy (MBRT), a spatial fractionation technique, can generate highly personalized dose distributions and create an immune-activating microenvironment. This approach induces distinct spatiotemporal T-cell redistribution patterns. Studies in mouse models have confirmed that 2 days after MBRT irradiation, $CD8^+$ T cells rapidly infiltrate the tumor core, while $CD4^+$ Th cells significantly accumulate at the tumor periphery. By 7 days post-irradiation, $CD8^+$ T cells and $FOXP3^+$ Tregs exhibit high-density distribution at the tumor margin. More importantly, animals cured by MBRT showed no tumor growth after re-implantation of tumor cells, suggesting that this therapy can induce durable antitumor immune memory. Furthermore, the combination of MBRT and immune checkpoint inhibitor (ICIs) exhibited lower toxicity than conventional radiotherapy regimens [75,76]. This finding provides important evidence for reducing the side effects of radiotherapy and maximizing its therapeutic efficacy.

Yeo et al. prospectively monitored peripheral blood immune dynamics in GBM patients receiving standard chemoradiotherapy. The results showed that both radiotherapy alone and radiotherapy combined with TMZ increased Granzyme B^+CD8^+ T cells within the tumor, indicating a transient window of cytotoxic effect. However, this beneficial effect was accompanied by a concurrent expansion of Tregs, which may explain the limited durability of clinical benefit under standard treatment [77]. More importantly, glucocorticoids such as dexamethasone, which are administered to treat cerebral edema or neurological symptoms caused by treatment side effects, act as "immunosuppressive amplifiers" during this phase. By targeting hormone-responsive pathways, inhibiting NF-κB activity, and suppressing T cell proliferation, they lead to a significant decline in $CD4^+$ T cells and contribute to the persistence of the immunosuppressed state [78,79].

TMZ-based adjuvant chemotherapy further reshapes T-cell states across different time windows, providing a theoretical basis for optimizing the timing of its combination with immunotherapy. Following TMZ treatment, antitumor-associated cytokines such as IL-12 and TNF-α transiently increase, breaking the host's immune tolerance to tumor antigens, relatively enhancing effector T cell activity, reducing the proportion of Tregs, and improving survival [80]. However, this effect often wanes with continued antigen exposure and ultimately leads to T cell exhaustion and diminished effector function [81,82]. In the late phase of TMZ-adjuvant therapy, MDSCs significantly expand in peripheral blood, accompanied by decreased in the proportion of IFN-γ^+ $CD8^+$ T cells; this inverse correlation is particularly pronounced in non-survivors [83]. Furthermore, the local physical microenvironment further exacerbates immune dysfunction. Studies using microfluidic models have shown that temozolomide treatment enhances antitumor immune responses but impairs the motility of immune cells. High expression of genes associated with ECM remodeling is closely linked to altered immune cell–tumor cell interactions, and increased ECM stiffness can further amplify the barrier to immune cell infiltration in the context of TMZ treatment [84,85]. Comba et al. demonstrated in preclinical models that inhibiting COL1A1 in glioma cells represents a potential therapeutic strategy that reduces microglia/macrophage proliferation and perivascular mesenchymal-like cell infiltration, attenuates mesenchymal transition, and remodels the TME, thereby improving animal survival [38].

Overall, the timing of treatment is a key variable determining the potential for T cell reactivation. The standard treatment phase generates a "biphasic immune effect", despite persistent lymphocyte exhaustion, a transient window of enhanced immunogenicity still exists [86]. Therefore, optimizing treatment timing, minimizing unnecessary glucocorticoid exposure, and refining radiotherapy dose distribution are all beneficial for minimizing T cell depletion during the immune stimulation window and are expected to become important strategies for improving the responsiveness to immunotherapy.

3.1.3. T cell dynamics under immunotherapy intervention

Although immunotherapy has revolutionized the treatment landscape for various solid tumors, its clinical translation in GBM has repeatedly faced setbacks [87]. These challenges stem from the characteristics of GBM, including sparse T cell infiltration, profound T cell exhaustion, and insufficient antigenic drive, as well as the robust physical and functional barriers formed by myeloid suppressor cells [88]. To address these obstacles, various combination immunotherapy strategies have entered preclinical and clinical evaluation for GBM. The following sections will primarily focus on how immune checkpoint blockade (ICB), neoadjuvant therapy, cancer vaccines, and oncolytic viruses reshape the spatiotemporal dynamics of T cells in GBM.

3.1.3.1. Evolution of T cell subpopulations following ICB. ICB restores T cell function by inhibiting T cell exhaustion pathways mediated by PD-1, PD-L1, and CTLA-4. A particularly responsive target is the precursor-exhausted T-cell subset, which overexpresses costimulatory molecules CD28 and CD226, possesses self-renewal capacity and potential antitumor function, and is significantly associated with prolonged overall survival in recurrent glioblastoma (rGBM) patients, suggesting that this subset may serve as a predictive biomarker for ICB treatment response [89]. Consistent with this, GZMB expression slightly increased in patients treated with pembrolizumab [90]. However, resistance mechanisms remain spatially and temporally complex. Although RT-concurrent ICB can increase the total number of tumor-infiltrating T cells, $CD103^+$ Tregs accumulate in the TME and exhibit metabolic reprogramming with upregulation of cholesterol and lipid metabolism. These adaptations can mediate resistance to radioimmunotherapy and restrict the antitumor response of $CD8^+$ T cells [91].

3.1.3.2. Neoadjuvant immunotherapy reveals a "time-sensitive" activation window for T cells. Clinical studies in rGBM indicate that neoadjuvant anti-PD-1 therapy exposure is associated with the suppression of cell cycle genes and upregulated chemokines involved in immune cell recruitment to the TME. These changes correlate with enhanced immune activation, including cDC1 infiltration and activation, T-cell clonal expansion, interferon response upregulation, increased cytotoxicity, and partial survival benefits [92–94]. Some studies indicate that monotherapy with pembrolizumab or nivolumab for PD-L1 positive rGBM yields limited overall benefit. This may be due to the fact that its effects on TAMs remain insufficient. Relying solely on T cell activation is not enough to overcome the myeloid-dominated immune barrier of GBM. Particularly in the recurrence phase, the myeloid suppression network often becomes a key factor determining the upper limit of treatment efficacy [95,96]. However, following treatment with ruxolitinib, a JAK-STAT inhibitor that blocks the secretion of IL-10 by myeloid cells, a driver of T-cell exhaustion—the patient showed a significant increase in effector and effector memory T cells, along with improved survival rates [93,97].

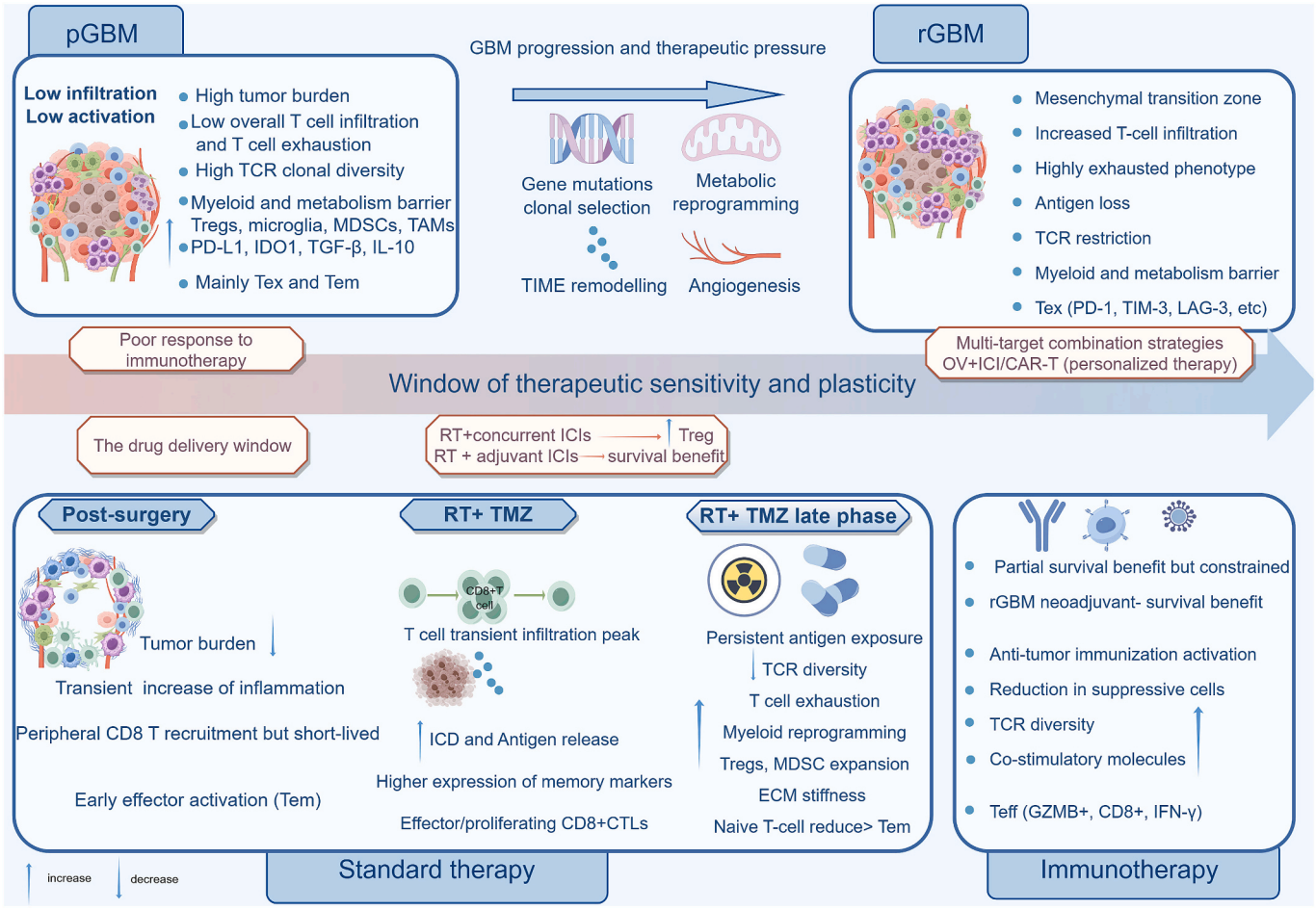

Fig. 3. Temporal evolution of T cell landscapes across GBM disease course and therapy. Schematic depicting the dynamic remodeling of T cell states throughout the clinical trajectory of GBM, from primary tumor to post-surgical, RT + TMZ, post-RT + TMZ, recurrent GBM, and post-immunotherapy phases. The T cell compartment undergoes continuous phenotypic and functional transitions, including early activation, progressive exhaustion, clonal contraction/expansion, and potential reinvigoration. Key therapeutic windows currently under preclinical investigation or clinical evaluation are indicated, highlighting opportunities for timely immunomodulatory interventions to sustain T cell fitness and counteract therapy-induced immune evasion. Abbreviations: TCR, T cell receptor; Tex, exhausted T cell; Tem, effector memory T cell; Teff, effector T cell; ICD, immunogenic cell death; RT + TMZ, radiotherapy plus temozolomide; ICIs, immune checkpoint inhibitors; OV, oncolytic virus.

3.1.3.3. Sustained T cell activation induced by cancer vaccines and oncolytic viruses. Cancer vaccines are designed to induce T cell-mediated immune responses within the immunosuppressive TME. DC vaccines involve loading autologous DCs, generated ex vivo, with tumor-associated antigens and infusing them into patients. These cells present antigens to mobilize peripheral T cells, triggering T cell-mediated adaptive immune response. DC vaccine targeting single tumor-associated antigens, such as EGFRvIII and IDHmut peptides, can stimulate antitumor immune responses and has been shown association with longer survival in preclinical models and early-phase clinical trials [98,99]. A phase III clinical trial combined a DC vaccine loaded with autologous tumor lysate (DCVax-L) with SOC treatment, and the results showed a significant improvement in patients' overall survival [100]. Fecci et al. demonstrated in a mouse model of glioma that the combination of anti-CD25 monoclonal antibodies and a DC vaccine reduces the ability of immunosuppressive $CD4^+CD25^+FOXP3^+$ $GITR^+$ Tregs to suppress $CD8^+$ T cells, significantly enhancing antitumor immunity [101].

Local oncolytic viruses may restore immune activation in situ despite T-cell deficiency or exhaustion. First, virus-mediated inflammatory response recruits T cells from perivascular regions into the tumor area. Second, the virus selectively lyses tumor cells to release tumor antigens that promote cross-presentation and T cell activation. Then, viral therapy can reverse T cell exhaustion and restore their cytotoxic function [102]. Clinical trial directly captured spatial evidence in human GBM tissue showing that a single oncolytic virus treatment correlates with persistent T cell activation and cytotoxic responses. Moreover, the survival benefits are associated with sustained increases in $CD8^+$ and $CD4^+$ TILs and systemic T cell stimulation [103]. Phase I and II trials of oncolytic herpesviruses such as G47Δ have also demonstrated that, treatment of residual lesions or rGBM yields biopsies with sustained increases in tumor-infiltrating $CD4^+$ and $CD8^+$ lymphocytes. Furthermore, the combination of G47Δ and systemic anti-CTLA-4 antibodies upregulated genes associated with lymphoid lineage, and T cell activation, demonstrating certain survival benefits and acceptable safety in rGBM, thereby offering a promising local immune-priming strategy for rGBM [104,105]. The significance of this strategy for T cell time-course analysis lies in the fact that it does not rely solely on the existing T cell pool but instead attempts to restore an activatable state in the low-responsive niche through in situ immunogenicity reconstruction.

3.2. T cell state atlas from primary to recurrent GBM

Patients with primary GBM (pGBM) recruit T cells to the tumor site in response to tumor-associated antigens. However, compared with those from healthy donors, these cells s may be subjected to sustained

immunosuppression by TAMs, MDSCs, Tregs, and diverse immunosuppressive factors within the TME, exhibiting substantial functional impairment and clonal restriction. [106]. Specifically, co-stimulatory molecule expression is downregulated, and tumor-infiltrating T cells gradually adopt an exhausted-like phenotype, accompanied by a decline in cytotoxic potential.

Cross-sectional analyses indicate that compared to pGBM, rGBM is not a simple continuation of the primary lesion but rather a new niche formed after selection by standard therapy and other therapeutic pressures. Tumor cell states in rGBM become more heterogeneous, and the immune microenvironment appears to further evolve toward a more stable inhibitory network. Studies have shown that rGBM is often accompanied by a MES-like phenotypic shift in tumor cells and exhibits more pronounced treatment resistance [107,108]. In analyses of paired primary and recurrent samples, the infiltration of T cells in recurrent lesions, particularly antitumor $CD8^+$ T cells, $GZMK^+$ effector T cells, and Tregs may be higher than in matched pGBM specimens [109]. While T cell infiltration increases during recurrence, this quantitative change does not translate into functional recovery, as the inhibitory network in rGBM is simultaneously reinforced. Although the overall immune cell composition appears relatively conserved between pGBM and rGBM, TILs exhibit a continuum of immune exhaustion, with upregulation of PD-1, TIGIT, CD39, TIM-3, and HLA-DR. rGBM exhibits higher PD-1 expression relative to pGBM, accompanied by reduced cytotoxicity and proliferative capacity, as well as TCR clonal restriction. Furthermore, $CD8^+$ T cells in pGBM TILs primarily exhibit a transitional memory phenotype, whereas those in rGBM are predominantly effector memory phenotype [110–112]. Multomics studies suggest that, relative to pGBM, spatial co-localization of tumor cells with $CD206^+$ macrophages and $CD163^+$ myeloid cells is significantly increased in rGBM, and interactions between MDM and Tregs with $CD8^+$ T cells are enhanced [113,114]. Concurrently, the myeloid population in the primary stage is predominantly enriched with resident microglia, whereas recurrent lesions shift toward an enrichment of monocyte-derived TAMs, MDSCs, and granulocytes. These myeloid cells further promote Tregs accumulation through signaling axes such as IL-10, TGF-β, CCL2, and colony-stimulating factor 1 (CSF1), thereby inhibiting antigen presentation, limiting T cell activation, and exacerbating T cell exhaustion [115–117]. Notably, preclinical studies have shown that the $HMOX1^+$ myeloid cell subset is predominantly localized in MES-like tumor regions. In rGBM, increased HMOX1 expression is associated with STAT3 pathway activation and enhanced IL-10 secretion; these alterations correlate with T cell exhaustion and poor overall survival [118].

Overall, cross-sectional comparisons between primary and recurrent GBM indicate that the evolution of T cells is a dynamic remodeling process associated with therapeutic pressure, tumor cell plasticity, myeloid network expansion, and systemic immune exhaustion. These further reveal that although neoadjuvant regimens may elicit transient intratumoral T cell activation, the dominant inhibitory network precludes durable responses, partly explaining the limited clinical efficacy of PD-1/PD-L1 monotherapy in rGBM. Nevertheless, true longitudinal trajectories require prospective tracking of spatial niches and clonal dynamics within individual patients through serial sampling integrated with spatial profiling. Accordingly, rGBM immunotherapy should advance beyond checkpoint monotherapy toward rationally designed combination regimens to improve response rates (Fig. 3).

4. Driving mechanisms of the spatiotemporal heterogeneity landscape of T cells

Through the iterative development of cutting-edge technologies such as single-cell transcriptomics, spatio-omics, and T cell receptor sequencing, our understanding of T cell heterogeneity is evolving from traditional static, holistic analyses toward a new phase characterized by dynamic, high-resolution spatiotemporal niches. The mechanisms underlying T cell spatiotemporal heterogeneity in tumors such as non-small cell lung cancer (NSCLC) and ovarian cancer are gradually being unraveled [119,120]. However, research on this topic in GBM remains in its preliminary exploratory phase. Building upon the systematic discussion of spatial and temporal dimensions presented earlier, this section will delve into the coupling mechanisms between these factors by examining the convergence of tumor cell intrinsic characteristics and molecular regulation, myeloid immune suppression networks, metabolism and epigenetic reprogramming, and neuroimmunology, thereby providing insights into the immune evasion in GBM.

4.1. Core drivers: Tumor cell state and plasticity

Tumor cells in different states exhibit significant differences in their ability to recruit and regulate immune cells [121]. Integrative studies have suggested that the spatial organization of T cells primarily originates from the regionalized distribution of tumor cells themselves. GBM cells exhibit spatially distinct distributions across states such as neuroprogenitor-like (NPC-like), astrocyte-like (AC-like), and MES-like and are associated with both genetic background and microenvironmental stress to compartmentalize the immune microenvironment, forming subtype-specific patterns of immune suppression [122,123]. Vidhya et al. performed spatial weighted regression analysis method on scRNA-seq datasets, confirming a strong overlap between reactive hypoxia regions, particularly areas of tissue necrosis, and the MES-like subtype. And that there is a bidirectional, synergistic reinforcement between tumor cells in the core region and immune suppression. In MES-like tumor regions, $HMOX1^+$ myeloid cells release IL-10, leading to the exhaustion of neighboring T cells. Inflammatory factors released by immune cells can, in turn, spatially associated with the tumor toward an MES-like state. Spots exhibiting MES-like and AC-like characteristics colocalize with $CD8^+$ effector T cell and the $CD8^+$ Tex cluster. TAMs genes such as CD163, CCL4, APOE, and HLA-DRA, are strongly correlated with $CD8^+$ Tex and $CD4^+$ Th1 clusters. The average PD-1 protein level is higher than in OPC-like and NPC-like subtypes, indicating enhanced local immune suppression [124–126]. Furthermore, previous studies have demonstrated that OLIG2 recruits HDAC7 to inhibit CXCL10 transcription, inducing STAT3 activation in TAMs and reducing the infiltration and activation of $CD8^+$ T cells in the MES subtype [127]. In rGBM, AP-1 (activator protein 1) mediates the transition of tumor subtypes to MES, further exacerbating immune evasion [128].

4.2. Genetic and molecular brakes and accelerators

The emergence of spatiotemporal heterogeneity in T cells within GBM involves multi-level molecular regulatory networks. The hypoxic environment can increase genomic instability, suppress DNA repair mechanisms, and accelerate the diversification of tumor subclones and immune editing. Complex interactions exist between MGMT status, DNA repair processes, and the immune response in GBM [129,130]. An analysis by Wang et al. of 86 pairs of primary-recurrent specimens indicated that $CD8^+$ T cell abundance in primary tumors is typically low, with cells appearing isolated and often confined to perivascular spaces, mismatch repair expression is associated with increased T cell infiltration in pGBM. In contrast, high tumor mutation burden (TMB) was significantly associated with increased T cell abundance only at recurrence [131]. Furthermore, the efficacy of TMZ treatment was associated with a hypermutational state at recurrence [132,133]. Additionally, S100A4 colocalized with CD163 and FOXP3 in GBM tissue. Elevated S100A4 expression is significantly associated with poor prognosis in GBM patients. During the progression of rGBM, the absence of S100A4 in Tregs and exhausted $CD4^+$ T cells stimulates $CD4^+$ T cell proliferation and the secretion of high levels of IFN-γ [134].

4.3. The remodeled hypoxic microenvironment

Using digital spatial profiling analysis, Petterson et al. found

significant differences in immune checkpoint expression between hypoxic and normoxic regions in GBM. The hypoxic microenvironment promotes a reduction in T cell numbers and functional exhaustion in the core region by upregulating the immune checkpoint inhibitory molecules CD44 and B7-H3, suggesting that partial pressure of oxygen itself can serve as a key spatial variable determining T cell functional status [135]. Sattiraju et al. found that, during GBM progression, the tumor vascular network transitions from a dense, regular structure to an abnormal state characterized by sparse and tortuous vessels. T cells undergo spatial reprogramming in tandem with vascular remodeling and the expansion of hypoxic zones, with the spatial distribution of TAMs and T cells shifting from early perivascular regions to hypoxic necrotic areas. Hypoxic promotes TAMs toward an immunosuppressive phenotype by upregulating the CCL8 and IL-1β signaling axes, and contributes to $CD8^+$ T-cell dysfunction [40]. In hypoxic zones, immunosuppressive cytokines such as TGF-β and IL-10 are upregulated, while the expression of endothelial adhesion molecules such as ICAM-1 and VCAM-1 is reduced, further cementing the spatial isolation of T cells [136,137].

4.4. Metabolic reprogramming

At the level of myeloid and T cell metabolic competition, the hypoxic microenvironment in the tumor core induces tumor cells to adopt a glycolytic phenotype by activating the HIF-1α signaling pathway, leading to the production of large amounts of lactate. This results in acidification of the TME, which directly impairs T cell antitumor function through two mechanisms. First, they can suppress IFN-γ production and cytotoxic activity, directly impairing T cell effector function. Second, lactate can downregulate T cell glycolytic metabolism by inhibiting the PI3K/Akt/mTOR signaling pathway, thereby suppressing their proliferative capacity and cytotoxic function, while simultaneously driving myeloid cells toward a pro-tumor phenotype [138,139]. Additionally, PD-L1 blockade influences tumor glycolytic pathways by inhibiting PI3K/mTOR signaling and reducing GLUT1 expression, thereby promoting the metabolism of activated T cells and restoring IFN-γ production [140]. Furthermore, the HIF-1α-transcription-induced Legumain enhances the GSK-3β–STAT3 signaling cascade, promoting M2-like polarization of TAMs and immune evasion. Targeting this pathway restores $CD8^+$ T cell activity and renders tumors sensitive to anti-PD-1 therapy [141].

MDSCs acquire metabolic adaptability through lipid metabolism and glycolysis. By depleting essential amino acids for T cell activation, and generating ROS, they directly suppress the function of T cells involved in antitumor immunity and promote the accumulation of Tregs. Fatty acid metabolism-related genes are significantly upregulated in $CD8^+$ TILs, and lipid droplet accumulation correlates positively with the expression of exhaustion markers such as PD-1 and TIM-3, suggesting that lipid metabolism itself may act as a metabolic switch driving the transition from an effector state to an exhausted state. Meanwhile, Tregs adapt to glucose competition through fatty acid oxidation pathways, maintaining their survival and immunosuppressive functions in low-glucose environments [142–144]. Furthermore, in GBM, high expression of tumor-derived indoleamine −2,3-dioxygenase (IDO) mediates the conversion of tryptophan to kynurenine, thereby inhibiting $CD8^+$ T cell proliferation, promoting Tregs differentiation, and enhancing MDSC activity [145]. Mouse models demonstrate that IDO-deficient mice exhibit a greater survival advantage compared to IDO-expressing mice, and high IDO levels are associated with reduced overall survival (OS) in GBM patients [146].

4.5. Emerging regulatory dimensions: Epigenetic and neuroimmune interaction networks

Recent studies further indicate that GBM can acquire myeloid-like suppressive characteristics by reshaping the microenvironment through epigenetic immune editing, thereby enhancing its ability to evade the immune system [147]. Lactate actively secreted by TAMs via MCT4 can be taken up by GSCs. Lactylation of KU70 at lysine K317 in GSCs inhibits cGAS-STING-mediated IFN1 production, thereby blocking DC maturation and antigen presentation, ultimately leading to spatial exclusion and functional exhaustion of $CD8^+$ T cells. Targeting this TAM-GSC lactate axis can restore cGAS-STING signaling, enhance $CD8^+$ T cell infiltration and cytotoxicity, and produce synergistic antitumor effects with PD-1 antibodies, providing a new dimension for spatiotemporally precise combination immunotherapy in GBM [148]. Furthermore, spatial glycomics analysis revealed a significant enrichment of abnormal glycosylation modifications in GBM, which is associated with the preferential increase of immune cell types such as $CD209^+$ DCs or Macs, $CD4^+$ T cells, and Tregs [149].

Neurotransmitter-mediated neuro-immune interactions also contribute to the formation of T cell spatiotemporal heterogeneity. GABA, which is abnormally expressed in the GBM microenvironment, is the primary inhibitory neurotransmitter in the CNS. Single-cell analysis revealed that GABA-related signaling pathways are specifically activated in TAMs and T cells; the expression of GABA-related genes is closely associated with immunosuppressive macrophage polarization and T cell functional suppression, and is significantly correlated with patient prognosis and responsiveness to immunotherapy [150]. Additionally, astrocytes further exemplify how non-tumor, non-immune cells actively shape T-cell spatiotemporal dynamics. In GBM, IL-11–driven STAT3 activation induces TRAIL expression on peritumoral astrocytes, which engages death receptors DR4/5 to trigger $CD8^+$ T-cell apoptosis, a mechanism conserved in IFN-γ–licensed neuroinflammatory contexts [54,151]. These findings incorporate neuro-immune interactions into the regulatory network of the GBM immune microenvironment, providing a new perspective on understanding T cell spatiotemporal heterogeneity.

These interactions are spatially confined to perivascular and hypoxic niches and temporally reshaped by treatment, collectively constituting the ecosystem-level drivers of spatiotemporal T-cell heterogeneity.

5. Translational strategies in GBM clinical practice based on T cell spatiotemporal coupling

5.1. Unlocking patient prognosis stratification

Traditional prognostic stratification systems based on clinical and pathological features struggle to reflect individualized differences in the tumor immune microenvironment. However, the differences in infiltration abundance and the distribution of functional defects among T cells across different spatial regions of GBM exhibit significant heterogeneity and are strongly associated with patient prognosis. This suggests that relying solely on non-standardized random sampling may obscure critical prognostic information. Therefore, establishing standardized spatial partitioning and sampling strategies will aid in identifying key nodes in immune state transitions and the development of treatment resistance [152].

Based on scRNA-seq analysis of GBM, Deng et al. identified a Prolif-like T cell subset expressing proliferation markers such as PCNA, MKI67, and MCM2. These subsets form proliferative interaction networks with tumor cells via thymidine kinase 1 (TK1). The high expression of TK1 in Prolif-like T cells is associated with poor prognosis in GBM patients. The fact that TK1 inhibition suppresses GBM proliferation positions it as a promising biomarker and potential therapeutic target [153]. Furthermore, CD39 on microglia acts synergistically with CD73 on tumor cells, leading to increased local adenosine levels, which in turn inhibit T cell activation via the A2A receptor, the spatial proximity of CD39 and CD73 predicts poor outcomes in GBM [154–156]. Spatial transcriptomics analysis identified a distinct subpopulation of $VSIG4^+S100A10^+$ TAMs that is specifically enriched in the hypoxic core and spatially colocalizes with exhausted T cells. These TAMs can inhibit T cell activation and

cytotoxic functions through direct cell-cell contact. This subpopulation is significantly enriched in patients who do not respond to anti-PD-1 therapy, suggesting that it may serve as a spatial biomarker for predicting immunotherapy response [157].

More importantly, a single-time-point assessment of the immune status is insufficient to capture treatment-induced immune remodeling, whereas longitudinal monitoring can identify optimal treatment timing or potential beneficiary populations earlier. Dynamic monitoring of peripheral blood immune markers provides an accessible window for prognostic stratification and personalized intervention in GBM patients. Elevated levels of anti-inflammatory cytokines (IL-10, IL-4, IL-6) and relatively reduced levels of pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β) in both peripheral blood and tumor cells prevent effective activation of antigen-presenting cells within the tumor. TILs exhibit significantly higher expression levels of PD-1, CD39, and TIM-3 compared to peripheral blood T cells [158,159]. Compared to recurrent tumors, the detection rate of TLS is slightly higher in primary gliomas. In particular, TLS exhibiting features of an active immune response, such as coordinated T cell and B-cell responses, and, clonal expansion, are often associated with longer overall survival and a lower risk of recurrence [52]. Overall, TLS is not universally present in GBM. Therefore, it is more appropriately viewed as a specific manifestation of spatial immune heterogeneity in GBM. This provides a new perspective for immune stratification and predicting treatment response in GBM.

Chemoradiotherapy not only directly kills tumor cells but also remodels the peripheral and local immune microenvironment. Dynamic changes in MDSCs can serve as early prognostic indicators. Previous studies have shown that trends in peripheral blood PD-L1$^+$ MDSCs during the early stages of chemoradiotherapy predict two-year survival rates more accurately than baseline levels [83,117]. Furthermore, TCR sequencing technology provides a tool for tracking the spatiotemporal evolution of tumor-specific T cell clones and helps identify dominant clonal types with the potential for therapeutic response. Studies have shown that the extent of TCR clone expansion following neoadjuvant immunotherapy is positively correlated with patient survival, suggesting that dynamic TCR monitoring can serve as an important reference for guiding treatment decisions [160]. In the tumors of long-term survivors, CD8$^+$ T cells exhibit a naïve-like phenotype, with lower levels of exhaustion and preserved effector characteristics. This suggests that the key to GBM prognosis lies in whether T cells can maintain sufficient clonal diversity, low levels of terminal exhaustion, and sustainable effector differentiation potential. These characteristics can serve as prognostic indicators for patients [110].

In addition to tissue and fluid samples, machine learning-based multimodal radiomics can extract hidden features from macroscopic images that reflect tumor necrosis, vascular permeability, and immune cell infiltration, thereby enhancing the clinical reliability of spatial information. It is therefore emerging as a promising non-invasive tool to bridge the gap between the dynamic immune status of GBM and clinical decision-making. Evidence from NSCLC and hepatocellular carcinoma suggests that multimodal imaging may identify immunosuppressive phenotypes and predict radiotherapy-induced lymphocyte depletion [161–163]. In GBM specifically, machine learning-based T1-weighted MRI radiomics features have been associated with immune score in IDH-wild-type GBM, as well as with T cell infiltration, TAM enrichment, and immune checkpoint molecule expression, suggesting potential prognostic value [164]. Additionally, relative cerebral blood volume is positively correlated with CD68$^+$ or CSF1R$^+$ macrophage accumulation and checkpoint molecule expression. It can even predict the level of CD8+ T-cell infiltration preoperatively, further supporting its potential prognostic relevance in gliomas [165]. Nevertheless, challenges persist in extracting relevant patient information at different time points and integrating large-scale multicenter data to minimize bias. If multimodal imaging can dynamically identify immunosuppressive phenotypes before and after treatment and predict the risk of lymphocyte depletion following radiotherapy, it may help precisely identify transient windows of immune activation and inform more personalized, spatiotemporally guided treatment strategies [166].

In summary, a single biomarker cannot fully account for the complexity of immuneresponses to GBM. Longitudinal tracking of peripheral immune cell subsets and TCR profiles, combined with spatial omics and radiomics analyses to map the immune landscape of cerebrospinal fluid and liquid biopsy samples, is crucial for unlocking refined patient prognosis stratification and optimizing treatment timing.

5.2. *Spatiotemporally-coupled combination therapeutic strategies*

T cell antitumor immunity is a continuous process with distinct temporal and spatial dependencies. Single-modality therapies typically intervene in only one phase of this process and are insufficient to overcome the complex barriers within the TME. Achieving therapeutic benefits in GBM therefore requires rationally prioritized combination strategies. Such prioritization should be guided by specific biomarkers, spatial niches, optimized temporal windows, and hierarchical levels of clinical evidence. Precision interventions that integrate these spatiotemporal determinants to maximize T cell infiltration and functional activation are reshaping the immunotherapeutic landscape in GBM.

5.2.1. *Spatial dimension: Targeted interventions guided by microenvironment compartmentalization*

Ongoing advances in spatial profiling have revealed the spatiotemporal heterogeneity of T cells, offering new opportunities for niche-specific intervention strategies.

In the tumor core, hypoxia-induced T cell terminal exhaustion and abnormal ECM stiffness pose major challenges to T cell function and infiltration. Targeting HIF-1α or lactate metabolic pathways has been shown to restore T cell function in the hypoxic microenvironment. The combined use of hypoxia-activated prodrugs with ICI may selectively reprogram the immunosuppressive state in hypoxic regions [167]. Additionally, antifibrotic agents targeting ECM remodeling have improved drug delivery and immune cell infiltration in preclinical models [168]. However, these findings remain at the preclinical stage and require clinical validation of both efficacy and safety.

Alanio et al. found that the perivascular region is characterized by enriched activated T cells and reduced Tregs in rGBM, which is significantly associated with prolonged post-relapse survival [169]. This finding suggests that this niche may be a “hot zone” for immunotherapy response in rGBM, and localized immune activation strategies targeting this region may be superior to whole-tumor interventions. Theoretically, vascular normalization may improve T cell migration into the tumor stroma. Bevacizumab, an anti-VEGF therapy clinically approved for rGBM, can partially remodel vascular architecture [170]. However, available evidence indicates that vascular normalization produces transient and limited improvements in T cell infiltration and Phase III trials in newly diagnosed GBM shows limited overall survival benefit [171]. CSF1R inhibitors targeting perivascular TAMs represent a preclinical strategy to relieve T cell suppression and promote tumor stroma infiltration. Therefore, the perivascular microenvironment in rGBM presents a distinct therapeutic window compared with the newly diagnosed GBM. The HBI identified by Wang et al. exhibits both active immune infiltration and significant immunosuppressive characteristics, representing a functionally distinct peritumoral spatial target [49]. Postoperative radiotherapy planning may incorporate HBI-directed irradiation with appropriate margins to eliminate infiltrating tumor cells. At the surgical level, multimodal MRI navigation can identify HBI regions, guiding expanded resection beyond conventional enhancement boundaries. In the context of immunotherapy, localized intervention strategies can be designed for the HBI, aiming to activate and maintain T cell function at the microenvironmental, thereby preventing terminal exhaustion once they enter the core region.

Furthermore, preclinical local treatment platforms such as catheter-based local drug delivery, biomaterial-based sustained-release systems,

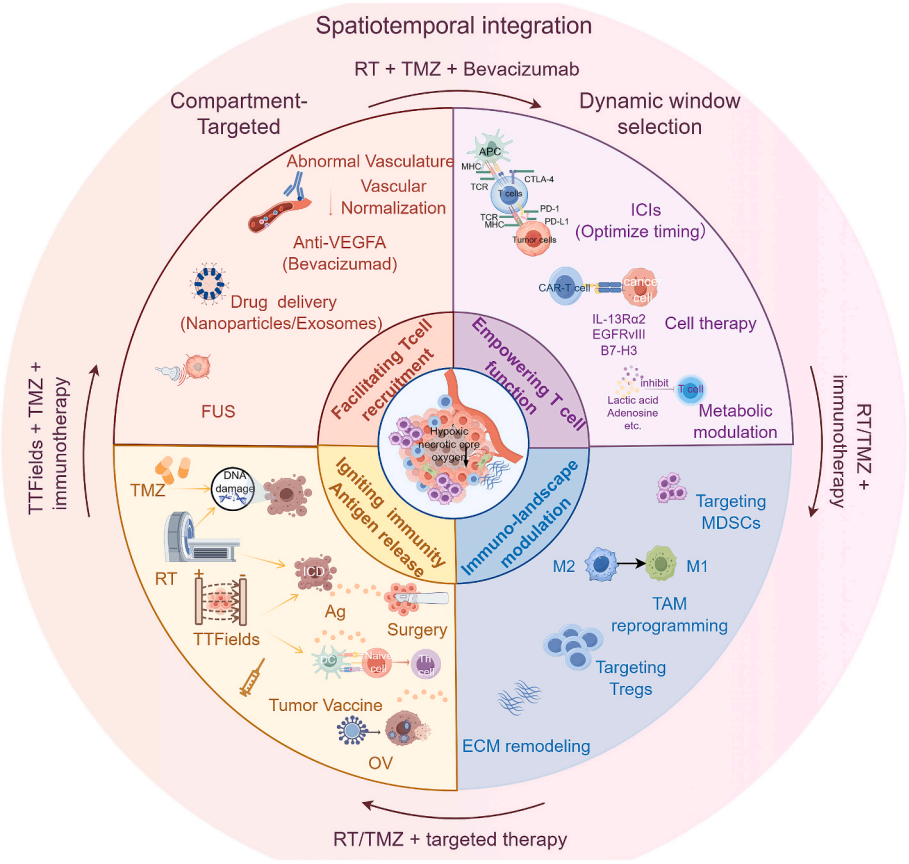

Fig. 4. Spatiotemporally-informed immunotherapeutic strategies for GBM. This figure illustrates a multi-dimensional therapeutic framework integrating spatiotemporal considerations to overcome T cell–centric immune evasion in GBM. The strategies are organized around four mechanistic axes: (1) priming antigen release and presentation, achieved by RT, OV, and tumor vaccines to generate T cell responses (neoadjuvant/perioperative window); (2) enhancing T cell recruitment and intra-tumoral infiltration, via optimized spatial drug delivery and vascular modulation (concurrent/early adjuvant window); (3) augmenting T cell effector function and countering exhaustion, through ICIs, adoptive T cell therapies, and metabolic/epigenetic reprogramming (adjuvant/recurrent window); and (4) remodeling the immunosuppressive microenvironment, by targeting TAMs, Tregs, MDSCs, and ECM barriers (recurrence window). Combinatorial regimens are positioned along a temporal axis spanning concurrent chemoradiotherapy, adjuvant, and recurrent phases. Importantly, this spatially and temporally coordinated framework provides the rationale for moving beyond isolated interventions toward multi-modal immunotherapies tailored to distinct GBM niches and disease phases. Abbreviations: FUS, focused ultrasound; CAR-T, chimeric antigen receptor T-cell therapy; RT, radiation therapy; TMZ, temozolomide; TTFields, tumor treating fields; OV, oncolytic virus.

implantable carriers, and convection-enhanced delivery enable precise immunotherapeutic delivery to the peritumoral region, enhance T cell infiltration and activation, and reduce glioblastoma initiator cells (GICs) to prevent postoperative GBM recurrence [172]. NIR-II engineered exosome nanotheranostic probes, another preclinical therapy technology, can effectively penetrate the blood-brain barrier and selectively target GBM cells, promote $CD4^+$ and $CD8^+$ T cell infiltration and enhance antitumor immune response [173].

5.2.2. *Spatiotemporally coupled sequential dynamic optimization*

Overall, the temporal evolution of T cells in GBM exhibits distinct phasic characteristics, providing important insights for optimizing the timing of T cell-targeted therapies. Below, strategies are organized by treatment phase, preclinical hypotheses and established clinical evidence are explicitly distinguished.

T cell-directed therapies should be administered as early as possible, during a phase when antigen presentation is intact and systemic immunity has not yet been severely compromised. It is worth noting that there is a treatment window of approximately one month between surgical resection and chemoradiotherapy initiation. During this period, the local immune microenvironment within the postoperative resection cavity undergoes remodeling, presenting a unique opportunity for therapeutic intervention. Intraoperative injection of an exosome-hydrogel platform can shift the treatment window to the surgical site. Supramolecular prodrug hydrogel that releases STING agonists in situ postoperatively, represent a preclinical strategy for precise spatial targeting of the drug within the surgical resection cavity. By dual activation of innate and adaptive immunity, it unlocks the potential of endogenous T cell responses, establishes durable immune memory, and suppresses tumor recurrence [174]. Equally important, $siNotch1^+$mitoxantrone represents a preclinical approach to selectively eliminate recurrence seeds, reshape the immune landscape via local IL-12, promote DC maturation, increase $CD8^+$ T cells and activated T cells, reduce Tregs and MDSCs, and upregulate IFN-γ/TNF-α expression, systematically reversing the immunosuppressive environment [172].

During the perioperative period following initial diagnosis and the early stages of radiotherapy, lymphocyte infiltration is limited but retains some antitumor potential, while the tumor antigen burden is largely preserved, presenting a valuable window of opportunity for immune activation. However, lymphocytes as a whole suffer significant numerical and functional damage due to the routine use of radiotherapy, TMZ, and corticosteroids, which weakens the efficacy of immunotherapy. Therefore, optimizing radiation fields and dose design, reducing corticosteroid exposure, and balancing the standard treatment-induced antigen release window with lymphocyte damage are essential to enhance the likelihood of effectively activating antitumor immunity. Immune protection during chemoradiotherapy should be an integral part of combination design to avoid inducing T cell exhaustion while

Table 1
Combination immunotherapy strategies under clinical trials in GBM.

Combination strategy	T-cell-related mechanism	Clinical trial number	Treatment timing	Design	Phase	Target population	Trial status/ outcome
ICI + SOC	Reversal of T cell exhaustion; antigen release and presentation	NCT02617589 [179] NCT02667587 [180]	Concurrent with RT/TMZ	Nivolumab + RT vs. TMZ + RT RT + TMZ + Nivolumab vs. RT + TMZ + Placebo	Phase 3	Newly diagnosed methylated GBM	Completed; mOS 13.4 vs. 14.9 months. Completed; mOS 28.9 vs. 32.1 months.
		NCT02866747	Concurrent with hFSRT	hFSRT vs. Durvalumab + hFSRT	Phase1	Recurrent GBM	Completed; Well tolerated in combination therapy [181].
		NCT02337686 [90]	Preoperative neoadjuvant and postoperative adjuvant	Pembrolizumab + surgery	Phase 2	Recurrent GBM	Active, not recruiting; mOS 20 months.
		NCT03197506	Neoadjuvant + adjuvant vs. adjuvant	Pembrolizumab + SOC	Phase 2	Newly diagnosed GBM	Active, not recruiting; mPFS 10.7 months.
Dual immune checkpoint blockade	Reversal of T cell exhaustion; enhances T cell priming and effector function; effector cytokine production	NCT02794883	Preoperative neoadjuvant and postoperative adjuvant	Tremelimumab vs. Durvalumab vs. Tremelimumab + Durvalumab	Phase 2	Recurrent GBM	Completed; mOS 7.3 vs. 11.7 vs. 7.7 months.
		ISRCTN84434175 [182]	Post-operative vs. alone after SOC	Ipilimumab + TMZ vs. TMZ	Phase 2	Newly diagnosed GBM	Completed; mOS 18 vs. 23 months.
		NCT04396860 [183]	Concurrent with RT	TMZ+ RT vs. RT + Ipilimumab + Nivolumab	Phase 2	Newly diagnosed GBM	Completed; mPFS 8.5 vs. 7.7 months.
		NCT03493932	Preoperative neoadjuvant and postoperative adjuvant	BMS-986016 (targeting LAG-3) + Nivolumab	Phase 1	Recurrent GBM	Completed; no IFN-γ response (0%).
		NCT03233152 [10]	Intraoperative intratumoral drug administration	Autologous CD1c (BDCA-1) + myDC and CD141 (BDCA-3) + myDC + Ipilimumab + Nivolumab	Phase 1/2	Recurrent GBM	Active, not recruiting (No results posted).
ICI and anti-angiogenic targeted therapy	Improving T cell recruitment and infiltration	NCT02337491 [184]	Recurrence after RT/TMZ	Pembrolizumab + Bevacizumab vs. Pembrolizumab	Phase 2	Recurrent GBM	Completed; mPFS 4.1 vs. 1.4 months. mOS 8.8 vs. 10.3 months.
		NCT02017717	Recurrence after RT/TMZ	Nivolumab vs. Bevacizumab	Phase 3	Recurrent GBM	Completed; mOS 9.8 vs. 10 months.
		NCT03291314 [185]	Recurrence after RT/TMZ	Avelumab + Axitinib (VEGFR-specific small-molecule tyrosine kinase inhibitor)	Phase 2	Recurrent GBM	Completed; (No results posted).
Adoptive T-cell therapy	Enhancing T cell cytotoxicity and prolongs persistence	NCT02208362 NCT02209376 NCT05660369		IL13Ra2-specific CAR T cells CART-EGFRvIII T cell CARv3-TEAM-E T cell	Phase 1	GBM	Active, not recruiting; mOS 10.2 months [186]. Terminated; (No results posted). Recruiting.
ICI + Oncolytic Virotherapy	Immunogenic cell death; reversal of T cell exhaustion	NCT04479241 NCT02798406 [187]		Lerapolturev (CED) + Pembrolizumab, DNX-2401(a genetically modified oncolytic adenovirus) + Pembrolizumab	Phase 2	Recurrent GBM	Completed; mOS 10.2 months. Completed; mOS 12.5 months.
ICI + Tumor vaccines	Antigen presentation and T cell priming	NCT02529072	Pre-Surgery	Nivolumab vs. Nivolumab + DC vaccine	Phase 1	Malignant gliomas (MGs)	Completed; mOS 8 vs.15.3 months.
		NCT04013672 [188]		Pembrolizumab + SurVaxM	Phase 2	Recurrent GBM	Completed; PFS-6 34.5%.
		NCT04888611	Preoperative neoadjuvant and postoperative adjuvant	Carilizumab (neoadjuvant) + surgery + GSC-DCV + Carilizumab (adjuvant) vs. Carilizumab (neoadjuvant) + surgery + placebo + Carilizumab (adjuvant)	Phase 2	Recurrent GBM	Unknown status.
ICI + TAM-targeted	Reshaping TAM-mediated T cell suppression	NCT02526017		Cabilizumab (Anti-colony stimulating factor-1 receptor) + Nivolumab	Phase 1	Recurrent GBM	Completed; mOS 8.1 months.
ICI + cytokine-targeted	Empowering T cell function, stimulating T cell proliferation	NCT04006119 [189]	Preoperative and postoperative	Ad-RTS-hIL-12 + Veledimex + Cemiplimab-RWLC	Phase 1	Recurrent GBM	Terminated; mOS 12.09 months.

(*continued on next page*)

Table 1 (*continued*)

Combination strategy	T-cell-related mechanism	Clinical trial number	Treatment timing	Design	Phase	Target population	Trial status/ outcome
Epigenetic immune regulation + SOC	Reprogramming exhaustion-associated epigenetic landscape	NCT03426891		TMZ + RT + Vorinostat (histone deacetylase HDAC inhibition)	Phase 1	Newly diagnosed GBM	Completed; mOS 12.2 months.
ICI + metabolic modulation + SOC	Removes metabolic barriers	NCT04047706		BMS-986205 (IDO1 inhibition) + Nivolumab + TMZ + RT	Phase 1	Newly diagnosed GBM	Active, not recruiting (No results posted).
TTFields + ICI + TMZ	Enhances immune recognition and anti-tumor immunity	NCT03405792 [190]	postoperative -conjunction	TTFields + Pembrolizumab + TMZ vs. TTFields + TMZ	Phase 2	Newly diagnosed GBM	Active, not recruiting; mPFS 11.79 vs. 6.7 months.
Gene therapy and virotherapy	Enhances local T cell priming and anti-tumor immunity	NCT01811992 [177]	Concurrent with RT/TMZ	Dose Escalation of Ad-hCMV-TK and Ad-hCMV-Flt3L	Phase 1	Newly diagnosed high-grade glioma	Completed; mOS 21.3 months.

Abbreviations: hFSRT, hypofractionated stereotactic radiation therapy; myDC, myeloid dendritic cells; CED, convection-enhanced delivery; GSC-DCV, glioma stem cell-loaded dendritic cell vaccine; mOS, median overall survival; mPFS, median progression-free survival; PFS-6, progression-free survival at 6 months.

pursuing theoretical synergistic effects. At the same time, radiation-induced transient T cell increases and ICD provide a "window of opportunity" for ICIs to access tumor antigens [87]. In preclinical mouse models, Van Hooren et al. further investigated the impact of the timing of ICB on radiotherapy efficacy. Adjuvant α-PD-1 therapy during the peak of T cell infiltration following radiotherapy maximized antigen exposure to effector T cells while avoiding negative feedback activation of Tregs, yielding superior survival benefits compared with concurrent α-PD-1 administration [175]. Additionally, targeting Tregs in the context of combined radiotherapy and immunotherapy induces the formation of TLS, enhances the infiltration and function of $CD4^+$ and $CD8^+$T cells, potentiating radioimmunotherapy efficacy [176].

Furthermore, in rGBM, TCR clonal expansion suggests the activation of a systemic antitumor immune response and the upregulation of the IFN-γ-related signaling pathways. However, TAMs gradually become entrenched and is difficult to effectively reverse. Clinical studies of neoadjuvant PD-1 blockade in rGBM have shown that preoperative administration of ICIs can induce stronger T cell activation signals in tumor tissue [94,160]. Currently, multimodal therapeutic strategies integrating myeloid and Tregs reprogramming with enhanced antigen presentation, alongside gene therapy combining cytotoxic and immunostimulatory effects that locally amplify inflammatory signaling, may delay or reverse T cell exhaustion over time [177]. Combining TLR9-targeted STAT3 antisense oligonucleotides with PD-1 blockade can simultaneously enhance innate immunity and lift immunosuppression [178]. Although these approaches show preclinical promise, their efficacy depends on mechanistic compatibility and spatiotemporal optimization, with clinical validation essential to avoid added toxicity without therapeutic benefit. Overall, future T cell intervention research should transition from traditional single-target, single-stage approaches toward stage-specific, time-sequenced, multi-target combination therapies spanning the entire trajectory from diagnosis to recurrence, prioritizing mechanistic compatibility and evidence stratification (Fig. 4, Table 1).

6. Integration and outlook: Opportunities and challenges from spatiotemporal profiling to precision intervention

Although spatiotemporally coupled combination strategies show great promise, several challenges remain for clinical translation. First, most mechanisms studies remain in the preclinical stage, and large-scale prospective trials validating safety and efficacy are lacking. Second, although organoid models can simulate spatiotemporal interactions between T cells and the microenvironment, thereby partially addressing the limitations of traditional cell line-based models, they still face constraints in accurately reproducing the complex functional immune components in vivo over the long term [191]. Meanwhile, microfluidic "tumor-on-chip" systems offer more precise control over oxygen and nutrient gradients but remain technically demanding [192]. In addition, the absence of standardized spatial partitioning and reliable biomarkers, coupled with limited real-time monitoring technologies, restricts the clinical translation.

Conclusively, future GBM immunotherapy should move beyond drug selection alone to integrate when to treat, which immune niche to target, and how to combine modalities. Converging high-throughput sequencing, live imaging, spatial multi-omics, immune monitoring, and AI-driven radiomics will enable the establishment of a T cell–based patient stratification, ultimately guiding personalized, spatiotemporal feature-guided dynamic targeted treatment regimens to improve the clinical outcomes with this lethal brain malignancy.

CRediT authorship contribution statement

Qingya Qiu: Conceptualization, Visualization, Writing – original draft. **Tingjun Zhang:** Conceptualization, Writing – review & editing. **Ping Song:** Writing – review & editing. **Hui Deng:** Writing – review & editing. **Yushu Liu:** Writing – review & editing. **Jiarui Bu:** Writing – review & editing. **Mengxian Zhang:** Supervision, Funding acquisition.

Funding

This study was supported by the National Natural Science Foundation of China (No. 81772680).

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.

Acknowledgements

The figures in the review were created with figdraw (https://www.figdraw.com).

Data availability

No datasets were generated or analyzed during the current study.

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