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Within and beyond the tumor: Mechanisms of glioblastoma-induced immunosuppression

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Immunotherapies have thus far proved of limited efficacy against glioblastoma. Failures can be attributed to a host of immunosuppressive mechanisms that are either directly employed by the tumor or are instead a convenient feature of the intracranial environment. This review aims to categorize glioblastoma immune-evasive tendencies, provide an update on our understanding of etiologies, and describe newer approaches to improving therapeutic responses.

Key Points:

- Glioblastoma employs multiple methods of immune-evasion and immunosuppression.
- Brain tumors proffer unique immunosuppressive mechanisms due to its central nervous system location.

Glioblastoma is the most aggressive and most common malignant primary brain tumor in adults, with an average survival of less than 21 months following diagnosis.[1] The 1-year survival rate is just 41.4% and 5-year survival is a dismal 5.4%.[2–4] More than 90% of glioblastomas recur following treatment,[5] and median survival following recurrence is only 3-9 months.[6]

Glioblastoma accounts for 57% of all gliomas and 48% of all primary malignant central nervous system (CNS) tumors. Standard of care remains maximally safe resection along with radiotherapy plus concomitant/adjuvant temozolomide.[7] This treatment paradigm has remained largely unchanged in the two decades since the publication of the Stupp protocol.[7]

While immunotherapies such as checkpoint blockade have become a mainstay of treatment for a range of solid tumors, successes have been limited in glioblastoma.[8,9] Failures can be attributed in large part to the profound immune dysfunction elicited by these tumors, both at a local and systemic level.[10,11]

This review will systematically describe the various immunosuppressive measures employed by glioblastoma (Figure 1). Mechanisms will be attributed and described within the context of 4 domains: the tumor cell (tumor-intrinsic), tumor microenvironment (TME), tumor location within the CNS (CNS-imposed), or peripheral to the tumor/tumor extrinsic (systemic). Intrinsic to the tumor, active mechanisms for immune evasion are augmented by notable tumor heterogeneity, which can be further exacerbated by the selective pressures imposed by therapy.[12–17] Locally, within the TME, glioblastomas foster evasion of T cell recognition, dysfunctional lymphocyte activity, and a disrupted cytokine milieu.[18–23] Active mechanisms for immune evasion are aided by notable tumor heterogeneity, which can be further exacerbated by the selective pressures imposed by therapy.[12–17] Glioblastoma's intracranial location presents unique challenges to immune access and avails of unique interactions, such as those between glial cells and neurons. Systemic alterations evoked by glioblastoma can include lymphopenia, lymphoid organ atrophy, sequestration of T cells, systemic T cell dysfunction, and altered hematopoiesis.[10,24,25] These systemic immune derangements are perhaps particularly surprising given that glioblastoma remains almost exclusively confined within the CNS. Ultimately, however, this combination of local and systemic immunosuppression promotes glioblastoma immune escape and severely limits the efficacy of immune-based treatment platforms.[18,26,27]

Tumor Intrinsic Factors

Glioblastoma can pass through the "cancer immunoediting" cycle, where it undergoes elimination by immune cells,

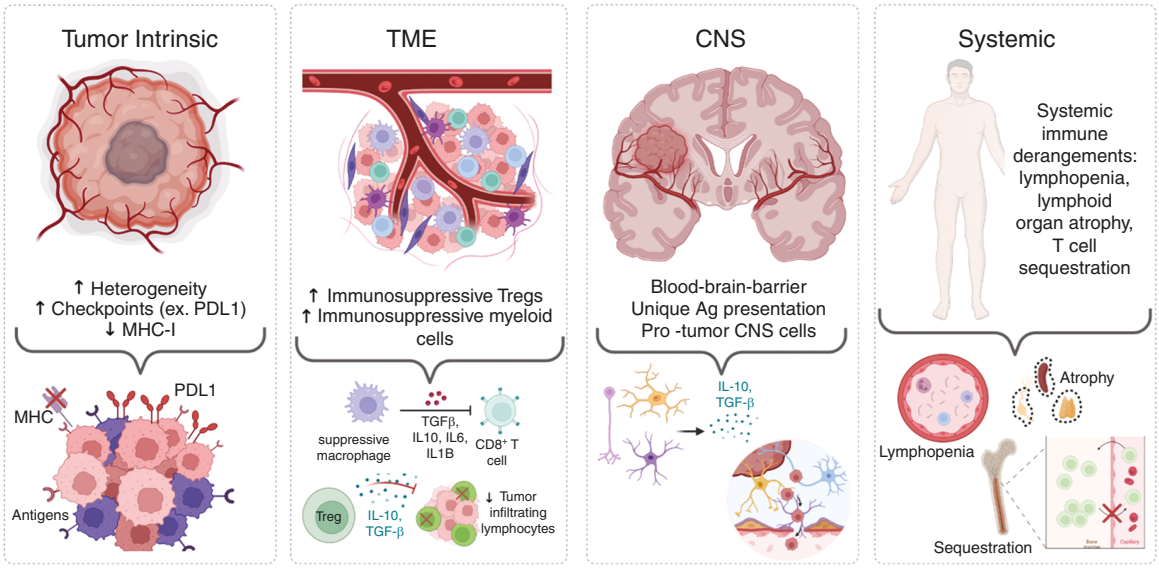

Figure 1. Overview of immunosuppressive mechanisms. At the tumor-intrinsic level, glioblastomas are markedly heterogeneous at even the single cell level and exhibit changes to gene expression or metabolic profiles that permit them to evade or counter the immune response. Within the tumor microenvironment, myeloid populations alter the tenor of the immune response, contributing to T cell exhaustion and an immunosuppressive milieu. The central nervous system (CNS) itself also provides safe harbor to tumors, creating challenges for antigen presentation and immune entry and forcing immune interactions with CNS-specific cell populations (microglia, neurons) that can restrict immune responsivity. Systemically, glioblastoma, and other intracranial tumors elicit such changes as lymphopenia, lymphoid organ involution, altered hematopoiesis, and T cell sequestration, despite being confined within the brain. Created in https://BioRender.com.

achieves equilibrium, and escapes an immune system attack via self-and immune-editing.[18,28] Self-editing at the tumor cell level can constitute a mode of tumor-intrinsic immune evasion. Common historical examples in the case of glioblastoma can include the upregulation of programmed cell death ligand 1 (PD-L1),[29–31] downregulation of major histocompatibility complex (MHC) molecules,[32,33] and various metabolic and epigenetic alterations[34–36] (Figure 2).

A well-recognized and tumor cell-intrinsic immunosuppressive strategy is the upregulation of PD-L1, which subsequently binds to the immune checkpoint PD-1 on T cells, limiting their function.[37] Therapies targeting the PD-1/PD-L1 axis, that is immune checkpoint blockade, represent some of the most successful immunotherapeutic strategies in solid tumors to date.[9] While anti-PD1 has failed to date in clinical trials in glioblastoma,[38] some more recent studies suggest that applications in the neoadjuvant setting may still bear fruit.[8] Cloughesy et al. for instance, observed improved immune parameters and a significant extension in overall survival (417 vs 228.6 days, HR 0.39, $P = .04$) when pembrolizumab was administered to patients with recurrent glioblastoma in the neoadjuvant, rather than adjuvant, setting.[8]

Interestingly, treatments incorporating anti-PD-1 have enjoyed tremendous success against brain metastatic melanoma,[39] suggesting that the CNS location is not a hindrance per se: it remains unclear whether the antibodies require brain access or may simply act systemically on T cells. Failures against glioblastoma then appear to result from features unique to these tumors. These can include an especially immunosuppressive microenvironment, limited T cell infiltration, and overall T cell dysfunction (particularly severe exhaustion),[40–45] all factors we will discuss in the following sections of the review. Additionally, T cells may develop adaptive resistance to checkpoint blockade therapy, upregulating alternative immune checkpoints, such as immunoglobulin mucin-3 (TIM-3).[46] TIM-3 serves a similar function to PD-1 in restricting T cell activity and may even induce T cell death following binding of exposed phosphatidyl serine on the tumor cell surface. As a result, anti-TIM-3 has been found to augment PD-1 blockade therapy to increase survival in patients with solid tumors, combating this adaptive resistance mechanism.[46] A clinical trial of anti-TIM-3 in combination with anti-PD-1 and stereotactic radiosurgery for recurrent glioblastoma is currently underway (NCT03961971).

MHC downregulation on tumor cells has historically been viewed as a cell-intrinsic mechanism of immune escape with varying relevance to glioma.[32,33,47] The loss of MHC and accompanying antigen presentation theoretically hides tumor cells from T cells and permits their unchecked outgrowth. Mutations leading to low or absent expression of β2-microglobulin (β2m), a crucial component to the MHC structure, have in particular been identified as harbingers of tumor immune-evasion.[32,33,48] Recent studies, in contrast, have also shown low β2m expression to actually be associated with favorable prognosis in gastric cancer and glioblastoma.[49,50] While elimination of tumor cells by CD8 + T-cells is thought to be hindered by MHC downregulation, there remain alternative mechanisms by which the immune system can attack tumor cells

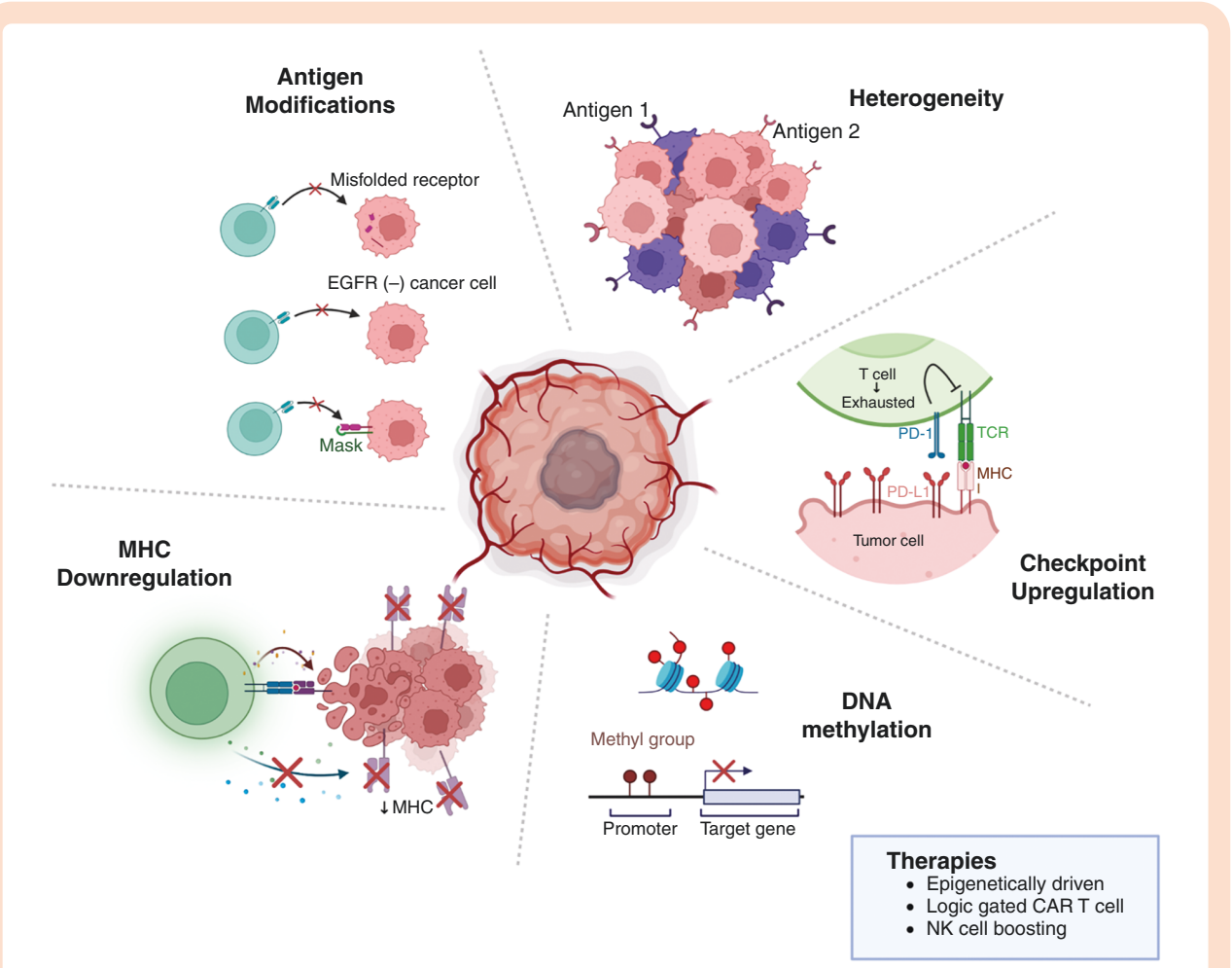

Figure 2. Tumor-intrinsic mechanisms of glioblastoma immune-evasion and suppression. Tumor cell-intrinsic mechanisms include antigen modifications, MHC downregulation, and antigenic and transcriptional heterogeneity that allow tumor cells to evade the immune system. Checkpoint upregulation and DNA methylation add further layers of suppression. Therapeutic approaches aim to modify gene expression or metabolism, target immune checkpoints, or sidestep heterogeneity. Created in https://BioRender.com.

that do not rely on T cells.[51] For instance, the loss of MHC class I can activate NK-mediated innate immunity and promote tumor cell expression of natural killer groups 2 member D (NKG2D) ligands (NKG2DL), which are typically upregulated following DNA damage and cellular.[52] The presence of such ligands can mark cells for destruction by NK cells in antigen-independent fashion.

NKG2DL may also seemingly mark tumors cells for destruction by CD8 + T cells in both MHC and antigen-independent fashion. In a true paradigm shift, it was recently revealed that MHC-I-negative glioma and melanoma cells remain susceptible to CD8 + T cell killing through the NKG2D/NKG2DL axis.[53] Importantly, MHC-I-negative tumor cell killing by CD8 + T cells was antigen-agnostic, though dependent on prior antigen-specific T cell receptor activation by antigen presenting cells (APCs) or even local MHC-I-positive tumor cells. These findings challenge the notion that loss of tumor MHC-I is synonymous with immune evasion.

The NKG2D/NKG2DL axis retains relevance here for other reasons as well. Soluble NKG2DL (ie, MICA or MICB) may be released by tumor cells and prove to be immunosuppressive in this context, competing for NKG2D and limiting the detection of tumor cells by NKG2D + immune cells.[54,55] Additionally, MICA and MICB may be transferred from the tumor cell surface to inhibit immune cell tumor-binding and activity.[34–36] Thus, therapies aimed at binding or removing soluble NKG2DL (such as soluble NKG2D), or at bringing NKG2D + T cells into better contact with tumor, may improve antitumor T cell function and/or counter tumor-imposed immunosuppressive mechanisms.

Despite its relatively high cellular and antigenic heterogeneity, glioblastoma possesses a low tumor mutational burden of ~1.5 mutations/megabase[1] with few coding mutations. As a result, there are relatively few neoantigens proffered for generating targeted adaptive immune responses. Likewise, those neoantigens present tend not to be homogenously expressed. Targeted therapies may successfully eliminate cells expressing the chosen target but be thwarted by outgrowth of antigen-negative variants. A classic example of this is found amidst therapies targeting the tumor-specific variant of the epidermal growth factor

receptor (EGFRvIII) on glioblastoma. EGFRvIII is expressed on 30% of glioblastomas, and on 37%-86% of the cells when present.[56] EGFRvIII-targeted therapies, such as EGFRvIII CAR-T cells, have exhibited limited efficacy, and even successful targeting of EGFRvIII + cells has seen antigen negative variants continue to grow.[20,57–59]

Further confounding therapy, treatments can also often increase intratumoral heterogeneity, as treatment-induced selective pressures can lead to hypermutation and the outgrowth of target-loss variants in the case of targeted therapies.[15–17] This is seen following alkylating chemotherapy, such as with temozolomide, where treatment induces mutations and genomic changes leading to further chemoresistance and immune evasion.[16,17,60] Tumor cells may also self-edit in response to targeted therapies, downregulating the expression of immunogenic antigens and fostering subsequent immune escape.[1]

Altering the metabolome is another tumor cell-intrinsic means for escaping immune-based platforms. In addition to perhaps providing tumors cells themselves a survival advantage, such alterations may serve to create a hostile environment for immune cells, fostering, that is, hypoxia and nutrient depletion that can lead to immune dysfunction. Metabolic alterations specific to glioblastoma include those in oxidative phosphorylation (OXPHOS), the pentose phosphate pathway (PPP), fatty acid biosynthesis, and more.[61] Fatty acid metabolism can promote tumor growth, and current work aims to target fatty acid oxidation with drugs such as Acyl-CoA binding proteins (ACBP, DBI) to hinder glioma growth.[62,63] The OXPHOS and PPP pathways play critical roles in tumor development through their influence on glycolysis, with OXPHOS inducing glioblastoma differentiation.[64] Glioma cells also frequently express indoleamine 2,3 dioxygenase, an enzyme that metabolizes the amino acid tryptophan, a process known to play roles in both enhancing tumorigenicity and recruiting immunosuppressive Tregs.[65]

A variety of epigenetic modifications, such as DNA methylation, can also help tumors evade the immune system by altering the expression of genes related to self-renewal and cell death.[66] Other epigenetic changes in subsets of glioblastoma can include mutations in complexes such as SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1 (SMARCAL1), normally involved in regulating chromatin structure and transcription. Such mutations can drive changes in chemokine expression and inflammatory cell recruitment to influence treatment resistance.[67–70] Ultimately, by modulating the expression of inflammasome components, tumors are able to manipulate the immune milieu and promote their survival.

In summary, there are several tumor-intrinsic features that may permit glioblastoma IDO IDO immune-evasion, including PDL1 upregulation, MHC downregulation, intratumoral heterogeneity, metabolic alterations, and epigenetic modifications (Figure 2). Such tumor cell-intrinsic changes are now the focus of a number of therapeutic platforms. For instance, metabolism-targeting agents include those inhibiting the OXPHOS pathway, with the compound gboxin aiming to inhibit the production of ATP in tumor cells and thus prevent proliferation.[71] As described above, immune checkpoint blockade targets receptors or ligands that limit CD8 + T-cell activation, with canonical targets to date including PD-1/PD-L1[72,73] and CTLA-4.[74] Additional targets have included TIM3,[75] LAG-3,[76,77] and TIGIT,[73,78] amongst others.

The most straight-forward attempts to side-step tumor heterogeneity simply employ multitarget strategies. For instance, multipeptide or neoantigen vaccines are designed to target multiple tumor-specific or tumor-associated antigens and may be customized to a patient's own tumor antigen expression profiles.[79–83] Tandem CARs targeting both IL-13Ra2 and/or EGFRvIII have likewise been developed and tested in clinical trials.[84,85] Concurrently, Boolean logic-gated CAR-T cells are beginning to be developed. These strategies equip CAR T cells with the capacity to respond only when certain combinations of targets are or are not expressed, in an effort to limit immune responses to normal tissues expressing tumor-associated (ie, not tumor-specific) antigens.[86]

Tumor Microenvironment Factors

The TME of glioblastoma is generally considered to be immunologically "cold" given a relative lack of T cell infiltration and fairly immunosuppressive milieu (Figure 3). The latter contributes a substantial degree of local T cell dysfunction within the TME that proves to be a significant barrier to effective antitumor immune responses. Most broadly, T cell dysfunction can be divided into the following 5 nonmutually exclusive categories: senescence, tolerance, anergy, exhaustion, and ignorance.[44]

T cell senescence is typically characterized by the loss of costimulatory markers and shortened telomeres resulting from chronic proliferation and stimulation.[87–89] Larger immune senescence may be marked as well by thymic involution, which can occur naturally with aging, but is also found in the context of chronic inflammation and leads to decreased T cell output.[90]

Tolerance is evolutionarily designed to limit T cell responses to self-antigens and is frequently therefore adaptive. It can either be central (ie, thymic deletion of autoreactive T cells) or peripheral (ie, Treg-imposed restrictions to autoreactive T cell responses) and is generally intended to completely curb cytotoxicity. In autoimmune diseases, however, tolerance may fail to properly induce T-cell unresponsiveness.[90] In the context of cancer, tolerizing mechanisms may instead be usurped by tumors to restrict responses to shared or even neoantigens. Glioblastoma cells, for instance, can overexpress FasL in order to delete T-effector cells peripherally, as well as to recruit regulatory T cells (Tregs) with the help of microglia, tumor-associated macrophages (TAMS), dendritic cells, and immunosuppressive cytokine secretion.[23,91–97] Tregs, in turn, serve as a means for propagating peripheral tolerance via direct contact-dependent inhibition of T cell responses or via the production of cytokines such as IL-10 and TGFB[98–100] and the inhibition of IL-2 production.[101,102] In the context of glioblastoma, Tregs become disproportionately represented among the CD4 compartment,[23,90] thus contributing to both local and systemic immunosuppression. Increased CCL2 within the TME has been shown to recruit both Tregs

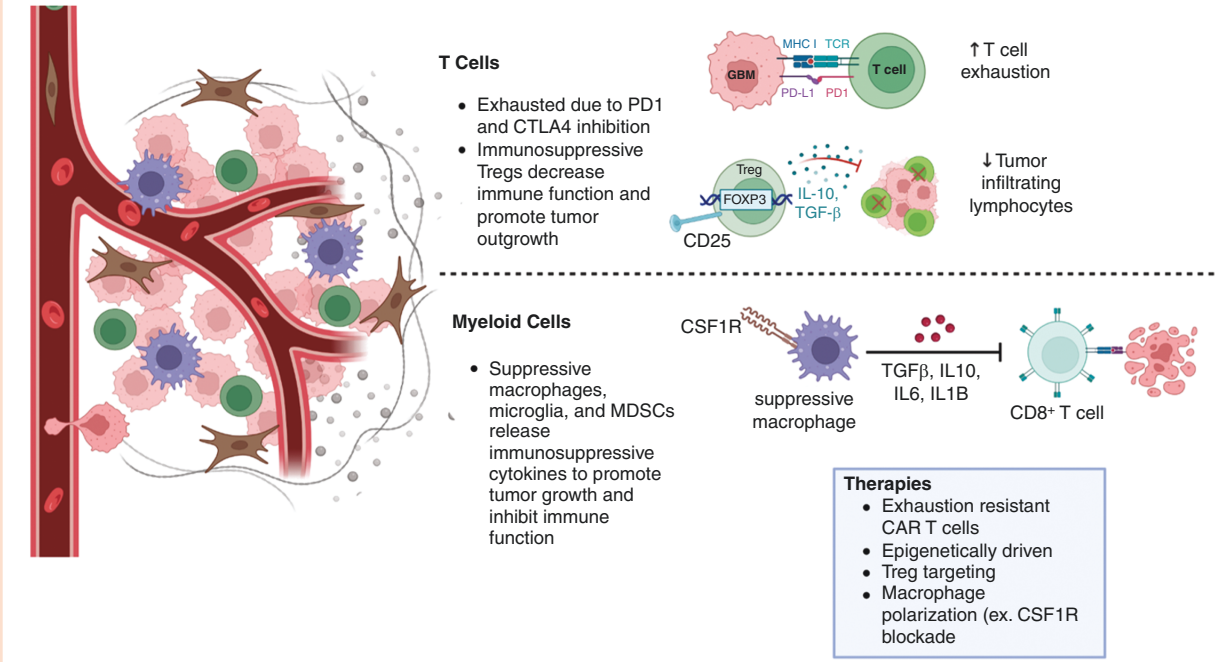

Figure 3. Glioblastoma tumor microenvironment-induced immune-evasion and immune-suppression includes mechanisms for locally eliciting various modes of T cell dysfunction (regulatory T cell-induced tolerance, exhaustion), much of which is aided by the activity of prominent populations of infiltrating myeloid cells. Created in https://BioRender.com.

and myeloid-derived suppressor cells.[23,94,103] Therapeutic strategies aimed at countering tolerance frequently focus on Tregs or their functional implications.

Anergy describes a fairly specific mode of T-cell inactivation after antigen binding and can be characterized by a lack of delayed-type hypersensitivity reactions upon secondary exposure to antigens. Clonal anergy follows insufficient costimulation from APCs leading to suboptimal antigen exposure, thus impairing T cell proliferation and preventing effective antigen recognition, respectively.[91,104–109]

Ignorance occurs when functional T cells remain inappropriately antigen-naïve, such as when targets are situated within immune "privileged" or "distinct" locations (such as the CNS), or conversely, when T cells become sequestered away from APC and/or targets and are not able to access their target antigen.[10,11,110–114] The T cell sequestration in bone marrow observed with glioblastoma and other intracranial tumors is a quintessential example.[10]

T cell exhaustion is a programmed hyporesponsive (but not nonresponsive) state that occurs often following chronic antigen exposure of appropriately primed T cells (ie, nonautoreactive) within the TME. It is characterized by the upregulation of various canonical and noncanonical immune checkpoint receptors (ie, PD-1, TIM3) on the T cell surface. Immune checkpoint receptor-ligand binding between T cells and tumor cells or APC elicits subsequent alterations to T cell metabolism and function and limits their capacity to clear antigen-expressing targets.[115,116] The result is the persistence of the target in a "stalemate" with the immune system.

Of the above modes of T cell dysfunction within the TME, exhaustion has become the most prominently studied of late, likely due to the frequent therapeutic focus on immune checkpoints. Likewise, T cell exhaustion is especially severe in glioblastoma.[11] Exhausted T cells are now divided into 2 subgroups: progenitor exhausted T cells (Tex_prog) and terminally exhausted T cells (Tex_term). Tex_prog (PD-1^{+}SLAMF6^{+}TIM3^{-}) can proliferate but have less cytotoxic potential, and Tex_term (PD-1^{hi}SLAMF6^{-}TIM3^{+}) are cytotoxic but nonproliferative, with higher expression of inhibitory receptors.[117] The master transcription factor regulator, thymocyte selection-associated high mobility group box factor (TOX), is expressed within exhausted T-cells, with levels increasing as exhaustion progresses.[117] TOX promotes chromatin remodeling at the promoters of genes driving T-cell exhaustion.[118] However, alone, it is insufficient to induce exhaustion and requires other functional contributors, such as PD-1 and SLAMF6.[119]

Recent studies have suggested that the classical definitions of exhaustion may be less relevant within glioblastoma. One such study, for instance, revealed unique transcriptional profiles among glioma-infiltrating lymphocytes, finding that clonally expanded T cells within the TME expressed lower levels of canonical exhaustion markers and instead terminally differentiated into a GZMK^{+} effector population with less cytotoxic capabilities.[120] Another study has highlighted a novel role for the receptor TNFR2 in marking the progression from Tex_prog to Tex_term within the glioblastoma TME, with blockade of the receptor prolonging survival in murine models of glioma.[121] Both studies advance novel phenotypes that may redefine the face of T cell dysfunction in the intracranial compartment.

While T cells are an expected focus of discussions surrounding immune dysfunction within the TME, more prevalent contributors within the glioblastoma TME are the various myeloid cell populations present. Tumor-associated macrophages and other myeloid cell populations play prominent roles in creating an immunosuppressive and/or pro-tumor TME. Tumor-associated macrophages found in tumors can be either microglia- or monocyte-derived and are self-renewing. Microglia-derived TAMs may be more prevalent in newly diagnosed tumors, whereas monocyte-derived TAMs may predominate amidst recurrence.[122] Altogether, they typically make up more than half of the cells within the glioblastoma TME, and they contribute significantly to immunosuppression via the secretion of immune-modulating cytokines,[123–125] such as transforming growth factor beta (TGFB), IL-10, IL-6, IL-1b, and others.[126] Likewise, numerous recent studies, including by our own group, suggest myeloid populations rather than tumor cells as the direct source of T cell exhaustion within the TME.[42,120,127,128] Altogether, these studies implicate antigen presentation by $CD163^+$ or $HMOX1^+$ myeloid cells as an initial event bringing them into contact with T cells, with secondary interactions involving, that is, IL-10 or SPP1 furthering the exhausted phenotype.

Additional myeloid-derived populations of relevance within the glioblastoma TME include infiltrating tumor-associated neutrophils (TANs). Neutrophils may play multiple roles that both support tumor growth directly while simultaneously limiting immune responsivity. For instance, TANs may release osteopontin, which stimulates the maintenance of stem-like glioblastoma cells.[129] These, in turn, can inhibit T cytotoxicity and promote proliferation in glioma stem cells through the activation of 3-phosphoinositide-dependent protein kinase 1.[130–133] Conversely, others have more recently identified a novel population of skull bone marrow-derived TANs that appear to possess APC-like features and can activate T cell cytotoxicity through antigen presentation on MHC II.[134] Thus, our newer understanding of neutrophils suggests increasing complexity surrounding their roles within the TME.

Current therapies aimed at modifying the TME most frequently address either T cell exhaustion or myeloid-induced immunosuppression (Figure 3). Regarding the former, approaches such as immune checkpoint blockade (discussed above) aim to target T cell exhaustion directly, while other therapies, such as CAR-T-cells, are increasingly being built with an eye toward conferring resistance to exhaustive mechanisms within the TME. Exhaustion-resistant CAR-T cells can be developed by genetically editing CAR-T cells, for example, via overexpression of specific genes. One such gene is BATF3, which has been shown to be associated with memory T cell features and improved cytotoxicity.[135] Other strategies include "armoring" CARs with cytokine support. Cotreatment with or coproduction of IL-15, for instance, can promote self-renewal of progenitor exhausted CAR-T cells, thus replenishing the cytotoxic T-cell compartment.[136] Other cytokine supports, such as IL-2 and IL-33,[137] have been shown to improve T cell polyfunctionality. Epigenetically focused therapies for exhaustion can target hypermethylation with DNA methyltransferase inhibitors. DNA methyltransferase inhibitors can be used to upregulate immune signaling, including a Type 1 interferon response.[138] Examples include the enhancer of zeste 2 polycomb repressive complex 2 subunit[139] inhibitors, as well as hyperacetylation with histone deacetylase[140] and bromo- and extra-terminal domain inhibitors.[139,140]

Therapies targeting myeloid cells to date have most typically aimed at impacting macrophage polarization. Such therapies include colony stimulating factor 1 receptor (CSF1R) blockade, which has been shown to deplete microglia and monocyte-derived TAMs[122] and to alter macrophage polarization toward more pro-inflammatory phenotypes.[141] Some groups have employed anti-CSF1R preclinically along with checkpoint blockade to elicit modest success against murine glioma.[142] Additional strategies for repolarization of TAMs have utilized CD40 agonists to improve dendritic cell T cell priming and TAM activation.[126,143,144] Likewise, inhibition of signal transducers and activation of transcription 3 (STAT3) within the TME may play a variety of antitumor roles, including restricting the immunosuppressive capabilities of infiltrating myeloid cells.[145–148] A Phase I trial of STAT3 inhibition in patients with glioblastoma was recently completed[149] (NCT02977780).

Looking to the future, the recent studies highlighted above delineating the importance of myeloid populations in driving T cell exhaustion may support newer strategies to block myeloid—T cell interactions within the TME.[42,120,127,128] Likewise, as newer roles for neutrophils are uncovered, novel approaches for impacting TAN recruitment or cytotoxicity may be justified. For instance, the discovery of a pro-inflammatory dendritic-like neutrophil population in the skull marrow insinuated a role for the CXCR4 antagonist AMD3100 for promoting their egress and recruitment.[134]

CNS Factors

Glioblastoma is unique among solid malignancies insomuch as it typically remains confined to the intracranial compartment. The CNS provides its own set of distinct challenges from an immunotherapy perspective (Figure 4). Historically, the CNS had been viewed as immune privileged: Harkening back to the 1940s, Peter Medawar demonstrated the absence of rejection when allogeneic skin grafts were implanted within the brain. What is less frequently recalled, however, is that Medawar's studies did actually observe rejection if the same skin grafts were previously grafted outside of the brain, making the notion of immune privilege somewhat less absolute.[1,150,151]

The blood-brain barrier (BBB) is also typically advanced as a feature of an immune-restrictive CNS, limiting access to both drugs and immune cells. However, the BBB deteriorates in glioblastoma,[152] and disruption likely allows many therapies to enter the brain space in some capacity.[153–156] Furthermore, an increasing participation of the brain with the immune system is now recognized. In more recent studies, for instance, Louveau et al. observed that meningeal lymphatics are an essential aspect of immune cell migration from the brain to the draining lymph nodes (dLNs).[157] The glymphatic system (glial-lymphatic)

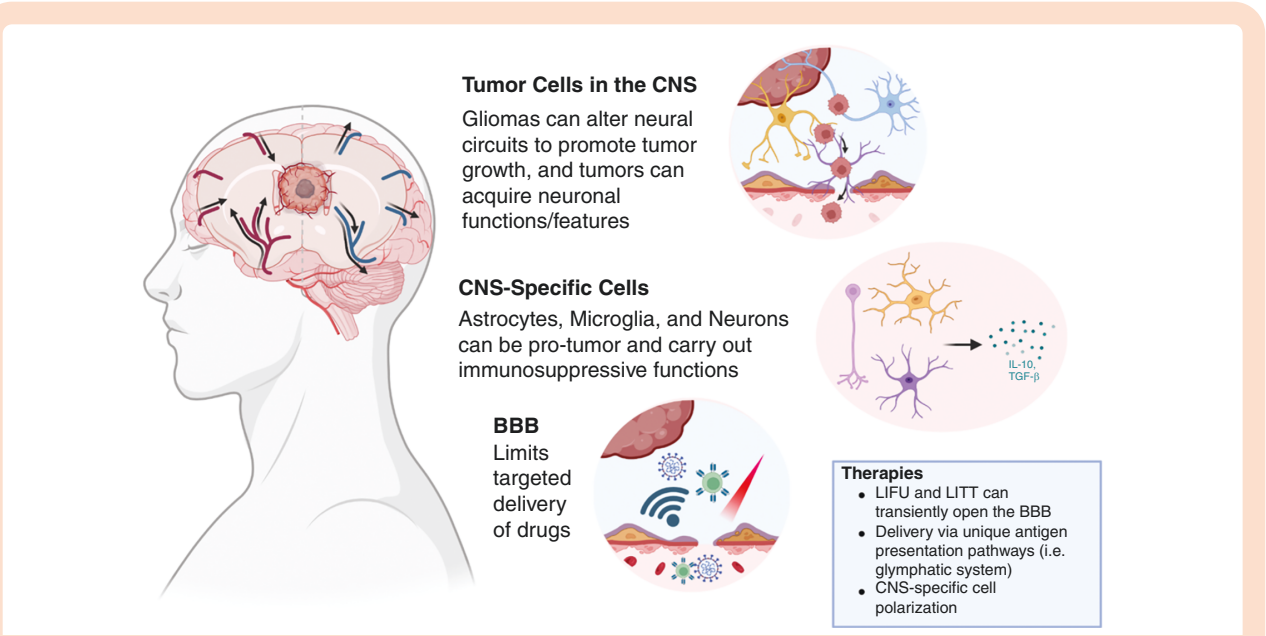

Figure 4. Central nervous system (CNS)-specific factors influencing glioblastoma immune-evasion and immune-suppression. The brain represents an immunologically "distinct" site, with unique aspects to antigen presentation and immune access. Microglia are CNS-resident cells that play an important immunomodulatory role. Glioblastoma also both alters and is influenced by surrounding neural circuits. Created in https://BioRender.com.

was identified as a mechanism of clearance from the brain where cerebrospinal fluid (CSF) could drain to venous perivascular spaces.[110,157–160] Functional lymphatic vessels have also been found in the meninges, allowing CSF to travel to cervical lymph nodes.[133–136] More recent research has shown that dural sinuses can also accumulate CNS antigens in the CSF, allowing APC-T cell interactions and promoting effector immune function.[161] The elucidation of these various CNS antigen drainage and presentation mechanisms has paved the way for newer therapies for several CNS pathologies such as Alzheimer's[157,162] and stroke,[163] incorporating novel therapeutic delivery routes, engineered particle delivery, and more.[164]

Although not as isolated as perhaps once thought,[165] the "immunologically distinct" brain still offers challenges to effective immunity against glioblastoma. Surrounding cell types unique to the intracranial compartment, such as microglia, astrocytes, and neurons, all can contribute to an immune-restrictive TME. While microglia and TAM were discussed above, tumor-associated astrocytes have also been shown to possess immunosuppressive activity, secreting cytokines such as IL-10 and TGFB.[166] Likewise, neurons have been shown to play a role in gliomagenesis, supporting tumor progression and infiltration.[167] The Monje group has recently shown that cholinergic neuron stimulation increases glioma proliferation, while neuron–tumor interactions promote tumor growth through glutamatergic and GABAergic neurons.[168] Furthermore, gliomas can alter neural circuits to promote proliferation by tumor cells[169,170] and promote hyperexcitability with the secretion of glutamate and neuroligin-3 (NLGN3).[169,171,172] Such activity suggests a crosstalk occurs between gliomas and neurons to promote tumor survival.[169] Recently, it has also been shown that radiotherapy can enhance tumor–neuron connections in a manner that actually contributes to therapeutic resistance, while virus-mediated ablation of these connections can instead decrease tumor proliferation.[173]

Therapies designed to address CNS-imposed limitations can employ such strategies as better delivery routes premised in newer understanding of antigen egress and presentation, or can perhaps further open the BBB to allow more efficient delivery (Figure 4). Regarding delivery routes, intrathecal and intraventricular injections have recently been used to deliver cellular therapies to the brain, allowing better access to the CSF and intracranial spaces.[85,174] Intratumoral injections have also been used for therapy administration: one recent clinical trial used this route to deliver a modified poliovirus (PVSRIPO) into recurrent glioblastomas.[175]

Regarding BBB opening, focused ultrasound has been used in patients to transiently open the BBB, permitting classically nonbrain penetrant therapies better intracranial access.[176] Laser interstitial thermal therapy has also been found to open the BBB in mouse models, thus proffering both tumor cell kill and subsequent improved therapeutic delivery.[177–179] With regards to brain-specific cell targeting, in addition to the virus-induced ablation of neuron–tumor connections mentioned earlier, targeting microglia via, that is, inhibition of nuclear receptor subfamily 4 group A member 2 (NR4A2) has been shown to synergize with immune checkpoint blockade.[180] Additional examples of novel strategies include nanoparticles designed to deliver various molecules such as small interfering RNA or chemotherapy with differing routes for administrations such as intranasal or intertumoral injections.

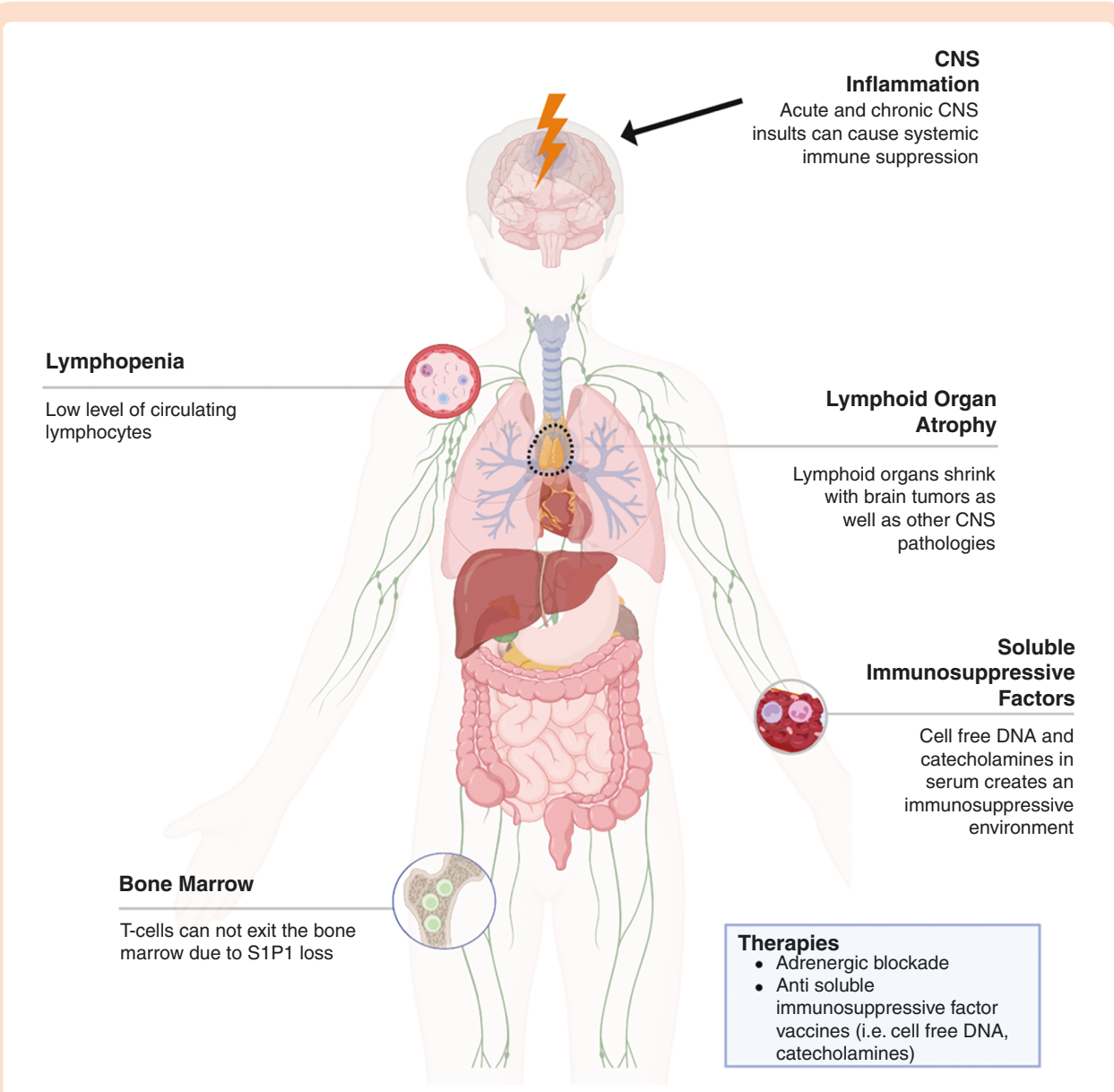

Figure 5. Glioblastoma and central nervous system-driven systemic immune derangements include lymphopenia, lymphoid organ atrophy, and bone marrow sequestration. The upstream mechanisms driving these systemic changes are an active area of investigation. Created in https://BioRender.com.

Systemic Factors

Various examples of systemic immune derangements have been documented in the context of glioblastoma and other intracranial tumors[10,25,181–185] (Figure 5). Early work by Brooks and Roszman in patients with glioblastoma first identified systemic immune dysfunction in the form of lymphopenia, impaired antibody production, and weakened lymphocyte function.[183,184,186–188] Regarding lymphocytes, studies have shown reduced counts and function of both CD4 + and CD8 + T cells,[189] as well as defects in T cell development.[190] IL-2 activity and signaling is diminished, leading to T cell proliferative defects.[189,191] Glioblastoma elaborates anti-inflammatory cytokines, such as TGFB, IL-10, and PGE2,[22,192,193] which serve to further suppress IL-2 secretion by T cells, reduce IFN-γ production, downregulate MHC expression/presentation, suppress Th1 cytokine synthesis, inhibit APC capacities, and suppression proinflammatory cytokine production. Tregs are also elevated both locally and systemically in patients with glioblastoma and serve to limit cellular immunity and promote immune escape.[23,65,194,195]

More recent work in this area has revealed that peripheral immunosuppression in glioblastoma patients and mouse models is characterized by T cell lymphopenia, splenic and thymic involution, sequestration of T cells within the bone marrow, and the presence of potent immunosuppressive

factors in circulation.[10,25,181] The role of serum-derived soluble factors as mediators of systemic immunosuppression in glioblastoma has been previously established.[25] Interestingly, systemic immune derangements, including peripheral lymphopenia mediated by serum-derived factors, are not unique to the glioblastoma setting and have also been described in other brain injuries, including stroke and brain viral infections.[25,196] Immunosuppressive factors in the serum of mice with intracranial pathologies are large in molecular weight and nonsteroidal in nature.[25] Notably, "systemic immune derangements" have been described across various intracranial pathologies, including brain tumors, demyelinating diseases, stroke, and traumatic brain injury.[25,181,197,198] These derangements include T cell lymphopenia and dysfunction, lymphoid organ atrophy/involution, and naïve T cell sequestration in the bone marrow,[10,181,197,199–201] suggesting a common mode of CNS-insult-driven immunosuppression.

Importantly, while much of the work described above was performed in treatment-naive patients and thus highlights tumor-imposed deficits, various components to standard of care therapy for glioblastoma further contribute to an environment of systemic immune dysfunction. While temozolomide assuredly contributes to lymphopenia, for instance, a perhaps even larger source of immune dysfunction is the typical dosing regimens of steroids such as dexamethasone, intended to curb cerebral edema. While such benefits are well documented, they come at a collateral cost to antitumor immune responses, restricting the number and function of lymphoid cells and hampering immunotherapeutic success.[202,203] It is a growing trend among immunotherapeutic clinical trials for cancers in general to place limits on the maximal dose of steroids that may be employed.

Several hypotheses exist as to the proximal causes of diminished systemic immunity amidst intracranial processes. One focuses on increased sympathetic activity, which appears to follow neuroinflammation and can impose adrenergic stress on immune cells.[204,205] One study showed that beta blockade in combination with immunotherapy was able to increase survival in a brain tumor model, as well as in lung cancer and melanoma brain metastases models. Likewise retrospective clinical data revealed extended survival in patients with glioblastoma or brain metastases who were prescribed beta blockade.[205]

Another potential mediator of systemic immunosuppression in serum may be cell-free (CF) DNA. Analysis of CF-DNA, especially that of circulating tumor DNA, is an active area of investigation; as such, "liquid biopsies" can potentially be noninvasive sources of prognostic biomarkers. However, the functional role of CF-DNA in immunity and its immune-modulatory roles in cancer and other intracranial pathologies remains poorly understood. Ayasoufi et al. have shown heightened levels of CF-DNA in serum of mice with glioblastoma,[206] which has also been observed in patients.[207,208] Furthermore, they demonstrated that CF-DNA isolated from the serum of mice with gliomas suppresses T cell function.[206] Roth et al. also recently showed that the presence of CF-DNA in the circulation of mice and humans poststroke conferred T cell immunosuppression indirectly through monocyte sensing of nucleic acids by Absent In Melanoma 2 (AIM2).[196] Distinct immune-modulatory roles of CF-DNA in various context are likely mediated through cell-type specific intracellular nucleic sensing mechanisms.

Overall, this common systemic immunosuppression seen across various CNS diseases and pathologies hints at a common mechanism, with several hypotheses as to the key drivers. Reversing systemic immunosuppression in the setting of glioblastoma will be an important step in improving global host immune dysfunction in a manner that better permits immunotherapeutic success (Figure 5). Strategies to address systemic immune derangements may well then synergize with and license systemically focused immune-stimulating therapies, such as checkpoint blockade.[205]

Conclusion

Immunotherapies for glioblastoma and other intracranial tumors continue to face unique challenges. These challenges exist at the level of the tumor cell itself, the TME, the CNS more generally, and even systemically. While we have discussed these 4 domains in isolation for the purpose of organization and clarity, they are by no means mutually exclusive and are ultimately overlapping and interconnected facets dictating glioblastoma's limited response to treatment. Likewise, while glioblastoma's intracranial locale poses specific immune-related considerations, the tumor exhibits particularly severe capacities for restricting immune function that make it more formidable than other brain-situated lesions, such as metastases. Glioblastoma presents a notable challenge to immunotherapy, proffering few neoantigens and eliciting marked local and systemic immune dysfunction. The latter includes such barriers as regulatory T cells-induced tolerance, severe T cell exhaustion, an immunosuppressive and myeloid-heavy TME, glial–neuronal interactions, lymphopenia, lymphoid organ involution, altered hematopoiesis, and T cell sequestration. These barriers ultimately serve to hinder T cell number, access, and function, all 3 necessary components to immunotherapeutic success. In such combination, the sum total of these immune obstacles is unique to glioblastoma, and immunotherapeutic approaches must include means for clearing some if not all of these hurdles. Alternative delivery routes, combinatorial approaches, epigenetic and metabolic manipulation, innovative cellular therapeutic modifications, and myeloid- or regulatory T cell-targeting approaches are just a few examples of strategies to be explored and expanded.

Keywords

glioblastoma | immune checkpoint blockade | immunosuppression |T cell exhaustion.

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Conflict of interest statement

The authors declare no competing interests with regards to the current work.

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