Proceedings of ICMMGH 2027 Symposium: Clinical OMICS for Drug Discovery and Personalized Medicine
DOI: 10.54254/2753-8818/2027.MB38477

Innate Immunity Suppression in Glioma, Reason, Mechanisms and Potential Treatments

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Abstract. Glioblastoma (GBM) is the most lethal primary central nervous system malignancy, with intrinsic immunosuppressive traits severely limiting the efficacy of conventional and immunotherapeutic regimens. This paper systematically elaborates the core causes, multi-layered molecular and cellular mechanisms, and targeted therapeutic strategies of innate immune suppression in GBM. It demonstrates that tumour-intrinsic oncogenic mutations, central nervous system immune privilege, and tumour microenvironment (TME) remodeling synergistically construct an immunosuppressive background to block innate anti-tumour surveillance. Mechanistically, GBM impairs innate immune activation via diminished DAMP release, defective pattern-recognition receptor (PRR) signaling transduction, and functional reprogramming of microglia, macrophages, NK cells and dendritic cells. This paper shows that innate immune suppression can not be reversed by single-target therapy using examples such as emerging PRR-targeted agonists and myeloid-modulatory interventions. It highlights the restoration of innate immune sensing and TME immune as the core direction for future GBM immunotherapy, providing systematic theoretical support for clinical translational research.

Keywords: Glioblastoma, innate immunity, tumour microenvironment, pattern recognition receptors, immune suppression

1. Introduction

Glioblastoma (GBM) is one of the most aggressive and highly heterogeneous primary malignant tumours in the human central nervous system (CNS). The prognosis is extremely poor and the recurrence rate is high. Although the emerging immune checkpoint inhibitors have achieved remarkable anti-tumour effects in solid tumours, their clinical efficacy in GBM patients is very limited. This is mainly due to the deep and multidimensional immunosuppression in the GBM tumour microenvironment (TME). On the other hand, innate immune tolerance and functional paralysis constitute the main barriers to early tumour surveillance and immune clearance, which fundamentally limit the activation of systemic anti-tumour immune response. Therefore, the key to breaking the immune resistance of GBM and developing new immunotherapy lies in clarifying the regulatory mechanism of innate immunosuppression.

Current research has preliminarily revealed the key link between GBM progress and innate immune disorders. Existing studies confirm that the immune privileged state of CNS constitutes an

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DOI: 10.54254/2753-8818/2027.MB38477

inherent immunosuppressive microenvironment. In addition, carcinogenic-driven mutations in GBM will inhibit the death of immunogenic cells and reduce the secretion of risk-related molecular patterns (DAMPs) required for the activation of innate immunity. Many studies have confirmed that abnormal modification of pattern recognition receptor (PRR) signaling pathways such as cGAS-STING and NLRP3 will destroy the transformation of dangerous signals into inflammatory anti-tumour responses. More and more evidence shows that GBM tumour microenvironment (TME) can induce phenotypic changes in innate immune cells, including small glial cells, tumour-related macrophages (TAMs), medullary inhibitory cells (MDSCs) and natural killer (NK) cells, thus forming tumour-friendly microenvironment. However, most of the existing studies mainly focus on independent molecular pathways or single immune cell subgroups, and lack systematic integration of the triggers, stratification mechanisms and targeted treatment strategies of innate immunosuppression [1]. Based on these research gaps, this review provides a comprehensive framework to examine the causes and molecular and cellular mechanisms underlying innate immune suppression in GBM. It also summarizes potential therapeutic strategies centred on PRR signaling activation and myeloid immune normalization, paying special attention to the limitations of monotherapy and the potential benefits of combined approaches.

2. Innate immunity suppression in glioma

GBM remains highly resistant to current treatments. A major challenge is the development of an immunosuppressive environment, where both tumour-intrinsic properties and the unique characteristics of the CNS restrict immune surveillance. Unlike highly immunogenic tumours, GBM exhibits limited response due to a combination of low immunogenicity, intrinsic oncogenic alterations and extensive remodeling of the surrounding TME [1, 2]. Together, these factors reduce the activation and function of innate immune responses, creating favorable conditions for tumour progression and immune escape.

At the intrinsic level of tumour cells, genetic changes and molecular heterogeneity can lead to immune escape of GBM. Comprehensive genome analysis identified different molecular subtypes associated with carcinogenic changes in pathways such as EGFR, PDGFRA, IDH1 and NF1. These genetic procedures not only affect the growth and survival of tumours, but also the composition and functional state of immune cell compartments. For example, different genomic backgrounds are related to differences in immune cell infiltration, allowing cancer cells to internally change to shape the GBM immune landscape. In addition, high intra-tumour heterogeneity enables different tumour cell populations to adopt different functional states to help them adapt to immune stress and treatment [2]. In addition to carcinogenic changes, the anatomical and immunological characteristics of the central nervous system provide another obstacle to immune-mediated tumour clearance. Recent studies have shown that there is a lymphatic structure associated with the central nervous system, but immune monitoring and activation in the brain are still more rigorous than peripheral tissue [1]. This limited immune channel can reduce the infiltration of immune cells, weaken the effective anti-tumour response, and provide an environment conducive to immune escape for GBM.

Apart from these intrinsic factors, GBM actively remodels its TME to support tumour survival and suppress immune activity. The GBM TME is a complex system composed of tumour cells, resident brain cells, infiltrating immune cells, vascular components and extracellular matrix elements. GBM cells continuously reshape surrounding cells and their functional states through direct cell–cell interactions and indirect communication mediated by cytokines, chemokines, growth factors and extracellular vesicles. Environmental factors such as hypoxia, altered pH and metabolic stress further influence cellular behavior within the tumour niche. These dynamic changes generate a

DOI: 10.54254/2753-8818/2027.MB38477

supportive environment that promotes tumour growth while impairing effective immune activation [1]. Together, these tumour-intrinsic alterations, CNS-specific immune constraints and TME remodeling establish the foundation of innate immune suppression in glioma. Understanding these factors provides the rationale for investigating the molecular and cellular mechanisms through which GBM actively suppresses innate immune surveillance.

3. Molecular and cellular mechanisms of innate immunity suppression in glioma

3.1. Modulation of immune-stimulatory ligands and danger-associated molecular patterns (DAMPs)

Innate immune surveillance depends on continuous availability of endogenous and exogenous signals that can be detected by PRRs. In GBM, suppression of innate immunity can therefore occur before the PRR itself is inhibited. Tumour cells can reduce the generation and release of immunostimulatory danger signals by resisting inflammatory forms of regulated cell death or limiting the accumulation or immunogenicity of cytosolic nucleic acids. These mechanisms decrease the upstream ligands required to initiate effective innate immune sensing and help establish an immunologically silent tumour environment.

Resistance to regulated cell death represents one major source of ligand depletion, as immunogenic cell death releases abundant damage-associated molecular patterns to trigger PRR-driven immune activation. A major source of endogenous danger signals is immunogenic regulated cell death. Ferroptosis, pyroptosis and necroptosis can cause oxidative membrane damage or membrane rupture, allowing intracellular DAMPs to become accessible to immune-sensing pathways. GBM exhibits substantial resistance to ferroptosis through enhanced antioxidant capacity, altered iron metabolism and lipid-peroxide detoxification. In particular, increased activity of the SLC7A11–glutathione (GSH)–GPX4 axis promotes cystine uptake, glutathione synthesis and removal of lipid peroxides, preventing the membrane damage associated with ferroptotic death [3]. Therefore, resistance to ferroptosis may reduce the endogenous danger signals available for PRR activation and contribute to immune silence in GBM. It should be noted that this description focuses on tumour-intrinsic ferroptosis resistance; therapeutic interventions such as chemotherapy can still trigger ferroptosis-dependent immunogenic cell death in GBM lesions.

Pyroptosis provides a second connection between tumour-cell death and innate immune activation. Canonical pyroptosis involves inflammasome activation, caspase-1-mediated cleavage of gasdermin D (GSDMD), formation of membrane pores and eventual cell lysis. This process allows the release of DAMPs such as HMGB1 and ATP, together with inflammatory cytokines including IL-1β and IL-18. In glioma, pyroptosis-related molecular patterns have been associated with immune infiltration, immune-related processes and potential responses to immunotherapy [4]. Thus, insufficient pyroptotic activity may reduce the generation of inflammatory signals that would otherwise reinforce innate immune activation.

Necroptosis similarly links tumour-cell destruction with inflammatory immune signaling. The RIPK1/RIPK3/MLKL axis promotes formation of the necrosome, MLKL phosphorylation and membrane disruption, resulting in the release of DAMPs and other intracellular contents. Evidence from glioma samples and experimental models indicates abnormal regulation of necroptosis-associated components in GBM, with alterations in RIPK1, RIPK3 and MLKL associated with tumour biology and therapeutic response [5]. Together, resistance to ferroptosis, pyroptosis and necroptosis allows GBM cells to reduce the immunogenic consequences of tumour-cell death while maintaining tumour survival.

DOI: 10.54254/2753-8818/2027.MB38477

Apart from cell death derived danger signals, nucleic acid based PRR ligands are also actively eliminated or modified by GBM cells to blunt upstream innate sensing. GBM can also suppress innate immune sensing by limiting the availability of nucleic-acid ligands. Cytosolic dsDNA is a principal ligand for cGAS, whereas endogenous dsRNA can activate RIG-I-like receptors, particularly MDA5. Following DNA damage, the abundance of cytosolic DNA is controlled by the exonuclease TREX1. SPOP-mediated ubiquitination promotes TREX1 degradation, whereas cancer-associated SPOP alterations or USP7 activity stabilize TREX1 and accelerate cytosolic DNA removal. Experimentally, reduced cytosolic dsDNA caused weaker STING and IRF3 phosphorylation, reduced cGAMP production and decreased expression of IFNB1, IFIT1 and CXCL10. This provides direct evidence that depletion of an upstream ligand can uncouple DNA damage from innate immune activation.

RNA sensing can be similarly restricted. GBM stem cells show increased ADAR1 expression and A-to-I RNA editing, particularly within dsRNA structures. This modification can alter endogenous dsRNA and reduce its immunogenic recognition by MDA5. In addition, PTEN-deficient GBM suppresses endogenous retrovirus transcription and the accumulation of immunostimulatory dsRNA, thus weakening the ERV–MAVS–IFN viral-mimicry pathway [6]. These mechanisms demonstrate that GBM can suppress innate immunity at the earliest stage of the sensing cascade: by reducing DAMP release and by eliminating or modifying DNA and RNA ligands before they can efficiently engage their corresponding PRRs.

3.2. Suppression of pattern-recognition receptor (PRR) signaling in innate immune cells

Even when immunostimulatory ligands are present, innate immune activation requires functional PRRs and intact downstream signaling. GBM can disrupt this surveillance by reducing PRR expression, altering receptor activation, interfering with adaptor-dependent signaling or shifting inflammatory outputs toward tumour-supportive states. In the GBM microenvironment, multiple PRR families, including Toll-like receptor (TLR) signals in myeloid cells, can be inhibited by different mechanisms. The change of TLR signal directly reflects the inhibition of innate immune cells in GBM. TLR4 is an important receptor for sensing endogenous danger signals and can regulate the inflammatory response in tumour cells and myeloid cells. Studies on GBM-related immune cells show that the expression level and function of TLR4 in TAMs are reduced. Further evidence comes from the GBM co-culture experiment, which shows that GBM cells can still inhibit the expression of TLR4 in macrophages and the activation of the TLR4-MD2 complex even after LPS stimulation. This finding shows that signals from GBM cells can actively reduce the ability of macrophages to respond to innate immune stimuli [7, 8].

Beyond TLR family members, the cGAS-STING axis represents another critical sensing node suppressed via epigenetic regulation. In the cGAS-STING system, STING in GBM tumour cells has been proven to be epigenetically silenced, and its promoter high methylation is closely related to the reduction of STING expression. Demethylation treatment can restore the expression of STING and its response to cGAMP, while restoring IRF3 and interferon-related signaling pathways. Although this evidence is mainly concentrated in GBM tumour cells rather than infiltrated innate immune cells, the decrease in STING expression in tumour cells may still affect the surrounding immune environment. This may be due to a decrease in the production of local interferon and other signals that can affect neighboring immune cells. Therefore, the inhibition of PRR inherent in the tumour may further lead to extensive immune dysfunction in the GBM microenvironment, rather than playing independently.

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Retinoic-acid-inducible gene-I-like receptor (RLR) signaling is also restricted at transcriptional and post-translational levels. It is similarly subject to suppression at several checkpoints. KAP1/TRIM28 can reduce the transcription of Ddx58 and Ifih1, which encode RIG-I and MDA5, by recruiting histone-modifying machinery and adding repressive H3K9me3 marks. As a result, GBM cells and stem-like populations show low basal RLR activity, while stimulation with poly(I:C) or 5′-triphosphate RNA can restore type I interferon and CXCL10 production and promote tumour-cell apoptosis. These findings suggest that RLR pathway can remain intrinsically competent but function at levels that are too low for effective activation. Post-translational regulation provides an additional checkpoint. TRIM38-mediated SUMOylation stabilizes RIG-I and MDA5 and facilitates their activation, whereas loss of this regulation reduces downstream TBK1 and IRF3 phosphorylation and interferon production.

Unlike the above-mentioned sensing defects, NLR-family-mediated inflammation highlights a key complexity: PRR pathway activation does not always generate anti-tumour phenotypes. NLR signaling demonstrates an additional form of dysregulation in which innate inflammatory activation is not necessarily equivalent to effective anti-tumour immunity. In GBM, NLRP3 activation can promote IL-1β and IL-18 production while expanding immunosuppressive myeloid populations. Pharmacological NLRP3 activation increased granulocytic MDSCs and antagonized the therapeutic benefit of STING activation, whereas NLRP3 inhibition prevented this effect [8]. NLRP3 expression has also been associated with an IL-1β/NF-κB p65 axis that promotes glioma proliferation and invasion. Notably, existing literature also documents context-dependent anti-tumour functions of NLRP3 in other glioma experimental systems; such contradictory observations suggest that NLRP3 output is highly dependent on tumour stage, cell type and local microenvironmental conditions. Therefore, the relevant defect is not simply insufficient PRR signaling. GBM can distort the output of innate immune pathways so that inflammatory signaling becomes tumour-supportive instead of producing productive anti-tumour immunity.

Overall, GBM suppresses PRR-associated immunity through multiple checkpoints, ranging from reduced sensor availability to impaired intracellular signaling and inappropriate inflammatory output. Among these mechanisms, suppression of TLR4 responsiveness in TAMs provides direct evidence of impaired PRR function within an innate immune population, whereas tumour-intrinsic cGAS–STING and RLR suppression demonstrates how malignant-cell signaling defects can further shape the surrounding immune environment.

3.3. Functional reprogramming of innate immune effector cells

3.3.1. Microglia and tumour-associated macrophages (TAMs) polarization

Myeloid cells constitute a major component of the glioma microenvironment, but their immunosuppressive activity cannot be adequately explained by conventional classification into microglia, macrophages or monocytes. In particular, 183,062 myeloid cells from 85 human gliomas were analyzed using single-cell RNA sequencing and identified four recurrent immunomodulatory programs: microglial inflammatory, systemic inflammatory, complement immunosuppressive and scavenger immunosuppressive programs [9]. Importantly, these programs were distributed across multiple myeloid cell types, indicating that functional state is not determined solely by cellular identity or developmental origin. Instead, glioma-associated environmental cues drive myeloid cells towards distinct functional states.

Among these programs, the two immunosuppressive states are particularly relevant to tumour-associated myeloid dysfunction. The complement immunosuppressive program was characterized by

DOI: 10.54254/2753-8818/2027.MB38477

expression of complement-associated genes including C1QA, C1QB, C1QC and C3, together with immunosuppressive markers such as VSIG4 and CD163. The scavenger immunosuppressive program showed increased expression of scavenger receptors such as CD163, LYVE1, MRC1/CD206, MSR1/CD204 and STAB1, consistent with enhanced tissue-remodeling and immunoregulatory activity. Interestingly, macrophages showed higher levels of both immunosuppressive programs, while microglia showed a wider range of inflammatory and complement-associated states.

Spatial transcriptomic analysis further demonstrated that these functional states are organized by the local tumour architecture. The scavenger immunosuppressive program was particularly enriched within hypoxic and vascular niches, while inflammatory programs were associated with inflammatory and vascular regions. Integration of spatial and transcriptomic data therefore supports a model in which local TME conditions actively instruct myeloid-cell function rather than merely determining which myeloid populations accumulate. Miller et al. further identified hypoxia, IL-1β, TGF-β and dexamethasone treatment as important environmental associations with these programs. Together, these findings indicate that GBM promotes a highly plastic myeloid compartment in which microglia and macrophages can acquire immunosuppressive functional programs in response to tumour-associated signals.

3.3.2. Myeloid-derived suppressor cells (MDSCs) accumulation

In addition to reprogramming resident and recruited macrophage-lineage cells, GBM promotes the accumulation of specialized myeloid-derived suppressor cell (MDSC) populations. Experimentally, 33 human gliomas were studied by single-cell RNA sequencing, identifying two immature bone-marrow-derived populations: early progenitor MDSCs (E-MDSCs) and monocytic MDSCs (M-MDSCs) [10]. They were strongly enriched in aggressive IDH-wild-type GBM but were largely absent from IDH-mutant gliomas. Both populations displayed metabolic and stress-adaptation programs, while M-MDSCs additionally showed increased expression of inflammatory, migratory and monocytic scavenger-associated genes.

The accumulation of these cells was closely associated with specific tumour niches. Spatial transcriptomics showed that E-MDSCs almost completely colocalised with a stem-like, mesenchymal tumour-cell population within the pseudopalisading regions surrounding necrosis, where hypoxia and nutrient limitation are prominent. Ligand–receptor analysis suggested that tumour cells actively contribute to MDSC recruitment through chemokine signaling, including CCL8–CCR1, CXCL1–CXCR1, CCL5–CCR1, CXCL8–CXCR1 and CCL4–CCR5, together with IL-6–IL-6R and CSF1–CSF1R interactions.

This tumour–MDSC interaction appears reciprocal. E-MDSCs express growth-promoting factors that can support the associated stem-like tumour cells, creating a local feedback loop that reinforces both MDSC accumulation and tumour aggressiveness. Functionally, isolated GBM-associated MDSC subsets reduced $CD4^+$ and $CD8^+$ T-cell proliferation in vitro, supporting their immunosuppressive function. Therefore, GBM-associated MDSCs are not simply an increased myeloid population, but a spatially and metabolically specialized suppressive compartment that is particularly prominent in the hypoxic niches of IDH-wild-type GBM.

3.3.3. Dysfunction of NK cells and dendritic cells

The functional reprogramming of innate immunity in GBM goes beyond the bone marrow population and extends to NK cells and dendritic cells (DC). NK cells account for a small part of

DOI: 10.54254/2753-8818/2027.MB38477

infiltrating inflammatory cells in GBM, and promote anti-tumour immunity through the production and regulation of cytokines of other immune cells through the direct cytotoxicity mediated by perforin and Gran enzyme B. Although they exist in tumours, NK cells associated with GBM show impaired functional activity. GBM-derived TGF-β can inhibit the activation of NK cells, and tumour-related MHC-I molecules can come into contact with the inhibitory receptors of NK cells, while reducing their cytotoxic antitumour activity.

DC provides another important component for innate immune monitoring by processing tumour-related antigens and initiating downstream immune responses. In GBM, DC can be recruited into TME through chemokines including CXCL1 and CCL5, but recruitment alone does not ensure effective anti-tumour response. Functional DC activation is necessary to produce anti-tumour cytokines such as IL-12 and support subsequent antigen-specific immune responses. Evidence from experimental DC activation and DC-based vaccination further shows that restoring DC function can partially improve the immune response of GBM. Overall, these findings indicate that GBM changes the composition and functional state of its innate immune compartment. GBM TME not only simply accumulates inhibitory cell populations, but also restricts the activity of innate cells involved in tumour monitoring and immune activation.

3.3.4. Soluble inhibitory mediators and metabolic reprogramming within TME

The functional inhibition of innate immune cells in GBM is not only determined by cell changes, but also strengthened by soluble mediators and metabolic constraints in TME. These factors provide lasting environmental clues and shape the functional state of innate immune cells. Soluble inhibitory mediator is an important mechanism for GBM to reshape the behavior of innate immune cells. Evidence shows that immunosuppressive bone marrow procedures are associated with specific TME-derived clues, including hypoxia, IL-1β and TGF-β signaling. This shows that inflammation and stress-related factors can actively shape the functional state of bone marrow, not just affect the recruitment of immune cells [9]. These signals form part of a broader network of cytokines and chemokines, which act on multiple innate immune groups. Therefore, continuous exposure to these factors can promote and maintain tumour-supported immune phenotypes.

Metabolic reprogramming provides an additional mechanism to enhance innate immunosuppression. GBM metabolism creates a hostile immune environment characterized by increased glycolysis, lactic acid accumulation, extracellular acidification, and competition for essential nutrients including glucose, glutamine and tryptophan [11]. These metabolic changes can change the survival and functional activities of immune cells, which is beneficial to inhibitory populations such as MDSC and M2-like macrophages, while limiting effective anti-tumour responses. Consistent with this, enhanced glycolysis and oxidative phosphorylation processes were found in tumour-infiltrated MDSC, indicating that metabolic adaptation supports their survival and inhibition functions in hypoxic and nutrient-restricted GBM niches [10]. These factors together produce persistent TME, in which congenital immune cells are continuously exposed to signals that are beneficial to tumour-supporting function.

4. Potential therapeutic strategies targeting innate immunity suppression in glioma

4.1. PRR-targeted agonists to restore innate immune sensing

Given that GBM suppresses innate immune activation through impaired tumour sensing and reduced inflammatory signaling, restoring PRR activity represents a promising therapeutic strategy. Among

DOI: 10.54254/2753-8818/2027.MB38477

these methods, the activation of the cGAS-STING pathway has become a potential method to transform the immunologically "cold" GBM microenvironment into a more immune-allowable state. Evidence shows that the use of agonist ADU-S100 to activate STING can reshape the GBM tumour microenvironment and enhance the innate immune response [12]. Although GBM cells showed limited responses to direct STING activation, human GBM explants still produced inflammatory cytokines after treatment, suggesting that stromal and immune cells within the tumour niche may also contribute to the response. In the intracranial GBM model, STING agonist treatment induces infiltration of innate immune groups, including inflammatory macrophages, bone marrow cells and NK cells, accompanied by an increase in type I interferon signaling. Importantly, the consumption of NK cells eliminates the therapeutic effect, indicating that NK cells are an important medium for STING activation response [12]. However, challenges including delivery across the CNS, excessive inflammatory activation and tumour heterogeneity are still important considerations in clinical translation.

4.2. Myeloid-cell-targeted therapy (MDSC depletion/inhibition)

Although PRR agonists aim to restore innate immune perception, when immunosuppressive medullary cell groups are still in a functional dominant position in TME, the use of PRR agonists alone may not be enough to overcome this immunosuppression. Therefore, targeting these cells represents another potential treatment strategy. GBM-related medullary cells can form different tumour-promoting transcription procedures, which indicates that selective reprogramming of these cells may be more effective than simply eliminating the infiltration of immune cells [9]. Potential treatment strategies include targeting pathways involved in macrophage maintenance, such as CSF1R signaling pathways, while reducing immunosuppressive MDSC groups or limiting their collection to tumour areas. However, it may not be ideal to completely clear the medullary cell group, because some macrophages and small glial cell subgroups still retain the function of inflammatory response and antigen presentation. Therefore, future treatments may require selectively reprogramming the state of medullary cells with immunosuppressive effects into immunostimulating phenotypes instead of non-selective clearance。

4.3. Combination therapy (chemoradiotherapy combined with innate-immune-targeted agents)

The limited efficacy of monotherapy in GBM shows that the activation of innate immunity alone may not be enough to overcome tumour-mediated multi-level immunosuppression. Therefore, combining traditional treatment with innate immune-targeted drugs may be a more effective treatment method. Traditional treatments such as radiotherapy and chemotherapy can change the stress state and antigen availability of tumour cells, which may provide additional opportunities for innate immune activation. Combining these treatments with PRR agonists or medullary cell targeted therapy may reduce the immunosuppressive barrier while enhancing immune recognition. However, the metabolic barrier in the GBM microenvironment, including hypoxia, nutrient competition and changes in the metabolite ability, may further limit immune cell function and therapeutic response [11]. Therefore, these factors should also be taken into account when designing a combined treatment plan. In general, effective GBM immunotherapy may require multi-target strategies, while restoring immune perception, reshaping immunosuppressive cell groups, and overcoming TME-mediated treatment resistance.

DOI: 10.54254/2753-8818/2027.MB38477

4.4. Current challenges and limitations of these potential treatments

Although the current preclinical research results are promising, innate immuno-targeted therapy still faces many challenges before achieving clinical transformation. Major limitations include effective drug delivery across the CNS, tumour heterogeneity, potential immune-related toxicity and the difficulty of maintaining sustained immune activation without inducing excessive inflammation. Future therapeutic development will require improved delivery systems, predictive biomarkers and rational combination strategies to achieve durable anti-tumour immunity in GBM.

5. Conclusion

This paper systematically clarifies the multi-factor causes and hierarchical mechanisms of innate immune suppression and summarizes corresponding targeted therapeutic strategies in GBM. Innate immune paralysis in GBM is synergistically induced by tumour-intrinsic oncogenic defects, inherent CNS immune privilege and comprehensive TME remodeling, rather than controlled by a single independent mechanism. At the molecular level, GBM hinders innate immune activation by reducing DAMP release and destroying core PRR signaling. At the same time, it can also reshape some immune signaling pathways, thus promoting tumour progression. At the cellular level, TME induces functional reprogramming of small glial cells, TAMs, MDSCs and other innate immune cells to form a stable immunosuppressive cell network. Hypoxia and metabolic disorders in the microenvironment further consolidate immune dysfunction and build a stratified and interrelated immunosuppressive ecosystem. At present, the treatment strategy for a single target cannot completely reverse innate immunosuppression, and the combined strategy of targeting immune perception recovery and TME normalization at the same time may have greater therapeutic potential. This review provides a systematic mechanism framework and research basis for understanding the innate immune escape of GBM and the development of new precise immunotherapy, which helps to break through the the immunotherapy bottleneck in refractory glioblastoma.

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