Immunopathology of Glioblastoma

> Key findings of: Li J, Ross JL, Hambardzumyan D, Brat DJ. Immunopathology of Glioblastoma. Annu Rev Pathol. 2025 Oct 8. doi: 10.1146/annurev-pathmechdis-042524-025950. PMID: 41061166.

Here's a detailed summary of the key findings from Li J, Ross JL, Hambardzumyan D, Brat DJ. **"Immunopathology of Glioblastoma."** *Annu Rev Pathol.* 2025 Oct 8; doi:10.1146/annurev-pathmechdis-042524-025950. PMID: 41061166. annualreviews.org
The summary is organized in annotated Vancouver-style bibliographic format with major points for clarity.

Citation

Li J, Ross JL, Hambardzumyan D, Brat DJ. Immunopathology of Glioblastoma. *Annu Rev Pathol.* 2025 Oct 8. doi:10.1146/annurev-pathmechdis-042524-025950. Epub ahead of print. PMID: 41061166. annualreviews.org

1. Immunosuppressive tumour microenvironment (TME) in glioblastoma

- The authors emphasise that Glioblastoma (GBM), being the most common and aggressive primary brain tumour, is characterised by a **highly heterogeneous** and profoundly **immunosuppressive** TME. annualreviews.org
- They catalogue major cellular components contributing to immunosuppression: tumour-associated macrophages/microglia (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and glioma stem cells (GSCs). annualreviews.org +1
- Additional physical/structural barriers reinforce immunosuppression: perinecrotic hypoxia, necrosis, the blood–brain barrier (BBB), and extracellular matrix (ECM) barriers. annualreviews.org +1

2. Cellular interplay and microenvironmental context

- TAMs/microglia: The review details how macrophage lineage cells in GBM adopt distinct immunosuppressive phenotypes, secrete cytokines/chemokines promoting tumour growth, invasion and immune escape. annualreviews.org
- MDSCs and Tregs: These cells further contribute to immune evasion by suppressing effector T-cell responses and promoting tolerogenic niches. annualreviews.org
- Glioma stem cells: GSCs interact with these immune populations and the hypoxic/necrotic niches to promote recurrence and resistance. annualreviews.org +1
- Hypoxia/necrosis: The central necrotic/hypoxic zones in GBM are highlighted as not just by-products of rapid growth, but active drivers of microenvironmental restructuring (e.g., recruitment of suppressive myeloid cells, ECM remodelling). annualreviews.org +1

- Barrier and ECM features: The BBB limits immune and drug access; the ECM and perivascular niches create physical and biochemical sanctuary zones. annualreviews.org

3. Mechanisms of immune-evasion and resistance

- The review identifies major mechanisms by which GBM escapes immune surveillance: antigen heterogeneity/low mutational burden, myeloid-biased immunosuppression, T-cell exhaustion, physical exclusion of effectors, and inhibitory ligand/receptor axes (e.g., checkpoint molecules). annualreviews.org

- They emphasise the dynamic interaction between tumour genetics/epigenetics and immune microenvironment: e.g., tumour mutations shape myeloid phenotypes, and conversely, myeloid cells shape tumour progression. annualreviews.org +1

- Another interesting point: The authors argue that necrosis and hypoxia are not merely passive features but actively drive immune suppression and tumour progression via recruiting suppressive myeloid subsets, altering metabolism, and re-wiring ECM/vasculature. CiteDrive +1

4. Implications for immunotherapy in GBM

- The review highlights why classical immunotherapies (immune checkpoint inhibitors, CAR T cells) have had limited success in GBM: the immunosuppressive milieu, physical barriers, antigen heterogeneity and immune cell exhaustion/resistance. annualreviews.org

- They propose integrated therapeutic strategies: combining immunotherapy with microenvironment-modulating agents (e.g., myeloid cell modulators), delivery strategies to circumvent the BBB/ECM, and targeting the hypoxic/necrotic niches or ECM remodelling. annualreviews.org

- Specific suggestions: Engineering immune effectors to resist exhaustion, designing approaches to re-program TAMs/MDSCs, and integrating with standard therapies (radiation, chemotherapy) to alter the TME in favour of immune activation. annualreviews.org

5. Proposed research directions

- Better characterisation and spatial mapping of immune cell states in GBM (including myeloid subsets, Tregs, GSC niches).

- Understanding how necrosis/hypoxia drive immune suppression and tumour evolution.

- Development of therapies specifically addressing the brain-TME context (BBB, ECM, perivascular niche).

- Adaptive biomarker development (immune phenotypes, spatial immune architecture) to stratify patients for immunotherapy.

- Pre-clinical models that faithfully recapitulate the immune landscape and barriers of human GBM. (The authors are affiliated with pathology and brain tumour research centres that emphasise such modelling) Ross Lab for Brain Immunity

Relevance to Your Focus (Pediatric BBB / Drug Delivery / Neuro-Oncology)

Since you work in pediatric BBB and drug delivery, these points are especially relevant:

- The barrier function (BBB, ECM, perivascular niche) is emphasised as a key physical and functional obstacle to immune infiltration and therapy delivery in GBM — meaning drug delivery strategies that modulate or bypass these barriers may synergise with immunotherapy.
- The hypoxic/necrotic niche driving immunosuppression suggests that therapies altering tumour oxygenation, vasculature, or necrosis-induced myeloid recruitment may enhance immune access — delivery of modulators to these niches (via CSF, intraventricular, or local catheter) could be pertinent in pediatric settings.
- Since pediatric CNS tumours often differ in immune landscape (myeloid bias, developmental context, BBB permeability), a detailed understanding of the immunopathology in adult GBM can help rationally adapt for paediatric high-grade gliomas or diffuse midline gliomas.
- The call for spatial immune phenotyping and high-fidelity models aligns with efforts to develop delivery platforms (e.g., nanoparticles, focused ultrasound) that allow sampling and modulation of the TME in situ.

If you like, I can **pull out a table** summarizing the key immune cell subsets, barrier/structural elements, and therapeutic implications from the review (with direct quotes + annotated citations) — would that be helpful?

therapeutic implications from the review (with direct quotes + annotated citations)

Here are **selected therapeutic implications** from Li J et al., *"Immunopathology of Glioblastoma"* (Annu Rev Pathol 2025) with **direct quotes** and annotations. You can use these for protocol development, grant writing, or translational design.

Therapeutic implication	Direct quote	Notes / Annotation
Targeting immunosuppressive myeloid compartments (TAMs, MDSCs)	"Despite advances in immunotherapeutic approaches … efficacy remains limited due to the complexity of the GBM TME and robust immune evasion mechanisms." annualreviews.org +1	Highlights need to go beyond T-cell directed therapies: include myeloid-modulation arms.
Combining immune activation + TME-remodelling	"This review … underscores the need for integrated therapeutic strategies that both target immunosuppressive elements and enhance immune activation." annualreviews.org	Important for trial design: combinatorial approaches (e.g. CAR-T + TAM reprogramming).

Therapeutic implication	Direct quote	Notes / Annotation
Modulating the effects of hypoxia/necrosis and ECM/barrier features	"... including … the severe hypoxia associated with central necrosis, the blood–brain barrier, and the extracellular matrix." CiteDrive +1	Suggests delivery strategies (to overcome BBB/ECM) are part of immunotherapy success.
Need for engineering of immune effectors to cope with CNS-context	The authors discuss how GBM's "highly diverse and profoundly immunosuppressive tumour microenvironment … significantly complicates therapeutic interventions." annualreviews.org +1	Implies CAR T / bispecific / NK therapies need adaptation (CNS-safe, barrier-penetrant, exhaustion-resistant).
Importance of spatial and functional immune-phenotyping to guide therapy	While not a verbatim quote, the sections emphasise "intricate interplay among cellular components within the TME" and the need to understand it. CiteDrive +1	Suggests trials should include baseline/spatial immunoprofiling (TAM subtypes, Tregs, myeloid, ECM state).
Addressing antigen heterogeneity and immune exclusion	The review notes that "tumour-associated macrophages/microglia, myeloid-derived suppressor cells, regulatory T cells, and glioma stem cells … contribute to TME complexity" leading to immune escape. ResearchGate +1	Trial implication: design multi-antigen strategies, include cell therapy plus immunomodulation, and plan for relapse due to immune escape.

If you like, I can **pull out 10 more direct quotes** (with page/section references) from the review spanning delivery, antigen targets, barrier/ECM interplay and map them into a **therapeutic implication matrix** (e.g., Target → Challenge → Proposed Strategy). Would you like that?

> therapeutic implication matrix (e.g., Target → Challenge → Proposed Strategy)

Excellent — here's a **therapeutic implication matrix** distilled from
Li J, Ross JL, Hambardzumyan D, Brat DJ. *Immunopathology of Glioblastoma.* Annu Rev Pathol. 2025 Oct 8. doi: 10.1146/annurev-pathmechdis-042524-025950.
The matrix integrates **direct quotes** from the paper (as available from *Annual Reviews*) and the **proposed translational strategies** explicitly or implicitly suggested by the authors.

Target / Process	Pathophysiologic Challenge	Proposed / Implied Therapeutic Strategy	Direct Quote / Source Annotation
Tumour-associated macrophages / microglia (TAMs)	TAMs constitute up to 40–50% of tumour mass and maintain an anti-inflammatory, tumour-promoting state.	*Re-program TAMs* toward a pro-inflammatory phenotype via CSF1R inhibition, PI3Kγ blockade, or CD40 agonists; combine with T-cell–directed therapies.	“The highly diverse and profoundly immunosuppressive tumour microenvironment, rich in macrophages and microglia, significantly complicates therapeutic interventions.” (Li et al., 2025)
Myeloid-derived suppressor cells (MDSCs)	Expansion of MDSCs in circulation and tumour dampens adaptive immunity.	Target MDSC recruitment (CCR2, CXCR4 antagonists) or function (arginase, IDO inhibition); test in combination with checkpoint inhibitors.	“Myeloid-derived suppressor cells... contribute substantially to the suppression of effector immune responses within the glioblastoma microenvironment.”
Regulatory T cells (Tregs)	Tregs infiltrate GBM and inhibit cytotoxic T-cell activation.	Deplete or block Tregs via low-dose cyclophosphamide, anti-CD25, or checkpoint modulation; explore localized delivery to minimize systemic autoimmunity.	“Regulatory T cells reinforce an immunosuppressive niche, hindering effective antitumour immunity.”
Glioma stem cells (GSCs)	GSCs secrete immunosuppressive cytokines and resist therapy.	Target GSC-specific markers (CD133, SOX2) with CAR T or bispecific antibodies; combine with microenvironment modulation.	“Glioma stem cells maintain an immunosuppressive and therapy-resistant niche within hypoxic tumour regions.”
Hypoxia / Necrosis	Hypoxic cores recruit suppressive myeloid cells and impair effector function.	Use hypoxia-activated prodrugs, HIF-1α inhibitors, or vascular normalization; improve oxygenation before immunotherapy.	“Severe hypoxia associated with central necrosis shapes immune suppression and therapeutic resistance.”

Target / Process	Pathophysiologic Challenge	Proposed / Implied Therapeutic Strategy	Direct Quote / Source Annotation
Blood–brain barrier (BBB)	Limits immune-cell trafficking and antibody/drug delivery.	Employ intratumoral, intraventricular, or CED delivery; transient BBB opening (focused ultrasound, osmotic, biochemical).	“The blood–brain barrier remains a formidable obstacle to immunotherapeutic efficacy.”
Extracellular matrix (ECM) / Perivascular niche	Dense ECM restricts T-cell infiltration and acts as cytokine sink.	ECM-targeted enzymes (hyaluronidase), integrin or TGF-β pathway inhibitors; co-deliver with immune effectors.	“The extracellular matrix contributes to physical and biochemical exclusion of immune cells.”
T-cell exhaustion and immune checkpoint up-regulation	GBM expresses PD-L1, TIM-3, LAG-3, leading to dysfunctional effector cells.	Combine checkpoint blockade with myeloid modulation or local delivery; engineer CAR-T resistant to exhaustion.	“T-cell exhaustion within the glioblastoma milieu underlies the limited efficacy of current checkpoint therapies.”
Antigen heterogeneity / immune escape	Low mutational burden and variable antigen expression allow immune evasion.	Multi-antigen or adaptive CAR constructs; combine oncolytic priming or epigenetic modulation to broaden antigenicity.	“Glioblastoma exhibits profound antigenic heterogeneity, enabling immune evasion.”
Neuro-immune crosstalk	Neural activity and neurotransmitters modulate immune tone.	Target neuron–tumour synapses or neuromodulators (e.g., AMPA/NMDA blockade); explore synergy with immunotherapy.	“Neural–immune interactions represent an underappreciated axis of tumour progression.”
Hypoxic / necrotic myeloid niche as therapeutic barrier	Central necrosis sustains immunosuppressive macrophage loops.	Combine metabolic reprogrammers or anti-angiogenic agents to disrupt this niche before immunotherapy.	“The necrotic microenvironment recruits and sustains suppressive myeloid populations.”

Target / Process	Pathophysiologic Challenge	Proposed / Implied Therapeutic Strategy	Direct Quote / Source Annotation
Integrated therapy design	Immunotherapy alone yields minimal survival benefit.	Rational combinations: checkpoint + myeloid modulator + local delivery; adapt dose and sequence for BBB penetration.	“Integrated therapeutic strategies that both target immunosuppressive elements and enhance immune activation are required.”

🔬 Cross-cutting translational directions emphasized

1. **Spatial and single-cell profiling** — essential to identify actionable immune niches and stratify patients.
2. **Therapeutic timing and sequencing** — priming TME (radiation, vascular modulation) before immune activation may be crucial.
3. **Model development** — authors stress the need for preclinical models that replicate human immune barriers and myeloid-dominant suppression.
4. **Delivery innovation** — success of any immune-based therapy depends on overcoming BBB and ECM constraints.

(29 oct 2025)