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Musatova O, et al., Immune checkpoints in immune response to glioma: two sides of the same coin.

Here is a summary of the **key findings and insights** from *Musatova O, Kumar V, Vinogradov K, Rubtsov Y. "Immune checkpoints in immune response to glioma: two sides of the same coin." Front Immunol. 2025 Aug 15;16:1639521* Frontiers+1

Overview & Rationale

- Gliomas (especially glioblastoma, GBM) create a strongly immunosuppressive tumor microenvironment (TME) which helps tumor cells evade immune elimination. PMC+1
- One of the major immune-regulatory systems exploited by tumors is the immune checkpoint network — i.e., ligands and receptors that restrain or modulate T cell activation and function. Frontiers+1
- This review examines both **canonical** (PD-1/PD-L1, CTLA-4) and **non-canonical / emerging** immune checkpoints in gliomas, their co-expression, signaling, prognostic relevance, and therapeutic implications. PMC+2Frontiers+2

Key Findings & Themes

1. **Diversity of immune checkpoints in glioma / TME**
    - Beyond PD-1/PD-L1 and CTLA-4, gliomas show expression (on tumor cells, immune infiltrates, or stromal elements) of alternative checkpoints or regulatory molecules, such as TIM-3, LAG-3, TIGIT, IDO1, CD39, CD73, adenosine/A2A receptor axis, B7 family members, and soluble or enzymatic mediators. Frontiers+1
    - Some of these molecules act via metabolic or enzymatic suppression (e.g., CD39/CD73 converting ATP to immunosuppressive adenosine) rather than only classical receptor–ligand inhibition. PMC+1
2. **Co-expression, synergy, and networked suppression**
    - Many immune checkpoints are co-expressed in gliomas (on the same or adjacent cells), forming a suppressive "network" rather than isolated axes. Frontiers+1
    - Such co-expression may result in redundancy and compensatory pathways of immunosuppression — blocking one checkpoint may lead to upregulation or compensation

by another. PMC+1

3. **Grade and molecular subtype associations**
    - High-grade gliomas (HGG) tend to have broader and higher expression of immune checkpoints compared to low-grade gliomas (LGG). PMC+1
    - Many checkpoint molecules correlate with “worse” molecular features (e.g. IDH wild type, mesenchymal subtype) and with poorer prognosis. Frontiers+1
    - Interestingly, one exception is **B7-H7 / HHLA2**, which in some LGGs is more frequently expressed and is associated with better prognosis (unlike most other checkpoints). PMC
4. **Prognostic correlations**
    - Expression levels of various immune checkpoints are often associated with patient survival metrics. For many checkpoints, higher expression correlates with worse prognosis in HGG and LGG. PMC+1
    - However, the picture is complex: the prognostic impact may depend on context (co-expression, tumor subtype, spatial localization) and may differ between grades. PMC
5. **Therapeutic implications and challenges**
    - **Checkpoint blockade (e.g. anti–PD-1, anti–CTLA-4)** is promising in principle but has had limited success in glioma to date. Frontiers+1
    - The authors argue that monotherapy blocking a single checkpoint is unlikely to be sufficient, due to **redundant immunosuppressive pathways** and compensatory mechanisms. PMC+2Frontiers+2
    - Combination therapies (e.g. dual checkpoint blockade, or combining checkpoint inhibitors with other immunotherapies) may be more effective. PMC+1
    - They note ongoing trials targeting LAG-3, TIM-3, TIGIT, IDO1, CD39, CD73 in GBM. PMC+1
    - The authors also highlight issues such as tumor heterogeneity, blood–brain barrier penetration, and potential adverse effects. Frontiers+1
    - Personalized approaches (e.g. based on transcriptomic, proteomic, metabolomic profiles) may be key to selecting optimal checkpoint combinations for individual patients. PMC+1
6. **“Two sides of the same coin” concept**
    - The title reflects the dual role of immune checkpoints: in normal physiology, they maintain immune homeostasis and prevent autoimmunity; in glioma, the same mechanisms are co-opted to foster immune evasion. Frontiers+1
    - That is, immune checkpoint pathways are not inherently “bad,” but contextually manipulated in cancer. This dual nature suggests careful therapeutic targeting is needed to avoid

unwanted side effects. PMC+1

Limitations & Gaps Highlighted

- Many of the discussed immune checkpoint associations are based on **expression / correlation data**, not causal or mechanistic proof, and often drawn from bulk tumor / transcriptomic datasets. PMC
- The functional roles of many non-canonical checkpoints in glioma remain incompletely understood. PMC
- Heterogeneity within tumors (both between patients and spatially within one tumor) complicates extrapolation and trial design. PMC+1
- The blood–brain barrier and CNS immune privilege pose special challenges for delivery of checkpoint inhibitors to gliomas. PMC+1
- The authors caution that targeting immune checkpoints carries risk of immune-related adverse events (as seen in other cancers) and that effects in the brain context may differ. PMC

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