Brain Metastases Immune Microenvironment

- Identification and characterization of tertiary lymphoid structures in brain metastases
- Population analysis and immunologic landscape of melanoma in people living with HIV
- Old players and new insights: unraveling the role of RNA-binding proteins in brain tumors
- A zinc transporter drives glioblastoma progression via extracellular vesicles-reprogrammed microglial plasticity
- Novel metabolic subtypes in IDH-mutant gliomas: implications for prognosis and therapy
- Current Understanding of the Exosomes and Their Associated Biomolecules in the Glioblastoma Biology, Clinical Treatment, and Diagnosis
- Hormonal and neuronal interactions shaping the brain metastatic microenvironment
- Improved overall survival in an anti-PD-L1 treated cohort of newly diagnosed glioblastoma patients is associated with distinct immune, mutation, and gut microbiome features: a single arm prospective phase I/II trial

Definition

The brain metastases (BrM) immune microenvironment refers to the **cellular and molecular composition of immune cells** within and around metastatic tumors that have spread to the brain. It includes both the **type and spatial distribution** of immune cells, as well as the **local immune activity and suppressive signals**.

Unique Features of the Brain Microenvironment

- The **blood-brain barrier (BBB)** limits immune cell trafficking
- The brain has a distinct **immune surveillance system**, including microglia and perivascular macrophages
- BrM can remodel the local environment, attracting or excluding systemic immune cells

Key Immune Components

- **CD8+ T cells** – cytotoxic lymphocytes that may infiltrate or be excluded from tumor parenchyma
- **CD4+ T cells and regulatory T cells (Tregs)** – modulate immune responses and may promote immune evasion
- **Tumor-associated macrophages (TAMs)** – often immunosuppressive in the CNS
- **Dendritic cells and B cells** – participate in antigen presentation and may contribute to local TLS formation

Recent Findings

- Transcriptome-wide gene expression profiling and spatial immune cell profiling have revealed that BrM from lung cancer and melanoma exhibit **higher immune cell infiltration** than those from breast cancer
- Presence of tertiary lymphoid structures (TLS) has been detected in some BrM, especially in treatment-naïve lung and melanoma metastases
- TLS presence is associated with **prolonged survival** and may serve as a **prognostic**

biomarker in BrM

Clinical Relevance

- BrM TIME influences **response to immunotherapy**
- Immune “hot” BrM (high infiltration and TLS presence) may respond better to **immune checkpoint blockade**
- Understanding the TIME helps stratify patients and guide CNS-targeted immunotherapies

Research Techniques Used

- RNA sequencing-based immune cell deconvolution
- Multiplex immunofluorescence staining
- Spatial immune cell profiling
- IHC for markers like CD3, CD8, CD20, PD-L1

Mughal et al. and Katrin Lamszus from the laboratory for Brain Tumor Biology, Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Germany performed transcriptome-wide gene expression profiling combined with spatial immune cell profiling to characterize the tumor immune microenvironment in 95 patients with BrM from different primary tumors. They found that BrM from lung cancer and malignant melanoma showed overall higher immune cell infiltration as compared to BrM from breast cancer. RNA sequencing-based immune cell deconvolution revealed gene expression signatures indicative of tertiary lymphoid structures (TLS) in subsets of BrM, mostly from lung cancer and melanoma. This finding was corroborated by multiplex immunofluorescence staining of immune cells in BrM tissue sections. Detection of TLS signatures was more common in treatment-naïve BrM and associated with prolonged survival after Brain metastases diagnosis in lung cancer patients. The findings highlight the cellular diversity of the tumor immune microenvironment in BrM of different cancer types and suggest a role of TLS formation for BrM patient outcome [1)]

Mughal et al. conducted a comprehensive study combining transcriptome-wide gene expression profiling with spatial immune cell profiling in 95 patients with brain metastases (BrM) from various primary tumor origins. Their goal was to better understand the heterogeneity of the tumor immune microenvironment (TIME) in BrM and its potential clinical implications.

Strengths

- **Multimodal approach**: The integration of RNA sequencing with spatial techniques provides both molecular and spatial resolution, offering a robust characterization of immune landscapes.
- **Cohort diversity**: Inclusion of BrM from multiple cancer types (lung, melanoma, breast) allows for cross-comparison and subtype-specific insights.
- **Novel findings**: Identification of tertiary lymphoid structure (TLS) signatures in BrM, especially from lung and melanoma, adds valuable data to the field and supports the idea that TLS may serve as a **biomarker** for favorable patient outcome.

- **Clinical relevance**: The association of TLS presence with **prolonged survival** in treatment-naïve lung cancer BrM patients is particularly significant and hypothesis-generating for future therapeutic targeting.

Limitations

- **Lack of functional validation**: While TLS presence was inferred via RNA sequencing-based immune cell deconvolution and confirmed with multiplex immunofluorescence staining, functional studies to prove TLS immunological activity (e.g., antigen presentation, T/B cell interaction) are lacking.
- **Cross-sectional design**: The study is primarily descriptive and cross-sectional; longitudinal tracking of TLS development or dynamic changes in TIME over treatment is not addressed.
- **Heterogeneity within tumor types**: Although BrM from lung and melanoma were grouped together, their internal heterogeneity (e.g., EGFR-mutant vs. KRAS-mutant lung cancer) may influence immune profiles and was not deeply stratified.
- **Limited exploration of immune suppression**: The study focuses on immune infiltration and TLS, but immunosuppressive elements of the TIME (e.g., Tregs, myeloid-derived suppressor cells) are not fully explored.

Conclusion

This study significantly advances our understanding of the immune contexture of brain metastases, emphasizing the **variability between tumor types** and the potential prognostic role of tertiary lymphoid structures. Mughal et al. provide a strong foundation for future work aiming to **modulate immune niches** within BrM, especially in the context of immunotherapy. However, the **mechanistic role** of TLS in anti-tumor immunity within the CNS remains to be elucidated, and follow-up studies should address **temporal dynamics**, **TLS function**, and **response to therapy**.

1)

Mughal SS, Reiss Y, Felsberg J, Meyer L, Macas J, Schlue S, Starzetz T, Köhrer K, Fehm T, Müller V, Lamszus K, Schadendorf D, Helfrich I, Wikman H, Berghoff A, Brors B, Plate KH, Reifenberger G. Identification and characterization of tertiary lymphoid structures in brain metastases. Acta Neuropathol Commun. 2025 May 3;13(1):91. doi: 10.1186/s40478-025-02007-x. PMID: 40319321.