OS05.5. A GLOBLASTOMA-INSTUCTED MICROGLIA TRANSIT TO HETEROGENEOUS PHENOTYPIC STATE WITH DENDRITIC CELL-LIKE FEATURES IN PATIENT TUMORS AND PATIENT-DERIVED ORTHOTOPIC XENOGRAFTS

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BACKGROUND: A major contributing factor to Glioblastoma (GBM) development and progression is its ability to evade the immune system by creating an immune-suppressive tumor microenvironment (TME). GBM-associated myeloid cells, including resident microglia, macrophages and other peripheral immune cells are generally geared towards tumor-supportive roles. It is however unclear whether such recruited myeloid cells are phenotypically and functionally identical. Here, we aim to understand the heterogeneity of the GBM TME, using an unbiased, marker-free approach to systematically characterize cell type identities at the molecular and functional levels. MATERIAL AND METHODS: We applied single-cell RNA-sequencing, multicolor flow cytometry, immunohistochemical analyses and functional studies to examine the heterogeneous TME instructed by GBM cells. GBM patient-derived orthotopic xenografts (PDOXs) representing different tumor phenotypes were compared to gloma mouse GL261 model and patient tumors. RESULTS: We show that PDOX models recapitulate major components of the TME found in high-grade GBM, and that they develop intra-tumoral compartments that create a GBM-specific TME. The most prominent transcriptomic adaptations are found in tumor-associated macrophages (TAMs), which are largely of microglial origin. We reveal inter-patient heterogeneity of TAMs and identify key signatures of distinct phenotypic states within the macroglia-derived TAMs across distinct GBM landscapes. GBM-educated microglia adapt expression of genes involved in immunosuppression, migration, phagocytosis and antigen presentation, indicating functional cross-talk with GBM cells. We identify novel phenotypic states with astrocytic and endothelial-like features. Identified gene signatures and phenotypic states are confirmed in GBM patient tumor tissue. Finally we show that temozolomide treatment leads to transcriptomic adaptation of not only the GBM tumor cells but also adjacent TME components. CONCLUSION: Our data provide insights into the phenotypic adaptation of the heterogeneous TME instructed by GBM tumor. We confirm a crucial role of microglia in supporting the immunosuppressive TME and show that PDOXs allow to monitor the highly plastic GBM ecosystem and its phenotypic adaptation upon treatment. This work further confirms the clinical relevance of PDX0 avatars for testing novel therapeutics including modalities designed to target the myeloid compartment.


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