Immunosuppressive microenvironment

The immunosuppressive microenvironment in glioblastoma (GBM) prevents an efficient antitumoral immune response and enables tumor formation and growth. Although an understanding of the nature of immunosuppression is still largely lacking, it is important for successful cancer treatment through immune system modulation. To gain insight into immunosuppression in GBM, we performed a computational analysis to model relative immune cell content and type of immune response in each GBM tumor sample from The Cancer Genome Atlas RNA-seq dataset. We uncovered high variability in immune system-related responses and in the composition of the microenvironment across the cohort, suggesting immunological diversity. Immune cell compositions were associated with typical alterations such as IDH mutation or inactivating NF1 mutation/deletion. Furthermore, our analysis identified three GBM subgroups presenting different adaptive immune responses: Negative, Humoral, and Cellular-like. These subgroups were linked to transcriptional GBM subtypes and typical genetic alterations. All G-CIMP and IDH-mutated samples were in the Negative group, which was also enriched by cases with focal amplification of CDK4 and MARCH9. IDH1-mutated samples showed lower expression and higher DNA methylation of MHC-I -type HLA genes. Overall, our analysis reveals heterogeneity in the immune microenvironment of GBM and identifies new markers for immunosuppression. Characterization of diverse immune responses will facilitate patient stratification and improve personalized immunotherapy in the future [1)].

Current clinical trials take a multifaceted approach with the intention of harnessing the intrinsic cytotoxic capabilities of the immune system to directly target glioblastoma cancer stem cells (gCSC) or indirectly disrupt their stromal microenvironment. Monoclonal antibodies (mAbs), dendritic cell (DC) vaccines, and chimeric antigen receptor (CAR) T cell therapies have emerged as the most common approaches, with particular iterations incorporating cancer stem cell antigenic markers in their treatment designs. Ongoing work to determine the comprehensive antigenic profile of the gCSC in conjunction with efforts to counter the immunosuppressive microenvironment holds much promise in future immunotherapeutic strategies against GBM. Given recent advancements in these fields, Esparza etal. believe there is tremendous potential to improve outcomes of GBM patients in the continuing evolution of immunotherapies targeted to cancer stem cell populations in GBM [2)].

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2)
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