mains largely incurable. While immunotherapies have been highly effective in some types of cancer, the disappointing results from clinical trials for GBM immunotherapy represent continued challenges. GBM is highly immunosuppressive and resistant to immunotherapy because of glioma cells escaping from immune surveillance by reprograming the tumor microenvironment (TME). However, understanding the mechanisms of immune evasion by GBM remains elusive. Based on unbiased approaches, we found that Chitinase-3-like-1 (CHI3L1), also known as human homolog YKL-40, is highly expressed in GBM, which is regulated by the CHI3L1-PI3K/AKT/mTOR signaling in a positive feedback loop. Gain- and loss-function studies reveal that CHI3L1 plays a predominant role in regulating an immunosuppressive microenvironment by reprogramming tumor-associated macrophages (TAMs). Using the liquid chromatography-mass spectrometry and orthogonal structure-based screening, we found that Galectin-3 binding protein (Gal3BP) and its binding partner, Galectin-3 (Gal3), can interact competitively with the same binding motif on CHI3L1, leading to selective migration of M2-like versus M1-like bone marrow-derived macrophages (BMDMs) and resident microglia (MG). Mechanistically, the CHI3L1-Gal3 protein complex governs a transcriptional program of NFκB/CEBPβ to control the protumor phenotype of BMDMs, leading to inhibition of T cell infiltration and activation in the GBM TME. However, Gal3BP can reverse CHI3L1-Gal3 induced signaling pathway activation and subsequent protumor phenotype in TAMs. Based on protein binding motifs, a newly developed Gal3BP mimetic peptide can attenuate immune suppression and tumor progression in the syngeneic GBM mouse models, including decreasing M2-like TAMs and increasing M1-like TAMs and T cell infiltration. Together, these results shed light on the role of CHI3L1 protein complexes in immune evasion by glioblastoma and as a potential immunotherapeutic target for this devastating disease.

OTME-21. THE ROLE OF GLIOBLASTOMA ASSOCIATED MESENCHYMAL STEM CELLS IN IMMUNE SUPPRESSION

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Glioblastoma (GBM) is an aggressive brain cancer, with an overall survival of 14.6 months. The tumor microenvironment in GBM plays major roles in immunosuppression and modulation of the response to therapies. GBM patients with higher levels of mesenchymal stem like cells (G-MSC) show poor overall survival as compared to patients with no/lower G-MSC levels. Our lab found that levels of G-MSC corelate with CD4+ T cells in humans and murine models of GBM, and with immunosuppressive molecules like PTGS2, the gene for cyclooxygenase 2. To investigate the mechanism by which G-MSCs promote immunosuppression, we isolated G-MSCs from an orthotopic mouse model of GBM and subjected them to RNASeq analysis to obtain an unbiased picture of transcriptomic changes occurring upon activation. We identified changes in multiple immune modulating pathways involving antigen presentation, leukocyte migration and activation, and immune checkpoints. Our findings indicate that G-MSCs represent a key immune modulating faction in the microenvironment. Further dissection of the role of these cells in immune modulation will aid us in understanding the biology of the brain tumor microenvironment and identifying potential combination therapies.

OTME-22. BIOINFORMATIC EVALUATION OF ECM MOLECULES AND ANGIOGENIC ASSOCIATE GENES IN DIFFUSE MIDLINE GLIOMA (DMG): MAPPING THE TUMOUR MICROENVIRONMENT

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Paediatric Diffuse Intrinsic Pontine Glioma (DIPG) is a devastating cancer of an extremely aggressive nature, located in the pontine area of the brain. DIPG primarily affects children, with the average age of diagnosis between 6 and 7 years. Unfortunately, the outlook and overall survival remains bleak. While there has been impressive progress in identifying genes that are central to and drive DIPG growth; there remains several gaps in documenting the DIPG microenvironment landscape. The focus of this study is to begin to examine mRNA expression of genes associated with blood vessel development, angiogenesis, and extracellular matrix molecules (ECM) in normal brain development and DIPG by utilizing publicly available genomic datasets. In-depth bioinformatics from GSE26576 dataset included differential expression and gene ontology (GO) with KEGG pathway analyses using Gene Expression Omnibus (GEO) and DAVID, which have revealed a number of significantly upregulated genes that may affect DIPG angiogenic processes ($p<0.05$). 38 of such genes from 9 different GO terms were then included in a protein-to-protein interaction network that revealed a surprising connection between *MMP16, CSPG4* and *COL11A1*. Subsequently, using R2 genomic visualisation platform from publicly available single cell RNAseq data we showcased the difference in their individual expression based on the molecular subtypes of DIPG histone 3 (H3) mutation (K27M, wild type and G34R) with a strong statistical significance ($p<0.05$). Interestingly, during normal paediatric development such genes showed consistent expression, suggesting their potential complications in DIPG angiogenesis. Overall, this bioinformatic approach has led to the identification of a set of interacting genes that will inform our *in vitro* and *in vivo* studies. This information will add to the documentation of the host/tumour microenvironment landscape and our plan is to continue to explore this area to map the spatial and temporal expression of these genes.

OTME-23. SINGLE-CELL TRANSCRIPTOMIC AND EPIGENOMIC IMMUNE LANDSCAPE OF ISOCITRATE DEHYDROGENASE STRATIFIED HUMAN GLIOMAS

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The brain tumor immune microenvironment (TIME) continuously evolves during glioma progression, but a comprehensive characterization of the glioma-centric immune cell repertoire beyond a priori cell states is uncharted. In this study, we performed single-cell RNA-sequencing (scRNA-seq) and single cell- Assay for Transposase-Accessible Chromatin using sequencing (sc-ATAC-seq) on ~100,000 tumor-associated immune cells from seventeen isocitrate dehydrogenase (IDH) mutation classified primary and recurrent human gliomas and non-glioma brains (NGBs). Our analyses revealed sixty-two transcriptionally distinct myeloid and lymphoid cell states within and across glioma subtypes and we noted microglial attrition with increasing disease severity concomitant with invading monocyte-derived cells and lymphocytes. Specifically, certain microglial and monocyte-derived subpopulations were associated with antigen presentation gene modules, akin to cross-presenting dendritic cells (DCs). We identified cytotoxic T cells with poly-functional cytolytic states mostly in recurrent IDH-wt gliomas. Furthermore, ligand-receptor interactome analyses showed a preponderance of antigen presentation and phagocytosis over the checkpoint axis in IDH-wt compared to IDH-mut gliomas. Additionally, our sc-ATAC-seq analyses revealed differences in regulatory networks in NGBs, IDH-mut and IDH-wt glioma associated immune cells. In particular, we noted abundant usage of inflammatory transcription factors (TFs) as exemplified by Nuclear factor kappa B and Activator Protein-1 TF family in IDH-wt microglia when compared with microglia from IDH-mut and NGBs. Unique features such as amplification of 11- Zinc Finger Protein accessibility were restricted to monocyte derived cells and were not observed in microglia. Finally, sc-ATAC-seq profiles of $CD8^+$ exhausted T cells from IDH-wt showed strong enhancer accessibility on Cytotoxic T-lymphocyte-associated protein 4, Layilin and Hepatitis A Virus Cellular Receptor 2 but no enrichment on PDCD1 (gene encoding Programmed cell death protein 1) was seen. In summary, our study provides unprecedented granular detail of transcriptionally defined glioma- specific immune contexture that can be exploited for immunotherapy applications.

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