adhesion and cytokine regulation pathways. Bulk transcriptomic data of human tumors and matching patient-derived xenografts (PDXs) showed that a group of secreted stromal factors acting as regulators of tumorigenic mechanisms, such as IGF2 and COL4A1, are lost after xenografting and replaced by the host murine microenvironment, suggesting that tumor cells are involved in paracrine and bivalent crosstalk with TME cells, impacting on tumor cell growth and progression. Finally, bulk deconvolution and cell-cell communication analysis were exploited to define, respectively, the stromal cell proportions and the key factors involved in the tumor-TME crosstalk; this latter can be considered as possible targets for tailored and more specific anti-tumor therapeutic strategies.

OTME-4. IDH MUTATED GLIOMAS PROMOTE EPILEPTOGENESIS VIA D-2-HYDROXYGLUTARATE DEPENDENT MTOR HYPERACTIVATION

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Epilepsy in the context of brain tumors provides a great burden in these patients, yet mechanisms underlying this process are poorly understood. It has been demonstrated that isocitrate dehydrogenase (IDH) mutations are an independent factor in epileptogenesis in patients with low grade gliomas. Here, using electrographically sorted human cortical tissue from patients with IDH mutated tumor related epilepsy and *in vitro* cortical cultures, we explore a metabolic paradigm and its impact on increased neuronal excitability. We hypothesize the IDH mutation promotes epileptogenesis through its neomorphic activity of D-2-hydroxyglutarate (D-2-HG) production in turn interrupts surrounding normal neuronal circuitry potentially through metabolic perturbations. We demonstrate D-2-HG increases neuronal spiking activity, promotes distinct metabolic profiles independent of neuronal spiking activity, as well as increases neuronal mTOR signaling, which is reflected in human peritumoral epileptic cortex. Increased mTOR signaling is sufficient to upregulate neuronal spiking activity and, reciprocally, inhibition of mTOR corrects neuronal activity as well as partially corrects metabolic reprogramming. Our results suggest D-2-HG can lead to mTOR activation within the peritumoral neurons, thereby suggesting an additional possible mechanism of epileptogenesis in patients with IDH mutated low grade gliomas. Ultimately, our results raise the possibility of mTOR inhibition may be a promising treatment of seizures in patients with these tumors.

OTME-5. MENINGIOMA LIQUID BIOPSY SPECIMENS EXHIBIT CONTRASTING IMMUNE-CELL LANDSCAPES ACROSS METHYLATION-SUBTYPES AND ESTIMATED RECURRENCE RISK SUBGROUPS

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BACKGROUND. Tumor-infiltrating immune cell compositions have been previously correlated to encouragement or inhibition of tumor growth. This association highlights immune-landscape profiling through non-invasive methods as a crucial step in approaches to treatment of patients with meningioma (MNG), a prevalent primary intracranial tumor. Genome-wide DNA methylation patterns can aid in definition and assessment of cell compositions in liquid biopsy serum specimens, and allow for development of machine-learning models with predictive capabilities. METHODS. We profiled the cfDNA methylome (EPIC array) in liquid biopsy specimens from patients with MNG (n = 63) and nontumor controls (n = 6). We conducted both unsupervised epigenome-wide and supervised analyses of the meningioma methylome. Estimation of immune cell composition was conducted using Python-based methodology, where a reference methylome atlas of chosen cell types (B-cells, CD4- and CD8T-cells, neutrophils, natural killer cells, monocytes, cortical neuron, vascular endothelial cells, and healthy meninge) was used to deconvolute the MNG samples. Recurrence risk was estimated using an existing methylation-based Random-Forest classifier previously reported and validated, adapted to our serum-based cohort through employment of translatable meningioma subgroup-specific methylation markers (differentially methylated probes). RESULTS. We identified four distinct genome-wide methylation subgroups (k-clusters) of MNG which presented differential tumor micro-environments across all cell types investigated. Application of the DNA methylation-based Random-Forest classifier allowed for categorization of primary MNG serum samples into estimated recurrence-risk subgroups. Significantly contrasting micro-environments for the subgroups were observed across several cell-types, with those MNG more likely to recur displaying depletion in cell types reported to improve anti-tumoral response in many tumors (e.g. T-Cells). CONCLUSIONS. DNA methylation based deconvolution allowed for detection of contrasting tumor microenvironment compositions across MNG methylation subtypes and recurrence-risk estimation subgroups. These results suggest that microenvironment profiling can be informative of probable tumor behavior and prognostic outcomes, helping guide therapeutic approaches towards treatment of patients with MNG.

OTME-6. DEEP SEQUENCING REVEALS HETEROGENEITY OF BRAIN METASTASIS-ASSOCIATED MACROPHAGES AND MICROGLIA AND UNCOVERS THEIR CELL TYPE-SPECIFIC FUNCTIONS WITHIN THE TUMOR MICROENVIRONMENT

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Macrophages represent a highly plastic cell type,indispensable for tissue and organ homeostasis, as well as innate immunity. Basic and translational research attributed tumor-promoting functions to macrophages, and their presence is often associated to poor patient prognosis and therapy resistance. While brain-resident macrophages, the so-called microglia (MG), represent the major immune cell type in the parenchyma under normal conditions, primary and metastatic brain tumors induce the recruitment of different immune cell types from the periphery, including monocyte-derived macrophages (MDM). Controversy remained about the redundancy of disease-associated molecular signatures and functions. The identification of markers that reliably distinguish brain-resident from blood-borne tumor-associated macrophages (TAMs) allowed the interrogation of molecular traits of different TAM populations in mouse and human brain tumors. Using RNA-Seq, we demonstrated that TAMs rapidly acquire disease-associated transcriptional programs upon initial tumor infiltration, while gene expression remained stable during different stages of BrM progression. Across different BrM models, disease-associated transcriptional changes revealed lineage-specific, non-redundant functions of TAM populations, which was further reflected by cell type-specific occupation of different niches within the BrM microenvironment. Furthermore, we observed dose- and cell type-specific immune modulatory effects of whole brain radiotherapy on myeloid cells in BrM leading to a transient loss of disease-associated transcriptional programs predominately in blood-borne myeloid populations. This effect can at least in part be attributed to a replenishment of the recruited macrophage pool. This observation was further supported by scRNA-Seq analyses revealing higher heterogeneity of TAM-MDM compared to TAM-MG under treatment-naïve conditions and in response to radiotherapy. Together, our results point towards the phenotypic plasticity of TAMs, especially MDMs, and the contribution of each compartment in instigating cancer-associated inflammation or the establishment of an immuno-suppressive TME. While TAM-MG exert functions related to pro-inflammatory responses, TAM-MDM are rather involved in tissue repair and regulation of adaptive immune cell functions.

OTME-7. CANCER - IMMUNE CELL INTERACTIONS DRIVE TRANSITIONS TO MESENCHYMAL-LIKE STATE IN GLIOBLASTOMA

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