Gene set enrichment analysis (GSEA) was performed to determine differentially expressed gene signatures in treated vs control mice. Gene expression clustering profiles were conducted using a Principal Component Analysis (PCA), and relative gene expression differences were analyzed by unpaired t-tests.

Results Our data shows differentially expressed antigen processing and cross presentation gene signatures in the ACT-treated compared to untreated tumors by GSEA analysis. We also observed that tumors treated with ACT cluster separately from control tumors in PCA analysis and they have several differentially expressed genes. Furthermore, we found downregulation of genes associated with the suppressive properties of regulatory T cells (Runx1 and TGF-β), and upregulation of dendritic cell characteristic genes (Batf3) in ACT-treated tumors vs control.

Conclusions These findings provide insights into the immune cell dynamics and specific genes and gene signatures that are differentially expressed within the tumor microenvironment after treatment. This could help improve current adoptive cellular therapies to treat brain tumors.


P09.14 THE ROLE OF IDO1 AND CELLULAR SENESCENCE IN THE EFFICACY OF PD-1 PATHWAY BLOCKADE AND RADIOThERAPY IN AGED MICE WITH GliOBlaSTOMA

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Background Glioblastoma is the most common primary brain tumor in adults with a median overall survival between twelve to fifteen months.1,2 The prognosis is worse for patients older than 63 years of age.1 Aging is associated with senescence, which leads to secretion of proinflammatory cytokines and increased levels of the immunosuppressive enzyme indole-amine-2,3-dioxygenase 1 (IDO1).3 Increased levels of IDO1 at an advanced age may attenuate the efficacy of immunotherapy.

Materials and Methods One hundred and seven mice between 79 and 92 weeks of age with differential Id01 expression were intracranially injected with syngeneic murine GL261 cells and treated with PD-1 monoclonal antibodies and radiotherapy. The mice have been monitored for ninety days. U87 glioblastoma cells were cultured and treated with interferon-γ and NU223612.

Results PD-1 blockade and irradiation were less effective when Id01 expression was preserved. Mouse lines with Id01 knock-out in dendritic and endothelial cells had better survival. There was a higher senescent cell burden within the brain tumor than the extra-tumoral tissue in mice reaching the humane endpoint. In U87 glioblastoma cells, interferon-γ induced upregulation of PD-L1 and ID01 in a similar pattern. ID01 degradation resulted in concomitantly lower levels of PD-L1.

Conclusions Taken together, these results suggest that the treatment protocol with PD-1 pathway blockade plus radiotherapy should be combined with ID01 inhibitors and potentially with senolytics to achieve a better therapeutic outcome in the elderly population with glioblastoma.

References


P09.15 PATIENT-DERIVED HEAD AND NECK TUMOR SLICE CULTURES – A VERSATILE TOOL TO STUDY ONCOLYTIC VIRUS ACTION

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Background Translating preclinical data from cell-based in vitro systems and syngeneic mouse tumor models to the clinically heterogeneous ecosystem of human tumors is a challenging task. Especially head and neck squamous cell carcinomas (HNSCC) show a highly diverse and complex architecture which makes the prediction of a treatment outcome quite difficult. To bridge this gap, we have established and employed a patient-derived HNSCC slice culturing system to assess immunomodulatory effects as well as permissivity and oncolytic virus (OV) action.

Materials and Methods HNSCC tumor biopsies from 12 patients were sectioned using a vibratome and cultured under different conditions for 48hrs. Tumor content and viability of the cultured slices was assessed by two independent pathologists. Characterization of the morphology and tumor microenvironment was done by immunofluorescence stainings. Presence and activation of T-cells upon stimulation either with a bispecific EpCAM-CDD3 antibody or a combination of α-CD3/α-CD28 antibodies was analyzed with flow cytometry and measuring IFNγ secretion. Permissivity of an oncolytic virus, VSV-GP, in these HNSCC slices was tested using a GFP-tagged OV by following the infection for 48hrs. Co-immunofluorescent studies were performed to analyze which cell populations could be infected by the OV.

Results The heterogeneous morphology of a human tumor could be retained in these slice cultures including the preservation of different cell types like tumor cells, immune cells and cancer-associated fibroblast. Upon stimulation with different antibodies the remaining cytotoxic T-cells showed functionality and could be activated. In addition, more than half of the HNSCC slice cultures were permissive to VSV-GP, so they were not only susceptible to the OV but could also produce new progeny. VSV-GP could not only infect epithelial tumor cells but also cells of the tumor microenvironment like stromal cells.