O16 Immunogenomic analysis reveals that tumor aggressiveness is associated with a decreased CD8 T cell signature in an in vivo prostate cancer model

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Introduction & Objectives: Prostate cancer is the most common diagnosed cancer in Dutch men. Most prostate tumors are typically slow-growing, but in a subset of patients the cancer will grow aggressively with metastatic spread. Despite the fact that immunotherapy is emerging as a promising treatment option in various solid tumors, the benefits in prostate cancer are limited to a small fraction of patients. Little is known about the factors that determine immune evasion, particularly in aggressive prostate cancer. Previously, we have established the PTEN knock-out MuCaP mouse prostate cancer model in which upon transplantation of epithelial cell lines we distinguish slow and fast-growing prostate cancer (van Duijn et al., 2018). In the current study, the MuCaP model is used to assess differential tumor-immune interactions in prostate tumors.

Materials & Methods: Transcriptomic analysis was performed on syngeneic tumors (n=16) and their corresponding epithelial MuCaP cell lines (n=8). Raw RNAseq data was mapped to the GrCm38/mm10 reference genome with STAR aligner. Data was further processed with FeatureCounts and differential gene expression analysis was performed with DESeq2. The relative immune cell distribution was determined with ImmuCC. Pathway analysis was performed with IPA (Qiagen Inc.), and gene set enrichment analysis was used to test the contribution of immune-related genes. Analysis of the T cell receptor repertoire was performed with MiXCR.

Results: Epithelial tumor cell line growth was similar in vitro, but corresponding syngeneic tumors had different growth rates in vivo. Two cell lines were highly tumorigenic with fast and aggressive growth rates, while the other two showed a more indolent phenotype. Analysis of immune cell distribution revealed that aggressive tumors had a higher frequency of macrophages, yet a lower frequency of CD4 T cells and B cells when compared to indolent tumors. Interestingly, pathways underlying T-cell influx, T-cell activation and T-cell co-stimulation were reduced in aggressive tumors compared to the indolent ones. Subsequent gene set enrichment analysis pointed to a low CD8 T-cell signature in the aggressive tumors, decreased expression of genes underlying antigen presentation and lower expression of co-stimulatory ligands. Notably, the diversity of T cell specific T cell receptors was lower in aggressive tumors.

Conclusions: In conclusion, the syngeneic MuCaP model is a unique model to study tumor growth in an immune competent setting. Data so far suggest that immune evasion in aggressive tumors is established through reduced T-cell influx, reduced antigen presentation and a decreased expression of co-stimulatory ligands. Further analysis of epithelial tumor cell lines as well as therapeutic interventions will contribute to the identification of the exact determinants underlying immune evasion.