PD-1 EXPRESSION ON TUMOR-INFILTRATING T-LYMPHOCYTES AS DETERMINANT OF THE HEAD AND NECK CANCER TUMOR IMMUNE MICROENVIRONMENT RATHER THAN ANATOMICAL SITE

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Abstract

Background The response rate to immune checkpoint inhibitors (ICI) targeting programmed cell death 1 (PD-1) receptor is 13–18% for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).1, 2 Detailed understanding of the tumor immune microenvironment (TIME) is crucial in order to explain and improve this. HNSCCs arise at various anatomical locations including the oral cavity, hypopharynx, larynx and oropharynx.3 Since the tumors originate at distinct locations in the upper aero-digestive tract with varying microenvironments, we questioned whether the immune composition varies across these HNSCC sites. Studies directly comparing immune infiltration between anatomical sites are scarce.

Methods Here we characterized the TIME of 76 fresh HNSCC tumor specimens using flow cytometry, and performed single cell RNA-sequencing (scRNA-seq) on nine samples. In addition, scRNA-seq data of 18 HNSCCs were analyzed from Cillo et al. (2020).4 To expand and verify our findings we performed deconvolution on The Cancer Genome Atlas (TCGA) bulk RNA-seq data (n = 354).

Results We found major differences in the composition of the TIME between patients. When comparing anatomical sites, tumors originating from the oral cavity had higher T cell infiltrates than tumors from other anatomical sites, which was confirmed in the TCGA cohort. Of the checkpoints investigated, PD-1 was most abundant on T cells across all sites, although the percentage of tumor-infiltrating T lymphocytes positive for PD-1 varied considerably between patients. Remarkably, the fraction of T cells expressing PD-1, rather than anatomical site of origin, dominated how HNSCC specimens were classified by unsupervised clustering analysis of cell surface markers. Moreover, a high proportion of PD-1+ CD8+ T cells was associated with an improved overall survival. Using scRNA-seq we observed that PD-1 expression was highest in the CD8-ENTPD1 tissue-resident memory T cell/exhausted T cell and CD4-CXCL13 type 1 T helper cell clusters. When comparing PD-1+ with PD-1- T cells we found CXCL13 being most differentially expressed, and highest in PD-1+ tumor-infiltrating T lymphocytes.

Conclusions We found that oral cavity SCCs have the highest frequencies of T cells. In addition, we observed a high variability in the fraction of T cells expressing PD-1 between patients. PD-1 expression on T cells within the TIME, rather than HNSCC anatomical location, determined the clustering of patient samples, and correlated with overall survival. Whether the fraction of T cells positive for PD-1 within the TIME enables ICI response prediction for patients with head and neck cancer, remains to be determined.

REFERENCES

Ethics Approval Written informed consent was obtained from all patients from whom fresh tumor biopsies were used for research, as part of the HNcol protocol at the Department of Otolaryngology|Head and Neck Surgery of Amsterdam UMC (VUmc) as approved by the Institutional Review Board (2008.071|A2016.035).

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