HPV33-DRIVEN OROPHARYNGEAL SQUAMOUS CELL CARCINOMAS ARE INCREASING IN PREVALENCE AND ARE CHARACTERIZED BY LOW CD8 INFILTRATION AND EPITOPE PRESENTATION DEFICIENCIES

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Background The evolving dynamics of human papillomavirus (HPV) genotypes has the potential to impact the prognosis of HPV-associated malignancies. HPV33+ oropharyngeal squamous cell carcinoma (OPSCC) patients in particular may have inferior survival rates compared to the other high-risk HPV subtypes. Despite heterogeneity in disease biology and varying clinical outcomes, ambiguity exists for the optimal clinical management of non-HPV16 high-risk subtypes. Here, we interrogated tumor from HPV33+ HNSCC patients to gain an in-depth understanding of cellular heterogeneity, identify high-risk MHC alleles, and explore disease-relevant targets that may inform strain-specific disease management.

Methods Treatment-naïve HPV+ OPSCC patients (n=19) were prospectively enrolled under an institutional review board (IRB)-approved tissue collection protocol (DF/HCC#09-472) for collection of surgical specimens. Subtype was assessed using TTMV-HPV DNA. Multiplexed, barcoded peptide-MHC-I tetramer libraries containing epitopes derived from the HPV33 genome were used to probe dissociated tumors followed by single cell RNA sequencing using the 10x Genomics platform. SingleR and published gene marker sets were used to phenotype and perform broad lineage assignment. Bulk RNA-sequencing data from additional HNSCC dataset was interrogated to validate select findings.

Results Our cohort (Total patients n=237; HPV33+ n=17, 7.2%) showed a ~2.4 fold higher rate of HPV33-driven OPSCC compared to published reports (3%). Single cell RNA-seq of tumor cells revealed that HPV33+ tumors exhibited a distinct HPV gene expression profile compared to HPV16+ tumors. HPV33+ tumors showed evidence of less infiltration of cytotoxic T-cells, exhausted T-cells and overall CD8+ T-cells. Interrogation of an independent HPV+ OPSCC cohort confirmed an overrepresentation of A*02:01 allele in HPV33+ OPSCC patients compared to HPV16+ OPSCC. Comparative epitope prediction analysis revealed that HPV33 lacks a key epitope found in HPV16 that is known to play a key role in immune recognition in A02:01+ patient samples.

Conclusions Targeted therapeutic trials have focused on HPV16+, rather than other high-risk HPV subtypes such as HPV33. Our data highlight reduced CD8+ T cell infiltrates as a potential correlate to poor outcomes in these patients. In addition, the observed A*02:01 ratios demonstrates potential immunoediting in HPV16+ patients. Increasing prevalence underscores an unmet need and presents a unique opportunity to design novel precision-based immunotherapeutic approaches for HPV33+ malignancies and potentially improve clinical outcome in this growing patient subpopulation.