SPECIFIC INNATE AND ADAPTIVE IMMUNE EFFECTOR SUBSETS IMPORTANT FOR ANTITUMOR ACTIVITY IN HPV POSITIVE CANCERS

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Background
High-risk type human papillomaviruses (HPV) are associated with genital and oral cancers, and the incidence of head and neck squamous cell cancers is fast increasing in the USA and worldwide. Survival rates for patients with locally advanced disease are poor and variable after standard of care (SOC) chemoradiation treatment (CRT). Identifying the antitumor host immune mediators important for treatment response and designing strategies to promote them are essential for improving clinical outcome. Antitumor immunity comprises of adaptive and innate immune effectors. Among these, cytotoxicity from CD8 T and NK cells is essential for controlling/elimination of tumor cells. The effector function of these cells is modulated by various receptors via a wide array of activation or inhibitory signals. Among these receptors is HLA-DR, a recognized activation marker on CD8 T cells.

Methods
We analyzed tumor brushings from HPV+ cervical cancer patients undergoing chemoradiation for immune correlates, specifically the CD8 and NK cell subsets using multiparametric flow cytometry.

Results
We obtained evidence showing that functional subsets of CD8 T as well as NK cells expressing HLA-DR are associated with response to standard of care chemoradiation. In a cohort of 27 patients, we observed 34 percent of CD8 T cells with this phenotype prior to treatment. Subsequent to treatment, we observed those with poor response to SOC exhibited a 1.4-fold drop in these subsets while those that responded showed 1.3-fold enhancement. In mice, NK cells expressing CD11c, the dendritic cell marker are analogous to the HLA-DR positive subset in humans. We observed a positive correlation of this subset of NK cells, in addition to antigen specific CD8 T cells, with antitumor response to a therapeutic peptide vaccine comprised of potent clinically relevant adjuvants in preclinical models of HPV cancers. The underlying mechanism includes vaccine adjuvant-mediated production of cytokines IL-15 and IL-18 in vaccinated animals. Importantly, in ex vivo studies employing normal donor as well as HPV patient peripheral blood cells the combination of IL-15 and IL-18 promoted significant expansion of HLA-DR positive NK subsets with high cytotoxic function.

Conclusions
Together, these results emphasize the importance of HLA-DR expressing subsets of CD8 T and NK cells for protection in HPV cancers and support designing strategies to expand this population of highly cytotoxic immune cells subsets for harnessing their role in antitumor immunity.

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