ESSENTIAL ROLE OF INNATE EFFECTOR IMMUNE RESPONSES FOR THE THERAPEUTIC EFFICACY OF PEPTIDE VACCINE TO TREAT HPV+ TUMORS

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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 after standard of care chemoradiation treatment, while immune therapeutic strategies including vaccines that target the virus-encoded E6 and E7 oncoproteins have mostly been ineffective in inducing regression of established HPV+ tumors despite promoting antigen-specific adaptive immunity. Therefore, vaccination strategies to significantly enhance antitumor immune responses with multiple effector functions to overcome the prevailing immunosuppressive tumor microenvironment are necessary to achieve curative efficacy against established HPV+ tumors. We present here preclinical evidence for the essential role of innate immune effector responses induced by a therapeutic HPV peptide vaccine incorporating two clinically relevant adjuvants QS-21 and CpG-ODN to induce sustained, complete regression of oral HPV tumors.

Methods We used mEER and TC-1, two mouse tumor cell lines expressing HPV-16 E6 and E7 along with h-Ras for tumor induction in the tongue and vaginal mucosa in syngeneic C57BL/6J mice. All animal studies were pre-approved and carried out in accordance with the University of Texas MD Anderson Cancer Center Institutional Animal Care and Use Committee (IACUC) guidelines. At days 5 and 11 following tumor implantation vaccine was administered via intranasal route and tumor growth monitored by MRI (for oral mEER) and IVIS (for vaginal TC-1). Around 15 or 16d post-tumor challenge, mice were euthanized and TIL analyses was performed to determine correlates of protection.

Results Vaccination resulted in robust induction of antigen-specific anti-tumor CD8 effector T cell responses along with expanded repertoire of innate cytotoxic effector responses that included unique natural killer cell subsets. The therapeutic efficacy of the vaccine was dependent on CD8 T cells and in addition required NK cells subsets as shown by in vivo antibody depletion and adoptive transfer to HPV peptide vaccine non-responsive oral tumor bearing mice. The combined polyfunctional populations of cytotoxic CD8 and NK cell subsets producing IFNg and granzyme B significantly outnumbered suppressive immune cell repertoire. Notably, the vaccine was effective in treating HPV tumors at both the vaginal and oral mucosal tissues.

Conclusions Overall, these data provide strong support for therapeutic strategies promoting innate immune responses along with antigen-specific immunity, as evidenced by the therapeutic HPV peptide vaccine formulation in the present investigation, for potential clinical assessment in patients with HPV + cancers.

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