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Therapeutic vaccination against cancers associated with human papillomaviruses

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Cervical cancer associated with infection by high-risk human papillomaviruses (HPV) is the major mucosally transmitted human infectious disease in women. Barrier immune protection at the mucosal portal of viral entry is essential. Two vaccines are currently approved worldwide to prevent infection and cervical intraepithelial neoplasia (CIN) caused by high-risk HPV in young females. However, these prophylactic vaccines based on viral L1 proteins are unsuitable for treating HPV+ cancers that express viral E6 and E7 oncogenes. We discovered two synthetic polypeptides corresponding to the E6 and E7 of high-risk HPV16 as potential therapeutic vaccine candidates because corresponding cellular immune responses correlated with recurrence-free patient survival post-ablative treatment for CIN. We formulated these HPV E6/E7 peptides with novel adjuvants: a non-toxic cholera toxin mutant, CT-2* and a-galactosylceramide (a-GalCer), a glycolipd that links innate and adaptive immunity by activating NKT cells and dendritic cells. Intranasal or oral-sublingual vaccination with the HPV peptides admixed with these adjuvants elicited strong antigen-specific systemic and mucosal immunity as well as protection against tumor challenge in mouse models. Additional studies in macaques, mucosal delivery of antigens along with the CT2* or a-GalCer adjuvant proved safety and effectiveness for inducing antigen-specific effector and memory $CD4^+$ and $CD8^+$ T cells in the mucosal and systemic compartments. As more data emerge linking HPV infection to other genital lesions such as penile, anal, vulvar, and vaginal cancers as well as squamous cell carcinoma of the oropharynx (SCCOP) results from our investigations may have a broader application to treat many other HPV^+ cancers.

Biography

Dr. Sastry is a Professor in the Department of immunology in Houston, TX, with joint appointment in the department of Veterinary Sciences, Bastrop, TX, at The University of Texas M. D. Anderson Cancer Center. His research over the past 20+ years supported by NIH and private funding in the broad areas of viral oncology and immunology focuses on understanding the biology, pathology and genetics of HPV-associated cancers and HIV-induced AIDS. The overall goal is to develop procedures and reagents for prediction, treatment and prevention by developing vaccines and therapeutics. He serves on NIH study panels and editorial boards of journals.