

Robust T-cell responses and clinical responses following long peptide vaccination against high risk HPV-16

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Abstract

A therapeutic vaccine was designed based on long overlapping peptides covering the complete amino acid sequence of the HPV16 E6 and E7 oncogenic proteins, thereby harboring all potential T helper and CTL epitopes. Previously, we demonstrated that HPV16 specific T-cell immunity induced by this vaccine delivered in Montanide ISA 51 adjuvant was able to terminate persistent infections and eradicate established HPV16+ tumors in rabbits.

Currently, 12 patients with histologically proven HPV16+ vulvar intraepithelial neoplasia (VIN) grade III were vaccinated 4 times with a 3-week interval by s.c. injection of the long peptides emulsified in Montanide ISA 51. Immunological monitoring was performed at the systemic level by the analysis of blood samples, drawn before each vaccination and after the last vaccination, and at the local level by the analysis of HPV16-specific T cells in tissue biopsies of the VIN lesion (before and after vaccination) as well as a biopsy from the last vaccination site.

In all 11 patients, already after 2 vaccinations, strong and broad vaccine-induced systemic proliferative responses accompanied with the production of IFN γ and IL-5 were detected. This type of response is similar to the memory T-cell responses observed in healthy individuals with HPV16-specific immunity. Importantly, circulating HPV16 E6 and E7 specific T-cells produced IFN γ upon stimulation with naturally processed and presented antigen. Notably, vaccination resulted in the induction of both CD4+ and CD8+ HPV16-specific T cells. Multiple epitopes were recognized in each patient. Analysis of the local immune response demonstrated the presence of HPV16-specific Th1/Th2 cells infiltrating both the vaccination site and the VIN lesion after vaccination in 6 out of 9 patients analyzed. A complete clinical response was seen in 4 out of 12 patients, as determined by complete clearance of lesions by macroscopy and microscopy. In 3 of these patients HPV 16 was also cleared as determined by PCR.

Further improvement of T-cell responses against the E7 component was achieved by delivering the E6 and E7 peptides into different SC locations, thereby avoiding immunodominance of E6 over E7.

In conclusion, our peptide-based vaccine elicits a strong and broad HPV16-specific T-cell response that displays the capacity to migrate into the persistently HPV16-infected lesion of patients with high grade VIN and causes complete regressions in a substantial proportion of patients.

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