Therapeutic dendritic cell vaccination against human papillomavirus

AKADEMISK AVHANDLING

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Avhandlingen baseras på följande arbeten:


II Chandy AG, Nurkkala M, Josefsson A, Eriksson K. Therapeutic dendritic cell vaccination with Ag coupled to cholera toxin in combination with intratumoural CpG injection leads to complete tumour eradication in mice bearing HPV 16 expressing tumours. *Vaccine* 2007 Aug; 10;25(32):5037-46

III Nurkkala-Karlsson M, Wassén L, Nordström I, Gustavsson I, Slavica L, Josefsson A, Eriksson K. Conjugation of HPV16 E7 to cholera toxin enhances the HPV-specific T-cell recall responses to pulsed dendritic cells *in vitro* in women with cervical dysplasia. *Submitted for publication*

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Cervical cancer, which is caused by infection with human papillomavirus (HPV), is the second most common cancer among women worldwide, leading to 230 000 deaths annually. The two currently available HPV vaccines can only be used prophylactically, so they are of no use to the 291 million women who are already infected and at risk of developing cancer. Early stage cervical cancer can be treated with surgery, chemotherapy, and radiation, although the treatment outcomes for patients with recurrent disease are poor. The main goals of this thesis were to develop and evaluate a possible treatment against HPV-induced cervical disease.

HPV uses several different mechanisms to evade elimination by the immune system, e.g., suppression of inflammation in the infected epithelium and down-modulation of the presentation of HPV antigens on MHC molecules, thereby avoiding recognition by immune cells. The use of TLR ligands as local treatments to overcome HPV-induced down-modulation of immune responses has been investigated. The results show that intravaginal or intratumoural administration of TLR ligands enhances the expression of both MHC molecules and chemokines, and promotes the influx of immune cells into the targeted tissues.

Dendritic cells (DCs) sense danger and activate antigen-specific T cells in the adaptive immune system, leading to the killing of virus-infected cells. The use of DCs as a therapeutic cancer vaccine was assessed in mice with tumours that expressed the HPV16 E7 antigen. The antigen used, E7, was chemically conjugated to cholera toxin (CT-E7), to enhance both antigen uptake and presentation and DC maturation. Vaccination with CT-E7-DCs primed for tumour-specific cytotoxic T cells led to a significantly reduced tumour burden. Complete tumour eradication was achieved by combining CT-E7-DC vaccination with intratumoural administration of a TLR ligand. The CT-E7-DCs also activated E7-specific human T cells, as demonstrated in vitro using blood cells from patients with HPV-induced cervical disease. The CT-E7-pulsed DCs produced IL-12 and induced E7-specific CD4+ T-cell responses, including the production of IFN-γ, which is crucial for a robust anti-tumour response. Indoleamine 2,3-dioxygenase (IDO), which is an enzyme produced by DCs, is proposed to affect negatively the outcome of DC vaccination owing to its down-regulation of T-cell responses. The results presented in this thesis show that exposure of DCs to CT does not induce IDO transcription or activity, whereas it does prime DCs for CD40 ligand-induced IDO production.

The results outlined in this thesis highlight the potential of a combinational immunotherapeutic treatment against HPV-induced cervical disease, indicating that it may be possible in the future to treat patients who have HPV-induced malignancies.

Keywords: human papillomavirus, therapeutic dendritic cell vaccination, cholera toxin, T cells, TLRs and CpG