

Development of novel immunization approaches to generate immunity in the female genital tract with special reference to genital herpes

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av

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Avhandlingen baseras på följande delarbeten:

- I **Tengvall S**, Josefsson A, Holmgren J, Harandi AM.
CpG Oligodeoxynucleotide augments HSV-2 glycoprotein D DNA vaccine efficacy to generate T helper 1 response and subsequent protection against primary genital herpes infection in mice.
Journal of Reproductive Immunology 2005 Dec;68(1-2):53-69
- II **Tengvall S**, Lundqvist A, Eisenberg RJ, Cohen GH, Harandi AM
Mucosal administration of CpG Oligodeoxynucleotide elicits strong CC and CXC chemokine responses in the vagina and serves as a potent Th1-tilting adjuvant for recombinant gD2 protein vaccination against genital herpes.
Journal of Virology 2006 Jun;80(11):5283-91.
- III **Tengvall S**, Derek O'Hagan, Harandi AM
Rectal immunization confers a sex hormonal- and MyD88- independent protective immunity against genital herpes simplex virus type 2 infection in mice.
Submitted for publication
- IV **Tengvall S**, Harandi AM
Importance of the adaptor molecule MyD88 in innate and adaptive immune protection against genital herpes infection in mice.
Manuscript

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Development of mucosal vaccines for inducing immunity in the female reproductive tract would have profound implications for the prevention of sexually transmitted diseases. Despite numerous efforts, no such vaccines are currently available for human use. The main objective of this doctoral thesis was to develop novel immunization approaches to generate immunity in the female genital tract with special emphasis on immunity against genital herpes.

Mammalian innate immune systems sense and respond to pathogens through a series of pattern recognition receptors such as Toll-like receptors (TLRs). Detection of pathogen associated molecular patterns by TLRs triggers a signaling pathway mainly through adaptor protein MyD88, which results in a coordinated set of immune responses that includes both innate and acquired immunity. By using a well-established mouse model of genital HSV-2 infection, it was shown in this thesis that the efficacy of intramuscular immunization with a DNA vaccine encoding glycoprotein D (gD) from HSV-2 can be improved with a timely administration of synthetic oligodeoxynucleotide (ODN) containing immunostimulatory CpG motifs, a TLR9 ligand. Another important finding in this thesis work was introduction of CpG ODN as a potent vaginal adjuvant for induction of acquired immunity in the female genital tract as well as for systemic immune response. Thus, vaginal immunization with HSV-2 gD in combination with CpG ODN induced a potent gD specific antibody as well as cellular immunity, and conferred protection against subsequent vaginal challenge with a lethal dose of HSV-2.

The potential of rectal immunization route to induce protective immunity in the female genital tract was also investigated. Thus, rectal immunization with a live attenuated HSV-2 TK⁻ was shown to confer antibody and cellular response as well as protection against an otherwise lethal vaginal challenge with a virulent HSV-2 strain. Importantly, unlike intravaginal route, rectal route was shown to be independent of sex hormonal influence. It was also documented that TLR/MyD88 signaling pathway is important for innate immune protection against primary genital herpes. By contrast, the usage of MyD88 was shown to be dispensable for induction of acquired immune protection induced by vaginal or rectal immunization with HSV-2 TK⁻. In addition, while rectal immunization with the TLR/MyD88 targeting adjuvant CpG ODN in combination with gD failed to elicit protective immunity, rectal immunization with cholera toxin and gD conferred a potent antibody and cellular immune responses as well as protection against genital herpes. These results have implications for the development of vaccines to generate immunity in the female genital tract against sexually transmitted infections.

Keywords: female genital tract immunity, genital herpes, mucosal adjuvant, TLR, MyD88 and CpG ODN

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