Immunization approaches and molecular signatures for mucosal immunity to primary and recurrent herpes

Akademisk avhandling

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av
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Avhandlingen baseras på följande arbeten:

I. Wizel B, Persson J, Thörn K, Nagy E, Harandi AM.
Nasal and skin delivery of IC31® -adjuvanted recombinant HSV-2 gD protein confers protection against genital herpes.
Vaccine 2012; 30(29): 4361-8.

II. Persson J, Zhang Y, Olafsdottir T, Thörn K, Cairns TM, Wegmann F, Sattentau Q, Eisenberg RJ, Cohen GH, Harandi AM.
Nasal immunization confers high-avidity neutralizing antibody response and immunity to primary and recurrent genital herpes in guinea pigs.
Submitted

III. Persson J, Nookaew I, Mark L, Lindqvist M, Harandi AM.
Molecular and cellular imprints of live attenuated herpes simplex virus type 2 in the murine female reproductive tract
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Immunization approaches and molecular signatures for mucosal immunity to primary and recurrent herpes

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Genital herpes is most commonly caused by herpes simplex virus type 2 (HSV-2), and is a prevalent sexually transmitted infection worldwide. Despite numerous efforts, there is currently no licensed vaccine against the disease. This thesis evaluates the potential of different immunization strategies to engender protective immunity to genital herpes, using animal models of HSV-2 infection. Studying early molecular and cellular signatures of vaginal immunity to genital herpes represents the secondary objective of this thesis.

A well-established mouse model of genital herpes was used to investigate immunogenicity and protection against primary genital HSV-2 infection. A guinea pig model, which displays a HSV-2 infection that closely resembles the pathogenesis and symptoms of the disease in humans, was employed for studying the impact of immunization on the establishment of latency and recurrent genital herpes. Surface plasmon resonance technology was used to study the avidity and neutralizing epitope profile of IgG antibodies raised towards HSV-2 envelope glycoprotein D (gD) by immunization. Whole-genome microarray analysis combined with systems biology, protein array analysis and flow cytometry were used to identify early immune events in the murine vagina after delivery of a live attenuated HSV-2 strain, known as the gold standard for induction of protective immunity in mice.

Main results presented in this thesis include: I) Nasal and skin immunization with recombinant HSV-2 gD antigen in combination with the clinically tested adjuvant IC31® was highly efficient for induction of specific B and T cell responses and protection against primary genital herpes in mice; II) Nasal immunization elicited a high avidity, HSV-2 neutralizing IgG antibody response as well as protective immunity to both primary and recurrent genital herpes infection, with partial reduction of viral latency, in guinea pigs; and III) Identification of local inflammatory imprints connected to immune cell recruitment after vaginal immunization with live attenuated HSV-2 in mice.

The results presented in this thesis provide evidence on the potential of nasal and dermal immunization for induction of protective immunity to genital herpes as well as early molecular and cellular signatures of the protective immune response in the vaginal mucosa. These results may inform rational development of a vaccine to counter genital herpes infection in humans.

Keywords: Genital herpes, HSV-2, vaginal immunity, female reproductive tract, vaccine, adjuvant, systems biology.

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