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Mucosal adjuvants and their mode of action in the female genital tract

AKADEMISK AVHANDLING

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av
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Avhandlingen baseras på följande delarbeten:

I. Lindqvist M, Persson J, Thörn K, Harandi AM.
The mucosal adjuvant effect of alpha-galactosylceramide for induction of protective immunity to sexually transmitted viral infection.
J Immunol. 2009 May 15;182(10):6435-43.

II. Lindqvist M*, Navabi N*, Jansson M, Samuelson E, Sjöling A, Orndal C, Harandi AM.
Local cytokine and inflammatory responses to candidate vaginal adjuvants in mice.
Vaccine. 2009 Dec 10;28(1):270-8.

III. Del Campo J, Lindqvist M, Cuello M, Bäckström M, Cabrerra O, Persson J, Perez O, Harandi AM.
Intranasal immunization with a proteoliposome-derived cochleate containing recombinant gD protein confers protective immunity against genital herpes in mice.
Vaccine. 2010 Feb 3;28(5):1193-200.

IV. Lindqvist M, Brinkenberg I, Samuelson E, Thörn K, Harandi AM.
A genome-wide transcriptome profiling unravels molecular correlates of mucosal adjuvants in the female genital tract
Manuscript

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Mucosal adjuvants and their mode of action in the female genital tract

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Abstract:
Sexually transmitted infections (STIs) cause a socioeconomic burden, morbidity and even mortality in a large part of the human population all over the world today. One of the most common genital ulcerative diseases is caused by herpes simplex virus type 2 with over 536 million people infected world-wide. Despite tremendous efforts, there are only vaccines against sexually transmitted human papillomavirus available today. The lack of success in vaccine development against STIs has partly been due to insufficient knowledge about how to induce protective immunity in the female genital tract.

Development of new vaccines is largely based on the use of highly purified or recombinant antigens, with limited immunogenicity. This has generated a need for development of potent vaccine adjuvants. Although a few adjuvants are included in the licensed vaccines, they are all administered systemically and their mode of action is poorly defined. In this thesis we have identified two new potent mucosal adjuvants for induction of immunity against genital HSV-2 infection, the glycosphingolipid alpha-galactosylceramide (α-GalCer), which is a potent agonist of invariant natural killer T (iNKT) cells and AFCo1, a cochelate structure of proteoliposome derived from *Neisseria Meningitides* serogroup B, with a combined immunostimulatory and delivery system function.

By employment of genome-wide gene expression microarray analysis combined with a bioinformatics approach we assessed the molecular signatures of two classes of immunostimulatory mucosal adjuvants, namely α-GalCer and the Toll-like receptor 9 agonist CpG ODN, both of which have been shown by our group to induce comparable immune protection against genital herpes infection in mice. Local administration of the adjuvants elicited expression of a number of core genes among which several were cytokines and chemokines as well as inflammasome associated genes. “Inflammatory response” was identified as the common main bio-function with Tnf as the common key regulator of gene expression. An adjuvant-induced enhancement in the frequency of vaginal dendritic cells and macrophages was also observed.

In summary, results presented in this thesis could identify two new mucosal adjuvants with the ability to confer protective immunity against genital herpes, as well as the molecular signature of mucosal adjuvants in the mouse female genital tract. These results may contribute to the future development of safe and potent mucosal adjuvants to be included in novel vaccines against STIs.

Keywords: mucosal adjuvants, genital tract, HSV-2, alpha-galactosylceramid, CpG ODN, proteoliposome-derived cochleate, inflammation, bioinformatics, mouse

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