

Functions of Glycoprotein G of Herpes Simplex Virus Type 2

Akademisk avhandling

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av

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Avhandlingen baseras på följande arbeten:

- I. **Görander Staffan, Svennerholm Bo, Liljeqvist Jan-Åke**
Secreted portion of glycoprotein g of herpes simplex virus type 2 is a novel antigen for type-discriminating serology. *J Clin Microbiol.* 2003;41(8):3681-6
- II. **Görander Staffan, Mbwana Judica, Lyamuya Eligius, Lagergård Teresa, Liljeqvist Jan-Åke**
Mature glycoprotein g presents high performance in diagnosing herpes simplex virus type 2 infection in sera of different tanzanian cohorts. *Clin Vaccine Immunol.* 2006;13(6):633-9.
- III. **Liljeqvist Jan-Åke, Görander Staffan, Elias Per, Aslani Alireza, Bergström Tomas.**
Glycoprotein G of herpes simplex virus type 2 is essential for neuronal spread of genital infection in mice. In manuscript.
- IV. **Görander Staffan, Lindqvist Madeleine, Harandi Ali, Liljeqvist Jan-Åke.**
Vaccination with the mature glycoprotein G of herpes simplex virus type 2 protects against genital and neurological disease. In manuscript.

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Functions of Glycoprotein G of Herpes Simplex Virus Type 2

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Abstract

Background: Herpes simplex virus type 2 (HSV-2) is a common sexually transmitted infection with more than 500 million individuals infected world-wide. A major global health problem is that HSV-2 infection facilitates the spread of HIV. This epidemiological situation warrants the development of a vaccine to reduce the spread of HSV-2. As HSV-2 often is transmitted without symptoms type specific serology is valuable in diagnosis of the infection. The envelope glycoprotein G (gG-2) of HSV-2 is cleaved intracellularly into a membrane bound portion (mgG-2) and a secreted portion (sgG-2). Although the function of mgG-2 is unknown the protein induces a type specific antibody response. This feature is utilized in several serological HSV-2 type specific assays. A general problem is that assays which are reliable in Western world country populations show lower performance for sera from African countries.

Aims: To evaluate sgG-2 as type specific antigen in ELISA for detection of HSV-2 infection in a Swedish cohort and define the performance for both sgG-2 and mgG-2 in ELISA for high HSV-2 prevalence cohorts in Tanzania (paper I and II). To elucidate the function of mgG-2, using HSV-2 mutants, in a genital mouse model (paper III) and to evaluate mgG-2 as a vaccine candidate against genital HSV-2 infection in mice (paper IV).

Methods: Natively produced sgG-2 and mgG-2 proteins were purified by immunosorbent columns from HSV-2 infected cell cultures. For the vaccine studies mgG-2 was purified using *Helix pomatia* lectin affinity chromatography. A frame shift HSV-2 mutant devoid of mgG-2 and an emerald green fluorescent protein labelled sgG-2 and mgG-2 negative HSV-2 were used for functional studies in C57BL/6 mice. Viral load was estimated by virus isolation and by real time PCR. C57BL/6 mice were immunized with mgG-2 and CpG as adjuvant and challenged genitally with wild type HSV-2.

Results: We showed that sgG-2 is a novel antigen that can be used for type specific serological diagnosis of HSV-2 infection and that an ELISA based on mgG-2 can improve the detection of HSV-2 infected individuals from Africa. Both mgG-2 deficient HSV-2 mutants were severely attenuated and all mice survived a genital infection. The viral mutants infected the genital mucosa but did not induce genital disease and were not propagated to the sensory ganglia or to the CNS. Finally, mice immunized with mgG-2 and adjuvant were highly protected against a lethal dose of wild type HSV-2. Protection was associated with an enhanced Th1 response and IFN- γ production in re-stimulated CD4⁺ T cells.

Conclusion: Native sgG-2 and mgG-2 proteins induce type specific antibody responses and perform well in ELISA in low as well as in high HSV-2 prevalence populations. The mgG-2 protein has an important function in the ability of HSV-2 to infect nervous tissue. As vaccination with mgG-2 protects mice from lethal disease mgG-2 constitutes a promising vaccine candidate against HSV-2 infection. In human trials detection of anti-sgG-2 antibodies may be a valuable tool to discriminate between vaccine induced immunity and natural HSV-2 infections.

Keywords: Herpes simplex virus type 2, glycoprotein G, type specific serology, vaccine, Tanzania.

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