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Herpes simplex virus type 1 infection in the central nervous system – Experimental and clinical studies

Akademisk avhandling

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Fakultetsopponent:
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Avhandlingen baseras på följande delarbeten

I. Jennische E*, **Eriksson CE***, Lange S, Trybala E, Bergström T.
The anterior commissure is a pathway for contralateral spread of herpes simplex virus type 1 after olfactory tract infection. *J Neurovirol* 2015; 21(2): 129-147.
*Equal contribution

II. **Eriksson CE**, Studahl M, Bergström T.
Acute and prolonged complement activation in the central nervous system during herpes simplex encephalitis. *J Neuroimmunol* 2016; 295-296: 130-138

III. **Eriksson CE**, Agholme L, Trybala E, Nazir FH, Satir TM, Zetterberg H, Bergström T, Bergström P.
Transient cytopathogenicity despite increasing infectivity of herpes simplex virus types 1 and 2 during neuronal differentiation. *Manuscript*

IV. Altgärde N, **Eriksson C**, Peerboom N, Phan-Xuan T, Moeller S, Schnabelrauch M, Svedhem S, Trybala E, Bergström T, Bally M.
Mucin-like Region of Herpes Simplex Virus Type 1 Attachment Protein Glycoprotein C (gC) Modulates the Virus-Glycosaminoglycan Interaction.
J Biol Chem 2015; 290(35): 21473-21485

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Herpes simplex virus type 1 infection in the central nervous system – Experimental and clinical studies

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Abstract

Alphaherpesvirus infections in the central nervous system (CNS) are rare but severe, and many patients show remaining neurological sequelae. While antiviral treatment has reduced the mortality, morbidity has not been diminished to the same degree, and the immune system activation might contribute to the pathogenesis. Clinical symptoms have often been in focus in previous studies of such infections, while the entry and spread of viral agents is less thoroughly elucidated. Therefore, the aim of this thesis was to investigate aspects of the pathogenesis of herpes simplex virus type 1 (HSV-1) infections in the CNS, including viral properties related to virulence, transport and tropism, and to host immune responses in this compartment.

Infection in a rodent model of herpes simplex encephalitis (HSE) revealed that HSV-1 can enter the brain via the trigeminal nerve or the olfactory bulb. Furthermore, HSV-1 was found to utilize the anterior commissure (AC), a bundle of nerve fibres between the two brain hemispheres, for transport to the contralateral hemisphere. In the AC, HSV-1 targeted cells morphologically resembling oligodendrocytes, which could suggest that virus may utilize additional cells to neurons for rapid transport.

Cerebrospinal fluid (CSF) samples from HSE patients and controls were analysed for concentrations of CNS aquaporins (water channels) and complement components participating in the innate immune response. Increased concentrations were found in HSE patients for aquaporin 9 (AQP9) and complement components C3a, C3b, C5 and C5a as compared with healthy controls, indicative of an increased intrathecal immune activity in HSE. For C3a and C5a, the activity was increased both in acute and convalescent stages of HSE, further contributing to previous observations of increased immune activity in convalescence.

In a cell culture model for differentiation of induced pluripotent stem cells into cortical neurons, reflecting neuronal development, the susceptibility of differentiating cells to infection with HSV-1 or herpes simplex virus type 2 (HSV-2) was investigated. Despite production of high viral titres and high viral DNA quantities both early and late in differentiation, the cell viability of cells in late differentiation was higher than for cells in early differentiation. Thus, neuronal progenitor cells were more vulnerable to infection than mature cortical neurons.

The role of the mucin-like region of glycoprotein C of HSV-1 was studied in cell culture and surface binding resonance experiments. Here it was found that the mucin-like region facilitated both viral attachment to cell surface glycosaminoglycans upon infection and, more importantly, to egress and release of newly produced virions from infected cells.

Altogether, the findings in this thesis supported previous findings of viral and immunological factors contributing to the CNS infectivity and outcome in HSE. In addition, a novel pathway for HSV-1 transport in the brain in form of AC was discovered. Finally, the importance of the complement system activation in the CNS in HSE patients, and a role for mucin-like region of gC in HSV-1 attachment and egress *in vitro* was demonstrated.

Keywords: herpes simplex virus; herpes simplex encephalitis; central nervous system infection; complement system; aquaporin 9; glycoprotein C; differentiating neuronal cells; mucin-like region

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