

# Chemokine responses and T cell recruitment in central nervous system alphaherpesvirus infections

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien,  
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av **Liza Lind**

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Avhandlingen baseras på följande delarbeten

- I. **CXCL11 production in cerebrospinal fluid distinguishes herpes simplex meningitis from herpes simplex encephalitis**  
Lind L, Studahl M, Persson Berg L, Eriksson  
*Journal of Neuroinflammation*. 2017; 14(1):134
- II. **Chemokine production and T cell trafficking into the central nervous system of mice with herpes simplex meningitis: accumulation of recently degranulated cytotoxic CD4 CD8 double positive T cells**  
Lind L, Thörn K, Krzyzowska M, Svensson A, Eriksson K, *Manuscript*
- III. **Chemokines and matrix metalloproteinases in cerebrospinal fluid of patients with central nervous system complications caused by Varicella zoster virus**  
Lind L, Eriksson K, Grahn A, *Manuscript*
- IV. **Role of interferon- $\gamma$  and interleukin-1 $\beta$  in CXCL11 induction in herpes simplex neuroinflammation**  
Lind L, Svensson A, Thörn K, Studahl M, Schlüter K, Eriksson K, *Manuscript*

# Chemokine responses and T cell recruitment in central nervous system alphaherpesvirus infections

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## Abstract

This thesis is focused on members of the alphaherpesvirus family; the two herpes simplex viruses and varicella zoster virus. Herpes simplex virus type 1 mainly causes cold sores and type 2 gives rise to genital blisters. Varicella zoster causes chickenpox in children and shingles in adults. The viruses are chronic and incurable, and very common. Both herpes simplex and varicella zoster virus are mostly harmless but can in rare cases cause inflammations of the central nervous system with various degree of severity. We have studied the immune system in neuroinflammation caused by alphaherpesviruses, with a special focus on how T cells, an important cell type in fighting off infections, reach the central nervous system. The central nervous system is immune privileged, thus immune cells entry is highly restricted and mediated by several factors. Interferons and interleukins amplify the immune response. Chemokines are attracting cells to the site of inflammation. Matrix metalloproteinases rearrange the membranes separating the central nervous system from peripheral blood.

Herpes simplex virus type 2 meningitis (HSM), an inflammation of the membranes surrounding the brain, is a more benign disease compared to herpes simplex virus type 1 encephalitis (HSE), an inflammation of the entire brain. In *Paper I* we found that in the cerebrospinal fluid of patients with HSE or HSM chemokines CXCL8, CXCL9 and CXCL10 are strongly induced. In HSM two additional chemokines were induced; CCL8 and CXCL11. In *Paper II* we characterized T cells in the central nervous system of mice infected with herpes simplex virus type 2. We found a subset of T cells expressing both CD4 and CD8 surface markers which were highly virus-specific and activated. Returning to humans we examined levels of chemokines and matrix metalloproteinases in patients with neuroinflammations caused by varicella zoster virus (*Paper III*). We found that CXCL11 increased in meningitis patients, but not in patients with encephalitis or Ramsay-Hunt (facial palsy). Matrix metalloproteinases 2 increased in all patient groups, whereas other matrix metalloproteinases were disease exclusive. In *Paper IV* we further investigated chemokine and cytokine contribution to inflammatory response. We found that CXCL11 levels correlated with expression of IL-1 $\beta$ , which was higher in cerebrospinal fluid of HSM patients. We also wanted to investigate the source of CXCL11 and found that neither astrocytes nor microglia produced CXCL11 upon stimulation with any herpes simplex virus, but microglia upregulated CXCL11 mRNA.

In this thesis we suggest that CXCL11 is a marker of viral meningitis, induced by interferon- $\gamma$  and IL-1 $\beta$ . We find CD4 and CD8 double positive T cells in the CNS of mice with herpes simplex virus type 2 infection, which are degranulated, highly virus-specific and secreting cytotoxic factors.

**Keywords:** herpes, varicella, encephalitis, meningitis, chemokines, matrix metalloproteinases, central nervous system