Cellular recognition of herpes simplex virus infection and virus-induced cytokine production

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ABSTRACT

The aim of the PhD dissertation was i) to determine the cytokine expression profile after herpes simplex virus (HSV) infection, ii) describe cellular mechanisms of viral recognition, and iii) identify viral proteins that inhibit or enhance cytokine production. The dissertation includes five papers published and two manuscripts intended for publication.

HSV is a very common virus that clinically may manifest in gingivostomatitis, herpes labialis, keratitis, encephalitis, and genital herpes. Normally the infection is self-limiting but in immuno-compromised individuals, such as newborn babies, transplantation patients, and AIDS patients the virus may spread throughout the body and result in encephalitis, which is associated with high mortality and morbidity.

i) The PhD study showed that HSV infection in dendritic cells and macrophages induces a number of well known proinflammatory cytokines, chemokines, and interferons, including the recently discovered type III interferons IL-28 and IL-29. The study also presents the first evidence that IL-29 has potential antiviral activity against HSV in human cells. Furthermore, selective production of the chemokine RANTES was seen in murine macrophages.

ii) A group of recognition receptors, termed Toll-like receptors (TLRs), were investigated, and it was found that HSV infection was recognised through both TLR-dependent and TLR-independent mechanisms. Downstream of recognition, HSV-induced activation of the transcription factors IRF3 and NF-kappa-B was essential for chemokine and interferon expression. Furthermore, the kinases IKK-beta, TAK1, MEKK1, and PKR also play important roles for the virus-induced cytokine expression.

iii) HSV evades the antiviral cytokine response through the viral protein infected cell protein (ICP) 27. Infection of macrophage cell cultures with ICP27-defective virus resulted in enhanced production of antiviral cytokines and an enhanced activation of NF-kappa-B and IRF3. However, the study also showed that virus replication is essential for cytokine expression and that viral ICP0 positively affects the expression of cytokines, such as the chemokine RANTES. In conclusion, viral gene products both enhance and restrict cytokine production.

The project contributes with new knowledge on the progress of virus infections and may eventually contribute to better design of treatments and vaccines.