The role of interferon-lambda in host defence during herpes simplex virus infection

Nina Ank, MD

This PhD dissertation was accepted by the Faculty of Health Sciences of the University of Aarhus, and defended on June 20 2008.

Official opponents: Jens Bukh, Thomas Michiels, and Lars Iversen.

Tutors: Søren R. Paludan and Søren C. Mogensen.

Correspondence: Nina Ank, Institute of Medical Microbiology and Immunology, Bartholin Building, Wilhelm Meyers Allé, University of Aarhus, 8000 Århus C, Denmark.

E-mail: na@microbiology.au.dk

Dan Med Bull 2008;55:160

ABSTRACT

The PhD dissertation originates from the Faculty of Health Sciences of the University of Aarhus, and it is based on three papers.

Herpes simplex virus (HSV) is a widespread virus which causes a range of diseases. The best known disease is the common cold sores. HSV can also give rise to the sexually transmitted genital HSV infection. The current treatment for HSV shortens the period of illness, but cannot eliminate the virus. Apart from the classical manifestations of HSV, HSV can also give rise to for instance keratitis and encephalitis.

The innate immune response recognizes HSV using different conserved receptors. Among these receptors are the Toll-like receptors (TLR), with especially TLR numbers two and nine playing a significant role in the recognition of HSV. When the virus has been recognised, a process is initiated leading to the elimination of the virus. One of the first factors produced in the process of elimination is interferon (IFN). There are three classes of IFNs, among these type III IFN (IFN-γ), a recently identified IFN. The three classes of IFN all contribute to combating viral infections. Type I IFN and type III IFN directly induce a so-called antiviral state in cells and indirectly contribute to the elimination of viruses by influencing the slower evolving adaptive immune response.

This dissertation investigates the role of type III IFNs. Both cell types producing and responding to IFN-γ have been examined. In addition, the antiviral activity of IFN-γ both in in vitro and in vivo experimental settings has been investigated. These investigations showed that IFN-γ had limited antiviral activity against HSV under the applied in vitro settings; in contrast IFN-γ provided complete protection against genital HSV infection in mice. Likewise it has been endeavoured to clarify the mechanisms behind the antiviral activity, by examination of the genes induced by IFN-γ. The genes in focus have been genes with an already known antiviral activity. IFN-γ did induce genes with known antiviral activity.

As the first study of its kind, this dissertation investigates the role of IFN-γ using mice deficient for the receptor for type III IFNs. Studies in these mice showed that IFN-γ was dispensable in combating systemic viral infections. On the other hand, studies in mice deficient for the receptor for IFN-γ showed that IFN-γ is needed to obtain the already described protective effect against genital HSV infection of a ligand for TLR9. The mechanisms behind this were further investigated by examinations of bone marrow chimeric mice and mice depleted of plasmacytoid dendritic cells.

Altogether, the data suggest that IFN-γ especially plays a role during local infections on mucosal membranes, whereas IFN-γ has not been shown to play a role under systemic infections.