ROLE OF NATURAL KILLER T CELLS (NKT) CELLS IN IMMUNITY TO HERPES SIMPLEX VIRUS TYPE 1

by

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Summary

Herpes simplex virus type 1 (HSV-1) produces acute muco-cutaneous infections, followed by spread to sensory nerve ganglia, and establishment of latency. In the peripheral nervous system, primary sensory neurons, which are found in dorsal root ganglia of the of the spinal nerves, are the target for HSV and they may undergo either productive or latent infection. Productive infection of sensory neurons generates the potential for lethal spread of virus through the nervous system but in immunocompetent hosts, viral replication is terminated by timely development of an adaptive immune response. The infection of dorsal root ganglia that follows cutaneous inoculation of the flanks of mice with HSV provides a well-characterized model of peripheral nervous system infection. The mechanisms responsible for clearance of HSV are complex. At mucosal and cutaneous sites, local innate immune mechanisms act to interrupt the initial spread of virus to the nervous system, while adaptive immunity is important in limiting replication in the ganglia and extension of the virus to adjacent dermatomes. Thus actions of both the innate and the adaptive immune systems are vital in defence against replicating HSV-1, while it is thought that latent infection in the ganglia is contained by the surveillance of the adaptive immune system.

Natural killer T (NKT) cells are a conserved subpopulation of lymphocytes that recognize glycolipid antigens presented by the invariant MHC class I-like molecule CD1d. Upon activation through their semi-invariant T cell receptor, these cells rapidly release large amounts of immuno-modulating Th1 and Th2 cytokines. NKT cells have, therefore, been implicated in immune responses controlling various diseases, including infection, cancer, and autoimmunity, as well as having an involvement in allo-graft survival. Consideration of the important contributions of innate and adaptive immunity to clearance of HSV prompted this investigation of the role of CD1d and of CD1d-restricted NKT cells in the pathogenesis of HSV infection.

The first part of this thesis (Chapter 3 and 4) describes investigations into the role of NKT cells in immunity to HSV-1, using a zosteriform model of infection and two gene knockout strains of C57BL/6 mice. CD1d GKO and Jα18 GKO mice, which are deficient in NKT cells,

are compromised in controlling HSV-1 as evidenced by mortality, virus loads in skin and dorsal root ganglia, presence and size of skin lesions, persistence of HSV antigen, neuronal damage and extent of latency. Comparisons between wild type (NKT cell replete), Jα18 GKO (deficient in invariant Vα14^{+} NKT cells) and CD1d GKO (deficient in all CD1d-dependant NKT cells) mice allowed assessment of CD1d-dependant NKT cell subsets in defence against the virus at various stages of infection. It was concluded that both subsets play important roles in controlling the virus and in preventing lethal neuro-invasive disease, that both are vital adjuncts to the adaptive immune response and that without them, low doses of neuropathogenic HSV-1 can establish quickly and cause fatal infections.

The NKT-cell population appears to be quite dynamic in its response to a range of pathogens and other disease processes. The study described in Chapter 5 presents evidence suggesting that the response of NKT cells during HSV infection is no less dynamic. In the axillary lymph nodes, observations on numbers of cells expressing NK1.1 antigen and the invariant TCR suggest that NKT cells are activated in the regional lymph nodes draining the infection site. Observations on lymphocytes prepared from liver and spleen also suggested activation of NKT cells, indicating that NKT cells at these sites are also activated during the course of acute HSV infection.

The role of NKT cells in the control of HSV infection was further examined by adoptive transfer studies, to investigate whether the defect in handling of HSV-1 by Jα18 GKO mice could be complemented by the adoptive transfer of lymphocytes from wt mice (Chapter 6). Finally, the relevance of activated NKT cells in the anti-HSV response was examined by observing the effects of α-GalactosylCeramide therapy on the severity of HSV-1 infection (Chapter 6). Activation of NKT cells by this compound delayed the onset of HSV disease, decreased prevalence and severity of zosteriform lesions and reduced viral titres in skin and ganglia. The beneficial effects of α-GalactosylCeramide on the outcome and severity of HSV infection in the skin were dose-dependent.

Collectively, the studies described in this thesis provide insights into how NKT cells, normally a rare population of cells, has the ability to regulate the protective immune response

to HSV-1. As more understanding is gained about how NKT cells become activated during HSV-1 infection, and how they mediate their antiviral effects, other ways may be developed to modulate and activate this interesting subset to the benefit of infected individuals.