

## Herpes Simplex Keratitis

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Herpes simplex keratitis remains a blinding problem of major epidemiological importance to ophthalmologists in all developed countries, despite the development over the past 35 years of anti-viral agents effective in the treatment of active episodes of herpes simplex keratitis. Both viral and host immune response factors influence the severity of the inflammatory response that develops in the cornea infected by HSV. It is the unraveling of the details to the immunologic response that have been most difficult in the research community's attempts to better understand, and hence better treat this clinical problem. We have focused our attention on study of a murine model of HSK over the past decade, and this has helped us define the role of the immune response to HSV in both protection from, and in creation of blinding keratitis after HSV exposure to the cornea.

At least one gene locus, closely linked to or identical to the Igh-1 locus on chromosome 12 of the mouse tightly regulates the mouse immunologic response to corneal inoculation with HSV (and, for that matter, to anterior chamber inoculation with this virus). Thus, mice which are genetically identical except for a very limited amount of their DNA at and around the Igh-1 locus exhibit dramatically different inflammation responses to HSV inoculation. Igh -1e and Igh -1d mice develop necrotizing stromal keratitis after HSV corneal inoculation, but Igh -1b mice are highly resistant to such destructive keratopathy. Additional mapping studies recently by our laboratory group has strikingly narrowed the candidate gene to the Igh-1c gene, the gene encoding for the synthesis of the constant region of immunoglobulin IgG2b.

The molecular and cellular details of the immunologic response to HSV which create a complex drama whose finale is either one of protection from or development of keratopathy are incompletely understood. An extraordinarily complicated interplay between the components of the natural immune response and the humoral and cellular components of the acquired immune response occurs, regulated by a product or products encoded by the "susceptibility gene." The replicating virus is attacked and destroyed in all instances. As the immunologic attack on the virus develops, however, innocent bystander damage to delicate ocular structures critical for good vision hangs in the balance. The mystery is why some mice (Igh-1b) consistently are spared the vision-limited keratopathy that other mice (Igh-1d and Igh-1e) so routinely develop as a consequence of this inflammatory response. The cellular and molecular differences between Igh-1 disparate congenic mice that exhibit differential susceptibility to necrotizing HSK are the following:

1. Resistant mice make an earlier and more vigorous IgG2 anti-HSV antibody response than do susceptible mice.
2. Resistant mice develop HSK susceptibility if they are treated in such a way that they are rendered B cell-deficient and hence make a deficient anti-HSV antibody response after corneal inoculation with HSV.
3. Susceptible mice are "hyperactive" in their natural killer cell response, in their macrophage responses, and in their CD4 T cell responses to HSV inoculation.
4. Keratopathy seen in HSK susceptible mice is produced by CD4 cells, natural killer cells, macrophages, and neutrophils.
5. The T cell population in the peripheral cornea and in the limbal conjunctiva of susceptible mice is rich in CD4 lymphocytes and is deficient in CD8 regulatory T cells.
6. Resistant mice have an abundance of CD8 regulatory cells in the corneal periphery and in the limbal conjunctiva, and few CD4 cells in these areas.
7. In vivo natural killer cell depletion or macrophage depletion of HSK-susceptible mice converts them into HSK resistant mice.

8. Passive immunization of HSK susceptible mice with IgG2 anti-herpes antibodies confers complete protection against subsequent development of HSK.
9. Passive immunization of HSK susceptible mice with HSV-immune CD8 regulatory T cells confers protection against subsequent development of HSK after corneal inoculation with HSV.
10. Adoptive transfer of T cells into athymic (nude) congenic Balb/c mice, ordinarily resistant to developing HSK, transforms them into HSK susceptible mice, and the T cells responsible for this are CD4 rather than CD8 T cells.

Interestingly, we have shown in a paper published in Nature in 1995, that the susceptible mice, in addition to developing keratopathy secondary to the effects of the virus and secondary to the effects of the overly exuberant immune response to the virus, also develop an autoimmune keratitis!

We show that HSK is mediated, at least in large part, by T cell clones specific for corneal cell antigens which also recognize peptide present in IgG2a, and exposure of HSK-susceptible mice to a soluble form of this peptide confers complete resistance to HSK after subsequent inoculation of the cornea with HSV. Shared expression of peptide sequences between sequestered tissue proteins (for example, in the cornea) and circulating proteins (for example, on IgG2a immunoglobulin) may be important for maintenance of cell tolerance and prevention of autoimmunity.

These results, taken together, emphasize the critical importance of developing new therapies, above and beyond steroid therapy, which can safely modify an overly exuberant inflammatory response in the cornea, can suppress an autoimmune inflammatory response which has developed in the face HSV exposure, while at the same time not inhibiting the immune system's capacity to "clear" the infectious component. (HSV infection). Preliminary results from our laboratory suggest that the active ingredient from a Chinese herbal remedy may well possess this capacity.