Commentary: Targeting herpetic keratitis by immunomodulation of IL-27 signaling

Herpetic stromal keratitis (HSK) is a chronic inflammatory disease triggered by infection of the cornea with HSV-1.[1] Evidence from mouse models of HSK suggest that the inflammation is mediated preferentially by CD4+ T cells in part through the production of Th1 cytokines (IFN-γ and IL-2).[2] A prominent component of counter-inflammation is the activity of regulatory T cells (Treg), especially those that can be identified because they express the Foxp3 transcription factor, which controls their regulatory activity. When the Treg response is absent or impaired, stromal keratitis lesions are more prolonged and consequential. Unfortunately, the function of Treg can be unstable in an inflammatory environment, with the cells themselves losing their regulatory function and even taking on a pro-inflammatory role and then contributing to tissue damage.[3] Because HSK is an immunopathological process, knowledge of the underlying immunological mechanisms is a prerequisite for the design of immunology-based therapeutic intervention.

In this issue of the *Indian Journal of Ophthalmology*, Xia *et al*. investigate the role of IL-27 signaling in HSV-1 infection using a mouse model of HSK.[4] IL-27 is a heterodimeric cytokine composed of the subunits p28 and EBI3, which bind to the heterodimeric IL-27Rα/gp130 receptor.[4] Although it was initially linked with the development of Th1 responses, it is now recognized as a potent antagonist of different classes of inflammation through its ability to directly modify $CD4^+$ and $CD8^+$ T cell effector functions, to induce IL-10, and to promote specialized T regulatory cell responses. Xia *et al.* provide evidence that IL-27 acts as a pathogenic pro-inflammatory cytokine and upregulate $CD4^+$ $Foxp3^+$ Tregs production during the $CD4^+$ T-cell mediated immunity against HSV-1, which ultimately resulted in promoting the progression of HSK and poor prognosis. The data also suggested that administration of anti-IL-27 antibody decreases the severity of HSK and inhibits $CD4^+$ T Cells infiltration in infected corneas but did not affect the expression of IL-17, IFN-γ, and IL-10 in the cervical DLNs of HSK mice which confirmed that the amelioration in inflammatory response observed in anti-IL-27-treated mice was not associated with the altered Th1, Th2, Th17 responses. Additionally, anti-IL-27 treatment did not alter the viral burden in the cornea as well which proved that the corneal pathological lesions in HSK mice are not the direct aftermath of viral replication in the cornea. Maertzdorf *et al.* have previously also reported that Th17 cells also infiltrate to the HSV-infected cornea and possibly are involved in HSK pathogenesis.[5]

These data provide important guidance to therapeutic approaches in the HSV-1 cure agenda. Currently, the acute and epithelial forms of SK are usually controlled using anti-viral drugs. However, chronic forms of stromal keraritis, which are inflammatory in nature, require the addition of a topical corticosteroid to the anti-viral treatment regimen. The present results indicate that the ocular surface provides a readily accessible site for DNA immunization and is suitable for both immune induction and modulation of the nature of the immune response that is induced. The maturation of this literature should be accompanied by attempts to translate these findings from experimental models into human diseases and by efforts to define where IL-27 might represent a viable therapeutic target.

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Joveeta Joseph

Jhaveri Microbiology Centre, Brien Holden Eye Research Centre, L. V. Prasad Eye Institute, Hyderabad, Telangana, India

Correspondence to: Dr. Joveeta Joseph, Jhaveri Microbiology Centre, Brien Holden Eye Research Centre, L. V. Prasad Eye Institute, Hyderabad - 500 034, Telangana, India. E-mail: joveeta@lvpei.org

References

1. Hendricks RL. Immunopathogenesis of viral ocular infections. Chem Immunol 1999;73:120-36.
2. Abramson O, Qiu S, Erle DJ. Preferential production of interferon- gamma by CD4+ T cells expressing the homing receptor integrin alpha4/beta7. Immunology 2001;103:155-63.
3. Suvas S, Azkur AK, Kim BS, Kumaraguru U, Rouse BT. CD4+CD25+ regulatory T cells control the severity of viral immunoinflammatory lesions. J Immunol 2004;172:4123-32.
4. Xia L, Tan T, Li Y, Zhong Q, Shi M. Blockade of IL-27 signaling ameliorates herpes stromal keratitis with upregulated $CD4^+$ $Foxp3^+$ regulatory T cells influx in mice. Indian J Ophthalmol 2019;67:1821-8.
5. Maertzdorf J, Osterhaus AD, Verjans GM. IL-17 expression in human herpetic stromal keratitis: Modulatory effects on chemokine production by corneal fibroblasts. J Immunol 2002;169:5897-903.

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