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COMMENTARY

Targeting Autophagy in Dendritic Cells as a Mechanism to Limit Immunopathogenesis in Herpetic Stromal Keratitis

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ABSTRACT **In a recent *mBio* article, Y. Jiang, X. Yin, P. M. Stuart, and D. A. Lieb [mBio 6(6):e01426-15, 2015, doi:10.1128/mBio.01426-15] presented an elegant set of experiments that utilized a transgenic, knockout strain of mice whose dendritic cells (DCs) are incapable of undergoing autophagy, to dissect out the aspects of the chronic inflammatory response following viral infection of corneal epithelial cells. The authors' results provide a potential proof of concept that the DC autophagy pathway may be a valid target for therapeutic drug design in certain inflammatory pathologies.**

It is well-known that herpes simplex virus type 1 (HSV-1) is the primary infectious cause of blindness in the United States. While HSV-1 infects corneal epithelial cells, disease presentation as herpetic stromal keratitis (HSK) is predominantly driven by immune responses to the replicating virus, particularly those responses mediated by CD4$^+$ T cells. These responses include Th1 and Th17 types and are mediated by interleukin-2 (IL-2), gamma interferon, IL-17, and other cytokines. These effects may linger and persist long after the virus is no longer detected. That HSV-1 is capable of undergoing a subsequent latent infection, only to reactivate at the initial site of infection, exacerbates the situation. Repeated chronic leukocytic infiltration ultimately leads to irrevocable tissue damage.

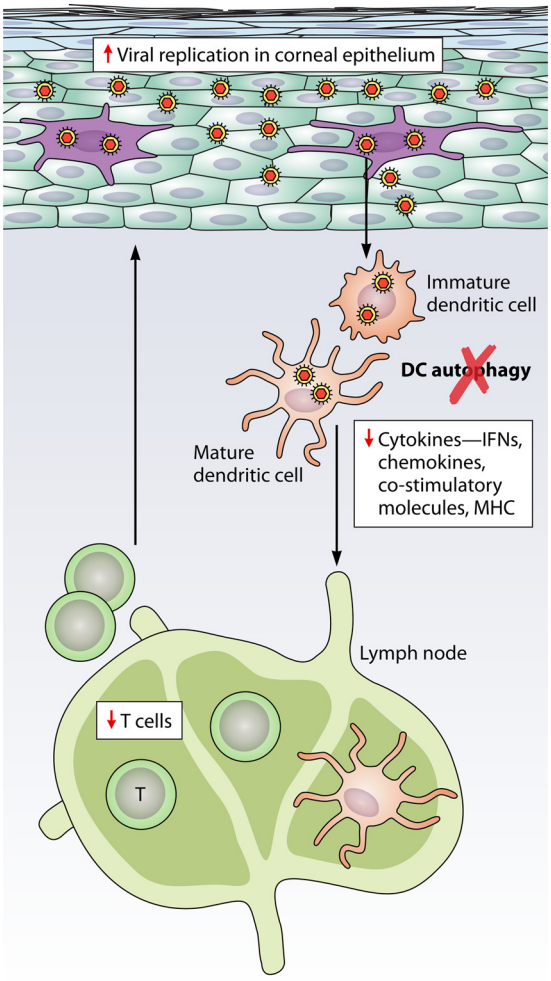

FIG 1 DCs residing in epithelia are activated in response to HSV-1 infection. Activation involves production of inflammatory cytokines and ultimately leads to an increase in B and T cells. Jiang et al. showed that HSV-1-infected animals with autophagy-deficient DCs are reduced for CD4$^+$ T cell activation and cytokine production. While HSV-1 replicates slightly better in the corneal epithelia of these animals, there is less overall disease. These effects are noted with red arrows. Adapted using data from references 2 and 3.

While recognition of this immunological component of the corneal pathogenesis might infer an anti-inflammatory intervention, the virulent nature of this infectious agent demands caution. Accordingly, the recommended treatment for HSK involves frequent initial topical corticosteroid doses in combination with a modified nucleoside antiviral agent. The rationale behind this treatment is that the corticosteroid suppresses inflammation and the antiviral slows down the viral replication so that the patient's immune cells can clear the infection. The paradox here is that systemic immunosuppression is not an option in this situation, due to the potential for a life-threatening viral infection. It is this exact conundrum that Jiang, Yin, Stuart, and Lieb investigated in their recent *mBio* article (1).

Jiang and colleagues reasoned that an alternative approach might be to limit signaling upstream of the CD4$^+$ T cell response. Thus, they focused on dendritic cells (DCs). DCs are professional antigen-presenting cells required for optimal innate and adaptive immune responses (Fig. 1). The team utilized an existing mouse strain with DCs knocked out for the *Atg5* locus, whose product plays a major role in membrane formation of the autophagosome. In control studies, the authors demonstrated that the absence of DC autophagy had limited effects on innate immunity, consistent with previous studies. Importantly, CD4$^+$ T cell activation was indeed reduced in the DC autophagy-null animals. Additionally,

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viral replication slightly increased when DC autophagy was absent.

The key finding of this body of work is that following productive primary viral replication, corneal disease was significantly decreased when DC autophagy was absent. That finding implies a role for DC autophagy in HSK pathology. The authors therefore appear to have succeeded in threading the needle between dampening the $CD4^+$ T cell response to limit corneal disease without losing control of the viral infection. These results clearly dictate a need to more fully understand the mechanism through which DC autophagy regulates DC biology. It is conceivable that drug targets exist within the DC autophagy regulatory pathway that could be exploited to modulate the DC response. An intriguing implication of such finidngs is that future attempts at viral vaccine development might also utilize DC autophagy modulation as a mechanism to manipulate the immune response.

Jiang, Yin, Stuart, and Lieb have provided us with some interesting observations to consider. Additional biochemical and molecular genetic analyses will be required to define the specific details of the mechanism through which DC autophagy is regulated, so that these findings can potentially be leveraged in an attempt to reduce HSK disease. The future in this interesting research area remains bright indeed.

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