Role of Th17 cells in the immunopathogenesis of dry eye disease

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To the editor: The article "IL-17 disrupts corneal barrier following desiccating stress" by De Paiva *et al.*[1] provides additional evidence that interleukin-17 (IL-17) is associated with disruption of the corneal epithelial barrier function, which is the most sight-threatening complication of dry eye disease (DE), arguably the most common ophthalmologic condition. It reports an increased expression of Th17-cell inducers, including IL-6, transforming growth factor-β, IL-23, and IL-17A on the ocular surface of DE patients, as well as an increased concentration of IL-17 in tears and an increased number of Th17 cells on the ocular surface of experimental animals with DE. In addition, the authors show that IL-17-induced secretion of MMP-3 and -9 by epithelial cells causes a significant increase in corneal epithelial permeability, which is ameliorated by *in-vivo* neutralization of IL-17.

However, the precise etiopathogenesis of DE, particularly the nature of ocular surface autoantigen(s), and the site and mechanism of generation of these self-reactive T cells are still not very clear.[2–4] In a recent article,[5] we have shown not only the involvement of Th17 cells in dry eye pathogenesis but also the mechanism of induction of autoimmunity in the draining lymph nodes (LN) using a mouse model of DE. In addition to the expression of Th17 profile on the ocular surface, we showed increased frequency of Th17 cells in the draining LN, where these cells show specific resistance to regulatory T cell (Treg)-mediated suppression. In agreement with De Pavia *et al.*,[1] the functional relevance of Th17 cells in the pathogenesis of DE was fundamentally confirmed by an observation that the *in-vivo* neutralization of IL-17 results

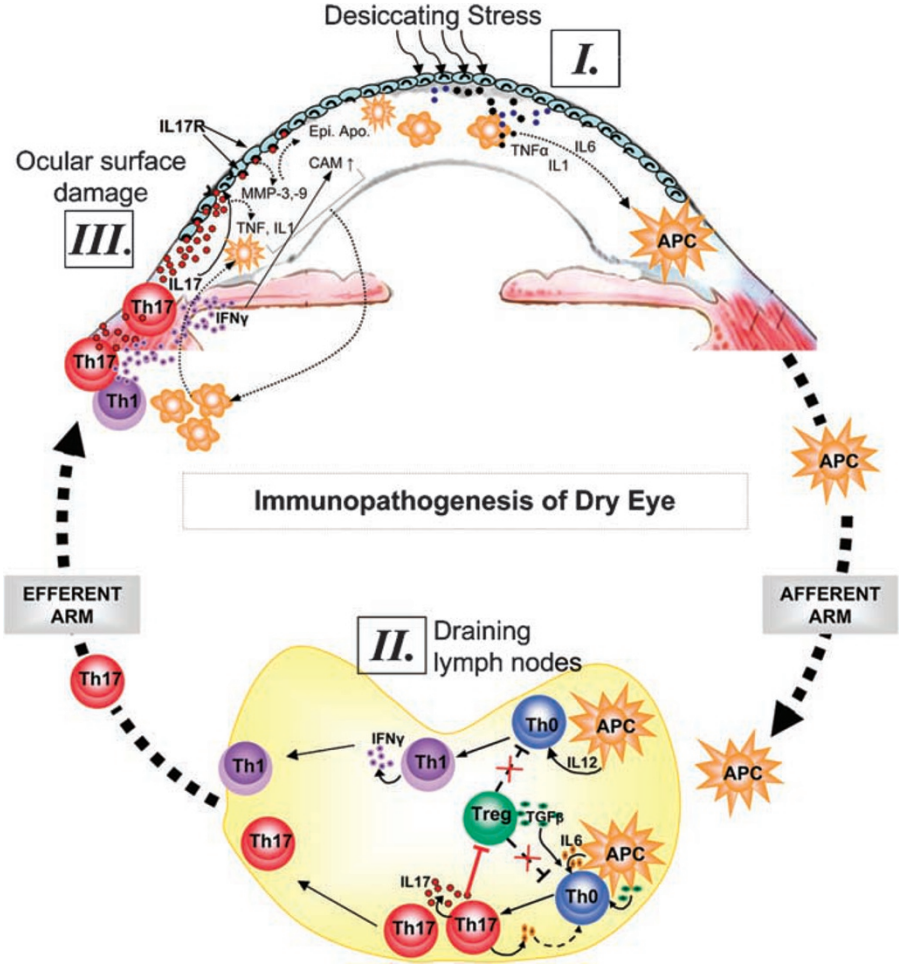

Figure 1 Immunopathogenesis of dry eye disease. Ocular surface inflammation in dry eye disease (DE) is sustained by ongoing activation and infiltration of pathogenic immune cells, primarily $CD4^+$ T cells in the conjunctiva and $CD11b^+$ monocytic cells in the cornea.[1–5] (**I**) Desiccating stress induces secretion of inflammatory cytokines, especially interleukin (IL)-1, tumor necrosis factor-α, and IL-6 by ocular surface tissues, which facilitate the activation and migration of resident antigen presenting cells (APCs) toward the regional draining lymph nodes (LN). (**II**) In the LN, these APCs stimulate cognate naïve T cells (Th0), leading to the expansion of IL-17-secreting Th17 cells and interferon (IFN)-γ-secreting Th1 cells. IL-17 in turn antagonizes the regulatory T cell (Treg) function by facilitating further expansion of Th17 cells, which may compete with Tregs for transforming growth factor (TGF)-β available in the milieu. (**III**) Once these effectors are generated in the LN, they migrate to the ocular surface and secrete effector cytokines. Interaction of IL-17 with its receptors on the ocular surface leads to epithelial damage through increased secretion of matrix metalloproteinases (MMPs) and inflammatory cytokines. In addition to apoptosis and metaplasia of ocular surface epithelia, IFN-γ causes upregulation of chemokine ligands–receptor and adhesion molecules (CAM), which facilitate the increased ingress of immune cells to the ocular surface tissues.

in a markedly attenuated induction and severity of disease. Interestingly, DE amelioration was paralleled by a reduction in the expansion of Th17 cells and by the prevention of the loss of Treg function in the draining LN, suggesting that the Th17 cell-secreted IL-17 antagonizes the Treg function, which in turn unleashes Th17 and Th1 cells to expand further, migrate to ocular surface, and cause epithelial damage. Together, these studies suggest that Th17 cells are the dominant pathogenic effectors in DE. On the basis of the current data[1,5] and data published earlier[2–4], an overarching hypothesis about the mechanism(s) involved in the pathogenesis of DE is illustrated in **Figure 1**. DE affects the visual performance and the quality of life of >10 million people in the United States alone. The current finding that IL-17 blockade leads to diminished disease severity suggests potential new approaches for the treatment of DE.

ACKNOWLEDGMENTS

This work was supported in part by National Institutes of Health grant NEI R01-12963.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. De Paiva, C.S. *et al.* IL-17 disrupts corneal barrier following desiccating stress. *Mucosal Immunol.* **2,** 243–253 (2009).
2. Pflugfelder, S.C., de Paiva, C.S., Li, D.Q. & Stern, M.E. Epithelial-immune cell interaction in dry eye. *Cornea* **27** (Suppl 1), S9–S11 (2008).
3. Research in dry eye: report of the Research Subcommittee of the International Dry Eye WorkShop. *Ocul. Surf.* **5,** 179–193 (2007).
4. Barabino, S. & Dana, M.R. Dry eye syndromes. *Chem. Immunol. Allergy* **92,** 176–184 (2007).
5. Chauhan, S.K. *et al.* Autoimmunity in dry eye is due to resistance of Th17 to Treg suppression. *J. Immunol.* **182,** 1247–1252 (2009).

doi:10.1038/mi.2009.21