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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

All Hands on Deck: Commensals, Th17 Cells, and Neutrophils Provide Short-term Compensation of Constitutive Permeability Defects Against Acute Infection

Although ample evidence has been generated that increased intestinal permeability contributes to many inflammatory and disease phenotypes, both in the intestines and in extra-intestinal sites such as the liver, it also has been shown in several model systems that a barrier defect alone generally is insufficient to induce chronic inflammatory conditions such as ulcerative colitis and Crohn's disease. This is reflected in clinical data showing that a subset of healthy first-degree relatives of Crohn's disease patients show increased intestinal permeability but do not go on to develop full-blown disease, even though increased permeability can serve as a predictor of disease relapse.[1,2] This conundrum has perplexed investigators for many years as to how some people with a compromised intestinal barrier evade being condemned to a fate of chronic inflammatory disease that many others endure. Clues to this puzzle have been gleaned from several studies using genetically manipulated rodent models that identified that a permeability defect precedes intestinal inflammation but required a second-hit to manifest disease. The consistency of these observations indicated that a safety mechanism existed to prevent random breaches of epithelial junctional integrity from precipitating chronic autoimmune disease. The assortment of genes studied that give rise to a permeability defect range from specific tight junction proteins junctional adhesion molecule A to anti-inflammatory cytokines (interleukin 10) to a number of inflammatory bowel disease candidate genes[3,4] (reviewed previously[5]). Although the capacity of the epithelium itself to rapidly repair discreet disruptions, such as occurs during cell shedding, are well documented, the consequences of targeted disruption of tight junction permeability in the absence of epithelial cell loss have been somewhat unpredictable, with several models yielding conflicting results. Adding to the complexity of this system is the well-recognized dual role of innate and adaptive immune cells in both aiding and compromising epithelial barrier function in a context-dependent manner. Moreover, our increasing understanding of the intricate and essential interactions of the host mucosa with the intestinal microbiome for overall intestinal homeostasis also underlines how dynamic and interdependent this relationship is.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Edelblum et al[6] have identified a novel mechanism that may explain some of the key questions in this field. The investigators used a constitutively active myosin light-chain kinase (CA-MLCK) transgenic mouse that shows increased macromolecule permeability without evidence of epithelial damage or hyperproliferation. This group previously showed that this mouse shows subclinical inflammation and is more susceptible to experimental colitis ($CD4^+CD45^+$Rb(hi) T-cell transfer) than control mice.[7] Here, the investigators made the surprising finding that the presence of an underlying barrier defect did not lead to an immediate increase in susceptibility to infection with protozoan or bacterial pathogens, as predicted previously. On the contrary, CA-MLCK mice showed an immune response—mediated by T-helper 17 $CD4^+$ T cells and subsequent recruitment of neutrophils—that reduced acute *Toxoplasma gondii* and *Salmonella typhimurium* translocation across the epithelial barrier.

The protective response in CA-MLCK mice was the result of enhanced mucosal immune activation that required $CD4^+$ T cells and interleukin 17A, with no apparent requirement for increased overall or microbe-specific IgA production. This indicates a key mechanistic difference between the mode of immune compensation in this model and a previous study showing that mice lacking expression of the tight junction protein junctional adhesion molecule A also showed a compensatory adaptive $CD4^+$ T-cell immune response to an underlying permeability defect. This response, which protected against injury-induced colitis, required IgA secretion driven by increased transforming growth factor-β production.[3] The protective response in CA-MLCK mice was lost in germ-free conditions but was restored by introduction of a fecal microbe community rich in segmented filamentous bacteria. Therefore, commensal microbes were able to promote a mild Th17 response that limits early pathogen translocation. A key finding of the study was that this protective immune response was effective only against acute, but not chronic, infection because chronic *S typhimurium* infection resulted in a more severe outcome in CA-MLCK mice, suggesting that despite activation of protective mucosal immunity, barrier defects ultimately resulted in enhanced disease progression after a more sustained challenge. The study further underlined the differing and context-dependent responses of T cells to pathogen infection in conditions of an intact vs a compromised epithelial barrier. These data provide new insight into the mechanisms by which mucosal immunity adapts to epithelial tight junction defects, and how this compensation eventually fails in the context of chronic inflammatory disease. As concluded by the investigators, these mechanisms may explain both the absence of disease in relatives of Crohn's disease patients, despite barrier loss, as well as the increased disease susceptibility induced by barrier dysfunction and the potential link between enteric

infection and the subsequent development of inflammatory bowel disease.

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Conflicts of interest
The author discloses no conflicts.

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2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2017.06.004