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**“ $\gamma\delta$  intraepithelial lymphocyte migratory behavior  
modulates intestinal barrier integrity in response to infection  
and inflammation”**

by  
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## ABSTRACT

The intestinal epithelium is the first line of defense against the trillions of bacteria located within the intestinal lumen. Pathogenic bacteria which invade the epithelium must be quickly eliminated to prevent infection. Failure to rapidly clear invasive bacteria may also lead to the activation of an excessive adaptive immune response, as seen in inflammatory bowel disease (IBD), a relapsing-remitting disease characterized by a vicious cycle of barrier loss, microbial invasion, and chronic inflammation. Intraepithelial lymphocytes expressing the  $\gamma\delta$  T cell receptor ( $\gamma\delta$  IEL) provide immunosurveillance of the intestinal epithelial compartment by migrating dynamically along the basement membrane and into the lateral intercellular space (LIS) between adjacent epithelial cells. This migration-mediated immunosurveillance is a central component of antibacterial defense. Though  $\gamma\delta$  IELs are critical for the maintenance of an intact epithelial barrier, many of the mechanisms surrounding  $\gamma\delta$  IEL regulation of mucosal homeostasis remain unclear. To address this gap in knowledge, we have identified a novel role for IL-15 in promoting  $\gamma\delta$  IEL chemokinesis at steady state. Intravital microscopy of mice following *in vivo* antibody blockade of the IL-15 receptor IL-2R $\beta$  showed reduced  $\gamma\delta$  IEL motility and stalling of these cells within the LIS. As a result, mice treated with anti-IL-2R $\beta$  were significantly more susceptible to acute transepithelial *Salmonella* Typhimurium invasion as compared to control mice, demonstrating that IL-15 regulation of  $\gamma\delta$  IEL migratory behavior is critical for  $\gamma\delta$  IEL-mediated immunosurveillance and epithelial barrier maintenance.

Furthermore, we have defined a previously unknown role for  $\gamma\delta$  IELs in facilitating pathological cell shedding, a process by which epithelial cells undergo apoptosis and are extruded into the lumen in response to pro-inflammatory cytokines. We have found that  $\gamma\delta$  IELs often make prolonged contact with shedding epithelial cells prior to their extrusion, and that blockade of CD103 ( $\alpha^E\beta^7$  integrin), which mediates retention of  $\gamma\delta$  IELs within the LIS through binding of E-cadherin, abrogates LPS-induced cell shedding. Moreover, we have shown that granzymes A and B, which are abundantly expressed by  $\gamma\delta$  IELs, are required for LPS-induced cell shedding via a perforin-independent mechanism, indicating that extracellular granzyme activity may facilitate  $\gamma\delta$  IEL-mediated cell shedding.

Overall, we have elucidated several mechanisms through which  $\gamma\delta$  IELs influence epithelial barrier integrity. Ultimately, these findings may enable the development of novel therapies that promote  $\gamma\delta$  IEL immunosurveillance to maintain mucosal homeostasis and prevent disease relapse in IBD patients.