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"Spatiotemporal changes in γδ IEL surveillance of the ileal epithelium precede Crohn's disease-like ileitis."

By

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B.S. 2017, University of Michigan

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Friday, October 18th, 2024
10:00 A.M.
Cancer Center, G1196

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ABSTRACT

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract, commonly affecting the ileum. Analysis of ileal tissue from patients with CD revealed a loss of intraepithelial lymphocytes expressing the γδ T cell receptor (γδ IELs) during active and quiescent disease. At homeostasis, γδ IELs continuously survey the intestinal epithelium to protect against inflammation and infection; however, the role of γδ IELs in ileitis pathogenesis remains unclear. Profiling the ileal IEL compartment of $TNF^{\Delta ARE/+}$ mice revealed a reduction in frequency and absolute number of γδ IELs preceding onset of CD-like ileitis. Remaining γδ IELs also displayed significantly impaired motility prior to active disease, indicating that γδ IEL-mediated epithelial surveillance is diminished. Furthermore, investigation of γδ T cell localization along the crypt-villus axis revealed fewer γδ T cells in the mid-villus region in pre-ileitis $TNF^{\Delta ARE/+}$ mice compared to WT. This reduction corresponded with a decrease in villous $V\gamma7^+$ IELs and reduced epithelial expression of *Btnl1/6*, which are critical for the maturation and expansion of this γδ IEL subset. Interestingly, while villous $V\gamma1^+$ IEL number declines during active ileitis, the number of crypt $V\gamma1^+$ IELs remains constant throughout the development of disease. These $V\gamma1^+$ IELs are found near Paneth cells (PC), secretory epithelial cells that regulate the luminal microbiota through the production of antimicrobial peptides. Although PC number and antimicrobial function are markedly reduced during active inflammation, PC granule disorganization was observed prior to disease onset. Thus, crypt $V\gamma1^+$ IELs may influence PC pathology in the context of ileitis. In $TNF^{\Delta ARE/+}$ mice that develop accelerated disease in response to an altered microbiota, the onset of inflammation correlates with an earlier reduction of γδ IELs and *Btnl1* expression. These findings suggest that decreased γδ IEL number and surveillance, coupled with altered distribution along the crypt-villus axis, leads to the development of CD-like ileitis. Understanding mechanisms by which γδ IELs are involved in the onset and progression of CD may inform novel therapeutic strategies to restore γδ IEL epithelial surveillance and prevent disease relapse in patients.