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"An altered microbiota enhances CD39 expression on γδ intraepithelial lymphocytes through TCR-dependent IL-2Rβ signaling."

By

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Tuesday, March 18th, 2025
Cancer Center, G1196
1:00 P.M.

Join Zoom presentation

https://rutgers.zoom.us/j/92621190936?pwd=0OgiAs2XZCVUNsQdHOyiXh5lFbMhHn.1

Meeting ID: 926 2119 0936
Password: 164194

ABSTRACT

A single layer of epithelial cells separates the gut lumen, home to 4 trillion commensal bacteria and other microbes, from the underlying immune system. Intraepithelial lymphocytes (IEL) expressing the γδ T cell receptor (TCR) provide continuous surveillance of the barrier to limit pathogen invasion. We recently identified a hyperproliferative γδ IEL ($\gamma\delta^{HYP}$) phenotype that is transmissible via the gut microbiota and protects against enteric infection. Despite increased IEL number, $\gamma\delta^{HYP}$ mice display no overt intestinal pathology; therefore, we hypothesized that additional regulatory mechanisms may be in place to prevent aberrant IEL activation. In addition to their enhanced proliferative and migratory capacity, we now report an expansion of a $CD39^{hi}$ population within the $\gamma\delta^{HYP}$ IEL compartment. CD39 is an ectoenzyme that hydrolyzes extracellular ATP into ADP/AMP, which in turn, is broken down by CD73 into the immunoregulatory molecule adenosine. Transcriptomic analyses indicate that $CD39^{neg}$ γδ IELs exhibit a more naïve-like phenotype whereas the activation of TCR and IL-15 signaling promotes enhanced CD39 expression. In support of this, we found that IL-15 receptor complexes are elevated in $\gamma\delta^{HYP}$ small intestine, and that CD122 expression is the highest among $CD39^{hi}$ γδ IELs. TCR activation was observed among less mature $\gamma\delta^{HYP}$ IELs, and is required to drive CD122, and subsequently, CD39 expression in these cells. Notably, constant exposure to the $\gamma\delta^{HYP}$-associated microbiota is necessary to sustain γδ IEL CD122 and CD39 expression leading us to hypothesize that these commensals activate the TCR. In addition to inducing CD39 expression, increased IL-15 signaling promotes IEL survival via Bcl-2 upregulation and enhances the bioenergetic profile of $\gamma\delta^{HYP}$ IELs to support elevated protein production following stimulation. Despite this, $CD39^{hi}$ γδ IELs exhibit reduced pro-inflammatory cytokine production, thus providing one possible explanation for the lack of inflammation in $\gamma\delta^{HYP}$ mice. Overall, our study identifies a novel mechanism by which an altered microbiota amplifies CD39 expression on $\gamma\delta^{HYP}$ IELs, leading to the expansion of γδ IELs with regulatory potential. Further understanding of the mechanisms regulating γδ IEL effector function may ultimately allow fine tuning of mucosal immunity to ensure protection against intestinal injury or infection while limiting aberrant cytotoxicity.