How T cell-derived interleukin-22 promotes antibacterial defense of colonic crypts

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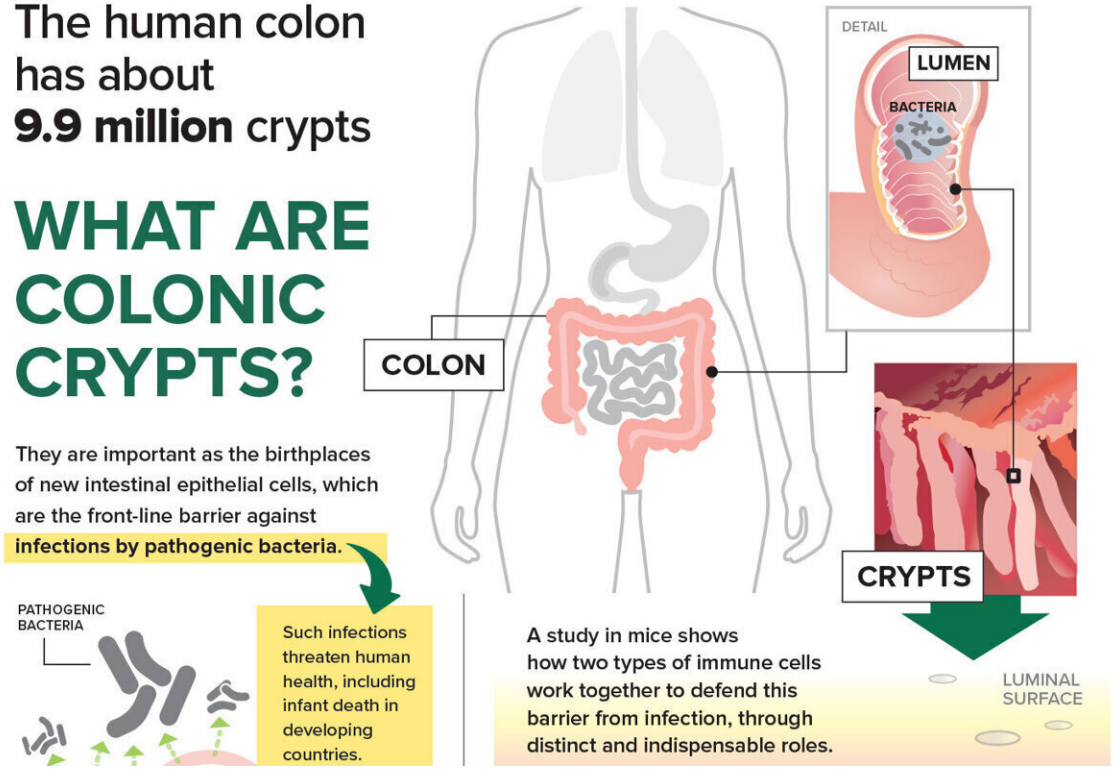

Credit: Jody Potter, University of Alabama at Birmingham

Intestinal epithelial cells line the inner wall of the gut, creating a barrier to dangerous bacteria like enteropathogenic E. coli that seek to attach and efface that barrier, causing diarrhea. Such pathogens pose

significant risks to human health and cause infant death in developing countries.

In a study published in the journal *Immunity*, Carlene L. Zindl, Ph.D., and Casey T. Weaver, M.D., of the University of Alabama at Birmingham Department of Pathology show how two types of immune cells—one a part of the innate immune system and the other a part of the adaptive immune system—play distinct and indispensable roles to defend that barrier.

"In this study, we define a nonredundant role for interleukin-22-producing T cells in antibacterial defense of colonic crypts," Weaver said. "Our findings address a central, unresolved issue regarding the coordination of innate and adaptive immunity and specialization of innate lymphoid cells, or ILCs, and CD4 T cells. Since the discovery of ILC subsets and appreciation of their functional parallel with T cell subsets, it has been unclear what functions are unique to each immune cell population."

The study used mice with bacterial infection of the colon by Citrobacter rodentium, which models human disease caused by enteropathogenic and enterohemorrhagic E. coli. Colons of mice and humans have surface intestinal epithelial cells, or surface IECs, that face the lumen of the colon and line the mouths of colonic crypts. The colonic crypts are the numerous tiny indentations in the colon that are shaped like thick-walled test tubes; at the bottom of each crypt are stem cells that give rise to all new IEC subsets.

Each crypt is only about 75 to 110 cells deep and 23 cells in circumference, and the human colon has about 9,950,000 crypts. Crypt IECs line each crypt.

Interleukin-22, or IL-22, is a cytokine signaling protein produced by

cells to initiate an immune response. The UAB researchers developed mice that have a reporter gene in IL-22, so they could tell which cells produced IL-22. They also were able to target a deficiency of IL-22 to different immune cell populations, to learn the effect of that loss of IL-22 production in a subset of cells upon the progress of C. rodentium infections.

The researchers found that the ILC3 subset of innate immune cells were the dominant IL-22-positive cells at steady state, before any infection. During early infection with C. rodentium, days 3 to 6, ILC3s produced the greatest amount of IL-22. During late infection, days 7 to 14, T cells had increased 50-fold in number and were the dominant IL-22 producers. Furthermore, the two types of cells had distinct microanatomic niches—ILC3s were confined to small, isolated lymphoid follicles, at some distance from crypts, and they did not increase in number during infection. The rapidly growing T cells surrounded the crypts, in closer proximity to IECs compared to ILC3s.

By knocking out IL-22 production in both or either of the immune cell types, researchers could discern their particular roles—both by visualizing infection in living mice using a bioluminescent strain of C. rodentium, and by looking at which IECs were activated by IL-22.

In mice with intact immune systems, some growth of C. rodentium in the colon was seen at days 3 to 7; but the mice survived the infection. In mice without IL-22 production by both ILC3s and T cells, heavy C. rodentium infection was seen at days 3 to 7, and all the mice thereafter succumbed to the infection.

Mice that had no IL-22 production by the ILC3s, but still maintained IL-22 production in T cells, began to succumb to infection as quickly as the total IL-22 knockout mice; but 40 percent survived, presumably rescued by later IL-22 production from the T cells. Mice with loss of

IL-22 production only in the T cells began to succumb to infection at a later time than the other two mouse strains, and they showed 60 percent survival.

"These data establish that innate cell-derived IL-22 acts to limit C. rodentium colonization during the early phase of infection," said Weaver, the Wyatt and Susan Haskell Chair of Medical Excellence in Pathology, "but is unable to compensate for T cell-derived IL-22 in bacterial restraint and host protection later."

Microscopic examination of colon sections showed that mice with intact immune systems had bacterial attachment to surface IECs at days 4 to 9, but no bacterial growth inside the crypts. In mice without IL-22 production by all immune cells or by T cells only, heavy infection was seen inside the crypt lumen, and C. rodentium was attached to crypt IECs by day 9.

When the IL-22 produced by the immune cells binds to IECs, it activates the STAT3 signaling pathway in the target cells, which in turn activates or represses specific genes in the target cells.

Microscopic examination of colon sections stained for STAT3 activation showed that, despite their critical role in restraining bacterial colonization over the early course of enteropathogenic bacterial infection, ILC3s only induced weak STAT3 signaling, and that signaling was limited to the surface IECs. In contrast, T cells contributed to colon barrier defense by delivering IL-22 to both crypt IECs and surface IECs as an infection progressed, inducing robust, sustained STAT3 signaling in both IEC populations. "Our data determine that 'specialized' T cell immunity is required for protection of the colonic crypts during C. rodentium infection," Zindl said. "This may reflect the ability of T cells, unlike ILC3s, to migrate to the crypt epithelium and engage in direct contact with IECs via peptide-MHC and/or surface adhesion molecule

interactions."

Zindl is a UAB Scientist I and the lead researcher in the study.

The resulting gene expression changes in the IECs included heightened expression of messenger RNAs for antimicrobial peptides, neutrophil-recruiting chemokines and enzymes that altered the protective mucins produced by colon goblet cells and enterocytes. All of these help fight a bacterial infection. In contrast, interferon gamma-induced proinflammatory genes were repressed. "These data reveal a dual role of T cell-derived IL-22," Zindl said, "in both promoting antibacterial defense of the crypts and limiting tissue damage caused by uncontrolled IEC and immune cell activation."

"Our findings demonstrate spatiotemporal differences in the production and action of IL-22 by ILCs and T cells during infection," Weaver said, "and they reveal an indispensable role for IL-22-producing T cells in the protection of the intestinal crypts."

More information: Carlene L. Zindl et al, A nonredundant role for T cell-derived interleukin 22 in antibacterial defense of colonic crypts, *Immunity* (2022). DOI: 10.1016/j.immuni.2022.02.003

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