A T-cell stimulatory protein and interleukin-10 synergize to prevent gut inflammation

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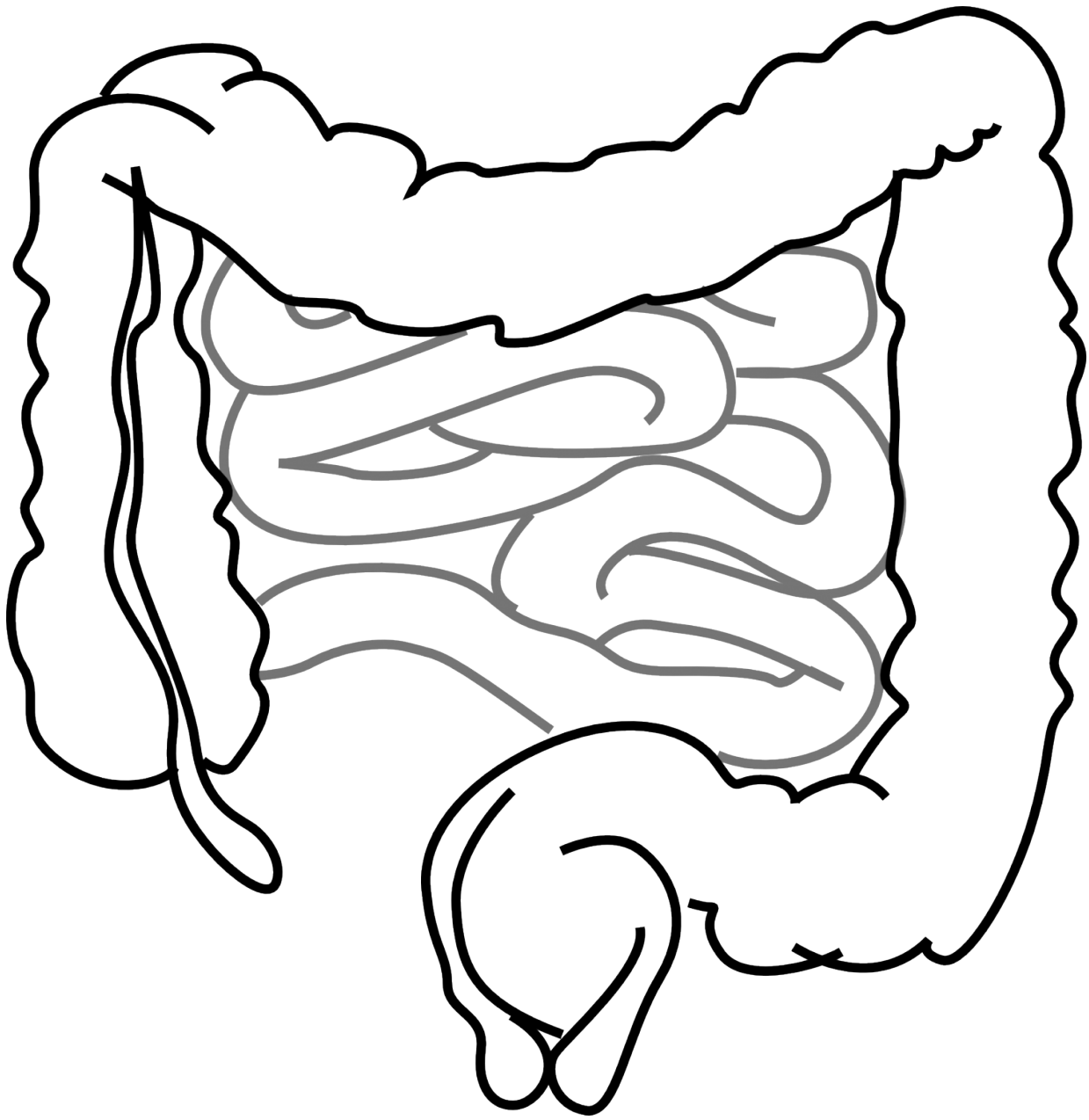

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Researchers have found an unexpected synergy between a T-cell stimulatory protein—the ICOS ligand—and interleukin-10, an immunoregulatory cytokine, to prevent inflammatory bowel disease in

mice. The study will aid the understanding of, and future research into, this immune disorder, which includes Crohn's disease and ulcerative colitis. About 1.6 million Americans have inflammatory bowel disease.

Interleukin-10, or IL-10, was already known as a major player to prevent gut inflammation by establishing and maintaining immune homeostasis in the gut, where it is vital for the host to have a peaceful coexistence with normal intestinal microbes, while the immune system still stands guard against pathogens. IL-10 is produced by CD4+ T-regulatory cells in the gut.

ICOS ligand, or ICOSL, is expressed on B cells and dendritic cells of the immune system, and it helps to control T-cell activation and differentiation, two steps of the host immune response to microbes and microbial pathogens. Both IL-10 and ICOSL were known risk alleles for inflammatory bowel disease, but their synergistic interaction was not known.

The research, published in the *Proceedings of the National Academy of Sciences,* was led by Craig Maynard, Ph.D., assistant professor in the University of Alabama at Birmingham Department of Pathology.

"Collectively, our data identify a synergy between two inflammatory bowel disease-related pathways—T-cell-derived IL-10 and ICOSL-dependent anti-commensal antibodies—that promotes mutualism with the gut microbiota," Maynard said. "Furthermore, we identify ICOSL deficiency as an effective platform for exploring the functions of anti-commensal antibodies in host-microbiota mutualism."

In humans, complete deficiency of ICOSL or the ICOS receptor that ICOSL bind to causes a combined immunodeficiency with repeated bacterial and viral infections. In contrast, mice with ICOSL or ICOS receptor deficiencies maintain a healthy gut homeostasis under specific

pathogen-free conditions.

In the current study, the UAB researchers found that ICOSL-deficient mice—like the ICOS receptor-deficient mice Maynard's group has previously studied—harbored increased frequencies and numbers of IL-10-producing CD4+ T cells, particularly in the proximal colon.

When researchers transiently depleted the IL-10-producing cells in the ICOSL-deficient mice, they saw a striking change—rapid onset of severe inflammation in the proximal colon.

While the number of IL-10-producing CD4+ T cells was increased in the ICOSL-deficient mice, the numbers of colon-associated T-follicular helper cells and the plasma cells that produce immunoglobulin A and immunoglobulin G, or IgA and IgG respectively, were decreased.

The mice also had dramatic reductions in antibodies against normal gut microbes, which included a limited recognition of antigens implicated in the progression of inflammatory bowel disease. These included flagellin antigens derived from several members of the family Lachnospiraceae. These bacteria are known to enrich in the mucus-associated communities of the gut, and Crohn's disease patients have antibodies against two of the Lachnospiraceae flagellin antigens. The mice also had reduced IgA and IgG antibodies that targeted antigens from multiple species of anaerobic bacteria known to be associated with active inflammatory bowel disease.

Simultaneous ablation of both pathways, ICOSL and IL-10, in newborn mice caused severe colitis with evidence of disease as early as four weeks, if the mice were fostered with ICOSL-deficient dams. However, this early onset intestinal inflammation was delayed when the newborn mice were fostered by ICOSL-sufficient dams, showing a protective role for maternal antibodies.

Maynard says the overall results suggest that induction of ICOSL-dependent antibodies and T-cell-derived IL-10 may be simultaneous host adaptations to microbial occupation of a niche near the epithelium in the gut. "Future exploration of the specific microbes that drive these responses," he said, "could potentially identify novel antigen-specific approaches to bolster mucosal immune defenses."

More information: Ashley E. Landuyt et al, ICOS ligand and IL-10 synergize to promote host–microbiota mutualism, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2018278118

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