New study reveals how T cells gain and maintain tolerance to gut bacteria

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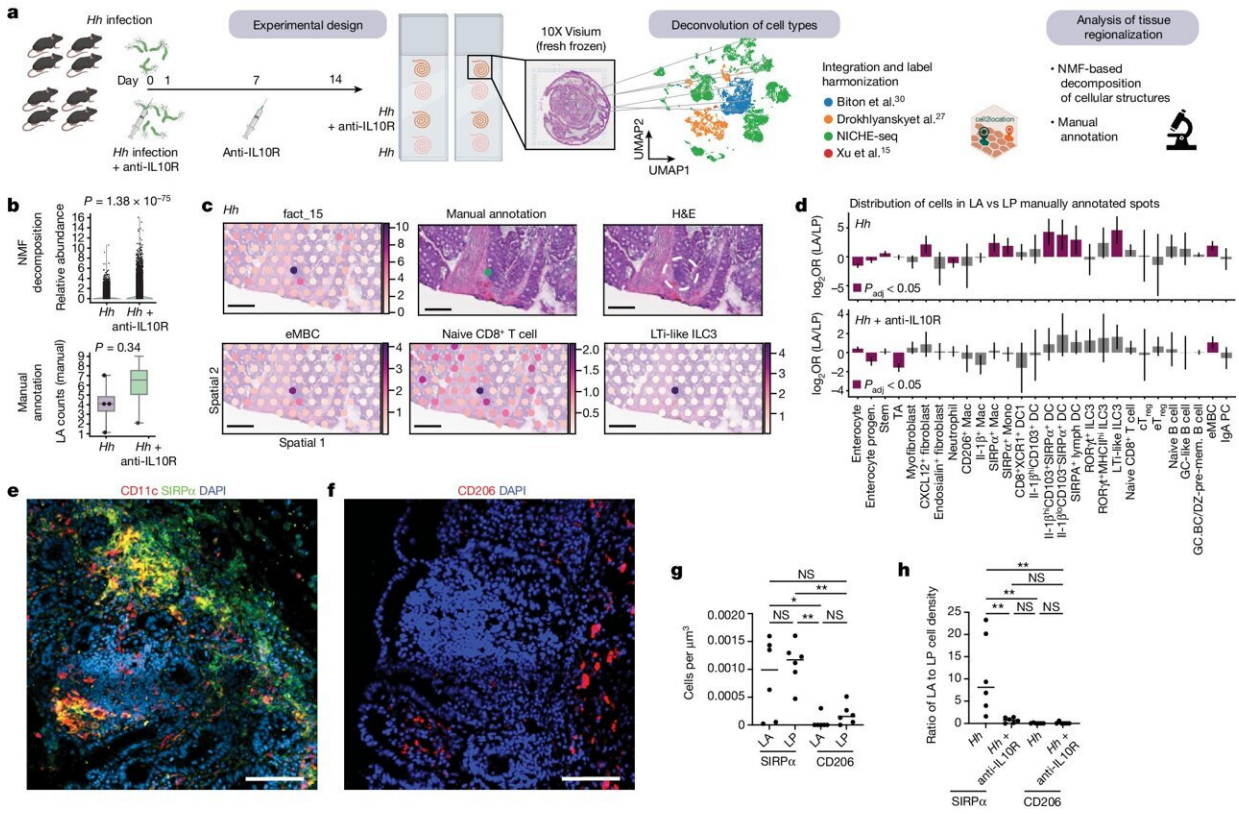

Enrichment of the LA cell signature by spatial transcriptomics analysis is diminished in inflammation. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07251-0

The immune system in the intestine maintains a careful balance, tolerating our long-term resident (commensal) gut bacteria while

defending against invading pathogens. Under certain circumstances, dysregulation of our intestinal immune response to commensal and pathogenic microbes can drive inflammatory disease.

Regulatory T (T_{reg}) cells are a subpopulation of white blood cells which control how the immune system responds differently to pathogens and to commensal bacteria. They play a role in preventing autoimmune disease but are disrupted in inflammatory diseases of the gut like ulcerative colitis.

Not much is known about the compartmentalization of cells in the gut that supports T_{reg} cells to maintain tolerance to commensal bacteria or why they lose it. If it was better understood, we might be able to develop therapies to re-establish this tolerance for patients with intestinal inflammation.

A new study published in *Nature* explored the immune landscape that affects T_{reg} function. To do this, researchers from the Kennedy Institute looked at how T_{reg} cells in the intestine acquire and maintain tolerance to Helicobacter hepaticus, a pathobiont bacteria that establishes lifelong infection in the gut.

By tracking the cells over time and space using live-cell imaging, RNA sequencing and spatial transcriptomics, the researchers were able to carefully unpick how T_{reg} cells interact with other cells to establish tolerance to H hepaticus.

While T_{reg} cells can become stimulated by H hepaticus anywhere in the intestine, the researchers found that the lamina propria, a thin layer of tissue which lines the intestine, was the main area where T_{reg} cells promote tolerance to this pathobiont. This finding challenges the existing paradigm that this activation occurred mainly in small lymphoid aggregates in the caecum and the colon.

Production of the cytokine IL-10 by T_{reg} cells was necessary for long-term tolerance to the bacteria. T_{reg} cells stably maintained this tolerance after acquiring it, but the tolerance could be broken down when the intestine became inflamed. During this inflammation, a subset of dendritic cells expressing CD103 and SIRPα became dominant and interacted with T_{reg} cells, seemingly disrupting the homeostasis within the tissue.

The researchers also identified distinct interactions between macrophages and T_{reg} cells in the intestine which seem to govern tolerance to H hepaticus. Specifically, they identified pairs of ligands and receptors on the T_{reg} cells and macrophages which likely govern this interaction.

In combination, the study reveals new insights into where (the lamina propria) and how (compartmentalization of dendritic cells, specific interactions with macrophages) tolerance to novel intestinal microbes may be gained and maintained.

The findings from the study could be used to design better therapies for patients with inflammatory diseases of the gut and beyond. They could also support the development of novel therapies that target T cells (T-cell therapies) and could inform on strategies for oral vaccinations which need to work in the intestinal niche.

Dr. Emily Thornton, co-corresponding author of the study said, "This work focuses on the intestine, but effector T_{reg} cells are key to maintaining tolerance across the body and promoting tissue repair. While the interactions we have shed light on here are important for tolerance in the intestine, the goal is to harness these pathways to restore tolerance in inflammatory diseases more broadly."

Dr. Yisu Gu, first author of the study said, "This work ... also provides

an atlas of intestinal micro-niches in homeostatic and inflammatory settings, allowing other groups to use this publicly available resource to answer their scientific questions without the need for further experimentation.

"I'm really excited on the potential of these findings to inform on an ongoing clinical interest of mine—graft versus host disease—and how we can design better cellular therapies to improve patient outcomes."

More information: Yisu Gu et al, Immune microniches shape intestinal T_{reg} function, *Nature* (2024). DOI: 10.1038/s41586-024-07251-0

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