Putting the brakes on chronic inflammation: Study discovers link between two key pathways

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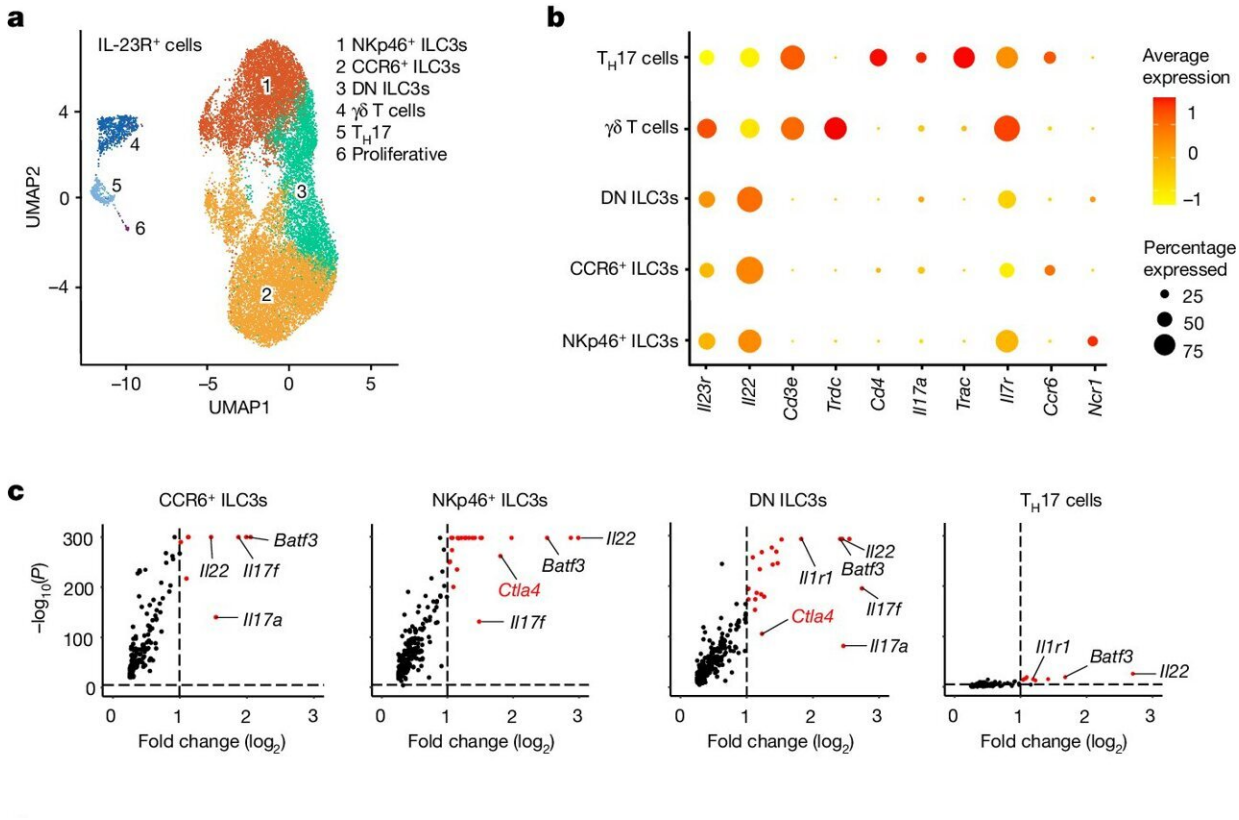

A single-cell atlas of IL-23 responses in the small intestine identifies CTLA-4$^+$ ILC3s. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07537-3

Scientists at Weill Cornell Medicine have discovered a previously

unknown link between two key pathways that regulate the immune system in mammals—a finding that impacts our understanding of chronic inflammatory bowel diseases (IBD). This family of disorders severely impacts the health and quality of life of more than 2 million people in the United States.

The immune system has many pathways to protect the body from infection, but sometimes an overactive immune response results in autoimmune diseases including IBD, psoriasis, rheumatoid arthritis and multiple sclerosis. Interleukin-23 (IL-23) is one such immune factor that fights infections but is also implicated in many of these inflammatory diseases. However, it was unknown why IL-23 is sometimes beneficial, and other times becomes a driver of chronic disease.

In the study, published June 12 in *Nature*, the team found that IL-23 acts on group 3 innate lymphoid cells (ILC3s), a family of immune cells that are a first line of defense in mucosal tissues such as the intestines and lungs. In response, ILC3s increase activity of CTLA-4, a key regulatory factor that prevents the immune system from attacking the body and beneficial gut microbiota. This interaction critically balances the pro-inflammatory effects of IL-23 to maintain gut health, but is impaired in IBD.

The findings identify ILC3s as a critical link between potent IL-23 driven inflammatory response and checkpoints for immune regulation in the intestine. It also provides clues on how to harness this pathway to fight cancer and alleviate a serious side effect of cancer immunotherapy.

"We were surprised to uncover the unexpected connection between these two major immune pathways that control health, immunity and inflammation," said senior author Dr. Gregory Sonnenberg, the Henry R. Erle, M.D.-Roberts Family Professor of Medicine, head of basic research in the Division of Gastroenterology & Hepatology and a

member of the Jill Roberts Institute for Research in Inflammatory Bowel Disease at Weill Cornell Medicine.

"Until now, most research on CTLA-4 focused on T cells, another type of immune cell. By uncovering that it is selectively upregulated on ILC3s by IL-23, this demonstrates that we should be thinking about these pathways more broadly to develop more selective therapeutics."

When inflammation is out of control

"IL-23 normally provides tissue protection in the gut, but something changes in chronic inflammatory diseases which makes IL-23 a key driver of tissue pathology, and that's what we decided to investigate," said the paper's lead author, postdoctoral researcher Dr. Anees Ahmed.

The investigators used single-cell RNA sequencing to study the effects of IL-23 on different types of immune cells in the healthy intestine. This analysis revealed that IL-23 in the healthy gut potently turns on the CTLA-4 pathway in ILC3s. They then showed that blocking the CTLA-4 pathway in those cells led to severe intestinal inflammation.

To see if their results applied to humans, the investigators turned to the Jill Roberts Institute Live Cell Bank, which includes deidentified samples from people with IBD as well as healthy individuals.

"This unique resource enabled us to quickly confirm that our findings in mice were relevant to IBD patients," said Dr. Sonnenberg.

They then verified this finding in patients through collaboration with Dr. Robbyn Sockolow, professor of clinical pediatrics and chief of the Division of Pediatric Gastroenterology, Hepatology and Nutrition in the Department of Pediatrics at Weill Cornell Medicine and a pediatric gastroenterologist at New York-Presbyterian Komansky Children's

Hospital and Center for Advanced Digestive Care.

With Dr. Sockolow, they found evidence that this novel immunologic pathway exists in the healthy human intestine and becomes impaired in the inflamed intestine of IBD patients. "This may provide a new explanation of why IL-23 becomes a driver of intestinal inflammation in human IBD," said Dr. Sockolow.

Implications for cancer and associated immunotherapy

This study also suggests that this pathway may be harnessed to fight cancer and may explain why people receiving certain immunotherapy drugs often experience inflammation in the gut as a side effect. Immunotherapy drugs that block CTLA-4 are used to take the brakes off the immune system—allowing it to fight cancer. These new results suggest that CTLA-4 on ILC3 cells and other related innate or innate-like lymphocytes should be considered in fighting cancer. Further, it suggests that blocking CTLA-4 on ILC3s may lead to severe gut inflammation which can cause patients to discontinue their cancer treatment.

Much more research is needed before these findings can be applied to new treatments. Dr. Ahmed said that eventually it may be possible to develop more targeted treatments that avoid ILC3s in the gut or simultaneously block IL-23.

"In the future, we may be able to find ways to selectively block CTLA-4 or IL-23 in specific immune cells," he said. "If we could manage it, that could lead to a breakthrough in fighting cancer while protecting the gut from inflammation."

The findings could also have long-term applications in developing new treatments for a range of autoimmune diseases known to be mediated by IL-23. Drugs that target IL-23 already exist, and potentially we could make next-generation therapies that don't completely block IL-23 since it is still needed to fight infection but instead control the underlying mechanisms of IL-23–driven chronic inflammatory diseases, Dr. Sonnenberg said.

More information: Anees Ahmed et al, CTLA-4-expressing ILC3s restrain interleukin-23-mediated inflammation, *Nature* (2024). DOI: 10.1038/s41586-024-07537-3

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