Gut Microbes' Fatty Acid Gifts Enable Specialized Immune Defenders

By YAN Fusheng (Staff Reporter)

Our trillions of gut microbes aren't just along for the ride – they actively shape our health in unseen ways. Now, a research team, jointly led by Dr. SONG Xinyang from the Shanghai Institute of Biochemistry and Cell Biology (SIBCB) of the Chinese Academy of Sciences and Dr. Dennis L. Kasper from the Harvard Medical School, illuminates a hidden immune pathway sparked by bacterial fatty acids.

Gut microbes can convert linoleic acid – a common fatty acid that is relatively abundant in vegetable oils, nuts and seeds – to conjugated linoleic acids (CLAs), which boost certain immune cells that reside in the small intestine. (Credit: *Pixabay*)

Published in *Naure* on June 28, 2023, a new study, entitled "*Gut microbial fatty acid isomerization modulates intraepithelial T cells*", uncovers an unappreciated role of microbial metabolites in immunity. The study was conducted by an international team jointly led by Dr. SONG Xinyang from the Shanghai Institute of Biochemistry and Cell Biology (SIBCB) of the Chinese Academy of Sciences and Dr. Dennis L. Kasper from the Harvard Medical School.

"I have long been fascinated by studying the immunomodulatory functions of gut symbiotic microbes, " explains Dr. SONG Xinyang when asked what drives him and his coworkers to explore the link between dietary fats, gut microbes and intestinal immunity. "Under steady-state conditions, changes in food composition are the dominant factor in shaping the microbe-immune interactions, as dietary components have a profound influence on both sides via tuning the metabolite pool size in the intestine."

At first, they discovered that certain dietary fatty acids serve as chemical precursors for gut microbes to metabolize. The resulting products then spur intestinal immunity by promoting the development of a unique population of intraepithelial lymphocytes (IELs) in the gut lining.

Like guards along a castle wall, IELs nestled in the gut lining provide an intimate immune defense. These IELs act as first responders to sound the alarm against pathogens that breach the intestinal barrier.

The IELs can be classified into two groups: the natural IELs that develop independently of the microbiota, and the induced IELs that are more relevant to the gut microbes. Within the group of induced IELs that carries the CD4 receptor on their surface, there is a novel subset that also carries the CD8 receptor. Most IELs express either CD4 or CD8, enabling them to recognize and interact with other cells. Some of these induced IELs carry both $CD4^+$ and $CD8\alpha\alpha^+$, where $CD8\alpha\alpha^+$ indicates the presence of two joined CD8α protein chains. This special subset of IELs tends to preferentially express many genes important for maintaining gut barrier function.

"They are incorporated into the host's first-line defense system in the gut lining. We observed that mice with lower levels of these IELs more readily succumbed to infection, indicating the critical roles played by the IELs in fighting off intestinal pathogens," says Dr. SONG Xinyang, one of the lead scientists of the study.

Notably, the IELs develop from naive $CD4^+$ T cells entering the gut environment. Without the right cues from gut microbes, the $CD4^+CD8\alpha\alpha^+$ IEL population dwindles – leaving gaps in the immune garrison.

Now, researchers have uncovered how bacterial enzymes and dietary fats team up to induce $CD4^+CD8\alpha\alpha^+$ IELs.

The small intestine absorbs fats from our food, alongside an ensemble of gut microbes. These bacteria can chemically tweak fats using enzymes called linoleic acid isomerases (LAIs). In particular, LAIs convert dietary fat linoleic acid into unique isomers called conjugated linoleic acids (CLAs).

The team confirmed that CLA levels inside the gut depend on both the richness of the diet and the right microbes being present. Mice fed with a minimal diet lacking fat diversity had fewer CLAs in their small intestines. So did mice raised germ-free – without any gut microbes. This highlighted the interplay between the diet, gut microbes, and biochemical tinkering that shapes our intestinal terrain.

"A Western-style diet, characterized by its highly refined foods with low-fiber ingredients, might dampen our gut ecosystem by reducing the diversity of gut microbes and their metabolic capacity. Losing such microbial cues – *e.g.*, gut CLAs in this study – is likely to stunt mucosal immunity in humans, thus predisposing us to many gastrointestinal diseases," comments Dr. SONG.

The researchers introduced different gut bacterial strains back into the germ-free diet for mice, and found that only CLA-producing LAI^+ microbes could restore high levels of $CD4^+CD8\alpha\alpha^+$ IELs in these model animal. In contrast, stripping LAI genes from these bacteria prevented them from inducing IELs.

Together, these findings revealed that bacterial CLA production is essential for building the ranks of first-line intestinal defenders. But how do these modified fats train immune cells?

Further experiments uncovered an intracellular receptor called HNF4γ, which recognizes CLAs as they enter IELs. The binding with CLA switches on HNF4γ's activity. This triggers the expression of a cytokine receptor, IL-18R1, to receive immune signals from its ligand IL-18.

"Early work in mice has shown that IL-18 signaling protects the host from infection by intestinal pathogens. Herein, we identified that gut microbes can convert common dietary linoleic acid into its isomer forms," adds Dr. SONG Xinyang. "These byproducts then serve as an immune cue to spur the development of the $CD4^+CD8\alpha\alpha^+$ IELs via modulating IL-18 signaling in $CD4^+$ IELs."

The CLA-HNF4γ-IL-18 cascade they revealed implies that a rational tuning of common dietary nutrients, or their microbial byproducts, might boost downstream immune signaling, and thus help with the medications to common foodborne pathogens.

Blocking any part of this CLA-HNF4γ-IL-18 cascade – through diet, microbial mutations, or gene knockouts – would disrupted $CD4^+CD8\alpha\alpha^+$ IEL homeostasis. Mice became more susceptible to intestinal infections like Salmonella without these frontline defenders.

In essence, gut microbes have learned to utilize our own dietary fats and immune wiring for mutual benefit – theirs and ours. By converting fatty acids into CLAs, they stimulate the development of specialized immune cells lining the intestinal border. This microbial ingenuity highlights how deeply intertwined gut microbes are with immune function. Through clever metabolic tricks, they transform dietary nutrients into immune-modulating signals, demonstrating an intimate biochemical dialogue between microbes and immunity. Far from passive bystanders, gut microbes actively nurture our defenses – if we nourish them appropriately in return.

Indeed, the interplay between food, gut microbes, and immunity is intricate.

"Our findings in mice indicate that the microbial fatty acid isomerization process can enhance gut barrier functions by modulating a specific IEL subpopulation. Many of common probiotics – *e.g.*, *Lactobacillus* and *Bifidobacterium* – also harbor the linoleic acid isomerase that is required for CLA production. It is intriguing to speculate that, in humans, a proper combination of a healthy diet and the right probiotics is the potential to benefit gut barrier integrity via the immune cascade we uncovered here," envisions Dr. SONG Xinyang.

Reference

Song, X., Zhang, H., Zhang, Y., Goh, B., Bao, B., Mello, S. S., . . . Kasper, D. L. (2023). Gut microbial fatty acid isomerization modulates intraepithelial T cells. *Nature*. doi:10.1038/s41586-023-06265-4