Mouse study shows how diet altered by gut microbes spurs development of immune cells

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The notion that diet and health are inextricably linked is hardly novel. For millennia, people have known that poor nutrition is responsible for many health problems. But the precise mechanisms that explain just how diet alters the function of our cells, tissues, and organs have remained poorly understood.

Now, a study led by Harvard Medical School researchers sheds light on

this process, pinpointing a critical intermediary between food and health—the gut bacteria that make up our microbiome, or the collection of microorganisms that live in symbiosis with humans.

The work, which was conducted in mice and published June 28 in *Nature*, shows that gut microbes feast on common fatty acids such as linoleic acid and convert them to conjugated linoleic acid (CLA). This byproduct then serves as a signal for a biological cascade that ultimately spurs a specific type of immune system to develop and reside in the small intestine.

In the study, the researchers observed that mice in whom this cascade was interrupted more readily succumbed to a common foodborne pathogen.

The findings, the team said, detail an intricate interplay between gut microbes, food, and immunity. They also underscore the importance of understanding how individual microbial species in the gut could alter specific organ functions and exercise important effects on health.

"The triad of diet-microbes-immune system has attracted considerable attention, with a paucity of detail to demonstrate how these three components work together," said study senior author Dennis Kasper, the William Ellery Channing Professor of Medicine at Brigham and Women's Hospital and professor of immunology in the Blavatnik Institute at Harvard Medical School. "We have found one of the clearest demonstrations here of a mechanism underlying how diet and the microbiome build the immune system."

In the new study, Kasper worked in collaboration with Xinyang Song, a former postdoctoral researcher in the Kasper lab, now a principal investigator at the University of Chinese Academy of Sciences; and colleagues from HMS, Massachusetts General Hospital, Tufts

University, and the UMass Chan Medical School.

The team initially noticed that germ-free mice—a common lab model that is not naturally colonized by microorganisms, and thus has no microbiome—were missing a subset of immune cells known as $CD4^+CD8aa^+$ intraepithelial lymphocytes (IELs), which normally reside in a specific part of the small intestine.

Interestingly, mice that were not germ-free but ate a minimal diet composed of just the essential nutrients to keep them alive were also deficient in these cells. However, $CD4^+CD8aa^+$ IELs were present in non-germ-free mice fed a typical rich commercial diet composed of many different nutrients.

Suspicious that an interplay between diet and the microbiome might be responsible for the presence or absence of $CD4^+CD8aa^+$ IELs, the researchers examined which nutrients were lacking from the minimal diet, eventually homing in on various fatty acids. After feeding individual fatty acids to mice on minimal diets with typical microbiomes, they discovered that animals that ate a long-chain fatty acid known as linoleic acid began growing $CD4^+CD8aa^+$ IELs in their small intestines.

Kasper explained that many bacteria that reside in the gut produce an enzyme called linoleic acid isomerase (LAI) that converts linoleic acid into a conjugated form, with some linoleic acid double- and single-chemical bonds rearranged. Further investigation showed that CLA—the conjugated form of linoleic acid—was abnormally low both in mice with a typical microbiome fed a minimal diet or in germ-free mice fed a rich diet, suggesting that bacteria were necessary to convert linoleic acid into CLA.

When the researchers colonized germ-free mice with bacteria that

produced LAI and fed them a rich diet, these animals developed $CD4^+CD8aa^+$ IELs in their small intestines. Conversely, when the researchers colonized them with bacteria that had been genetically modified to not produce LAI, they did not develop these immune cells, showing that CLA produced by this bacterial enzyme was essential for these immune cells to grow.

Further investigation revealed a more complete mechanism behind why CLA spurred $CD4^+CD8aa^+$ IEL development: The researchers found that some immune cells in the small intestine produced a protein called hepatocyte nuclear factor 4g (HNF4g) on their surfaces, which serves as a receptor for CLA. When CLA attached to these receptors, the cells produced a different protein called interleukin 18R (IL-18R), which in turn lowered the production of a third protein called ThPOK. The less ThPOK produced, the more $CD4^+CD8aa^+$ IELs developed.

This complex pathway has clear implications for immunity to infection, Kasper said. Indeed, when the researchers tampered with any part of the cascade—for example, preventing production of IL-18R or HNF4g—mice in whom the cascade was turned off didn't produce $CD4^+CD8aa^+$ IELs and were unable to fight off infection with Salmonella typhimurium, a bacterial species commonly responsible for cases of food poisoning.

"One of the reasons that more examples of the diet-microbes-immune system triad have not yet come to light is that these pathways are so complicated," Kasper said. "By investigating these intricate pathways, we will have a better understanding of how our microbiomes keep us healthy and how to intervene when they don't."

More information: Xinyang Song et al, Gut microbial fatty acid isomerization modulates intraepithelial T cells, *Nature* (2023). DOI: 10.1038/s41586-023-06265-4

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