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Bugs in the gut trigger production of important immune cells

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A new study reveals that specific types of bacteria in the intestine trigger the generation of pro-inflammatory immune cells, a finding that could eventually lead to novel treatments for inflammatory bowel disease and other diseases. The study by NYU Langone Medical Center researchers is published in the October 16 issue of the journal *Cell Host and Microbe*. The new finding adds to the growing body of research showing that the kinds of bacteria in our intestine, and in our stomach, have an impact on our health.

"There is more and more evidence that gut flora have a tremendously important influence on human health," says Yasmine Belkaid, Ph.D., chief of the mucosal immunology unit in the laboratory of parasitic diseases at the National Institutes of Health "If some set of microbes induces a specific immune response, this points to a way to manipulate the immune system,"
says Dr. Belkaid. "This new study is the first report that has associated a defined set of gut flora with the induction of specific immune cells."

The new research is from the laboratory of Dan Littman, M.D., Ph.D., the Helen L. and Martin S. Kimmel Professor of Molecular Immunology at NYU School of Medicine and a Howard Hughes Medical Institute Investigator. "It's not the amount of microbial flora but the kind of microbial flora that seems to count," says Dr. Littman.

The new study found that cytophaga-flavobacter-bacteroidetes (CFB) bacteria were associated with the creation of Th17 cells in mice.

Typically, in both mice and humans, most of the bacteria found in the gut fall into the CFB phylum or another phylum called Firmicutes. These bacteria play many roles, such as aiding in digestion and protecting against pathogens by outcompeting harmful bacteria.

Inflammatory bowel disease (IBD) affects as many as 700,000 people each year and is one of the most prevalent gastrointestinal diseases in the United States. Treatment with antibiotics has had limited success. But pinpointing the specific species of bacteria that influence the balance of inflammatory cells, says Dr. Littman, could lead to more sophisticated treatments that fine-tune bacteria in the intestine and, in turn, dampen the production of inflammatory cells.

The Yin and Yang of Immunity

A healthy immune system is a balancing act between two opposing yet intimately connected forces, one calming, the other inflammatory. Sometimes called the yin and yang of adaptive immunity, pro-inflammatory cells (the "yang") dominate when the body needs protection, and regulatory cells (the "yin") soothe the immune system when it doesn't.

When this balance is disrupted and there is an overload of fiery yang cells, inflammatory disease results. In recent years, scientists have linked a striking number of autoimmune disorders to excess pro-inflammatory cells, including psoriasis, inflammatory bowel disease, and multiple sclerosis. "The number of inflammatory diseases known to involve T helper 17 (Th17) cells," – the fiery yang cells – "seems to be growing every week," says Dr. Littman.

For this reason, Dr. Littman has been studying the molecular pathways that stimulate the production of these cells. Recently, his team reported on a promising potential therapeutic target that may help ameliorate

diseases associated with overproduction of Th17 cells.

In the new study, Dr. Littman's team observed that newborn mice that remain isolated from bacteria never generate any of these cells. Normally, newborn mice are born without any bacteria or Th17 cells in their intestines. They begin to generate the cells only after they begin to eat food and ingest bacteria. These observations suggested that the introduction of bacteria in the gut is associated with the creation of Th17 cells.

To determine if the bacteria actually cause the generation of Th17 cells, the team gave normal, bacteria-filled mice antibiotics that selectively killed some of the bacteria in their small intestine. Some of these antibiotics also depleted their Th17 cells, indicating for the first time a causal link between specific bacteria and the generation of inflammatory cells.

Littman's team then found a colony of mice that have intestinal bacteria but do not have Th17 cells. This colony, it turned out, had different bacteria in their guts than other colonies. "The same way people from different countries have different bacteria in their guts, mice from different colonies will have different bacteria," explains Dr. Ivaylo Ivanov, an author of the study and a post-doctoral fellow in Dr. Littman's laboratory. In this case, "one colony has the bacterial species associated with Th17 cells and the other doesn't."

By comparing the intestinal bacteria in mice, the team discovered that cytophaga-flavobacter-bacteroidetes (CFB) bacteria were associated with the creation of Th17 cells. Dr. Littman's team is now working to determine the specific bacteria that induce pro-inflammatory immune cells in mice. They will use this information to help determine the bacterial species in the intestines of humans that trigger the overproduction of these cells.

Dr. Littman also is interested in identifying the signals emitted by bacteria that influence the innate immune system, which responds to immediate threats from foreign pathogens and produces substances that spur naive or unspecialized T cells to develop into Th17 cells. Manipulation of the bacteria or their products, says Dr. Littman, could then be used to shift the balance of pro-inflammatory and regulatory immune cells.

Source: NYU Langone Medical Center