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MICROBIOLOGY

Bacterium Proves Essential to Immune System Development

Carbohydrate on Bug's Coat Tips the System Toward Cell-mediated Response

Bacteria: friends or enemies? Historically, medicine has focused on the antagonistic role of pathogenic bacteria, and most of us will use antibiotics at some point in our lives. But as scientists probe further into the multitude of bacterial species in our bodies and our environment, the view of man against microbe is appearing increasingly limited.

The bacteria living in our digestive tract have been shown to help digestion, protect against infection, and aid the development of the intestine after birth. But a new study suggests that one common intestinal bacterium, *Bacteriodes fragilis*, may do even more. In the July 15 *Cell*, a team led by Dennis Kasper and Sarkis Mazmanian at the Channing Laboratory reports that *B. fragilis* contributes to the development of the immune system. "This organism isn't just living in us passively, nor is it causing

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Photo by Graham Ramsay

The bacteria in our bodies are more than just freeloaders. A study led by Dennis Kasper (left) and Sarkis Mazmanian suggests that proper immunity may depend on them.

Immune Development

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any detriment," said Mazmanian, HMS instructor in microbiology and molecular genetics. "It's actually helping us." Furthermore, the team has identified a specific molecule on the bacterium's outer coat that promotes proper immune function in mice. The carbohydrate is the first known "symbiosis factor" responsible for carrying out a beneficial relationship between mammals and bacteria.

Bacterial Bounty

The normal mammalian gut is teeming with bacteria, on the order of a thousand different species and one trillion bacterial cells to every gram of intestinal contents. To examine how specific bacteria affect the immune system, the team studied germ-free mice that are raised in a sterile environment where they are never settled by bacterial swarms. Kasper, the William Ellery Channing professor of medicine at Brigham and Women's Hospital and professor of microbiology and molecular genetics at HMS, and his colleagues found that these mice have a lower proportion of CD4+ T cells in their immune system, suggesting that bacteria somehow play a role in the development of these cells. When the researchers allowed only one species, *B. fragilis*, to colonize the mice, their CD4+ T cell levels were restored to normal levels. "Colonizing those animals with one species, one single organism, we were able to completely restore that defect in the T cell numbers," Mazmanian said.

Furthermore, the team found that one molecule could account for this ability. Last year, another team in Kasper's lab announced the surprising finding that certain kinds of bacterial carbohydrates could be taken up by antigen-presenting cells of the immune system and recognized by T cells, a role that was formerly reserved solely for proteins (see *Focus* June 4, 2004). These carbohydrates have a zwitterionic structure—containing both a positive and negative charge on each repeating unit—that allows them to interact with immune cells the same way a protein antigen would.

B. fragilis has two zwitterionic carbohydrates on its outer coat. Kasper and Mazmanian found that if the mice were colonized with a strain of *B. fragilis* that lacked one of these carbohydrates—polysaccharide A (PSA)—the bacteria could no longer restore T cell levels in the mice. "If you delete that one antigen, you completely lose the ability to restore the defects in the immune system," Mazmanian said.

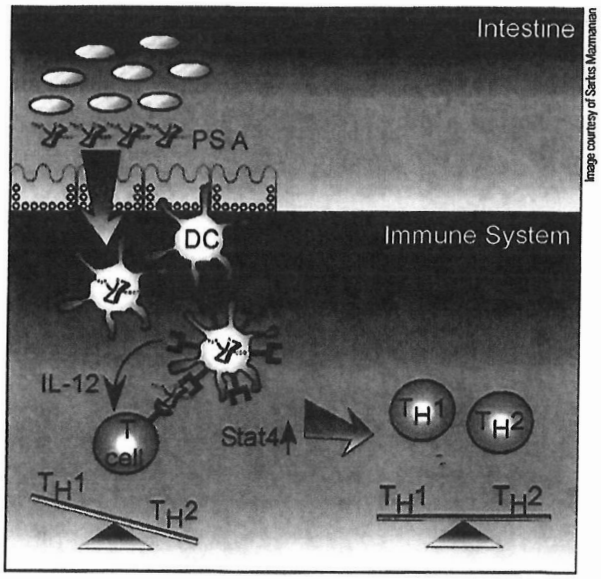

Image courtesy of Sarkis Mazmanian

***Bacteria put the immune system in balance. B. fragilis* lining the surface of the intestine (at top) express a carbohydrate, PSA, that is taken up by dendritic cells of the immune system. The antigen is then presented to T cells, where it signals them to adopt a Th1 subtype. This action can correct the imbalance of Th1 and Th2 responses in mice born into an otherwise sterile environment.**

Using mice and cultured cells, the team found that PSA induces the Th1 subset of T cells—those that are responsible for cell-mediated immunity. Normally, the immune system relies on a balance between these cell-mediated responses and antibody-mediated, or Th2, responses. Kasper said that mice and humans who grow up in sterile environments have immune systems that are skewed toward Th2 responses, suggesting that Th2 may be a "default" pathway for the body. If bacterial factors like PSA are necessary for development of the Th1 arm of the immune system, it would be a clear sign that we depend on bacteria for proper immune function.

"No one has previously described in mammalian systems a single molecule that causes symbiosis," Kasper said.

The effect of PSA extends beyond T cells. The researchers noticed tissue abnormalities of the thymus and spleen in germ-free mice and in mice colonized by *B. fragilis* that lacked PSA. But a normal strain of *B. fragilis* corrected these abnormalities. "Organ development actually depended on the presence of this molecule," said Kasper. Although bacteria have been

known to contribute to the normal development of structures in the intestine, this is the first indication that they can affect organs beyond their residence.

Microbial Role Reversal

Though the exact pathway of this symbiosis is unknown, initial experiments in culture showed that the bacteria's message is relayed by dendritic cells, which line surfaces like the digestive tract and help coordinate early Th1/Th2 decision-making. Future work will help determine whether mammals have dedicated genetic pathways to respond to bacterial signals.

Kasper said that his team's results fit with what has become known as the "hygiene hypothesis"—the idea that decreased exposure to bacteria may be spurring the rise of modern-day maladies like asthma, allergies, and autoimmune diseases. It may be that without the guidance of bacteria, our immune systems develop the wrong responses. Not just killers, bacteria serve as coaches.

"If you look at my career and most of my colleagues' in the Microbiology Department," Kasper said, "we've all spent our years studying pathogens. And here's an amazingly important biologic function—the development of the immune system—and it has nothing to do with a pathogen, but it does have to do with bacteria." There is a growing recognition that medicine must expand its limited view of bacteria as the enemy. Even the notion that the tiny organisms are just sitting passively inside us may miss the mark. By cell count, we are 99 percent bacteria. Having evolved alongside vast numbers of bacteria for millennia, we may in fact, as this study suggests, rely on them for our health.

—Courtney Humphries