Biologists link gut microbial equilibrium to inflammatory bowel disease

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We are not alone -- even in our own bodies. The human gut is home to 100 trillion bacteria, which, for millions of years, have co-evolved along with our digestive and immune systems. Most people view bacteria as harmful pathogens that cause infections and disease. Other, more agreeable, microbes (known as symbionts) have taken a different evolutionary path, and have established beneficial relationships with their hosts. Still other microbes may be perched somewhere in between, according to research by biologists at the California Institute of Technology (Caltech) that offers new insight into the causes of inflammatory bowel disease (IBD) and colon cancer.

A paper about their work appears in the April 22 issue of the journal *Cell Host & Microbe*.

"It has been proposed that the coupled equilibrium between potentially harmful and potentially beneficial bacteria in the gut mediates health versus disease," says Sarkis K. Mazmanian, assistant professor of biology at Caltech. "If the balance is altered," say, by changes in diet, the effects of stress, or the use of antibiotics, "then the immune response in the intestines is also changed." This altered host-microbe relationship, called dysbiosis, has been linked to IBD and colon cancer as well as to obesity and diabetes.

Close to a thousand different species of bacteria reside in the gut, which makes understanding the consequences of dysbiosis a challenge. One way of studying the effects of a balanced host-microbe relationship, and

how it arises in the first place, is to change experimentally the relative population size of the microbe. That's exactly what Mazmanian and graduate student Janet Chow accomplished in a bacterium called Helicobacter hepaticus.

Helicobacter hepaticus has an unusual modus operandi. It is not an opportunistic pathogen like the bacteria that cause diseases such as tuberculosis or strep throat, nor is it a beneficial symbiont. While H. hepaticus can persist for a lifetime in the gut of a healthy organism without causing any ill effects, it causes syndromes similar to IBD in immunocompromised mice—animals with artificially depressed or inactive immune systems. "Perhaps this organism is somewhere within the evolutionary spectrum between pathogen and symbiont," says Mazmanian. The authors have coined the term "pathobiont" to describe the unique lifestyle of H. hepaticus and the relationship it establishes with its host.

Mazmanian and Chow suspected that the effect of the bug's presence—whether it lives in quiet coexistence with its host or causes disease—may be determined by its ability to communicate with and, more importantly, to modify the immune system of its host.

To examine this possibility, Chow genetically altered the bacterium to inactivate its "secretion system." The secretion system is a collection of proteins the microbe uses to send chemical messages to its host; Mazmanian says it represents a biological "needle and syringe" that delivers bacterial molecules directly into eukaryotic cells. Although the specific functions and identities of these chemicals are unknown, they appear to establish a truce between the bug and the host's immune system.

When Chow genetically disrupted the secretion system—shutting off this communication—she saw two unexpected and intriguing effects. First,

the size of the H. hepaticus population expanded dramatically, leading to dysbiosis. In turn, the host immune system ramped up its activity. This manifested in inflammation—the body's response to infection or injury.

"The bacteria appear to have struck a deal with their host," Mazmanian says. They keep their own numbers low so they don't overwhelm the immune system, and in return, the immune system leaves them alone. "The bacteria need the secretion system to put the host in 'don't attack' mode." In return, the presence of the bacteria does not induce inflammation, as would be the case with a pathogen that has not evolved a similar "agreement."

"There has to be communication. It could be peaceful—as is the case for symbionts—or it could be an argument—as is the case for pathogens. But when this molecular dialogue breaks down, it's probably harmful to both microbe and man," Mazmanian says.

Disrupt that communication, and the balance gets thrown out of whack. "Inflammation leads to cancer, and this bacterium has been associated with inflammation and colon cancer in animals," he says. Understanding if dysbiosis causes disease in humans could lead to therapies based on restoring the healthy microbial balance in the gut.

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