A Delicate Balance

The traditional understanding of how the immune system distinguishes the body's own cells (self) from genetically different cells (nonself) suggests that our molecular defenses should be in a constant state of war against these myriad interlopers. Why the intestines, for example, are not the scene of more pitched battles between human immune cells and the trillions of bacteria present is one of the great, as yet unsolved mysteries of immunology.

The few clues that exist offer tantalizing insights into the balancing act between the microbiome and human immune cells that has taken some 200,000 years to calibrate. Over the eons the immune system has evolved numerous checks and balances that generally prevent it from becoming either too aggressive (and attacking its own tissue) or too lax (and failing to recognize dangerous pathogens).

For example, T cells play a major role in recognizing and attacking microbial invaders of the body, as well as unleashing the characteristic swelling, redness and rising temperature of a generalized inflammatory response to infection by a pathogen. But soon after the body ramps up its production of T cells, it also starts producing so-called regulatory T cells, whose principal function seems to be to counteract the activity of the other, pro-inflammatory T cells.

Normally the regulatory T cells swing into action before the pro-inflammatory T cells get too carried away. "The problem is that many of the mechanisms that these proinflammatory T cells use to fight infection— for example, the release of toxic compounds— end up blasting our own tissues," says Caltech's Mazmanian. Fortunately, the regulatory T cells produce a protein that restrains the proinflammatory T cells. The net effect is to tamp down inflammation and prevent the immune system from attacking the body's own cells and tissues. As long as there is a good balance between belligerent T cells and more tolerant regulatory T cells, the body remains in good health.

For years researchers assumed that this system of checks and balances was generated entirely by the immune system. But in yet another example of how little we control our own fate, Mazmanian and others are starting to show that a healthy, mature immune system depends on the constant intervention of beneficial bacteria. "It goes against dogma to think that bacteria would make our immune systems function better," he says. "But the picture is getting very clear: the driving force behind the features of the immune system are commensals."

Mazmanian and his team at Caltech have discovered that a common microorganism called **Bacteroides fragilis,** which lives in some 70 to 80 percent of people, helps to keep the immune system in balance by boosting its anti-inflammatory arm.

Their research began with observations that germ-free mice have defective immune systems, with diminished function of regulatory T cells. When the researchers introduced B. fragilis to the mice, the balance between the pro-inflammatory and anti-inflammatory T cells was restored, and the rodents' immune systems functioned normally. But how?

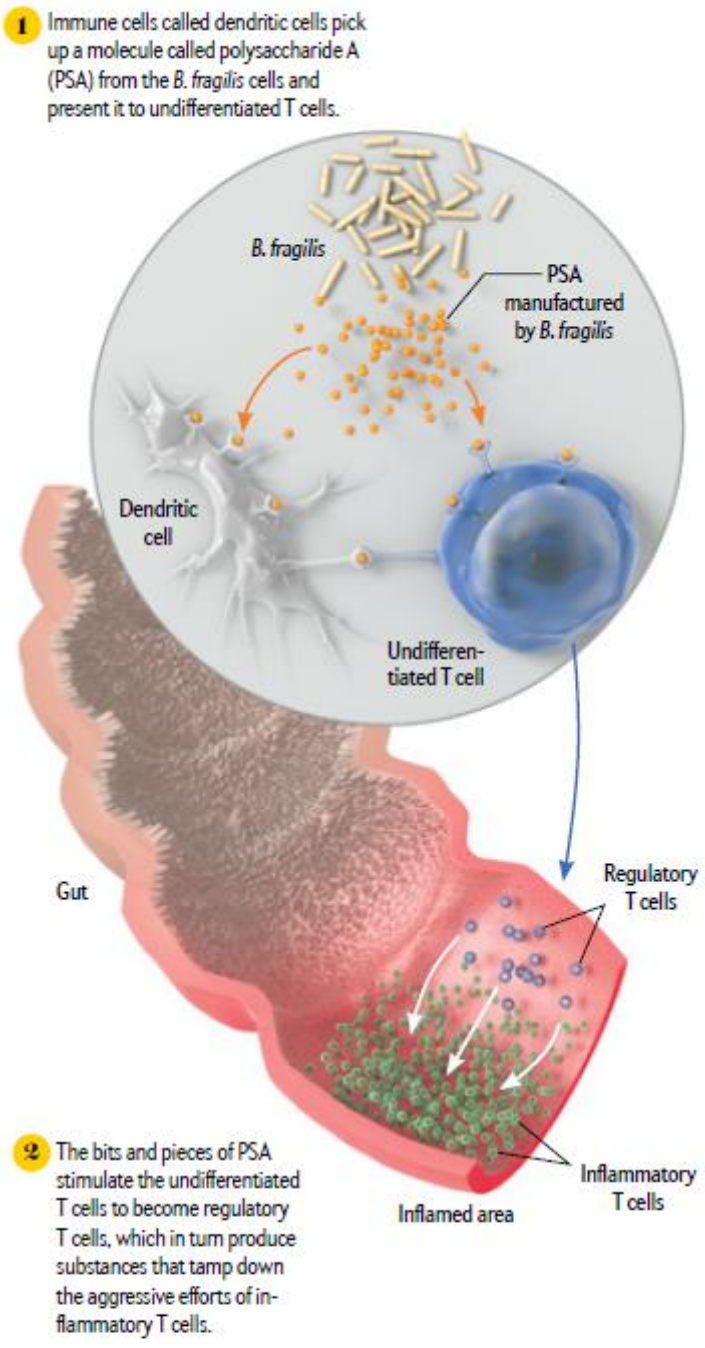
In the early 1990s researchers started characterizing several sugar molecules that protrude from the surface of B. fragilis— and by which the immune system recognizes its presence. In 2005 Mazmanian and his colleagues showed that one of these molecules, known as polysaccharide A, promotes maturation of the immune system. Subsequently, his laboratory revealed that polysaccharide A signals the immune system to make more regulatory T cells, which in turn tell the pro-inflammatory T cells to leave the bacterium alone. Strains of B. fragilis that lack polysaccharide A simply do not survive in the mucosal lining of the gut, where immune cells attack the microbe as if it were a pathogen. In 2011 Mazmanian and his colleagues published a study in Science detailing the full molecular pathway that produces this effect— the first such illumination of a molecular pathway for mutualism between microbe and mammal. "B. fragilis provides us with a profoundly beneficial effect that our own DNA for some reason doesn't provide," Mazmanian says. "In many ways, it co-opts our immune system— hijacks it." Unlike pathogens, however, this hijacking does not inhibit or reduce our immune system performance but rather helps it to function. Other organisms may have similar effects on the immune system, he notes: "This is just the first example. There are, no doubt, many more to come."

Alas, because of lifestyle changes over the past century (use of antibiotics), B. fragilis, like H. pylori, is disappearing. "What we've done as a society over a short period is completely change our association with the microbial world,"

Mazmanian says. “In our efforts to distance ourselves from disease-causing infectious agents, we have probably also changed our associations with beneficial organisms. Our intentions are good, but there’s a price to pay.”

In the case of B. fragilis, the price may be a significant increase in the number of autoimmune disorders. Without polysaccharide A signaling the immune system to churn out more regulatory T cells, the belligerent T cells begin attacking everything in sight— including the body’s own tissues. Mazmanian contends that the recent sevenfold to eightfold increase in rates of autoimmune disorders such as Crohn’s disease, type 1 diabetes and multiple sclerosis is related to the decline in beneficial microbes. “All these diseases have both a genetic component and an environmental component,” Mazmanian says. “I believe that the environmental component is microbiotic and that the changes are affecting our immune system.”

The microbial shift that comes with changes in how we live— including a decrease in B. fragilis and other anti-inflammatory microbes— results in the underdevelopment of regulatory T cells. In people who have a genetic susceptibility, this deviation may lead to autoimmunity and other disorders. Or at least that is the hypothesis. At this stage in the research, the correlations in humans between lower microbial infections and increased rates of immune disease are only that— correlations. Just as with the obesity issue, teasing apart cause and effect can be difficult. Either the loss of humanity’s indigenous bugs have forced rates of autoimmune diseases and obesity to shoot up or the increasing levels of autoimmunity and obesity have created an unfavorable climate for these native bugs. Mazmanian is convinced that the former is true— that changes in the intestinal microbiome are contributing significantly to rising rates of immune disorders. Yet “the burden of proof is on us, the scientists, to take these correlations and prove that there is cause and effect by deciphering the mechanisms



Case Study: How One Bacterial Species Helps

Studies on mice raised in sterile conditions reveal that *B. fragilis* bacteria are crucial to maintaining the health of the intestines. In one experiment, germ-free mice that were given a strain of *B. fragilis* bacteria that produced the complex carbohydrate polysaccharide A did not develop inflammation of the intestine (colitis), whereas mice that were given a strain of *B. fragilis* bacteria that did not make PSA developed chronic inflammation of the gut. Investigators showed that the presence of PSA stimulated the development of regulatory T cells that in turn switched off the inflammatory T cells, thereby restoring health.

.

Scientific American. The Microbiome: Your Inner Ecosystem