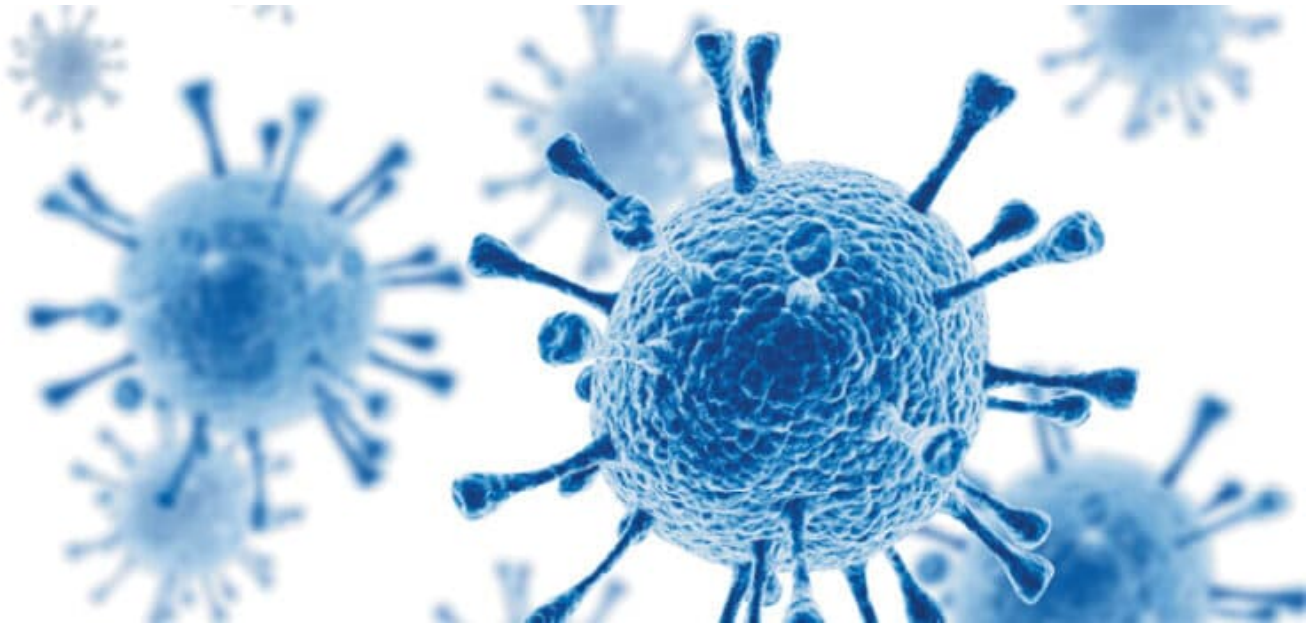
Gut bacteria may play a role in MS



Bacteria could affect immune responses.

by Mary E King, PhD

For the last few years, scientists have been learning more about different types of bacteria that live in our guts—and which may play a role in multiple sclerosis. Certain bacteria can encourage or suppress inflammation, according to some leading investigators, including two who presented their work at the September 2016 European Committee for Treatment and Research in MS (ECTRIMS) meeting in London. Gut bacteria may also influence whether pro- or anti-inflammatory types of immune cells circulate in the human bloodstream.

Sergio Baranzini, PhD, professor at the University of California at San Francisco School of Medicine, and Dr. Lloyd Kasper, professor at the Geisel School of Medicine at Dartmouth, discuss what these results in animal models mean for people with MS and how future research might shape therapeutic approaches.

Effect on immune cells

“My laboratory [at UCSF] has been studying the genetics of MS for a long time,” Dr. Baranzini says, “but genetics alone cannot explain all aspects [of MS].” He became interested in the genetics of the bacteria that live in the human intestines, he says, and in particular, how those bacteria might influence our immune systems.

Sergio Baranzini, PhD.
Photo courtesy of Dr. Baranzini

Dr. Baranzini points out that several thousand different species of bacteria can live in the gut, comprising much of what is called the “gut microbiome” (together with other tiny living organisms like viruses and yeasts).

Furthermore, Dr. Baranzini explains: “The gut contains particular tissue specializations called Peyer’s patches. These are places where circulating immune cells meet microbes that go through the intestinal tract.”

This natural interaction between immune cells and bacteria, he says, has led researchers to ask whether gut bacteria could be important in shaping our immune responses. Dr. Baranzini also cites earlier groundbreaking work where Dr. Kasper showed that using antibiotics to treat mice with experimental autoimmune encephalomyelitis (EAE)—an animal disease similar in some aspects to human MS—not only eliminated certain bacteria in the gut but made the mice more resistant to brain inflammation.

Pulling these lines of thought together, Dr. Baranzini states, “We hypothesized that there might be different populations of bacteria inhabiting the guts of people with MS compared to those in healthy individuals. Those bacteria might affect the immune response in MS.”

Experiments with human gut bacteria
Dr. Baranzini and his collaborators in the National MS Society-sponsored MS Microbiome Consortium (MSMC) and in the International MS Microbiome Study (iMSMS) collected stool and blood samples from 64 people with MS and 68 healthy controls in order to conduct four sets of experiments.

First, the scientists made extracts of the bacteria present in the stool samples. They also isolated immune cells (including B and T cells) from each blood sample. They incubated each

donor's bacterial extract with that individual's immune cells under conditions that enable T regulatory cells to grow; these cells are known to reduce inflammation. The combination of bacterial extract and immune cells from people with MS were less able to produce these T regulatory cells than were the combinations from healthy people.

"We didn't know why, but we saw that the bacteria from people with MS somehow affected the growth of the type of T cells needed to control inflammation," Dr. Baranzini explains. "We wanted to know which bacteria were causing this."

So, in the second experiment, researchers assessed the bacterial DNA in each stool extract to identify which species were present and in what amounts. A few types of bacteria were more prevalent in stool samples from people with MS than in healthy people, and a few were less prevalent.

"We wanted to understand what those specific species of bacteria would do," Dr. Baranzini continues, "so we grew two strains of the bacteria that were more prevalent and one of the less prevalent kind."

In this third experiment, researchers again made extracts of the bacteria, and incubated each of the three strains with immune cells from healthy individuals. "We found that the more prevalent strains of bacteria favored the growth of the types of immune cells, called Th1 and Th17, which support inflammation. The strain that was less prevalent in people with MS favored the growth of T regulatory cells, which dampen inflammation," Dr. Baranzini says.

In the fourth experiment, Dr. Baranzini's team looked at what live bacteria from the stools of people with MS and from controls would do to mice with EAE, so they transferred bacterial samples to the guts of those mice. The mice that received bacteria from the people with MS developed much more severe EAE than mice receiving bacteria from individuals without MS.

Dr. Baranzini points out that for all of these experiments, the individuals with MS who provided stool samples were not on MS disease-modifying medication. They were either newly diagnosed with MS or had chosen not to take disease-modifying medications. "It is also important to know whether medications used affect the gut bacteria," he explains, "and that will be the subject of future research."

He also cautions that the work needs to be reproduced in a larger number of individuals. That work is ongoing with the help of iMSMS. Dr. Baranzini and his team are funded by a Collaborative MS Research Center Award from the National MS Society.

Bacteria and a model of progressive MS

Dr. Kasper and his colleague, Javier Ochoa-Reparaz, PhD, are looking more deeply into the specific effects of gut bacteria in mice that have had EAE induced, and at disease progression in another mouse model that more closely mimics secondary progressive MS (SPMS).

Lloyd Kasper, PhD. Photo courtesy of Dr. Kasper

In one study, Dr. Kasper took a molecule called polysaccharide A (PSA), which is produced by certain human gut bacteria that are present in everyone, and gave it to mice with EAE. As he explains, “PSA induces regulatory T and B cells (also called Treg and Breg), which are important in reducing the severity of EAE in mice.”

Dr. Kasper continues, “In fact, PSA increases not only the Treg and Breg populations in the circulation and immune tissue around the gut, but also survival in these mice.” This shows that a particular molecule made by one type of human gut bacteria has a positive effect on an animal model of MS.

It’s currently believed that people with MS have ample numbers of regulatory cells (particularly Tregs) that do not function properly compared to individuals without MS.

Dr. Kasper says that additional studies (as yet unpublished) demonstrate that PSA also stimulates the proliferation of human T and B cells that are associated with the production of an important anti-inflammatory immune molecule, interleukin-10, which is known to be deficient in those with relapsing-remitting MS.

In their second study, Dr. Kasper’s laboratory used non-obese diabetic mice with EAE. These mice develop a disease that has two phases, such as in relapsing-remitting MS, with an acute phase and a phase that mimics secondary progressive MS. Dr. Kasper explains, “If you give these mice antibiotics to wipe out their existing gut bacteria, both phases of their disease are less severe. So, we can protect against disease progression in a mouse model of secondary progressive MS.”

Dr. Kasper took this research one step further and gave these mice PSA, and it also reduced disease severity to about the same extent as antibiotics. This work was funded by a research grant from the Society, funded with support from the Conrad N. Hilton Foundation.

“The clinical significance [for people with MS] is that it is possible that not only the initial phase but also the secondary progressive phase of MS is affected by the gut microbiome. While it is speculative to say this, it could mean that changes over time occur to the gut flora that may result in the secondary progressive part of the disease,” he says.

Possible role of diet

What could all of this mean for people with MS? “These results suggest that the microbiome has both the capacity to drive disease and to regulate disease,” states Dr. Kasper. “We now know that the microbiome induces both regulatory T cells and Breg cells. The bacteria inside of us are really important.” He adds, “If you reduce risk factors [for MS progression] through weight loss, less alcohol, less smoking, adequate vitamin D levels, etc., and you eat a healthy diet, you may be able to alter the bacterial colonization in a way that will produce more of the immune regulatory cells that reduce inflammation.

“For example,” Dr. Kasper continues, “[we may find that people with MS] who have suboptimal response to therapy, rather than changing medications, may need to pay attention to the gut microbiome and to other risk factors.”

More research is needed to help map out favorable and unfavorable microbiomes and the best approaches for altering them. Dr. Baranzini adds that future therapies might involve altering the composition of gut bacteria to reduce the number of immune cells that create inflammation, and increase the number of immune cells that reduce inflammation. That might be done by a stool transplant (a technique already used for certain types of severe gastrointestinal infection) or with changes in diet or probiotic approaches.

Dr. Baranzini’s next study will examine dietary habits along with stool samples in hopes of learning more about which types of changes in diet might be effective.

Mary E. King, PhD, is a freelance medical writer in Boulder, Colorado.

To learn more about Dr. Baranzini’s study, and to see which centers in your area may be participating, visit The International MS Microbiome Study.