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Scientists successfully treat new mouse model of inflammatory bowel disease

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Researchers trying to improve cancer immune therapy have made an unexpected find: They've produced the most accurate mouse model to date of inflammatory bowel disease (IBD), a cluster of conditions that afflict approximately 1.4 million Americans with abdominal pain, constipation and diarrhea.

The two most common forms of IBD are Crohn's disease and ulcerative colitis (UC); in extreme cases, they can be fatal. The mouse model closely resembles the most serious form of human UC and is uniformly fatal. But scientists successfully treated the mice with a pair of broad-spectrum antibiotics, easing gut inflammation and increasing survival. The results, reported this week in Public Library of Science-Medicine, have researchers eager to follow up both in the clinic and the lab.

"The antibiotics we gave the mice were used individually in unsuccessful clinical trials as ulcerative colitis treatments, but now we have colleagues who are thinking of giving combined therapy an informal try," says co-senior author Thaddeus S. Stappenbeck, M.D., Ph.D., assistant professor of pathology and immunology and of developmental biology. "The antibiotics probably won't be a cure by themselves, but they may provide us with a potent new approach to combine with other therapies."

The mice may also allow scientists to learn which species of gut microorganisms are becoming embroiled in battles with host immune systems, triggering the symptoms of UC. That information could allow the development of stronger and more specific treatments.

Silvia Kang, a former graduate student in the laboratory of co-senior author Paul Allen, Ph.D., the Robert L. Kroc Professor of Pathology and Immunology, created the mouse model by crossbreeding two mouse lines they had developed for cancer immune therapy research. Each mouse line had one protein knocked out that restrained immune T cells from shifting into attack mode.

"The idea was to see if we could create super killer T cells we could use to attack tumors," says Allen. "But all the mice became sick early on, started to lose weight and we soon realized that they all had serious gastrointestinal issues."

Allen decided to consult with Stappenbeck, an expert in IBD.

"I've looked at quite a few proposed mouse models of IBD, and I recognized right away that this had the potential to be outstanding," says Stappenbeck. "The colons of the mice were incredible. They were filled with inflammatory T cells. We found the mice almost exactly replicated the most acute types of ulcerative colitis."

Unlike prior models of IBD, the mice consistently develop gastrointestinal problems within a short time period and at a predictable point in their lifespan. When researchers treated the mice at three weeks with the antibiotics ciprofloxacin and metronidazole, colon inflammation was reduced and the mice were able to gain weight and survive longer.

Scientists believe IBD results from the host immune system damaging the tissues of the gut while erroneously attacking food and gut microorganisms that aid food digestion. There are an estimated 500 different species of microbes living in the gut, so sorting out which species are being attacked by the immune system has been an imposing challenge.

The new model may significantly ease that challenge. Although the dual antibiotics used to treat the mice are broad-spectrum, they didn't sterilize the guts of the mice, suggesting that the treatment happened to eliminate the microorganisms causing IBD.

"We'd like to treat the mice and then reintroduce candidate microorganisms into their guts to see if this restarts the inflammatory reaction," says Stappenbeck.

Stappenbeck and Allen plan continued collaborative study of the model.

Source: Washington University in St. Louis