Giving the NOD2 microbiota

By Kai-Jye Lou, Staff Writer

Disruption of enteric microbiota occurs in inflammatory bowel diseases, but whether this is a cause or result of the condition is unclear. Now, European researchers have shed light on the process by showing that a deficiency in an immune system–related receptor, NOD2, can disrupt enteric microbiota and set the stage for colitis and colitis-associated cancer.[1]

The group now is looking for bacterial strains that could help correct the microbial imbalance and is trying to better understand why a deficiency in caspase recruitment domain family member 15 (NOD2; CARD15) causes the disruption in the first place.

NOD2 is a pattern-recognition receptor for bacterial peptidoglycans that facilitates the host immune response against pathogens. It also has been shown to regulate the composition of enteric microbiota in mice.[2]

Mutations in the gene encoding NOD2 predispose individuals to Crohn's disease, which is one of the two major subtypes of inflammatory bowel disease (IBD). Patients with Crohn's disease also show imbalances in their enteric microbiota[3,4]—a condition called dysbiosis—and have an elevated risk of colorectal cancer.[5]

In the current study, a team co-led by Mathias Chamaillard sought to flesh out the relationship between NOD2 dysregulation, imbalances in enteric microbiota and susceptibility to colitis, and the development of colitis-associated colorectal carcinomas.

Chamaillard is a research director and team leader at the Center of Infection and Immunity of Lille at the **Pasteur Institute in Lille**. He has been studying the role and function of NOD2 and NOD2-related proteins in the host immune system, tumorigenesis and IBD for more than a decade.

The researchers showed that knockout of *Nod2* in mice increased susceptibility to chemical-induced colitis and colitis-associated colorectal carcinomas compared with no knockout.

Surprisingly, the disease-vulnerable state was transmissible. Wild-type mice cohoused with *Nod2*-deficient mice also showed increased susceptibility to colitis and colitis-associated colorectal carcinomas compared with wild-type mice cohoused with other wild-type mice. This result implicated the transmission of disease-predisposing bacteria as the underlying cause.

Indeed, *Nod2*-deficient mice treated with a broad-spectrum antibiotic showed lower susceptibility to chemical-induced colitis than untreated *Nod2*-deficient controls.

To confirm enteric bacteria were the culprit, the researchers carried out a series of fecal transplant experiments. *Nod2*-deficient mice receiving a fecal transplant from mice with functional *Nod2* showed decreased susceptibility to chemical-induced colitis compared with deficient mice given transplants from other mice lacking *Nod2*. Conversely, mice with functional *Nod2* receiving a fecal transplant from *Nod2*-deficient animals showed increased susceptibility to chemical-induced colitis compared with *Nod2*-functional mice receiving transplants from other mice with functional *Nod2*.

Results were published in *The Journal of Clinical Investigation*.

"One of the important experimental priorities in this field is whether disruptions in the gut microbiome are causal or a result of the disease," said Peter DiStefano, SVP of R&D of **Second Genome Inc.** "I think this study provides a key piece of data that shows causality of the gut microbiome in IBD."

Second Genome is developing therapies that can alter the composition and activity of microbial communities in the body.

"This paper also reinforces the connection between risk factors for Crohn's disease and colitis-associated cancer and proposes a plausible role for microbial dysbiosis in connecting the two," added Bernat Olle, COO of **Vedanta Biosciences Inc.** and a principal at **PureTech Ventures**. "The described mechanisms are consistent with what has been suggested in the literature and reinforce our understanding of how certain genes, such as *NOD2*, can influence the gut microbial composition, which in turn can keep inflammatory responses in check."

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Olle also said the findings help dispel the notion that having an at-risk genotype that predisposes one to dysbiosis and IBD is an unalterable fate.

"The host genotype may be unalterable, but the dysbiosis is certainly not, and as shown by the authors, fecal transplantation and other microbiome manipulations can reverse alterations of the gut microbiota and improve disease outcomes," he told *SciBX*. "In the last decades, a lot of effort in drug development in IBD has gone toward modulation of inflammatory mediators, and this has led to breakthrough treatments like anti-TNFs. However, these approaches may not help address the underlying dysbiosis that helps drive chronic inflammation in IBD patients."

At least three anti–tumor necrosis factor (TNF) antibodies already are marketed to treat Crohn's disease. These are Humira adalimumab from **AbbVie Inc.**, Remicade infliximab from **Johnson & Johnson** and Cimzia certolizumab pegol from **UCB Group**.

Vedanta is developing an oral formulation of enteric bacteria to correct the deficiency of normal bacteria that occurs in IBD.

Bugs as drugs

With the causal relationship established, Chamaillard said the group now is screening for probiotic bacterial strains that could normalize enteric microbial populations in the IBD setting.

"The current study shows that changing the composition of microbial communities in the gut could have a beneficial effect, but exactly how one should go about selectively changing the microbiome is still unclear," said Christian Jobin, an associate professor in the Department of Medicine at **The University of North Carolina at Chapel Hill School of Medicine**. "They may also want to identify and go after the microbial entities that cause the increased susceptibility to disease. RNA and genome sequencing studies are going to be important for addressing these questions."

DiStefano said another avenue to search for potential therapeutic strategies is the metabolites produced by enteric bacteria as such molecules may help drive or prevent disease.

"The researchers may want to look at the metabolites these bacteria produce and run studies to determine what these molecules are doing to the host and how they affect disease pathology," he said.

Indeed, Chamaillard's group is trying to identify the cellular and molecular mechanisms underlying the disruption of enteric microbiota caused by the deficiency in NOD2 and how this leads to increased disease susceptibility.

Olle wanted to see studies to determine whether there is an ideal time window during which manipulating the enteric microbiome would have benefit in IBD- or colitis-associated cancer.

"This will require prospective studies following IBD- and colitis-associated cancer patients and determining the timing and order of events that conspire to create the conditions for the disease to develop," he said. "Another important question will be to clearly define patient subsets that are most likely to respond favorably to microbiome manipulation. This information will be very useful for clinical trial design and patient selection."

The work reported in the paper is unpatented. Chamaillard said the group plans to file for IP after identifying the key bacterial strains, genes and molecular mechanisms responsible for disrupting enteric microbiota.

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COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NYSE:ABBV), Chicago, Ill.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Pasteur Institute in Lille, Lille, France
PureTech Ventures, Boston, Mass.
Second Genome Inc., San Francisco, Calif.
UCB Group (Euronext:UCB), Brussels, Belgium
The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, N.C.
Vedanta Biosciences Inc., Boston, Mass.