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Study links intestinal microbial population to production of inflammatory proteins

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A study led by investigators at Massachusetts General Hospital (MGH), the Broad Institute of MIT and Harvard, and two academic medical centers in the Netherlands has begun to elucidate how differences in the gut microbiome - the microbial population of the gastrointestinal tract - affect the immune response in healthy individuals. The study is one of three related papers published in this week's issue of *Cell*, the other two looking at genetic and environmental influences, as part of the Human Functional Genomics Project (HFGP).

"The underlying premise of the HFGP is that the immune system is a perfect target for studying human variation and the intersection of genes and the environment," says Ramnik Xavier, MD, PhD, chief of the MGH Gastrointestinal Unit, an institute member at the Broad and a principal investigator of the HFGP. "We know that some people are more susceptible to infections than others; some develop autoimmune diseases while most don't. In these studies we wanted to see how genes affect the immune system, how environmental factors affect susceptibility and in this investigation, whether and how the gut microbiome influences the immune system's response to various pathogens."

The microbiome study - led by Xavier and Mihai Netea, MD, PhD, of Radboud University Medical Center in the Netherlands - analyzed blood and stool samples from 500 healthy Western European HFGP participants to look for individual variations in immune responses to pathogens, represented by production of molecules called cytokines;

variations in the gut microbiome, and how those two factors relate to each other.

Immune cells from individual participants were exposed to three bacterial stimulants - the commensal microbe B. fragilis, the common pathogen S. aureus, and a toxin produced by E. coli - and two forms of the Candida fungus. Their response was reflected in the production of cytokines, proteins through which immune cells exert many of their effects. Looking at possible relationships between immune responses and the microbiome in individual participants, the investigators found clear patterns by which both the population of the microbiome and its function, reflected in the production of proteins called metabolites, interact with the immune response. Some of those interactions depended on the particular pathogen, some on the cytokines, and some on both.

Among the team's observations was how, depending on the specific pathogenic stimulus, breakdown of the amino acid tryptophan into the metabolite tryptophol can inhibit production of the cytokine TNF-alpha. They also identified an effect of palmitoleic acid - a fatty acid found in several dietary oils and known to suppress some immune activities - on production of the cytokine gamma interferon, although the precise mechanism is yet to be discovered.

The Isselbacher Professor of Medicine in Gastroenterology at Harvard Medical School and a member of the MGH Center for Computational and Integrative Biology, Xavier says, "We still don't have all the components, but the overall picture suggests that variations in the gut microbiome change production of the metabolites that go on to educate or influence immune cells, leading to differential outcomes when immune cells are exposed to various infections." The accompanying studies, on which he is a co-author, found similar influences on immune response by environmental factors - including the season of the year as well as participants' age and gender - and most powerfully, by genetic

differences.

Among the next steps, Xavier notes, will be conducting similar studies in individuals with specific diseases and in participants from other parts of the world. "By understanding how all of these complex mechanisms - genetics, microbiome and environment - drive variations in the immune response, we may be able to identify factors responsible for individual patients' susceptibilities and better target therapies," he says.

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