How do interactions between gut bacteria and fungi exacerbate crohn's disease?

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Scientists have known that bacteria in the gut, along with environmental and genetic factors, contribute to the debilitating intestinal ailment of Crohn's disease (CD). But in 2016, Mahmoud A Ghannoum, Ph.D., FAAM, FIDSA, professor and director of the Center for Medical Mycology at Case Western Reserve School of Medicine and University Hospitals Cleveland Medical Center, was the first to identify a specific fungus in humans that interacted with bacteria in the development of the disease.

Now, to learn precisely how that fungus interacts with bacteria to trigger CD, Ghannoum has received a five-year, $3M grant from the National Institutes of Health. His investigation will involve innovative molecular and cellular technologies, to delete specific genes in the fungus and note the effects on the inflammation that is a marker for CD using powerful microscopic analysis.

"Uncovering how the connection between bacteria and fungus works will lead to a clearer understanding of why some people develop Crohn's disease," said Ghannoum. "Equally important, it can put us on the pathway to new treatments and even cures, including targeted probiotics."

In his earlier work, Ghannoum reported that among hundreds of bacterial and fungal species inhabiting the intestines, abundance of the single fungus Candida tropicalis was positively correlated with two types of bacteria in CD patients: Serratia marcescens and Escherichia coli.

Ghannoum further showed that the three pathogens joined forces to form a powerful biofilm—a thick, slimy layer of microorganisms resistant to antibiotics and antifungals which adheres to the intestines and can prompt the inflammation that causes the painful symptoms of CD.

Specifically, biofilms formed by the three microorganisms together were significantly thicker than biofilms formed by the three microorganisms individually, or in varying combinations of two. Ghannoum also found that substituting other fungi did not produce the same thick biofilms as Candida, indicating that this is a Candida-specific effect.

The new study has three aims. The first is to identify the genetic mechanisms underlying Crohn's-associated interactions between the three microorganisms identified in the earlier study. Ghannoum will examine the genes of the three microorganisms alone and together to see which genes increase their expression when the three microorganisms come together, compared to when they are in isolation. He will then delete these genes to see if the three-microorganism, extra-thick biofilm still forms.

In aim two, Ghannoum will examine certain small chemicals that are secreted by the biofilm when the three microorganisms are grown together. The chemicals, known as metabolites, increase the ability of the fungus to invade the gut lining. "Here we want to find which chemical or chemicals, known as metabolites, allow the organism to form the biofilm," said Ghannoum. "Once we understand this, we want to see how we can interfere with the formation of the biofilm by manipulating the metabolites."

Under the third aim, Ghannoum will determine how the three microorganisms individually and collectively influence inflammation and associated symptoms. He will do this by looking for the presence of pro-

inflammatory proteins called cytokines. An imbalance between pro-inflammatory and anti-inflammatory cytokines that occurs in CD can result in disease progression. He will try and determine whether exposure of the triple-microorganism biofilm to antibacterial, antifungal, and metabolite inhibitors modulates the severity of intestinal inflammation.

"The long-term goal of this project is to develop novel antifungal and probiotic strategies that can be tested in pre-clinical and clinical studies to decrease the occurrence and duration of symptoms in patients with irritable bowel disease including Crohn's disease," said Ghannoum.

Provided by Case Western Reserve University

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