

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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The Potential Role of the Gut Microbiome in IBD Pathophysiology

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G&H Can you explain the concept of the microbiome as an independent organ and its role in proper bodily function?

GW The composite communities of bacteria in the intestinal tract, known as the gut microbiome, is the most densely populated bacterial community on the face of the earth. We have co-evolved with our gut microbiome to exist in a commensal and sometimes symbiotic relationship, where the microbiome plays a role in educating the mucosal immune system and developing our immune responses to other types of pathogens. Amongst its many other functions, it also plays a significant role in metabolism and the extraction of additional calories from food, as well as the metabolism of bile acids and certain vitamins.

G&H What factors contribute to the population of the gut microbiome, in both the short and long term?

GW Prior to birth, in the womb, we are sterile. After birth, the gut is immediately colonized, and during the first year of life, the composition of the gut microbiome is chaotic, and then tends to stabilize. How much this determines the ultimate make-up of the gut microbiome is a question under active investigation. Animal studies suggest that to a certain degree we are imprinted at birth, through vertical (mother to child) transmission, but, again, the stability of that imprint remains unclear.

Cohabitation has been identified as possibly contributing to the make-up of the microbiome. Another growing area of interest is in the effect of diet. Fasting has an effect, at least in animal models, on the gut microbiome. Different types of diets have an impact as well. Investigators are also looking at genetic influences of the host on the composition of the gut microbiome. Finally, the phenotype of the host (for example, obesity) has also been shown to play a role.

We can also alter the composition of the microbiome medically, the best example being with the use of antibiotics, which clearly leads to dramatic alterations in the composition of the gut microbiome. However, once antibiotic administration is stopped, the microbiome largely returns to its baseline composition within a month, with modest changes remaining up to a year.

It is currently unclear whether bacterial communities located on other body surfaces, such as the skin or respiratory tract, have an influence on the composition of the gut microbiome. In this regard, it is important to remember that the colon is an anaerobic environment, and thus it is plausible to hypothesize that bacteria that colonize body surfaces exposed to an aerobic environment will have a very limited impact on the composition of the gut microbiome.

G&H Can you describe each of the 4 theories of how the gut microbiome could potentially play a role in the pathogenesis of inflammatory bowel disease? How are these theories interrelated?

GW The 4 main theories of a role for gut microbia in inflammatory bowel disease (IBD) were recently summarized in a review article by Balfour Sartor in 2008. The first involves the idea of microbial pathogens inducing intestinal inflammation. Over the past several decades, a variety of microorganisms have been suggested to play a role in the pathogenesis of IBD. For example, *Mycobacterium paratuberculosis*, which causes an intestinal inflammatory disease known as Johne's disease in cattle

and other ruminants, has been suggested to be a cause of Crohn's disease. More recently, strains of bacteria that penetrate the intestinal epithelium, such as invasive strains of *Escherichia coli*, have gained the interest of some investigators in the field. However, definitive evidence to support the notion that IBD can be induced by a single pathogenic organism is currently lacking. When considering the hypothesis that IBD may be an infectious disease process, it is important to remember that our most effective treatments for IBD are based upon immunosuppression. If IBD were caused by infection with a specific pathogen, immunosuppression would appear to be more deleterious than beneficial.

Regardless, we do not discount the idea of an infectious component to IBD onset. Genetic alterations can lead to a failure to protect the host from certain organisms that are benign in nonsusceptible hosts. In other words, genetic alteration could lead to a dysregulated immune response to the normal bacteria in the colon, rather than some specific pathogen.

This ties in with our second theory, which posits a host genetic defect. It is very clear, based upon genome-wide studies, that there are many genetic polymorphisms associated with the development of IBD, and these associations are particularly strong for Crohn's disease. A number of the identified genes are innate immune response genes, a fact that supports the notion of an alteration in the innate immune response to normal bacteria in the gut. Whether this leads to unrestrained inflammation in the presence of these bacteria or it prevents the host from protecting against invasion by these normal bacteria is unclear.

Immune regulation plays a part in the third theory as well. The normal gut mucosa remains constantly active in order to protect the host from all of the bacteria and antigens that are present in the gut lumen. IBD can be seen as a failure by the body to restrain that immune response, which may be caused by the same host genetic defects discussed above. This theory is supported by the observation that patients with IBD manifest immune responses to normal components of the gut microbiome. For example, patients with IBD can produce antibodies to *E. coli* (OmpC), *Pseudomonas fluorescens* (I2), and other gut commensal organisms in the *Firmicutes* phylum (CBir1). These abnormal immune responses suggest that patients who have IBD sense these microbes differently from healthy individuals.

The final theory is one of dysbiosis, an imbalance between "good" and "bad" bacteria in the gut. Research in animal models has demonstrated a role for protective species of bacteria, such as those found in some probiotic formulations, in reducing intestinal inflammation. Other types of bacteria in the microbiome may exacerbate

intestinal inflammation. It is possible that an imbalance between the "good" and "bad" bacteria may ultimately play a role in the development of chronic inflammation that leads to IBD. We know that the gut microbiome in patients with active IBD is intrinsically different from that in patients without ongoing inflammation. Numerous investigators, supported by an initiative funded by the National Institutes of Health called the Human Microbiome Project, are working to characterize these alterations in subjects with IBD.

G&H Given the lack of demonstrable efficacy in IBD that has been seen with past studies of probiotic formulations, has this avenue of research been abandoned?

GW It remains intriguing that probiotics appear to work in animal models. The reasons for our relatively poor experience with them in human studies remain to be understood. Is it because we are not utilizing the right organisms? Are the organisms not colonizing the gut for a long enough period of time? Are we not delivering enough of the organisms to the host? Is the entire hypothesis incorrect? There are many different aspects to this question that we still do not understand.

From the perspective of the dysbiosis theory, patients with IBD may have a proportional reduction of anti-inflammatory "good" bacteria or an increase in pro-inflammatory "bad" bacteria. Probiotic therapies may theoretically be of use in replenishing anti-inflammatory bacteria, but if the imbalance is a result of too much pro-inflammatory bacteria, adding more "good" bacteria may not be sufficient. Regardless, specific probiotic formulations have shown some benefit in patients with pouchitis, which is a significant advance from a conceptual standpoint. However, more investigation is needed to determine whether better formulations can be produced and what may ultimately be useful in the treatment of IBD.

G&H Is there any ongoing study of the use of antibiotics to alter the gut microbiome in patients with IBD?

GW I am not aware of any large-scale studies utilizing antibiotics for IBD therapy. However, physicians are already using courses of antibiotics, the most common being ciprofloxacin and metronidazole, as Crohn's disease therapy, with some modest success.

We know from animal studies that single antibiotics cannot reduce bacterial populations in the bowel by substantial numbers. In the laboratory, we have used combinations of antibiotics, sometimes 4 or 5 agents together,

which can dramatically reduce gut bacteria. Therefore, it may be that we are not using potent enough antibiotics. In any case, the long-term use of antibiotics is not an optimal therapeutic option for any patient, regardless of their illness.

G&H What are the next steps in research of the gut microbiome as it relates to IBD?

GW Gut microbiome research can be considered in 3 broad phases. First, we need to understand its association with the disease, which, to a large extent, is where we are now. We are still working to characterize the composition of the gut microbiome in patients with IBD compared to that of normal controls and look at the impact of genetics, diet, and the other variables discussed above. The next step will be to prove causality. We know that inflammation, in and of itself, can lead to alterations in the composition of the gut microbiome. What we do not know is whether the microbiome changes because of the inflammation or if the inflammation is caused by the altered composition of the gut microbiome. Once the notion of causality has been confirmed, we can concentrate our efforts on the third area of research, which is to permanently change the gut microbiome to eliminate symptoms and effectively control the course of disease.

Researchers are currently working on all of these questions. The association studies need to be performed

in humans. The causality question will need to be performed in animal models before extending them to humans. Other investigators are using very sophisticated methods to try and understand how we can permanently change the gut microbiome for therapeutic purposes. This remains a huge challenge, partially because the targets that we wish to modify remain unknown. Nevertheless, in an interesting related approach, investigators are engineering bacteria that are capable of secreting anti-inflammatory substances such as interleukin-10. If patients with IBD can be successfully colonized, these bacteria could serve as “factories” to produce anti-inflammatory molecules and essentially treat the diseased bowel by downregulating the immune response within the mucosa on a continual basis.

Suggested Reading

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