

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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The Genetics and Pathogenesis of Inflammatory Bowel Disease



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G&H What do we now know about the map of genetic regions in inflammatory bowel disease?

MA It is understood that inflammatory bowel disease (IBD) is a complex genetic disorder. As of the last meta-analysis published in *Nature* in November of 2012, there are, at present, 163 genetic loci that have been associated with IBD susceptibility and pathogenesis. Seventy-one of these genetic loci are new associations. The advances in our understanding have been achieved by being able to study large populations of patients and by performing genome-wide association studies in which a million different single nucleotide polymorphisms (the subtle differences in our genetic code that make each of us unique) can be examined at once. The information gleaned from all of the genes that we have identified, however, still only explains about 20% of the heritability of IBD. This means that, for any individual with IBD, there also may be contributors that are unrelated to genetics.

In addition, many levels of gene regulation are involved in pathogenesis. For example, miRNAs likely play a role in the pathogenesis of IBD. miRNAs are small, noncoding RNAs that bind to RNA and generally down-regulate their transcription and, therefore, the expression of proteins. Because miRNAs generally bind to multiple target RNAs, they can be master regulators of pathways. One can see how this may have a large effect on inflammation and likewise could be used to turn off inflammation.

G&H How far along are we in studying the association between biologic agents and disease modification?

MA The prospect of disease modification with biologic agents is an exciting area. The challenge is to define the targets that are measuring damage in the bowel. Development of a scoring system is in progress, but it needs to be validated. We know that mucosal healing is probably a very good surrogate marker, but we still do not know for sure how well mucosal healing reflects disease modification. Other major outcomes to explore include prevention of surgery, mortality, and hospitalization rates. Accumulating data can take 5–10 years, and a large patient cohort is needed, so these are challenges to the study of whether biologic agents are disease-modifying drugs.

G&H What benefits to clinical gastroenterology are derived from unraveling the genetic component of IBD?

MA For now, the advances that have been made in our understanding of genetics are more interesting from the standpoint of what the origins of the disease might be even though, admittedly, this information may not be directly useful in the clinical setting. The genetic burden in any given individual is not sufficient to make a diagnosis of IBD. Research on the genetics of IBD may be useful in predicting disease phenotype. For example,

NOD2 testing may help predict in whom stricture development is more likely and who will need surgery. It has been incorporated in some commercial testing for Crohn's disease (CD) phenotyping.

G&H Is there a genetic overlap between ulcerative colitis and CD in terms of single nucleotide polymorphisms?

MA Of the 163 genetic loci that have been described in IBD, only 21 are CD-specific, and 20 are ulcerative colitis (UC)-specific. The rest of these genetic loci are common to both CD and UC. We no longer can think of these as very different diseases—they are almost identical genetically. Therefore, it is very likely that environmental factors and microbial factors play an even larger role in shaping the expression of the disease in terms of CD versus UC.

G&H Can we now identify patients at risk for small bowel strictures?

MA Serologic markers such as anti-*Saccharomyces cerevisiae* antibodies, anti-CBir1 flagellin, and antibodies against I2 protein track quite well with risk for complications of CD. NOD2 is also a risk factor for strictures. In my mind, a stricture is not the worst thing that can happen to a patient, especially if the stricture takes a long time to develop. For example, when one takes a careful history, it is often found that patients have had subtle symptoms of CD for 10 or more years and then present with a stricture. Conversely, patients in whom strictures develop very rapidly are quite a different problem.

G&H Given the expanding data about IBD and genetics, would preemptive surgery be a treatment option?

MA A standard that includes preemptive surgery for IBD is highly unlikely, but a role for early surgery in patients with fibrostenotic CD is now being acknowledged. The phenotypic data that are paired with genetic data in the genome-wide association studies described in the aforementioned meta-analysis published in *Nature* are not very deep, considering that they looked at 75,000 patients at once. More careful studies are needed to examine whether the presence of some genes predict more aggressive disease and, thus, a need for early surgery in some patients. More aggressive IBD consists of the perforating type or disease that involves extensive segments of the small bowel or colon. The ability to predict whether aggressive disease will develop in a patient based on his or her genetic profile would be of great value, although it is likely that this aggressive expression of disease also involves unidentified environmental or

microbial risk factors, and until these can also be measured, genetics alone may not be sufficiently predictive.

G&H Are the genetic regions associated with IBD shared with other pathologies?

MA One of the interesting points that has been found in these genome-wide association studies is a link between IBD and infectious and immunologic diseases. Many genetic loci associated with IBD are shared with such immune-mediated disorders as ankylosing spondylitis and psoriasis, and considerable overlap in terms of genetic susceptibility loci was observed between IBD and mycobacterial infection. For example, leprosy shows many of the same genetic determinants as CD. This is interesting because it has often been suggested that CD has a mycobacterial cause. Findings from the genome-wide association studies suggest that patients with IBD might have some kind of chronic infection. The connection between IBD and primary immune deficiencies, on the genetic level, suggests that even subtle perturbations at the interface of luminal bacteria and the host can challenge the host's ability to handle bacteria and lead to disease.

G&H After 25 years of genetic studies, what advances have been made in connecting the dots between immune function and IBD?

MA In some ways—although we have made great strides in genetic discoveries—study of the human mucosal immune system could be much improved. Investigators such as Lloyd Mayer, MD, Professor of Medicine at the Mount Sinai School of Medicine in New York City, have come the furthest in specifically studying the human mucosal immune system as opposed to that of murine models. One of the limitations to investigations in humans is lack of access to the actual intestinal tissue and its cells. It is very clear that the gut is its own environment and that the gut is quite distinct from the rest of the systemic immune system.

G&H Is IBD the body's overzealous attempt to thwart bacterial infection?

MA I do not believe that IBD is an overzealous response to bacterial infection, at least not at its very beginning. At its core, IBD may very likely be related to a defective innate immune response, but compensation or overcompensation by the adaptive immune system ensues to try to control what it perceives as chronic infection. In my opinion, it is very possible that either normal commensals take on the role of pseudopathogens or specific situational pathogens are causing disease and need to be identified.

G&H In terms of studies on race and ethnicity, who is most at risk for IBD?

MA A study in Hispanics with IBD was recently performed by me and a team of researchers here at the University of Miami. The population of Hispanics in Miami is very diverse and represents all of Latin America and the Caribbean. The research team had the ability to look at patients who were born in Latin American/Caribbean countries and compare them with patients who were born of Hispanic parents in the United States. We found that the majority of immigrants who had IBD had UC and the majority of non-Hispanic white persons and the children of Hispanics born in the United States were more prone to CD. Immigrants were also older at the time of diagnosis than their American-born counterparts. Although it might be thought that diagnosis of IBD in immigrants was delayed because the immigrants did not have access to medical care in their country of origin, other factors may explain the age difference at diagnosis between immigrants and American-born study subjects.

UC is a disease in which patients have rectal bleeding, but several years may transpire before this symptom develops once the patient is in the United States. The patients in our study may have been asymptomatic while living in their country of origin. Upon settling in the United States, these immigrants may have been exposed to a series of events related to diet, antibiotic use, and other factors that then unmasked their genetic susceptibility to IBD. We are now in the process of finding out whether Hispanics have the same polymorphisms that are found in other European populations or whether polymorphisms are unique to the Americas. The genetics of American Indians are of particular interest. Obesity may be another risk factor for IBD. Obesity itself is a low-grade state of inflammation, and excessive calorie intake may be detrimental to patients in regard to IBD pathology.

G&H In terms of environmental factors plus genetics, who is most at risk?

MA Classically, the Ashkenazim and the Sephardim have been at greatest risk for development of IBD. As different

societies are becoming more westernized, an unfortunate consequence is a rising incidence of IBD. Risk factors include exposure to antibiotics early in childhood and a Western diet that contains a lot of processed foods. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) during childhood may be another risk factor. Cigarette smoking has been a classic risk factor for CD, but I have observed that, although the prevalence of smokers is decreasing, a concomitant decrease in the prevalence of CD does not appear to be occurring. I caution patients with IBD who have children to avoid needless antibiotic use, NSAIDs, and processed food in their children.

G&H How valuable, clinically speaking, would genetic testing be for IBD risk?

MA For now, there is a very limited role for genetic testing for IBD. NOD2 appears to add predictive value when combined with serologies to predict aggressive CD. With respect to genetic testing as a means of determining in whom IBD will develop, we do not yet have a definitive strategy for lessening the risk. Patients who have a family history of IBD need to be counseled about factors that might minimize risk, which would include—as mentioned—avoiding processed foods, cigarette smoking, NSAIDs, and needless antibiotic exposure. The risks these behaviors pose regarding development of IBD will not change by undergoing genetic testing. However, testing for susceptibility genes might ultimately be useful in making a diagnosis of IBD.

Dr. Abreu has no conflicts of interest to disclose.

Suggested Reading

Damas OM, Jahann DA, Reznik R, et al. Phenotypic manifestations of inflammatory bowel disease differ between Hispanics and non-Hispanic whites: results of a large cohort study. *Am J Gastroenterol.* 2013;108(2):231-239.

Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* 2012;491(7422):119-124.

Kenny EE, Pe'er I, Karban A, et al. A genome-wide scan of Ashkenazi Jewish Crohn's disease suggests novel susceptibility loci. *PLoS Genet.* 2012;8(3):e1002559.

Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol.* 2011;106(4):661-673.