Published in final edited form as:
Pediatr Res. 2008 August ; 64(2): 119–120. doi:10.1203/PDR.0b013e31818254b6.

Pediatric Inflammatory Bowel Disease Research: On the Cutting-Edge

David A. Ziring and **Jonathan Braun**

Recent groundbreaking collaborative efforts have brought the field of Pediatric inflammatory bowel disease (IBD) research to the threshold of a new era in our understanding of the pathogenesis and treatment of this condition. First, several multicenter collaborative research groups, each with computerized databases and large outcomes registries have agreed in principal to combine their efforts with regards to research in genetics, immunology, and infectious diseases. Our knowledge of the intestinal immune system and its communication with the resident luminal bacteria has increased dramatically. And genotyping technology has advanced to the point that it is now feasible to examine haplotype differences among thousands of patient samples in days and weeks instead of months and years.

Genome wide-association studies (GWAS) have been a boon to the understanding of the genetic components of complex diseases, and there is no better example of this than in the study of Crohn's disease (CD) (1). CD and ulcerative colitis are complex diseases involving the interplay of many genes and the environment. The responsible genes likely work in combination with each other to affect patient susceptibility. Earlier genetic linkage studies led to the identification of the nucleotide-binding oligomerization domain containing 2, the first susceptibility gene discovered in CD (2). But the search for susceptibility loci in IBD was slow and inefficient using traditional linkage analysis.

Clearly, newer more efficient technology was required to identify those genes contributing smaller, combined effects leading to disease susceptibility. This progress could not have been possible without the International HapMap project and the mapping of the human genome. Nor would our progress have been as rapid without technological advances that make possible the scanning of the genome of thousands of patients with IBD and controls for more than 500,000 single nucleotide polymorphisms. The resources provided by the pediatric IBD consortia include several thousand clinically well-characterized patient samples that provide statistical power to detect small genetic influences on outcome.

The as yet fully unrealized power of GWAS lies in combining the skills of the immunologist with the technology provided by geneticists. Immunologists who identify aberrant pathways in IBD pathogenesis are able to propose novel targets for candidate gene analyses. This strategy has been used with GWAS to provide evidence of disease association in the genes encoding TL1A (TNFSF15) and the IL-23 receptor. Using this same approach, a new groundbreaking aggregate analysis (3) has uncovered another 30 susceptibility genes accounting for about 20% of the heritability of IBD.

Immunologists identified new ways to characterize the pathogenesis of IBD beginning in the 1980s with the discovery of mouse models of mucosal inflammation that mirrored the human disease (4,5). This taught us that effector T cells in the intestinal mucosa responded abnormally to naturally occurring gut constituents. The ensuing years saw a great increase in our understanding of the mechanisms for maintenance of gut integrity and communication across the epithelial barrier, the sampling of luminal microbial antigens by resident dendritic cells, the sensing of these antigens by membrane bound and intracellular detection systems,

and the control of the inflammatory response by regulatory immune cells. Most recently, we have developed a better understanding about the communication between the innate immune system and the gut microbiome, learning that the colitigenic phenotype can be conferred by vertical transmission of the intestinal flora into a genetically intact host (6).

New techniques for 16s ribosomal RNA molecular fingerprinting now allows us to characterize the intestinal microbiome with remarkable specificity. For many years, our lack of access to appropriate tools has limited our understanding of numbers and characteristics of the organisms resident in the gut, as these were not easily culturable. But now we are not only able to identify particular species and serotypes of both bacterial and fungal organisms, but also we can compose large phylogenetic trees and characterize the relationships and abundance of the organisms.

Antibodies directed at specific gut microbial antigens can be identified in the sera of patients with IBD and reveal problems in barrier integrity, immune regulation, or both. These antibody titers can now be measured with greater specificity, run through complex algorithms and allocated into panels that enable clinicians to predict the natural history of disease (7) in some patients.

Investigators on the leading edge of IBD treatment will use these serologic values combined with genetic data and promising immuno-imaging modalities, ultimately to target therapeutics tailored for individual patients As one example, pediatric gastroenterologists have learned the value of using pharmacogenomics in our use of 6-mercaptopurine as an immunomodulator (8). In this case, we can determine the patient's level of metabolizing enzyme and use the drug at a more appropriate dose and time and improve the likelihood of a successful outcome. A recent study also showed that treating patients early in the course of their disease with the antitumor necrosis factor, biologic infliximab was shown to result in a statistically greater percentage of patients with intestinal mucosal healing at 26 wk follow-up (9). Using these new modalities, we hope to able to more carefully select those patients who would most benefit from the optimal use of biologics such as the antitumor necrosis factor antibodies or alpha-4 integrin antagonist and therefore not expose other patients who may be less likely to respond to these drugs. To this end, we will use either biologic or small molecule therapies to provide early, aggressive treatment to high-risk patients in an effort to prevent the eventual development of complications of chronic IBD, including intestinal scarring, narrowing, abscess, and fistula formation. These multidisciplinary advances in our understanding of the pathogenesis and treatment of pediatric patients with IBD has given us new reasons for hope for major improvements in care for this population in the next decade.

References

1. The Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007; 447:661–678. [PubMed: 17554300]
2. Mathew CG. New links to the pathogenesis of Crohn disease provided by genome-wide association scans. Nat Rev Genet. 2008; 9:9–14. [PubMed: 17968351]
3. Barrett. Nat Genet. in press.
4. Blumberg RS, Saubermann LJ, Strober W. Animal models of mucosal inflammation and their relation to human inflammatory bowel disease. Curr Opin Immunol. 1999; 11:648–656. [PubMed: 10631550]
5. Strober W. Animal models of inflammatory bowel disease—an overview. Dig Dis Sci. 1985; 30:3S–10S. [PubMed: 3905309]
6. Garrett WS, Lord GM, Punit S, Lugo-Villarino G, Mazmanian SK, Ito S, Glickman JN, Glimcher LH. Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. Cell. 2007; 131:33–45. [PubMed: 17923086]

7. Dubinsky MC, Lin YC, Dutridge D, Picornell Y, Landers CJ, Farrior S, Wrobel I, Quiros A, Vasiliauskas EA, Grill B, Israel D, Bahar R, Christie D, Wahbeh G, Silber G, Dallazadeh S, Shah P, Thomas D, Kelts D, Hershberg RM, Elson CO, Targan SR, Taylor KD, Rotter JI, Yang H. Western Regional Pediatric IBD Research Alliance 2006 Serum immune responses predict rapid disease progression among children with Crohn's disease: immune responses predict disease progression. Am J Gastroenterol. 101:360–367. [PubMed: 16454844]

8. Dubinsky MC, Lamothe S, Yang HY, Targan SR, Sinnett D, Theoret Y, Seidman EG. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology. 2000; 118:705–713. [PubMed: 10734022]

9. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, Vermeire S, Van de Mierop FJ, Coche JC, van der Woude J, Ochsenkühn T, van Bodegraven AA, Van Hootegem PP, Lambrecht GL, Mana F, Rutgeerts P, Feagan BG, Hommes D. Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club 2008 Early combined immuno-suppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 371:660–667. [PubMed: 18295023]