Decoding inflammatory bowel disease through the lens of immunodeficiency

The pathogenesis of inflammatory bowel disease (IBD), a chronic inflammatory condition involving the gastrointestinal tract, remains incompletely understood.[1] Genome-wide association studies (GWAS) have identified nearly 100 loci with single-nucleotide polymorphisms (SNPs) that are associated with altered risk for developing IBD. However, these SNPs are also often found in healthy subjects. Given that the currently identified genetic loci of common variants account for only 20–25% of the genetic risk for IBD, unanswered questions remain regarding the full composition of IBD genetic risk.[2,3] Recently, much attention has been focused on the presence of rare variants (with allele frequencies <5%) that may contribute to the remaining genetic risk.[4,5]

Children with genetically well-defined primary immunodeficiencies (PIDs) can present with IBD-like gastrointestinal pathology. Intestinal granulomas are found in nearly 50% of patients with chronic granulomatous disease (CGD), and up to 17% of CGD patients develop colitis.[6] Patients with mutations in interleukin-10 receptor (IL-10R) and IL-10 genes can develop early-onset enterocolitis.[7,8] Gastrointestinal inflammation can also be seen in patients with Wiskott–Aldrich syndrome (WAS), immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, and NFκB essential modulator defects. Because many PID patients with highly penetrant loss-of-function mutations (frequently involving pathways that have been identified by GWAS) present with aberrant mucosal immune homeostasis, study of these patients can provide an additional approach to deciphering the role of these immune pathways in IBD pathogenesis. Additionally, because many children with PIDs present with symptoms prior to gastrointestinal manifestations, these patients provide the opportunity to study initiating and early events leading to IBD in genetically predisposed patients.

Available murine models of human PIDs (that present with mucosal disease) complement human studies by permitting interrogation and manipulation of immune and microbial compartments not possible in patients. Mice lacking IL-10 or IL-10R have both innate and adaptive immune abnormalities and develop enterocolitis described in humans.[9,10] The gene encoding signal transducer and activator of transcription 3 (STAT3), which is defective in some PID patients with hyper–immunoglobulin E syndrome, has been linked to both ulcerative colitis and Crohn's disease; targeted deletion of STAT3 in the myeloid compartment in mice results in enterocolitis.[11–13] Altered WAS protein or foxp3 protein expression in mice or humans—associated with WAS and IPEX, respectively—can result in regulatory cell dysfunction, T helper type 2 cytokine skewing, and enteropathy.[14,15] A striking finding of most animal models of IBD is the absence of disease when animals are reared in germ-free conditions, highlighting the key interplay between the gut immune system and gut microflora.

A role for the human microbiome in IBD pathogenesis has been postulated for years, given the varied successes of antimicrobial therapy and diversion of the fecal stream in IBD patients. Subsets of patients with IBD have fewer Firmicutes and Bacteroidetes and less overall diversity of bacterial species,[16] but controversy exists as to whether these alterations are the driving force for initiating intestinal inflammation or simply a result of the inflamed microenvironment. In the T-bet$^{-/-}$RAG2$^{-/-}$ ulcerative colitis (TRUC) murine model of colitis, altered flora seems to result from the genetic abnormality and predate the development of disease. Most notably in this model, the colonic flora from TRUC mice are associated with altered microbial communities (including the presence of *Klebsiella pneumoniae* and *Proteus mirabilis*) and can induce colitis in normal mice.[17] Although the evidence for altered gastrointestinal flora in immunodeficient humans is lacking, children with PID afford the unique opportunity to investigate whether profound and highly penetrant genetic defects of the immune system are associated with alterations in the composition or diversity of the human microflora.

The study of IBD pathogenesis is challenging given the multitude of known and unknown genetic factors. Genetically defined PIDs allow for the study of immune pathways relevant to IBD risk and their downstream effect on the human microbiome and mucosal homeostasis. Moreover, these pathways may play an underestimated role in the onset of IBD, especially in children. Therefore, the knowledge gained from studying the genes (and pathways) implicated in PID and mucosal disease should offer unique insights into IBD pathogenesis.

Christopher J Moran
Athos Bousvaros
Scott B Snapper

1. Kaser, A., Zeissig, S. & Blumberg, R.S. Inflammatory bowel disease. *Annu. Rev. Immunol.* **28**, 573–621 (2010).
2. Cho, J.H. & Brant, S.R. Recent insights into the genetics of inflammatory bowel disease. *Gastroenterology* **140**, 1704–1712 (2011).
3. Franke, A. *et al*. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat. Genet.* **42**, 1118–1125 (2010).
4. Imielinski, M. & Hakonarson, H. Breaking new ground in inflammatory bowel disease genetics: genome-wide association studies and beyond. *Pharmacogenomics* **11**, 663–665 (2010).
5. Worthey, E.A. *et al*. Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genet. Med.* **13**, 255–262 (2011).
6. Guerrerio, A.L., Frischmeyer-Guerrerio, P.A., Lederman, H.M. & Oliva-Hemker, M. Recognizing gastrointestinal and hepatic manifestations of primary immunodeficiency diseases. *J. Pediatr. Gastroenterol. Nutr.* **51**, 548–555 (2010).
7. Glocker, E.O. *et al.* Inflammatory bowel disease and mutations affecting the interleukin-10

receptor. *N. Engl. J. Med.* **361**, 2033–2045 (2009).
8. Glocker, E.O. *et al*. Infant colitis—it's in the genes. *Lancet* **376**, 1272 (2010).
9. Kuhn, R., Lohler, J., Rennick, D., Rajewsky, K. & Muller, W. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell* **75**, 263–274 (1993).
10. Spencer, S.D. *et al*. The orphan receptor CRF2–4 is an essential subunit of the interleukin 10 receptor. *J. Exp. Med.* **187**, 571–578 (1998).
11. Franke, A. *et al*. Replication of signals from recent studies of Crohn's disease identifies previously unknown disease loci for ulcerative colitis. *Nat. Genet.* **40**, 713–715 (2008).
12. Takeda, K. *et al*. Enhanced Th1 activity and development of chronic enterocolitis in mice devoid of Stat3 in macrophages and neutrophils. *Immunity* **10**, 39–49 (1999).
13. Barrett, J.C. *et al*. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat. Genet.* **40**, 955–962 (2008).
14. Nguyen, D.D. *et al*. Lymphocyte-dependent and Th2 cytokine-associated colitis in mice deficient in Wiskott-Aldrich syndrome protein. *Gastroenterology* **133**, 1188–1197 (2007).
15. Khattri, R., Cox, T., Yasayko, S.A. & Ramsdell, F. An essential role for Scurfin in CD4+CD25+ T regulatory cells. *Nat. Immunol.* **4**, 337–342 (2003).
16. Frank, D.N. *et al*. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc. Natl. Acad. Sci. USA* **104**, 13780–13785 (2007).
17. Garrett, W.S. *et al.* Enterobacteriaceae act in concert with the gut microbiota to induce spontaneous and maternally transmitted colitis. *Cell Host Microbe* **8**, 292–300 (2010).