Inflammatory bowel disease

Does innate immune response defect underlie inflammatory bowel disease in the Asian population?

F Lanzarotto, A Akbar, S Ghosh

Lifestyle rather than key genetic defects might be responsible for the defective innate immune response in Asians with inflammatory bowel disease.

The normal intestine encounters a high concentration of foreign antigen, bacteria, and food, across a large surface area that approximates to that of a tennis court. Despite the fact that this antigenic load is separated from the largest complement of lymphocytes in the body (gut associated lymphoid tissue, GALT) by only a single layer of polarised intestinal epithelium, most people do not mount an immune response to foreign antigens. The mucosal immune system has evolved to balance the need to respond to pathogens while maintaining active tolerance to commensal bacteria and food antigens. In inflammatory bowel disease (IBD), this tolerance breaks down and inflammation supervenes driven by the intestinal microbial flora. Tolerance is based both on the protection offered by the evolutionary conserved innate immune response that is non-antigen specific and the antigen specific adaptive immune response that develops upon antigen exposure. Current key targeted therapeutic strategies are directed against important cytokines that drive the adaptive immune response (anti-TNF antibodies), prevention of trafficking of lymphocytes to the intestine (α4 integrin antibodies), or induction of apoptosis of lymphocytes.

“Permanent” tolerance, however, is not restored and relapses are virtually inevitable when treatment is withdrawn. Understanding the molecular mechanisms of the breakdown of tolerance resulting from a defect in the innate immune response would potentially permit identification of novel therapeutic strategies. Identification of specific genetic mutations affecting the innate immune response associated with IBD disease lends credibility and rationale for pursuing this line of research.

While it is now undisputed that enteric bacterial flora play a key part in the pathogenesis of IBD, both ulcerative colitis (UC) and Crohn’s disease (CD), the exact mechanism resulting in the loss of tolerance of the intestinal mucosa to its bacterial neighbours remains elusive. The role of host genetic regulation of the innate immune response in the pathogenesis of CD has been brought to sharp focus by the identification of the NOD2 (CARD15) mutations on chromosome 16q12 strongly associated with CD, especially with ileal involvement. The specific ligand of cytosolic NOD2 is identified to be muramyl dipeptide, a component of peptidoglycan, which is a constituent of Gram negative bacteria, leading to NF-κB activation. A novel association between TLR4 polymorphism with both UC and CD has been recently described in Belgian cohorts, and with CD (less strongly with UC) in Greek and with UC alone in German IBD populations. In the Belgian and Greek IBD populations, allele frequency of TLR4 Asp299Gly was increased, whereas in the German population, TLR4 Thr399Ile mutation was increased in frequency. In addition to TLR4, CD14 (a GPI anchored molecule on the cell surface of monocytes) is also involved in recognising LPS complexed with LPS binding protein (LBP), which is a component of Gram negative bacteria, in the Greek population the T allele and TT genotype frequencies of CD14 promoter were significantly higher in CD patients compared with healthy people. In a recent report, it was shown that in Hungarian CD patients, the frequency of TLR4 polymorphism was not increased compared with controls. In a German IBD population, the T allele and TT genotype frequencies of CD14 promoter were found increased in CD population but not in UC population, whereas in a Japanese population promoter polymorphism of CD14 gene seemed to confer a genetic predisposition to UC.

It is intuitive to hypothesise that innate immune response defects leading to permanent tolerance will be an important part in combating the invasion of pathogens as a frontline defence. TLRs are composed of an intracytoplasmic toll/interleukin1 receptor domain and extracellular leucine rich repeat region (LRR). TLR4 specifically binds the lipid A portion of lipopolysaccharide (LPS), which is a component of Gram negative bacteria, leading to NF-κB activation. A novel association between TLR4 polymorphism with both UC and CD has been recently described in Belgian cohorts, and with CD (less strongly with UC) in Greek and with UC alone in German IBD populations. In the Belgian and Greek IBD populations, allele frequency of TLR4 Asp299Gly was increased, whereas in the German population, TLR4 Thr399Ile mutation was increased in frequency. In addition to TLR4, CD14 (a GPI anchored molecule on the cell surface of monocytes) is also involved in recognising LPS complexed with LPS binding protein (LBP), which is a component of Gram negative bacteria, in the Greek population the T allele and TT genotype frequencies of CD14 promoter were significantly higher in CD patients compared with healthy people. In a recent report, it was shown that in Hungarian CD patients, the frequency of TLR4 polymorphism was not increased compared with controls. In a German IBD population, the T allele and TT genotype frequencies of CD14 promoter were found increased in CD population but not in UC population, whereas in a Japanese population promoter polymorphism of CD14 gene seemed to confer a genetic predisposition to UC.

Table 1 Toll-like receptor family

<table>
<thead>
<tr>
<th>TLR family</th>
<th>Chromosome</th>
<th>Function/ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR1</td>
<td>4</td>
<td>Regulates TLR2 response.</td>
</tr>
<tr>
<td>TLR2</td>
<td>4</td>
<td>Microbial lipoproteins and peptidoglycans. CD14 dependent and independent responses to LPS.</td>
</tr>
<tr>
<td>TLR3</td>
<td>4</td>
<td>Interacts with dsRNA. MyD88 dependent and independent response to poly (I:C).</td>
</tr>
<tr>
<td>TLR4</td>
<td>9</td>
<td>Interacts with microbial lipoproteins. CD14 dependent response to LPS.</td>
</tr>
<tr>
<td>TLR5</td>
<td>1</td>
<td>Interacts with microbial lipoproteins, response to salmonella.</td>
</tr>
<tr>
<td>TLR6</td>
<td>4</td>
<td>Interacts with microbial lipoproteins and regulates TLR2 response.</td>
</tr>
<tr>
<td>TLR7</td>
<td>X</td>
<td>Single stranded RNA, siRNA, synthetic ligands.</td>
</tr>
<tr>
<td>TLR8</td>
<td>X</td>
<td>Uncertain.</td>
</tr>
<tr>
<td>TLR9</td>
<td>3</td>
<td>Receptor for CpG bacterial DNA motifs.</td>
</tr>
<tr>
<td>TLR10</td>
<td>4</td>
<td>Regulatory to TLR1 and TLR6. Asthma candidate gene, allergens.</td>
</tr>
</tbody>
</table>

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn’s disease; TLR, toll-like receptor; UC, ulcerative colitis
Crosstalk between NOD2 and toll receptor pathways.

Figure 1

Microbial ligands recognised by TLRs are produced by both pathogenic and commensal microflora of the gut. Activation of TLRs by commensal gut flora is essential for protection against gut injury. We have shown cross-talk between the TLR and NOD2 signalling pathways in human peripheral blood mononuclear cells, although the data from animal models have been conflicting. Further evidence suggests that defective NOD2 function results in a pro-inflammatory cytokine bias after stimulation of mononuclear cells with TLR2 stimuli. NOD2 mutations may result in imperfect sensing of danger resulting in overdrive of the adaptive immune response in presence of bacterial PAMPS. We have already shown that intestinal epithelial-like Caco-2 cells provide a microenvironment for a tolerising gut-type DC phenotype. It has been recently shown that epithelial cell conditioned dendritic cells released IL10 and IL6, but not IL12 and promoted polarisation of T cells toward Th2 response even after exposure to a Th1 inducing pathogen. Mucosal DCs have the ability to preferentially promote Th2 polarisation and IgA secretion by B lymphocytes. Several key receptors are important in the innate immune response including pattern recognition receptors such as TLRs, NOD, C-type lectin CD205, mannose receptor, IgA receptor. The key adaptive immune response receptors include MHC class I and II, CD1 family, CD80, CD86, CCR7, and CD40. It would seem probable that a defect in any of the molecules involved in the innate immune system leads to an overdrive of the adaptive immune system in response to intestinal bacteria. In populations traditionally exposed to high bacterial loads, it is possible that innate immune response defects confer a survival disadvantage and are selected out. However, as economic affluence makes the environment more hygienic, the intestinal tolerance promoted by constant stimulation of PRRs by PAMPS is gradually eroded, permitting exaggerated response to appropriate bacterial triggers. We have recently seen that Scottish children from more affluent areas had a higher relative risk of developing CD. It is possible to speculate that we shall find a similar phenomenon in the Asian subcontinent as the lifestyle becomes more Western. Although the possibility that other innate immune response defects at a genetic level may be discovered in the Asian population with IBD, it is possible that the innate immune response intrinsically maintains homeostasis and immune tolerance for which bacterial exposure in early life is essential, and in the absence of such exposure at the right age, the innate immune response loses its ability to regulate the adaptive immune response. The defect in innate immune response in the Asian IBD populations therefore may have an intimate link with lifestyle rather than the key genetic defects identified in Western IBD populations.

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