Commensal gut microbiota, genetic and epigenetic factors and susceptibility to inflammatory bowel disease

The incidence of inflammatory bowel disease, an often debilitating disorder, is increasing. Recent data indicate that complex interactions between the commensal gut microbiota, genetic and epigenetic factors and mucosal immunity are important in pathogenesis. Ongoing studies into these interactions will continue to advance understanding of processes responsible for the development of inflammatory bowel disease, as well as inform new and more effective approaches to management.

Inflammatory bowel disease (IBD), including Crohn’s disease and ulcerative colitis, is an often debilitating disorder marked by chronic and relapsing intestinal inflammation that has a high incidence in Australia. Incidences have increased over the past five or so decades both in children and in adults and in both low-incidence and high-incidence geographic locations. Studies into factors responsible for intestinal inflammation in IBD implicate a disturbance in the otherwise symbiotic relationship between the host’s intestinal mucosal immune system and the commensal gut microbiota, with genetic predisposition, environmental influences and dysbiosis of the gut microbiota each likely contributing.

It is well established that genetic factors contribute to susceptibility to IBD and much recent work has centred on identifying specific loci involved. A recent meta-analysis of Crohn’s disease and ulcerative colitis genome-wide association studies, followed by validation of significant findings in 75,000 patients and controls, identified a total of 165 IBD loci, more than that reported for any other complex disease to date. Over two-thirds of these susceptibility loci are associated with both Crohn’s disease and ulcerative colitis, suggesting that shared genetic mechanisms contribute to their pathogenesis. Exceptions are particular risk alleles at two Crohn’s disease loci, namely nucleotide oligomerisation domain 2 (NOD2) and PTPN22, which demonstrate significant protective effects in ulcerative colitis. Many of the DNA polymorphisms and haplotypes shown to be associated with predisposition to IBD participate in the host’s innate and adaptive immune responses to microbial organisms, pointing to a key role for perturbation in the mucosal immune response to commensal gut bacteria in disease pathogenesis.

Despite the large number of genetic loci linked to IBD, however, only a minority of the variance in disease risk for both Crohn’s disease and ulcerative colitis can be explained on a currently identified genetic basis, indicative that environmental factors likely contribute substantially to aetiopathology. Indeed, evidence of disease concordance rates in monozygotic twins of only 50% and 20% for Crohn’s disease and ulcerative colitis, respectively, along with the documented increased incidence of IBD among migrants from low-incidence to high-incidence areas, within the same generation, suggest an important environmental influence.

Recent data suggest that a complex interplay between commensal gut microbiota and epigenetics, defined as hereditable changes in gene expression due to mechanisms other than variations in DNA sequence, such as DNA methylation and post-translational histone modifications, may be responsible for at least some of the apparent effects of environment on IBD pathogenesis. For example, expression by intestinal epithelial cells of the pattern recognition receptors, Toll-like receptor (TLR) 2 and TLR4 is regulated by DNA methylation and histone deacetylation, which, in turn, depend on the presence of commensal gut microbiota. Furthermore, the expression of the chemokine receptor ligand, CXCL16, in a murine model of IBD is regulated by DNA hydroxymethylation, which also is critically dependent on exposure to commensal gut bacteria, especially early in life. It is well established in various genetically susceptible animal models that IBD does not occur in a commensal gut bacteria-free environment.

Analyses of mucosa-associated and faecal bacteria have demonstrated that patients with established IBD have both qualitative and quantitative changes in the composition of the commensal gut microbiota, with a reduction in diversity of faecal bacteria and an
increase in number of mucosa-adherent bacteria\textsuperscript{13}. Reduced numbers of bacteria with anti-inflammatory properties, such as \textit{Faecalibacterium prausnitzii} and \textit{Bifidobacterium} spp and an increased number of pro-inflammatory Enterobacteriaceae, especially \textit{Escherichia coli}, have been reported in those with established Crohn’s disease, while alterations in the composition of Gram-negative bacteria with anti-inflammatory properties, such as \textit{Akkermansia muciniphila} have been reported in those with increased number of mucolytic bacteria such as \textit{Ruminococcus gnavus} and \textit{Ruminococcus torques} demonstrated in this setting\textsuperscript{18}. Recent data suggest that microbial function is also disturbed in IBD, with perturbations in oxidative stress pathways particularly affected\textsuperscript{19}.

Given that the composition of the commensal gut microbiota may be disturbed by inflammation\textsuperscript{20}, an important issue, for which little data are currently available, is whether the dysbiosis so far identified in established IBD is present at disease onset - and hence may play a role in initiation of the disorder – or, rather, develops as a consequence. A recent analysis performed in the paediatric IBD setting at diagnosis, limiting the likelihood that microbial changes may have evolved as a consequence of the disease, is noteworthy in demonstrating a significant reduction in bacterial diversity early in the clinical course of Crohn’s disease. However, no such trend was apparent in children with ulcerative colitis. Furthermore, an increase in \textit{Faecalibacterium prausnitzii} was evident in the early stages of Crohn’s disease, suggesting a more complex gut microbial dynamic in IBD than previously considered\textsuperscript{21}.

Ongoing studies into the complex relationships between the commensal gut microbiota, genetic and epigenetic factors and mucosal immunity will continue to advance understanding of the pathogenesis of IBD, as well as inform new and more effective approaches to management of this condition.

References


Biography

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