What Causes Inflammatory Bowel Disease?

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The inflammatory bowel diseases, comprising mostly ulcerative colitis and Crohn’s disease, are caused by a combination of genetic susceptibility, environmental or luminal factor(s), and a disregulation of the immune system.

Genetic Factors

The genetic contribution to both conditions is polygenic. Swedish twin studies have demonstrated a stronger genetic influence for Crohn’s disease than ulcerative colitis. The chromosomal loci for some of these susceptibility genes have been identified, but recently the first specific gene associated with Crohn’s disease has been identified on chromosome 16.

A gene location in the pericentromeric region of chromosome 16, IB1Q, that contributes to susceptibility to Crohn’s disease had been established through multiple linkage studies. NOD2, a gene that encodes a protein with homology to plant disease resistance gene products, is located in the peak region of linkage on chromosome 16. Three independent variants of the NOD2 gene have been associated with Crohn’s disease.

Permissive Factors such as Stress

Even if specific genetic abnormalities are present, and the response to bacteria are central to pathogenesis, other factors may play a role, especially in modifying the threshold for an inflammatory process to be initiated or perpetuated. For example stress may alter gut barrier function via CRF mediated effects on inflammatory cells, gut mucus, gut permeability, and even by shifts in the gut luminal bacterial population.

Immune Activation and Tissue Destruction

The combination of genetic susceptibility, the presence of bacteria (pathogenic or commensal), and facilitatory factors such as stress, may then allow an inflammatory process to be initiated and continue. Dendritic cells are important in this recognition and perpetuation, as are the wide spectrum of inflammatory cells. Cells are attracted to sites of inflammation. A broad range of inflammatory cytokines then drive the inflammatory response. These cytokines ultimately cause tissue enzymes, particularly metalloproteinases, to produce tissue destruction.

Using Knowledge of Pathogenesis to Treat Disease

Any of these components of the inflammatory process may be a suitable therapeutic target. One of the more interesting possibilities is that gut inflammation may be reduced by altering the gut bacterial population.

The greatest body of evidence for modifying the gut flora currently relates to the ingestion of probiotic bacteria, that is bacteria which confer health benefits or disease modifying characteristics in excess of their nutritional value. Classically various types of lactobacilli and bifidobacteria have been considered to have such properties, although even within these species the evidence for therapeutic benefit varies between strains. Other bacteria such as certain strains of E. coli have also been shown to have therapeutic value.

In the inflammatory bowel diseases the administration of probiotic bacteria have started to have a real therapeutic impact. Campieri, Gionchetti and colleagues have shown in controlled trials that the administration of a concentrated mixture of multiple strains of probiotic bacteria will maintain remission in patients with an ileo-anal reservoir in whom antibiotics have healed an acute episode of inflammation (pouchitis). Both the antibiotic healing of the acute inflammation, and the maintenance of a healthy mucosa by altering the luminal milieu, form convincing evidence for the primary role of bacteria driving the inflammatory process in this condition. This group has also shown a decreased endoscopic recurrence in post operative patients with Crohn’s disease given antibiotics and probiotics after curative resection.

Gionchetti and colleagues have evaluated the benefits of a probiotic preparation (VSL#3) containing 5 x 10^11 per gram of viable lyophilised bacteria of 4 strains of lactobacilli, 3 strains of bifidobacteria, and 1 strain of Streptococcus salivarius subsp. thermophilus compared with placebo in maintenance of remission of chronic pouchitis. Forty patients in clinical and endoscopic remission were randomised to receive either VSL#3, 6 g/day, or an identical placebo for 9 months. Patients were assessed clinically every month and endoscopically and histologically every 2 months or in the case of a relapse. Faecal samples were collected for stool culture before and after antibiotic treatment and each month during maintenance treatment. Three patients (15%) in the VSL#3 group had relapses within the 9-month follow-up period, compared with 20 (100%) in the placebo group (P < 0.001). Faecal concentration of lactobacilli, bifidobacteria, and S. thermophilus increased significantly from baseline levels only in the VSL#3-treated group (P < 0.01). These results suggest that oral administration of this new probiotic preparation is effective in preventing flare-ups of chronic pouchitis. This type of study opens up a whole new area of therapeutic possibility.

Conclusion

In conclusion, genetic, bacterial, stress, and immune factors are being defined which all contribute to the genesis of gut inflammation. This information is already being utilised to produce therapeutic benefit.

References


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**GENETIC FACTORS**

The genetic contribution to both conditions is polygenic. Swedish twin studies have demonstrated a stronger genetic influence for Crohn's disease than ulcerative colitis. The chromosomal loci for some of these susceptibility genes have been identified, but recently the first specific gene associated with Crohn's disease has been identified on chromosome 16.

A gene location in the pericentromeric region of chromosome 16, IBD1, that contributes to susceptibility to Crohn's disease had been established through multiple linkage studies. NOD2, a gene that encodes a protein with homology to plant disease resistance gene products, is located in the peak region of linkage on chromosome 16. Three independent variants of the NOD2 gene have been associated with Crohn's disease. Wild-type NOD2 activates nuclear factor NF-kappaB, making it responsive to bacterial lipopolysaccharides; however, this induction is deficient in mutant NOD2. NOD2 variants appear to be associated with increased susceptibility to Crohn's disease, involving the innate immune response to bacterial components. The NOD2 gene product confers susceptibility to Crohn's disease by altering the recognition of intracellular receptor for components of microbial pathogens and/or by over-activating NF-kB in monocytes.

The NOD2 gene abnormality is likely to be present in only about 20 percent of Crohn's patients, and even in these patients may be only one of several predisposing abnormalities.

**GUT BACTERIA**

Previous studies by Duchmann and co-workers had previously convincingly demonstrated that inflammatory bowel diseases are associated with loss of the normal tolerance to the normal indigenous gut flora. Identification of the NOD2 gene provides a genetic basis for this abnormal host - bacterial interaction.

Whether the abnormal T cell response to luminal bacteria involves normal bacteria, or so far unidentified abnormal enteric pathogens, remains unknown. Any pathogens have been implicated, but none have been convincingly shown to be responsible. These include measles virus, Mycobacteria paratuberculosis, adherent E.coli. New molecular techniques for identifying unknown bacteria may allow new light to be shed on this difficulty.

Recent studies have suggested that a particular microbial gene in the murine intestine, Il2, is associated with Crohn's disease. The Il2 protein is a new class of T cell superantigen. Colonisation by the Il2 micro-organism in susceptible hosts may provide a superantigenic stimulus pertinent to Crohn's disease pathogenesis.

**PERMISSIVE FACTORS SUCH AS STRESS**

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**IMMUNE ACTIVATION AND TISSUE DESTRUCTION**

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**USING KNOWLEDGE OF PATHOGENESIS TO TREAT DISEASE**

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The greatest body of evidence for modifying the gut flora currently relates to the ingestion of probiotic bacteria, that is bacteria which confer health benefits or disease modifying characteristics in excess of their nutritional value. Classically various types of lactobacilli and bifidobacteria have been considered to have such properties, although even within these species the evidence for therapeutic benefit varies between strains. Other bacteria such as certain strains of E.coli have also been shown to have therapeutic value.

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**CONCLUSION**

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**REFERENCES**


