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Current concepts of the pathogenesis of inflammatory bowel disease

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Over the past decade, the focus of the etiopathogenesis of chronic inflammatory bowel disease (IBD) has turned toward defining a deficit in immune regulation. The problem inherent in presenting IBD as the result of a disordered immune system is the lack of knowledge of what is primary to disease itself and what is secondary to disease effects. Whether the immune system plays an initiating or a perpetuating role in the pathogenesis of IBD, it is the local immune response that causes the tissue damage and is responsible for the clinical presentation in IBD.

Presently, the utility of stratification of CD and UC into pathogenetically homogenous groups remains a question. Thus, CD and UC may be a heterogenous set of diseases with similar, yet distinctive, clinical phenotypes, and each subgroup may have different clinical courses and require different treatment approaches. The basis for this heterogeneity is at the primary genetic level, but the expression of genetic susceptibility requires environmental triggers. Despite extensive research, a common etiological agent has not yet been defined. Consequently, the primary events, which initiate the inflammatory response, remain unknown and treatment is empirical.

Clinical, epidemiological and experimental animal model studies strongly suggest an important genetic influence in the development of IBD. Approximately 10%-20% of patients with CD or UC have affected family members, with the highest risk among first-degree relatives. Several studies have demonstrated a greater than expected concordance for site and clinical type within multiple affected relatives.

These results suggest the presence of genetically defined subsets of CD and allow classification of CD according to anatomical location, extent (localized or diffuse) and behaviour of disease (stenotic *vs* aggressive fistulizing disease), and operative history.

Genetic studies have recently identified alleles of genes that are associated with CD and UC. The Table shows recently described IBD susceptibility loci of interest, which involve chromosome 3, 6, 7, 12 and 16.

A number of genetically determined immune system characteristics, including HLA haplotype and IL-1ra, tumor necrosis factor, adhesion molecules, and complement subunit polymorphisms, have been associated with IBD. By using random microsatellite markers, it has recently been demonstrated that a specific area on chromosome 16 also possesses a gene or genes related to CD. Similarly, among patients with UC, several genes have increased associations and the allelic associations of each of these genes seem to vary depending on the ethnic background.

In recent years much has been learned from genetically engineered knock-out and transgenic rodents, in whom modulation of a single gene induces spontaneous colitis or increased susceptibility to experimental colitis.

The current concepts of the pathogenesis of IBD assume that Crohn's disease and ulcerative colitis are idiopathic disorders, which are immunologically mediated and caused by an unrestrained activation of the inflammatory response. This may be due to a defective immunosuppression. Patients with IBD also have abnormatilities in epithelial antigen presentation. The inflammation may be driven by ubiquitous antigens, including normal resident luminal bacteria, bacterial products and toxins.

Three theories of IBD etiology are currently under consideration: (1) reaction to a persistent intestinal infection, (2) existence of a defective mucosal barrier to luminal antigens, and (3) a dysregulated host immune response to ubiquitous antigens. IBD may develop as an appropriate reaction to a persistent specific infection of the intestine. In CD infectious agents under current consideration include *Mycobacterium paratuberculosis*, paramyxovirus—more specifically measles or the association of measles and mumps or vaccination with MMR within the first year of live, and *Listeria monocytogenes*.

Most work has concentrated on the role of mycobacterial infection, but the absence of acid-fast bacilli and the fact that the granulomas in CD are non-caseating, have dampened enthusiasm. In serological and immunohistochemical studies on CD sera, the results are overlapping and less than 65% positive signals are reported using sensitive polymerase chain reaction (PCR) to detect -Mycobacterium paratuberculosis.

Several investigators have suggested a possible etiological role for small cytopathic RNA vira. One group reported measles- like particles in cells adhering to the vascular endothelium in CD—and later, that the presence of primary antibodies indentified their target antigens. Others have found no evidence of target RN A with PCR-

technique, and the hypothesis that measles vaccination is a risk fac tor has not been confirmed.

In UC, some evidence supports an etiological role in abnormal *Escherichia coli*. Abnormal bacterial metabolites and products may also contribute to the etiology of UC. Hydrogen sulfied, which is a product of anaerobic colonic bacteria, is found in increased concentrations in the colonic lumen of patients with UC. This agent selectively inhibits butyrate metabolism in colonic epithelial cells.

A defective mucosal barrier between the intestinal lumen and the circulation may allow unrestrained uptake of antigens and pro-inflammatory molecules.

Enhanced mucosal permeability has been observed in relatives of CD patients, with evidence of excessive response to NSAIDs in some asymptomatic family members. Specific abnormalities in mucosal barrier function have been found in patients with UC. These include reduction in colonic mucin species Ⅳ and alterations in mucin structure and lectin binding. Spontaneous colitis is observed in chimeric m ice with defective epithelial tight junctions. Furthermore, reduced mucosal defence has been demonstrated in mice deficient of intestinal trefoil factor and excessive inflammation has been described in mice deficient of growth factors.

Finally, IBD may be the result of an abnormal host response to ubiquitous antigens.

In CD, the response may be elicited by luminal constituents, whereas in UC, an autoimmune response may be the causative factor. A disordered regulation of the mucosal and systemic immune system results in activation of a self-perpetuating inflammatory cascade.

The assumption that CD and UC are autoimmune diseases has very little immunological documentation. Most likely, anit-epithelial cell responses observed in UC are nonpathogenic, secondary responses. Anti-neutrophil cytoplasmatic antibodies with perinuclear nuclear staining (pANCA), which are produced within the mucosa and present in 60%-70% of UC patients and 10%-15% of CD patients, may, however, be subclinical markers of disease phenotype. The population of UC patients producing pANCA has a stronger association with the MHC class Ⅱ allele than the UC population as a whole. A second autoantibody, anti-Saccharomyces cerevisia antibody (ASCA), has been observed in 50%-60% of CD patients, but only 10%-15% of patients with UC. The combination of genotyping with stratification by subclinical markers has provided the existing evidence of disease heterogeneity.

The most important pro-inflammatory and anti-inflammatory mediators may be involved in the pathogenesis of IBD. An imbalance between stimulating and inhibiting factors can start the process. For example, mice lacking T-cell receptors develop spontaneous colitis, whereas mice that do not produce the anti-inflammatory mediators, TGFβ or IL-10, develop chronic intestinal inflammation.

An important immunoregulatory balance is the one between IL-1 and IL-1ra, an anti-cytokine that inhibits the activity of IL-1 by binding to IL-1 receptors without causing agonist activity. In IBD, the ratio of IL-1ra to IL-1 in mucosal biopsies is significantly decreased compared to the healthy controls—and the defective production of IL-1ra is genetically determined.

However, genetic susceptibility is modulated by environmental factors, because the incidence of IBD is altered when populations move to new locations, and colitis fails to develop in genetically susceptible rodents raised in a sterile environment. UC is negatively correlated to smoking, while CD is positively correlated to smoking. Other less well-documented influences, such as oral contraceptives, refined sugars, lack of dietary fibers, perinatal infections, domestic hygiene, and nonsteroidals (NSAIDs), have been implicated to explain the rising incidence of CD in the industrialized countries compared with third world environments .

The pathogenesis of IBD progresses through a series of steps. The initiating events are separate from the perpetuating events, so, in theory, intervention can be undertaken at either stage. The immunoregulatory abnormalities characteristic of IBD will amplify the inflammatory reaction, leading to tissue damage and finally the well-known clinical symptoms. Either an infectious or a non-infectious agent may start the process.Any agent capable of breaking the mucosal barrier or stimulating an inflammatory response can start the process in susceptible patients. Luminal microbial agents break through the mucosa, where they activate inflammatory cells, with in turn release cytokines, arachidonic acid metabolites, platelet activating factor (PAF), reactive oxygen metabolites (ROMs), and nitric oxide, thus perpetuating the inflammatory response. The importance of luminal resident bacteria, such as *bacteriodes species*, is illustrated by the lack of colonic and joint inflammation in germ-free transgenic rats (HLA-B27).

There is some evidence of dysregulation of pro and anti-inflammatory regulatory cytokines and T-helper lymphocyte subsets in chronic intestinal inflammation. The key aggressive regulatory cytokines appears to be IL-1, TNFα, IL-12, and interferon γ(INFγ),-whereas the most important immunosuppressive regulatory molecules are TGFβ, IL- 4, and IL-10.

Other immunoregulatory abnormalities in IBD are related to the activities of the T_{H1} and T_{H2} subsets of T_H lymphocytes. T_{H1} cells mediate cellular immune responses and macrophage activation (lymphokine and complement production, and antibody- mediated cytotoxicity), whereas T_{H2} cells mediate hypersensitivity responses and down-regulate macrophages (B-cell and mast cell activation, IgG1 and IgE production, and eosinophilia). In experimental colitis, blockade of INFγ- prevents inflammation, suggesting that T lymphocytes play an essential role in chronic colitis.

Patients with CD seem to have selectively activated T_{H1} lymphocytes, whereas those with UC have selectively activated T_{H2} lymphocytes, suggesting that the two disorders have different, genetically determined pathogenic pathways. Of clinical interest is the aggressive fistulizing and stenotic forms of CD seem to have different T_{H1} and T_{H2} lymphokine profiles.

The activation of macrophages and T lymphocytes results in outpouring of cytokines, which in turn amplify the inflammatory response by recruiting other inflammatory cells. Expression of adhesion molecules is increased, which allows adherence of neutrophils, monocytes, and lymphocytes to blood vessels and their migration through the vessel wall and interstitial matrix. The inflammatory response is further augmented as an increasing number of effector cells, epithelial cells, and mesenchymal cells are stimulated.

As cells are activated, they release soluble mediators of inflammation that induce tissue injury. Activated neutrophils and macrophages release for example TXs, LTs, and PAF—and in response to bacterial products, such as FMLP, lipopolysacc harides, and peptidoglycan-polysaccharide—reactive oxygen metabolites, which oxidize essential sulfhydryls, degrade proteins, carbohydrates, hyaluronic acid, and mucin, inactivate NADPH and NADH, peroxidate membrane lipids, and promote DNA breaks.

The clinical manifestations of IBD—diarrhea, bleeding, pain, and weight loss—are the end result of the pathogenic process described here.

In conclusion, CD and UC are two forms of intestinal inflam-mation with possible common genetic predisposition—and may be part of a spectrum, rather than two distinct diseases. Induction may be non-specific. Genetic susceptibility and uptake of bacterial products perpetuate inflammation. Genetic and environmental factors are critical, but neither alone is sufficient. Progression and resolution of CD and UC are dependent on the balance of pro- and anti-inflammatory mediators. Homeostasis or chronic inflammation depends on the balance between inflammatory luminal constituents and protective mucosal factors. Specific therapy directed at an immunoregulatory defect or an inciting agent could alter the disease course.

Current therapies, such as glucocorticolds and 5-aminosalicylic acid (5-ASA), inhibit raised concentrations of interdependent, soluble mediators of inflammation, which may amplify one another or have parallel effects. In remains, however, to be defined whether targeting multi-inflammatory actions or a single key pivotal process is the better therapeutic strategy. The type of new drugs being developed include (1) conventional pharmaceuticals, (2) receptor antagonists-agonists, (3) enzyme inhibitors, (4) bio-engineered compounds (monoclonal antibodies, chimeric-targeted toxins, receptor ligands-soluble receptors), and (5) gene therapy.

Future medical options for treatment of IBD should aim at removing perpetuating antigens, blocking entry of inflammatory cells, enhancing endogenous suppressive molecules or correcting genetic defects.

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