

Gut

Leading article

Are the inflammatory bowel diseases autoimmune disorders?

There has been speculation for many years concerning autoimmune involvement in the pathogenesis of the inflammatory bowel diseases. Is there sufficient evidence to label ulcerative colitis and Crohn's disease as autoimmune disorders?

Definition of autoimmunity

Strictly, classification of a disease as autoimmune requires the demonstration of autoreactive lymphocytes or auto-antibodies, or both, which are specific for the disease concerned, present in all cases, and, most important, capable of reproducing the disease on syngeneic transfer. This is not feasible for human disease, where the presence of less exacting criteria are considered suggestive of autoimmune involvement: (a) Circulating disease specific autoantibodies, which may or may not be of direct relevance to pathogenesis – for example, antibodies to the acetylcholine receptor in myasthenia gravis and to mitochondrial antigens in primary biliary cirrhosis respectively. (b) An association with other autoimmune disorders. (c) An association with one or more HLA haplotypes. (d) A prominent lymphocytic infiltrate at the site of active disease, with induced epithelial expression of HLA class II antigens. (e) Corticosteroid responsiveness.

Do ulcerative colitis and Crohn's disease fulfil these criteria? Certainly, a range of autoantibodies directed against antigens expressed by enteric epithelial cells and leucocytes have been described.¹⁻⁴ Disappointingly, most of these autoantibodies lack sensitivity or specificity for inflammatory bowel disease, suggesting that they are simply epiphenomena. Recent unconfirmed reports, however, have described autoantibodies to colonic epithelial cells which are closely and specifically associated with ulcerative colitis but not with Crohn's disease.⁵⁻⁷ There is no strong or consistent association between HLA phenotype and either ulcerative colitis or Crohn's disease.^{8,9} While mucosal lymphocytic infiltration,¹⁰ induced epithelial HLA class II antigen expression,¹¹ and corticosteroid responsiveness are prominent features of both diseases, they are perhaps the least compelling of the defined criteria.

Autoimmune disorders and inflammatory bowel disease

Are the inflammatory bowel diseases associated with 'established' autoimmune disorders? The latter may be broadly divided into two groups, the diseases within each group tending to cluster in the same individuals. The first group encompasses ankylosing spondylitis, sacroiliitis, entero-

pathic oligoarthritis, and anterior uveitis. Members of this group are associated with the HLA class I antigen B27, and with erythema nodosum. They are undoubtedly associated with both ulcerative colitis and Crohn's disease, one or more occurring in well over 10% of cases of inflammatory bowel disease.¹² Intriguingly, the prevalence of this group of disorders in Crohn's disease is related to the extent of colonic involvement.¹²

The second group includes a range of disorders such as autoimmune thyroid disease and systemic lupus erythematosus, many of which have HLA associations primarily with class II gene products. A series of published case reports suggest that members of this group might also be associated with inflammatory bowel disease. There is some support for this contention from population studies,¹³⁻¹⁵ but these studies have been limited either by size or by failure to include an appropriate control group.

A controlled study of over 1200 patients with inflammatory bowel disease has recently been reported from Oxford¹⁶ documenting the prevalence of a defined range of 'established' autoimmune disorders belonging to this second group. Among the patients with ulcerative colitis, 6.6% had at least one of these disorders, but in contrast, they were no commoner in patients with Crohn's disease (1.9%) than in outpatient controls (2.0%). There was no correlation between the prevalence of autoimmune disease and the extent of colonic involvement. There was generally no temporal or sequential relation between the onset or activity of ulcerative colitis and the associated autoimmune disorder. This suggests that the association is not causal, but is due rather to a common predisposition to both disorders.

There is increasingly compelling evidence that primary sclerosing cholangitis satisfies the criteria for inclusion in the second group of autoimmune disorders. It is associated with the HLA B8/DR3 haplotype¹⁷ and with other autoimmune disorders within this group.^{18,19} Furthermore, lymphocyte autoreactivity to biliary antigens and high titres of an autoantibody (directed against a neutrophil nuclear antigen) have been reported in patients with primary sclerosing cholangitis.^{4,20} Finally, the portal tracts in active primary sclerosing cholangitis show a prominent lymphocytic infiltrate, with induced HLA class II antigen expression on biliary epithelium.^{21,22} The classification of primary sclerosing cholangitis as an autoimmune disorder has major implications for the pathogenesis of inflammatory bowel disease because the two conditions are so strongly associated.^{19,23} As with the other disorders in the second autoimmune group, the association is predominantly with ulcerative colitis, and

there is no temporal relation between the activity of primary sclerosing cholangitis and the associated ulcerative colitis.²⁴

Aetiology of autoimmune disease

Fulfilment of the criteria for classification as an autoimmune disorder provides an explanation for disease pathogenesis but does not necessarily identify the aetiological event. While autoimmune disease might theoretically result from a primary immunoregulatory defect, an array of other mechanisms have been implicated.^{25,26}

Firstly, the concept of molecular mimicry between microbial and host antigens, as exemplified by rheumatic fever, has aroused much interest. The gut is a huge reservoir of microbial antigenic determinants and there is therefore considerable potential for cross reactivity with autoantigens. The presence of gut mucosal inflammation might be expected to enhance luminal antigen exposure to the immune system. Cross reactivity between antigenic determinants on *Escherichia coli* and enteric epithelium has been implicated in the pathogenesis of inflammatory bowel disease.^{27,28} This hypothesis, however, is flawed because animals immunised with *E coli* in Freund's adjuvant acquire anticolon antibodies yet fail to develop colitis.^{27,29}

Evidence suggests that the HLA B27 associated disorders may arise from immunological cross reactivity between epitopes on *Klebsiella* nitrogenase and the B27 antigen itself.³⁰ Such a mechanism might be expected to be independent of the cause of enteric inflammation enhancing luminal antigen exposure to the immune system, and would therefore be consistent with the recognised association of B27 related disorders with infective as well as inflammatory enterocolitis. It would also fit well with the association between B27 related disease prevalence and the extent of Crohn's disease of the colon, the major location of commensal bacteria in the gut. The extent to which molecular mimicry with gut luminal antigens is involved in the aetiology of other autoimmune disorders is not known, but recent studies suggest that it may be important in the development of autoimmune thyroiditis³¹ and primary biliary cirrhosis.³²

Secondly, the environment created by non-specific events causing cellular destruction may render autoantigens expressed by cells in the immediate vicinity immunogenic: Dressler's/postpericardiectomy syndrome^{33,34} is a classical example, but it may also be that some viral infections can induce organ specific autoimmune disease in this way.³⁵ This mechanism may account for the development of autoimmune epiphenomena, such as many of the autoantibodies to colonic epithelium and leucocytes found in patients with inflammatory bowel disease.¹⁻⁴

The final mechanism involves development of an immune response to 'pseudo' autoantigens – that is, acquired cellular antigens which are appropriately recognised by the immune system as foreign. While this mechanism is not strictly autoimmune, it has the potential to generate what appears to be autoimmune disease. Haptenic modification of autoantigens is one way in which this may occur, exemplified by a range of drug induced autoimmune diseases. Another theoretical possibility is cellular expression of viral antigens resulting from unrecognised latent viral infection. It is not known how common this is, but the mounting evidence of viral involvement in the pathogenesis of a range of autoimmune disorders including coeliac disease,^{36,37} chronic active hepatitis,³⁸ Graves' disease,³⁹ and primary sclerosing cholangitis⁴⁰ suggests that this may be a most important mechanism in the development of (apparent) autoimmune disease. While as yet there is no convincing evidence for viral involvement in the pathogenesis of inflammatory bowel disease, comprehensive tissue examination for latent viral genomic material has not yet been reported.

Conclusion

The inflammatory bowel diseases fulfil some of the criteria required for classification as autoimmune disorders. Substantial differences in the prevalence of associated HLA class II related autoimmune diseases and of certain autoantibodies suggest that autoimmune mechanisms are more likely to be involved in the pathogenesis of ulcerative colitis than of Crohn's disease. The extent of this involvement, however, remains to be determined. Furthermore, implication of autoimmunity in the pathogenesis of ulcerative colitis does not identify the underlying aetiological event.

There are epidemiological and histological grounds for considering that ulcerative colitis and Crohn's disease may form two ends of the same disease spectrum.⁴¹ Given a common aetiology, differences in disease expression may perhaps result from differences in the immunological mechanisms involved. The situation may be analogous to that found in leprosy, where the immune response determines whether focal granulomatous ('tuberculoid') or diffuse non-granulomatous ('lepromatous') disease develops in response to the same aetiological agent.⁴¹ In contrast to leprosy, however, it might be enhanced autoimmunity rather than deficient xenommunity that is responsible for the development of diffuse non-granulomatous disease of the bowel – ulcerative colitis.

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