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Leading article

Potential role of superantigen induced activation of cell mediated immune mechanisms in the pathogenesis of Crohn's disease

The aetiopathogenesis of the inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis, remains unknown. In recent years, however, considerable evidence has been generated that suggests that immunological mechanisms may play an important part in the tissue damage of Crohn's disease and ulcerative colitis.

T cell activation in inflammatory bowel disease

In vivo T cell activation has been shown to be a feature of several diseases believed to be immunologically mediated.[1 2] The histological features of inflammatory bowel disease are also consistent with increased T cell activation: diseases of the gut, such as coeliac disease, Crohn's disease, and ulcerative colitis are associated with an inflammatory cell infiltrate into the diseased tissue with increased numbers of T cells in the mucosa.[3 4] Immunophenotyping of T cells has failed to show any gross abnormalities in inflammatory bowel disease: the proportions of CD4+ and CD8+ cells being similar in diseased and normal tissue[4–6] and there are no obvious defects in function.[7]

The use of monoclonal antibodies to markers of T cell activation, however, has shown considerable changes in T cells in Crohn's disease compared with normal controls. There is a shift from CD45RA to CD45RO expression in cells from the lamina propria of patients with Crohn's disease,[8] a phenomenon associated with antigen driven T cell activation.[9] In addition, T cell and macrophage populations from the peripheral blood, mucosa, and lamina propria of patients with Crohn's disease contain a high proportion of cells expressing early activation markers: 4F2, T9 (transferrin receptor), and interleukin 2 receptor expression is increased in peripheral blood and intestinal lamina propria populations during active disease.[10] Interleukin 2 receptor expression has also been studied using a monoclonal antibody to CD25 (the p55 chain of the interleukin 2 receptor).[11] CD25+ T cells and macrophages were present below the epithelium and deeper in the mucosa of inflamed tissue from patients with Crohn's disease but were not seen in histologically normal tissue from the same patient. Interestingly, one of the few immunological findings that differentiate between Crohn's disease and ulcerative colitis is that the mucosal CD25+ cells in Crohn's disease are predominantly T cells whereas those in ulcerative colitis are phenotypically macrophages.

Further evidence of increased cell mediated immune activity in the gut associated lymphoid tissue is provided by the increased concentration of various cytokines seen in diseased tissue from patients with IBD: there are increased concentrations of interleukin 2 in serum, the mucosal macrophage population, and the tissue mucosa of patients with IBD.[12–14] In addition, spontaneous production of interferon γ is increased in the lamina propria of patients with Crohn's disease[15] and production of tumour necrosis factor α is increased in colonic cells from children with IBD.[16] This last finding is of particular interest in Crohn's disease because of the part that tumour necrosis factor α is thought to play in the development of granulomas.[17]

Despite this strong evidence of T cell activation in the gut of patients with IBD, it is difficult to find out if this is of primary or secondary importance in the pathogenesis of the inflammation: damage to the gut epithelium and subsequent exposure of the gut associated lymphoid tissue to the mass of antigenic stimuli in the gut lumen would be expected to give rise to polyclonal stimulation of large numbers of T and B cells: any contribution to the chronicity of disease would be secondary to the primary insult. The polyclonal nature of the lymphocytic infiltrate in IBD has been shown by the studies of Kaulfersch *et al.*[18] In vitro studies examining small intestine explants cultured with pokeweed mitogen or monoclonal anti-CD3 antibody suggest that activated T cells can induce an enteropathy in vitro that strongly resembles human gastrointestinal diseases[19]: crypt hyperplasia and villus atrophy develop rapidly and the morphological changes seen with increasing age of the explant are consistent with increased numbers of T cells being present. In addition, there is increased cytokine production (interleukin 2 and interferon γ) and, consequently, increased HLA-DR expression on epithelial cells and lamina propria accessory cells. These studies provide important evidence that activated

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T cells play a primary part in the pathology of IBD and emphasise that one of the major challenges to researchers in IBD is the characterisation of the antigen(s) provoking this activation of T cells in the gut associated lymphoid tissue.

Immunological evidence for the presence of a specific triggering antigen in Crohn's disease

Indirect evidence for a specific triggering antigen in the pathogenesis of IBD was provided in 1976 by the finding of increased numbers of cold reactive lymphocytotoxic antibodies in patients with IBD.[20] These antibodies are more prevalent in relatives of patients with IBD than the normal population, implying exposure to an environmental agent. The relevance of this finding has not been revealed. Other studies have suggested the presence of a Crohn's specific antigen: on inoculation with Crohn's disease tissues, T cell deficient mice develop lymph node hyperplasia or lymphoma. In immunoflourescence tests, serum samples from patients with Crohn's disease recognise an antigen(s) in these tissues.[21] These findings were confirmed by Peña *et al*,[22] but further studies showed that tissues from other intestinal diseases induced similar lymph node changes on inoculation into mice.[23 24] Furthermore, serum samples from Crohn's disease patients recognised antigens in the lymph nodes of animals inoculated with saline alone.[24] Interestingly, samples from patients with Crohn's disease recognised antigen(s) in these tissues to a much greater extent than samples from ulcerative colitis or control patients.

More recently, in a study of T cell antigen receptor Vβ gene usage in IBD, Posnett *et al* reported increased proportions of Vβ8+ T-cells in mesenteric lymph nodes from a subgroup of patients with Crohn's disease.[25] This phenomenon was not seen in patients with ulcerative colitis, in controls, or in peripheral blood mononuclear cell populations from the same patients. A later study, which failed to show raised proportions of Vβ8+ T-cells,[26] examined the same population of cells that were negative in the study of Posnett *et al*. Confirmation of these findings would provide more evidence of a role for a specific triggering antigen in the immunopathogenesis of Crohn's disease.

Antigen specific lymphocyte responses in IBD

Considerable effort has been exerted in attempting to determine a role for various bacteria, viruses, and dietary antigens in the pathogenesis of IBD. Extensive culture and serological studies, however, have failed to provide convincing evidence of the participation of any proposed aetiological agent, including mycobacterial species (reviewed in reference 27): antibody concentrations to a wide range of commensal and pathogenic enterobacteria are raised in IBD.[28–31] This is assumed to result from leakage of commensal organisms through a previously damaged mucosa with cross reactivity between enterobacterial species thus explaining the raised antibody levels to pathogenic organisms.

The strong evidence for a significant involvement of activated T cells in the immunopathology of IBD and the granulomatous nature of Crohn's disease implies that studies of cell mediated immunity may be more fruitful in searching for antigen specific responses in IBD. Few studies of cell mediated immunity directed at particular organisms/antigens have been performed and these have concentrated on peripheral blood mononuclear cell responses to mycobacterial antigens.[32 33] Although these studies provide little evidence of sensitisation to mycobacterial antigens in patients with IBD, it is probably more relevant to perform studies of cell mediated immunity using gut associated lymphoid tissue: mucosal and mesenteric lymph node mononuclear cell (MLNMC) populations from patients with IBD respond to a range of microbial antigens.[34–36] In our study,[36] and that of Fiocchi *et al*,[34] responses of lymphocyte populations from the gut associated lymphoid tissue were often far greater than responses of peripheral blood mononuclear cells from the same patient.

We failed to show any evidence of hyper or hyporesponsiveness to mycobacterial antigens but, against a raised background of responsiveness to enterobacterial species, there was a significantly greater response to *Yersinia enterocolitica* in lymphocytes derived from mesenteric lymph nodes draining inflamed tissue. Similar patterns of lymphocyte responsiveness occur in other diseases associated with gut inflammation: in reactive arthritis, proliferative responses of T cell populations derived from peripheral blood are generally low. Responses of synovial fluid mononuclear cells to the causative organisms and recall antigens are significantly greater.[37–39]

Recent studies in our laboratory, using peripheral blood mononuclear cell populations from patients with active infectious diarrhoea of various aetiologies, suggest that similar patterns of responsiveness occur in these diseases also: during active disease peripheral blood responses are very low. In infectious diarrhoea, as in reactive arthritis, responsiveness of peripheral blood T cells to various enterobacterial antigens returns during convalescence (unpublished data). In early convalescence, the proliferative responses were generally greatest to either the causative organism or to yersinial antigens. This shows that the increased responsiveness to *Y enterocolitica* of MLNMCs from patients with IBD is not specific, but may represent the superantigenic activity that antigenic preparations (probably membrane protein) from the organism have been shown to possess.[40]

Potential role for superantigens in the immunopathology of Crohn's disease

If the increased proportion of Vβ8+ T-cells in MLNMC populations from patients with Crohn's disease is confirmed, this would provide the first evidence of a potential role for superantigens in the pathogenesis of this disease: clonal expansion of T cells bearing particular Vβ gene families is a characteristic of T cell stimulation by superantigens.[41] A number of bacterial products have been shown to possess superantigenic activity including *Staphylococcus aureus* enterotoxins,[42 43] group A streptococcal M protein,[44] and *Mycoplasma arthritidis*.[45 46] As already mentioned, *Y enterocolitica* has been shown to produce superantigenic activity in studies using murine T cells.[40]

It has been proposed that exposure to superantigens may give rise to the development of autoimmunity resulting from expansion of autoreactive T cell clones that are suppressed in the normal state.[47] Most of the diseases thought to be mediated by superantigens have associated autoimmune sequelae: a factor derived from *Mycoplasma arthritidis* causes arthritis in rats and experimentally induced arthritis in other species[48] and, in addition to its possible role in rheumatic fever, streptococcal M protein is implicated in autoimmune disorders of a range of organs.[44 49] Gastroenteritis caused by *Yersinia enterocolitica*, in common with gut infections caused by other organisms, may lead to the development of autoimmune spondylarthropathies such as Reiter's syndrome or reactive arthritis.[50] It is of interest that a chronic form of yersiniosis

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has been described in which *Y enterocolitica* cannot be detected by culture and serological techniques routinely used in diagnostic laboratories.[51] This form of yersiniosis bears striking clinical and histological similarities to Crohn's disease, including a predilection for the terminal ileum and extraintestinal complications such as arthritis, uveitis, and erythema nodosum. In addition, ileocolonoscopic and immunohistochemical studies have shown that a high proportion of patients suffering from seronegative spondylarthropathies have lesions in the gut bearing strong histological similarities to those seen in Crohn's disease.[52 53] It was postulated that this may point to the presence of a subset of patients with Crohn's disease who present with arthritis as the major manifestation of disease, with no obvious gut symptoms.

The aetiopathogenesis of reactive and rheumatoid arthritis is still not clearly understood despite the known association with the HLA-B27 allele. Neither are the mechanisms whereby arthritis develops in patients with IBD. Overall, searches for evidence of autoimmune reactions in IBD, especially Crohn's disease, have been negative: antibodies have been detected in patients with ulcerative colitis and Crohn's disease, which cross react between an antigen of the colonic epithelium and the Kunin antigen of enterobacteria[54] but a role for these antibodies in the perpetuation of gut inflammation or development of autoimmunity has not been elucidated (reviewed in reference 55). The anti-Vβ8 monoclonal antibodies used by Posnett *et al*, however, were also reported to cross react with epithelial cells. An antigen expressed by an abnormal epithelial cell in Crohn's disease may have the potential to stimulate an anti-Vβ8 humoral response that leads to the expansion of Vβ8+ve T cell populations.[25]

Whereas expansion of T cells bearing particular Vβ gene families is antigen specific, there is evidence that expansion of populations bearing particular Vα gene families may be host specific.[44] It has been proposed that this may provide a mechanism whereby some people are prone to developing superantigen related disorders while others are resistant. There is strong evidence of a genetic predisposition of IBD.[56] Interaction between Vα and Vβ elements, or the MHC genotype of a subject, could provide a genetic mechanism whereby people are prone to development of Crohn's disease, ulcerative colitis or neither disease.

The clinical and histological similarities between yersiniosis and Crohn's disease; the associated disorders such as arthritis and erythema nodosum, which are assumed to be immunologically mediated; the finding that *Y enterocolitica* possesses superantigenic activity and the possible presence of raised proportions of Vβ8+ T-cells in mesenteric lymph nodes of patients with Crohn's disease, provides tantalising evidence that superantigen induced activation and expansion of T cells may be responsible for the immunopathology of Crohn's disease.

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