Interleukin 12 and Th1 responses in inflammatory bowel disease

Immune phenomena are believed to play a key role in the pathogenesis of tissue damage in Crohn’s disease and ulcerative colitis. Although some of the immunological perturbations seem to be shared by Crohn’s disease and ulcerative colitis, there are important distinguishing features, possibly reflecting different pathways of immune mediated intestinal inflammation. Evidence indicates that macrophage and T cell derived cytokines play a key role in the amplification and perpetuation of the inflammatory response in both disorders. No aberrant cytokine secretion has been documented in inflammatory bowel disease (IBD) and no convincing evidence has as yet been provided that cytokine changes occur as a result of disease specific immune activation. However, a number of quantitative changes in the secretion and/or activity of both proinflammatory and regulatory cytokines have been reported in Crohn’s disease and ulcerative colitis. Based on variation in the magnitude of these changes there seem to be different cytokine profiles into which the inflammatory process may fall during the course of the disease. Studies from murine models indicate that two T lymphocyte subsets may be defined depending on their cytokine secretion profiles: Th1 lymphocytes producing interleukin (IL) 2 and interferon γ (IFN-γ), and Th2 lymphocytes producing IL-4, IL-5 and IL-10. When taken together all available data from both human and experimental studies suggest that in Crohn’s disease the local immune response tends to be predominantly Th1 whereas in ulcerative colitis Th2 mediated phenomena tend to predominate. However, Desreumaux et al have suggested that this may not be the case in early lesions.

Morphological and immunohistochemical observations suggest that during chronic intestinal inflammation, recently recruited lymphocytes undergo functional differentiation within the gut. Some authors have suggested that locally induced cytokines contribute to the in situ acquired functional properties of infiltrating mononuclear cells and that the preferential differentiation of T helper cells toward defined cytokine secretion patterns is driven by cytokines released within the inflamed tissues. Since in experimental settings IL-12 proved to play an important role in the generation of Th1 type cell clones, it was conceivable that IL-12 was a key mediator in Th1 cell differentiation in IBD (fig 1). As expected bioactive IL-12 was found in the intestinal mucosal samples of patients with Crohn’s disease. IL-12 is a heterodimer consisting of two covalently linked polypeptide subunits (p35 and p40) and produced mainly by monocytes/macrophages in response to bacteria, bacterial products or their components. IL-12 plays a pivotal role in determining the outcome of the effector T cell response. IL-12 induces IFN-γ synthesis and promotes Th1 cell differentiation. As result of this ability to modulate T cell polarisation, IL-12 has been used as an effective treatment of experimental parasitic infections exhibiting a Th2 cytokine profile, whereas antibodies to IL-12 prevented Th1 mediated autoimmune disorders. Transcripts for both IL-12 subunits (p40 and p35) were detected in Crohn’s disease lamina propria mononuclear cells (LPMC) and immunohistochemical analysis data have shown that, in human intestine, IL-12 production is restricted to macrophages infiltrating lamina propria. Moreover, IL-12 synthesis seems to be compartmentalised in Crohn’s disease, because no IL-12 was found in the unstimulated autologous peripheral blood mononuclear cells. LPMC from either ileal and colonic mucosa were equally capable of expressing and releasing IL-12, suggesting that neither the mucosal microenvironment nor variation in the luminal content are involved.

In contrast to Crohn’s disease, IL-12 is rarely detected in normal intestinal mucosa and in unstimulated LPMC from patients with ulcerative colitis. However, normal LPMC are fully capable of producing IL-12 after appropriate stimulation (e.g. staphylococcal enterotoxin B). The data suggest, therefore, that in the normal human intestinal mucosa IL-12 synthesis is downregulated, as is also suggested by the demonstration that human intestinal epithelial cell lines do not express IL-12/p40 mRNA in response to bacterial stimulation. Lamina propria T lymphocytes (T-LPL) isolated from normal mucosal samples synthesise IFN-γ after exposure to recombinant human IL-12 (personal unpublished observations). In addition, antibodies to IL-12 inhibited the development of IFN-γ producing T cells in Crohn’s disease gut specimen cultures. Therefore, IL-12 may account for the predominance of the Th1 response in Crohn’s disease. The IL-12 induced synthesis of IFN-γ by T-LPL may be enhanced by other cytokines produced in human intestine, such as IL-7 and IL-15 (personal unpublished observations). Driven by IL-12, IL-7 and IL-15 may thus promote Th1 cell expansion and contribute to the breakdown of tolerance towards the resident luminal antigens described in either human and experimental colitis. As IFN-γ is capable of upregulating macrophage IL-12 production, an enhanced IL-12/IFN-γ loop is likely to be involved in perpetuating chronic inflammation within the intestine.

A critical question is what induces IL-12 production in Crohn’s disease. IL-12 has been detected in Crohn’s disease LPMC from both spared and involved intestinal samples (from either ileum or colon) indicating that IL-12 production may not be an epiphenomenon of active inflammation. No data, however, have been provided to lead to its production.
show whether Crohn's disease LPMC IL-12 production occurs as result of a disease specific stimulus or whether it reflects macrophage activation by T cell derived cytokines or luminal bacteria, or both. In addition, it is unclear which molecular mechanisms regulate IL-12 release, although defective production of counterbalancing molecules seems to be contributory.27 Taken together these data suggest that IL-12 may be involved in mediating the immune response in Crohn's disease and that inhibiting or blocking its biological effects may be a promising way of controlling the inflammatory process in Crohn's disease. This is further supported by the demonstration that experimental colitis, mediated by a delayed hypersensitivity reaction and exhibiting a Th1 type cytokine profile, may be successfully treated with antibodies to IL-12, even after the lesion is established.28 More recently, it has been shown that homodimeric IL-12 p40 may efficiently prevent the IL-12 mediated inflammatory response.29 Homodimeric IL-12 p40 specifically blocks the interaction of IL-12 with its receptor, antagonising IL-12-induced cellular activation.29 This suggests that IL-12 p40 homodimers may act as IL-12 receptor antagonists.

Supported by grant CNR 96.03133. CT04, from the Italian National Research Council.

F PALLONE
G MONTELEONE

Cattedra di Gastroenterologia,
Dipartimento di Medicina Sperimentale,
Policlinico Universitario,
Via T. Campanella,
88100 Catanzaro, Italy

Correspondence to: Dr Pallone (email pallone@unizc.thebrain.net).

Interleukin 12 and Th1 responses in inflammatory bowel disease

F PALLONE and G MONTELEONE

Gut 1998 43: 735-736
doi: 10.1136/gut.43.6.735

Updated information and services can be found at:
http://gut.bmj.com/content/43/6/735

These include:

References
This article cites 25 articles, 8 of which you can access for free at:
http://gut.bmj.com/content/43/6/735#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Crohn's disease (932)
Ulcerative colitis (1113)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/