Inflammatory mediators in inflammatory bowel disease: Clues for designer therapy

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JL WALLACE. **Inflammatory mediators in inflammatory bowel disease: Clues for designer therapy. Can J Gastroenterol 1993;7(2):121-126.** The etiology of inflammatory bowel disease (IBD) is poorly understood. Regardless of the initiating events, it is likely that soluble mediators of inflammation play a critical role in the pathogenesis of the mucosal injury characteristic of this group of diseases. These mediators are responsible for recruiting and activating granulocytes. Thus, it is possible that these mediators may be rational targets for the development of novel anti-inflammatory drugs for the treatment of intestinal inflammation. Recent advances in research into the roles of leukotrienes, thromboxane, prostaglandins, platelet-activating factor, interleukin-1 and interleukin-8 in the pathogenesis of IBD are reviewed.

Key Words: *Inflammation, Interleukin-1, Interleukin-8, Leukotrienes, Platelet-activating factor, Prostaglandins*

Médiateurs inflammatoires dans la maladie intestinale inflammatoire: orientation thérapeutique

RÉSUMÉ: L'étiologie de la maladie intestinale inflammatoire est encore mal comprise. Malgré la présence d'incidents déclencheurs, il est probable que des médiateurs solubles de l'inflammation jouent un rôle crucial dans la pathogenèse des lésions muqueuses caractéristiques de ce groupe de maladies. Ces médiateurs sont responsables de mobiliser et d'activer les granulocytes. Ils pourraient constituer des objectifs légitimes pour la recherche axée sur la découverte de nouveaux anti-inflammatoires dans le traitement de l'inflammation intestinale. Les progrès récents accomplis pour percer le rôle des leucotriènes, de la thromboxane, des prostaglandines, du facteur d'activation plaquettaire, de l'interleukine-1 et de l'interleukine-8 dans la pathogenèse de la maladie intestinale inflammatoire sont passés en revue.

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UNTIL THE ETIOLOGY AND PATHOgenesis of inflammatory bowel diseases (IBD) are more clearly understood, the therapy for this group of diseases will remain somewhat empirical. The most frequently cited theory for the etiology of IBD is that an infectious agent or a dietary antigen gains access to the lamina propria, perhaps through an abnormally permeable epithelium, and initiates an inflammatory response (Figure 1). It is also widely held that through a genetic disposition, the immune response to such a challenge is inadequate or uncontrolled. Regardless of the initiating factor, it is clear that much of the tissue necrosis which characterizes IBD is produced by the host inflammatory response itself. For example, recent studies utilizing an experimental model of colitis demonstrated that up to 80% of the colonic epithelial injury associated with the colitis could be inhibited by pretreating the animals with a monoclonal antibody which prevented granulocyte migration out of blood vessels (1). Various inflammatory mediators contribute significantly to this injury by promoting the recruitment of granulocytes to the site of injury, as well as by affecting the function of immune cells (T and B lymphocytes). In recent years, a great deal of

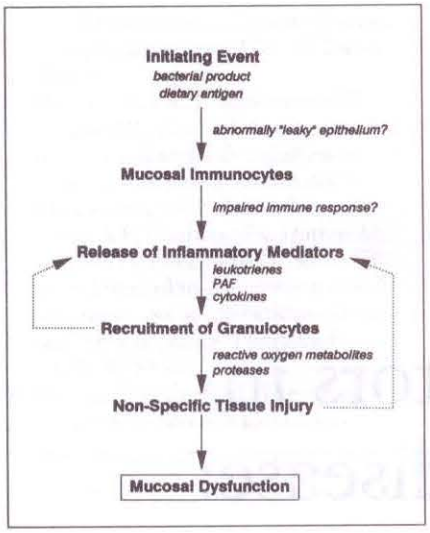

Figure 1) *Etiology (theroretical) of inflammatory bowel disease*

information has been gathered on the actions of soluble mediators of inflammation, and their potential role in intestinal inflammation. This paper reviews the experimental and clinical data which are available concerning the possible contribution of a number of classes of mediators to the pathogenesis of IBD: leukotrienes, thromboxane, prostaglandins, interleukin-1, interleukin-8 and platelet-activating factor.

LEUKOTRIENES

Of the multitude of inflammatory mediators, perhaps the one for which there is the most compelling evidence for a role in the pathogenesis of IBD is leukotriene (LT) B_4. LTB_4 is a potent chemotaxin for neutrophils and can activate neutrophils to release oxygen-derived free radicals and proteases (2, 3). LTB_4 also exerts immunomodulatory effects, stimulating the proliferation of B lymphocytes (4) and the production of tumour necrosis factor, interferon gamma and interleukin-2 by human mononuclear cells (3). In several animal models of IBD, LTB_4 synthesis has been shown to be greatly elevated soon after initiation of the inflammatory response (5-7), and in one model LTB_4 synthesis was shown to be elevated for as long as five weeks after induction of inflammation (5). LTB_4 has also been shown to exacerbate colonic injury induced by intracolonic ethanol (8).

In humans, LTB_4 synthesis is increased in ulcerative colitis and Crohn's disease patients by about 50-fold above normal levels (9). These tissue concentrations are within the range necessary to induce neutrophil chemotaxis; such a role is supported by the finding that 78 to 90% of the chemotactic activity present in samples of inflamed bowel was lipid in nature, co-eluted with LTB_4 on high performance liquid chromatography, and could be removed by preincubation of the extract with an antibody directed against LTB_4 (10). It has been suggested that one of the mechanisms through which 5-ASA or prednisone reduce colonic inflammation is by inhibiting LT synthesis, since these compounds were shown to reduce significantly rectal dialysate LTB_4 levels and clinical symptoms in a parallel manner (11). Interestingly, there was a subgroup of patients in this study who were unresponsive to therapy with 5-ASA and prednisone. These patients were found to have significantly higher pretherapy rectal dialysate LTB_4 levels than the patients who did respond to therapy, suggesting that high levels of LTB_4 in rectal dialysates may be predictive of how a patient will respond to anti-inflammatory therapy.

In recent years a number of specific inhibitors of LT synthesis have become available (Figure 2) and have been shown to accelerate healing in animal models of IBD (5,12,13). In each case the compound had to be administered early in the course of colitis for a beneficial effect to be observed. The ability of compounds to accelerate healing correlated well with their ability to inhibit colonic LT synthesis (14). LT synthesis inhibitors also significantly reduced the incidence of adhesions and diarrhea and improved the weight gain after induction of colitis (5,13).

The results of clinical trials with a specific inhibitor of LT synthesis have recently been reported. Laursen et al (15) reported that oral administration of the 5-lipoxygenase inhibitor, zileuton, inhibited rectal LTB_4 synthesis by approximately 67% for a period of 4 to 8 h. The compound was then assessed in a randomized, double-blind, placebo-controlled trial over a period of 28 days (16). Patients treated with zileuton showed significant improvement compared with placebo-treated controls, but not with patients treated with sulphasalazine. Unfortunately, the twice-a-day dosing regimen employed in this trial was not sufficient to achieve 24 h inhibition of colonic LT synthesis, so it is still unclear if effective inhibition of LT synthesis will represent an alternative approach to the treatment of active IBD.

THROMBOXANE

Thromboxane is derived from arachidonic acid via the actions of cyclooxygenase and thromboxane synthetase (Figure 2). The principal cellular source of this mediator is the platelet, although it is also made by macrophages and neutrophils. It is a potent vasoconstrictor and activator of platelets, and can induce lesions in the upper gastrointestinal tract when administered systemically (17). Interest in the role of thromboxane in IBD was first stimulated by reports that thromboxane production by cultured rectal biopsies from Crohn's disease patients (18) and thromboxane levels in rectal dialysates from ulcerative colitis and Crohn's disease patients were markedly elevated above controls (19). Using a rat model of colitis, Vilaseca et al (20) demonstrated that colonic production of many eicosanoids was elevated; however, while the production of most of the eicosanoids gradually returned towards control levels, thromboxane synthesis remained elevated throughout the 21-day study period. When the rats were treated with 5-ASA or prednisone at doses that significantly reduced the severity of injury, they observed a significant decrease in colonic thromboxane synthesis. They then assessed the effects of two thromboxane synthetase inhibitors in their model. Both compounds significantly inhibited the production of thromboxane, and significantly reduced the severity of the colitis. The authors suggested that the balance between prostaglandin and thromboxane synthesis

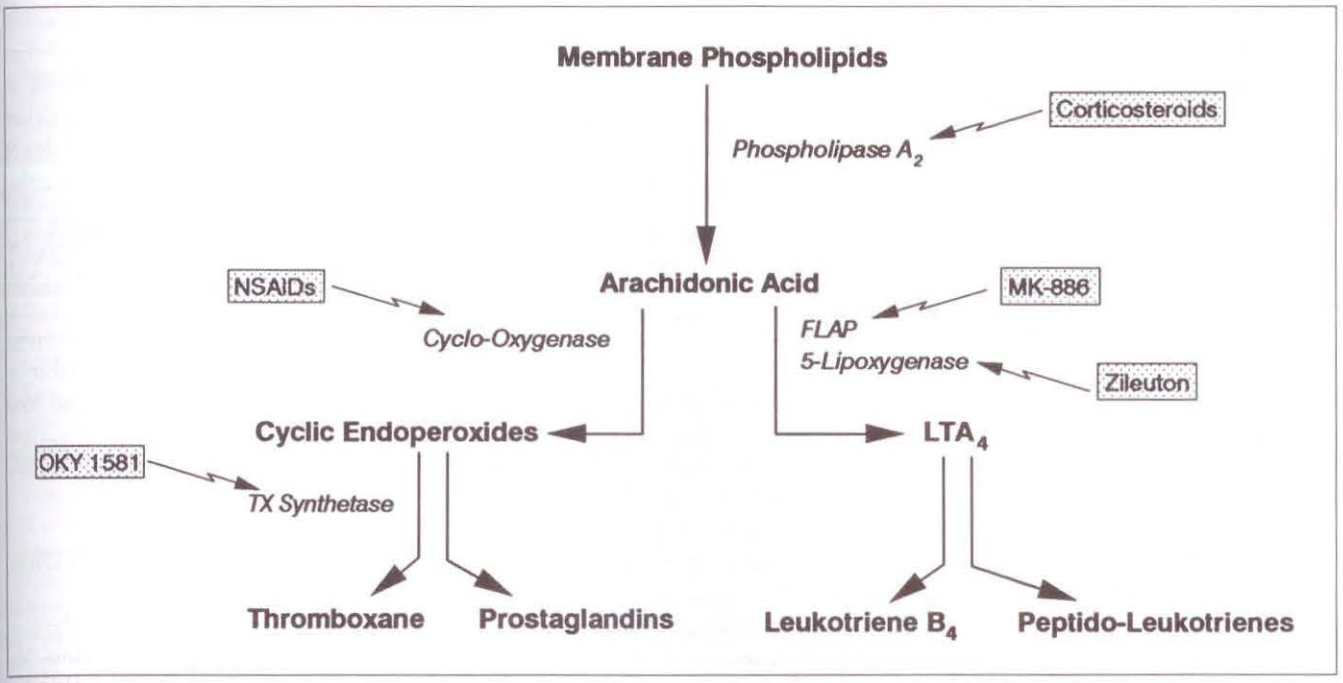

Figure 2) *Cascade of inflammatory mediators in IBD*

may be a critical factor in the pathogenesis of colitis, and that substances that reduce thromboxane synthesis or increase prostaglandin synthesis should have beneficial effects. A number of specific thromboxane receptor antagonists have been developed, but they have not been assessed in experimental colitis models or in humans.

PROSTAGLANDINS

Prostaglandins have traditionally been classified as inflammatory mediators based on their ability to potentiate edema formation in the presence of other mediators, such as bradykinin and histamine, and because of their hyperalgesic effects in various inflammatory diseases. In fact, there is considerable evidence to suggest that, for the most part, prostaglandins exert anti-inflammatory effects, and in the case of IBD, prostaglandins may play a critical role in 'dampening' the inflammatory response. As outlined in Table 1, prostaglandins exert anti-inflammatory effects at a number of cellular targets. For example, prostaglandins of the E and I series inhibit neutrophil activation and secretion as well as inhibiting their adherence and migration (21-23). Prostaglandins have also been shown to inhibit the production of other inflammatory mediators, including LTB_4 synthesis by neutrophils (24) and tumour necrosis factor synthesis by macrophages (25).

The evidence that prostaglandins exert anti-inflammatory effects in IBD comes primarily from animal studies. A number of groups have demonstrated that exogenous prostaglandins are capable of reducing the severity of injury and the extent of granulocyte infiltration in experimental models (5, 26-30). Pretreatment with prostaglandin E_2 was shown to dose-dependently reduce the severity of colonic injury in the rat induced by intracolonic instillation of 30% ethanol (26). Allgayer and Stenson demonstrated that administration of a prostaglandin E_2 analogue after induction of colitis in the rat with trinitrobenzene sulphonic acid resulted in a significant decrease in the migration of granulocytes into the affected region over the 24 h period that followed (27). Using the acetic acid model of acute colitis in the rat, Yamada et al (29) recently reported that misoprostol, a prostaglandin E_1 analogue, significantly reduced the infiltration of neutrophils into the colon and the changes in epithelial permeability. They suggested that the prostaglandin protected the proliferative zone of the colonic epithelium, allowing for more rapid establishment of an intact epithelium after the initial injury (31). The second type of evidence for an anti-inflammatory role of endogenous prostaglandins is the evidence that administration of nonsteroidal anti-inflammatory drugs to rats with colitis results in profound exacerbation of the injury, and significant mortality (a consequence of intestinal perforation) (12). This exacerbation of colitis was observed with doses of nonsteroidal anti-inflammatory drugs (NSAIDs) that did not produce gastrointestinal injury in healthy rats and was not attributable to increased LT synthesis.

There is also some clinical evidence consistent with these animal studies, including numerous anecdotal reports of exacerbation of IBD in patients ingesting NSAIDs (32). There has been only one clinical trial of a prostaglandin analogue in IBD. Goldin and Rachmilewitz (33) reported the failure of a prostaglandin E_2 analogue to improve the course of ulcerative colitis. In fact, they had to terminate the study prematurely because of a high incidence of diarrhea in the patients treated with the prostaglandin. Perhaps the potential utility of prostaglandins in the treatment of IBD deserves further

TABLE 1
Anti-inflammatory effects of prostaglandins

Target cell	Action
Neutrophil	Inhibit adherence, free radical production, LTB_4 synthesis, chemotaxis
Lymphocyte	Inhibit T cell proliferation, decrease cytotoxicity
Macrophage	Inhibit IL-1 and TNF synthesis, decrease cytotoxicity
Platelet	Inhibit aggregation, inhibit mediator release (degranulation)
Mast cell	Inhibit mediator release (degranulation)
Epithelium	Cytoprotective, accelerate repair

LTB_4 Leukotriene B_4; IL-1 Interleukin-1; TNF Tumour necrosis factor

evaluation, since some prostaglandin analogues which do not exert potent diarrheogenic effects have been developed.

INTERLEUKIN-1 AND INTERLEUKIN-8

In recent years, there has been a great deal of interest in the possible role of a number of cytokines in the pathogenesis of IBD. Perhaps the greatest interest has focused on interleukin (IL)-1 and more recently on IL-8. IL-1 is a pleiotropic molecule produced by numerous types of cells, including macrophages and mast cells (34). Among its many actions, IL-1 upregulates the expression of adhesion molecules on the vascular endothelium (35) and stimulates endothelial synthesis of IL-8. IL-8 is one of the most potent neutrophil chemotaxins yet described (36). IL-8 increases the expression of adhesion molecules, such as the, β_2-integrin family (CDll/CD18) on neutrophils. Thus, IL-1 and IL-8 act in concert to increase the recruitment of neutrophils to a site of inflammation.

IL-1 synthesis is not detectable in samples of normal colonic tissue, but can be detected in samples taken shortly after the induction of colitis in rats (37) or rabbits (38). These changes in IL-1 synthesis occurred before detectable changes in eicosanoid synthesis (38), suggesting that IL-1 might be the trigger for the production of these other inflammatory mediators. Treatment of rats or rabbits with an IL-1 receptor antagonist significantly reduced the severity of the necrosis and inflammation which are characteristic of their model of colitis (38-40).

The role of IL-1 and IL-8 in human IBD has been investigated by a number of groups in recent years. Ligumsky et al (41) reported that IL-1 synthesis was markedly elevated in colonic samples from patients with IBD, particularly when the tissue samples were taken from patients with active disease. Mahida et al (42) also demonstrated increases in IL-1 synthesis in human IBD, and further demonstrated that IL-1 synthesis could be inhibited by incubating the tissue samples with 5-ASA. The source of IL-1 production in the colon has also been examined. More recently, Mahida et al (43) demonstrated that IL-8 synthesis was elevated in colonic samples from patients with ulcerative colitis, but was not elevated in samples from patients with Crohn's disease, even though both groups of patients had comparable disease activity.

PLATELET-ACTIVATING FACTOR

Platelet-activating factor (PAF) is a phospholipid derived from membranes via the action of phospholipase A_2 and acetyl-CoA transferase. PAF is a potent ulcerogen in the stomach (44) and intestine (45), and is a potent chemotaxin and priming factor for neutrophils and eosinophils (46).

PAF synthesis by the rat colon is markedly elevated after induction of colitis (47,48). Treatment with one of three PAF antagonists resulted in a significant reduction in the severity of colonic damage and inflammation in one of these rat models (49). In another rat model, treatment with either of two structurally unrelated PAF antagonists produced a 43 to 53% reduction in neutrophil infiltration into the colon in a rat model of colitis (49).

Eliakim et al (50) extended these studies to human IBD. Colonic biopsies from patients with ulcerative colitis produced significantly more PAF than control biopsies when incubated in vitro and stimulated with calcium ionophore. PAF synthesis could also be stimulated by anti-IgE, suggesting that mast cells or other IgE-binding cells were the primary sources of PAF. PAF levels in the stool of patients with Crohn's disease were recently reported to be markedly elevated above control levels (51). Although a number of specific PAF receptor antagonists have been available for over five years, clinical trials of these compounds in IBD have not been reported.

IMPLICATIONS FOR FUTURE THERAPY

Until recently, the study of the roles of various eicosanoids, cytokines and PAF in the pathogenesis of IBD has been limited to animal models. However, specific and safe pharmacological probes are now becoming available which will permit similar studies to be performed in man. The results of trials with such compounds are eagerly awaited. Studies with these probes will provide information concerning the relative importance of each of these classes of mediators and, hopefully, will represent a new avenue for the therapy of inflammatory diseases of the intestine. However, it is always possible that these agents may prove to be too specific to be effective in a multifactorial disease such as IBD. Indeed, drugs such as corticosteroids and 5-ASA may be effective in the treatment of IBD because of their lack of specificity. By inhibiting the synthesis of a number of inflammatory mediators, as well as exerting other activities (eg, free radical scavenging), these compounds may have more profound effects in IBD than a drug which is targeted very specifically at a single inflammatory mediator. Of course, questions of this type can only be answered when appropriate clinical trials have been performed.

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