Cytokine interactions with epithelium

KIM E BARRETT PhD

KE BARRETT. Cytokine interactions with epithelium. *Can J Gastroenterol* 1996;10(5):323-328. Cytokines are a family of proteins that serve as intracellular messengers within the immune system and as growth factors for several cell types. Recent studies indicate that intestinal inflammation is accompanied by increases in a wide variety of cytokines and growth factors. Current knowledge in the area of cytokine-epithelial interactions, with particular reference to the involvement of such interactions in intestinal inflammation, is reviewed. Topics include epithelial functions subject to modulation by cytokines; effects of cytokines on epithelial damage, restitution and proliferation; effects of cytokines on the ability of the epithelium to express immune accessory and adhesion molecules; and effects of cytokines on the production of inflammatory mediators by the epithelium.

Key Words: Cytokines, Epithelium, Inflammation

Interaction des cytokines avec l'épithélium

RÉSUMÉ : Les cytokines sont une famille de protéines qui agissent à titre de messagers intracellulaires pour le système immunitaire et à titre de facteurs de croissance pour divers types cellulaires. De récentes études indiquent que l'inflammation intestinale s'accompagne d'augmentations d'une grande variété de cytokines et de facteurs de croissance. Les récents progrès enregistrés dans le domaine des interactions cytokine-épithélium, particulièrement en ce qui a trait à la participation de ces interactions dans l'inflammation intestinale, sont passés en revue ici. Les thèmes abordés sont entre autres, les fonctions de l'épithélium influencées par les cytokines, les effets des cytokines sur les lésions épithéliales, la réparation et la prolifération, les effets des cytokines sur la capacité de l'épithélium à exprimer les molécules immunitaires accessoires et adhésives et les effets des cytokines sur la production des médiateurs de l'inflammation par l'épithélium.

Cytokines are a family of proteins that serve as intracellular messengers within the immune system and as growth factors for several cell types. Recent studies indicate that intestinal inflammation is accompanied by increases in a wide variety of cytokines and growth factors (reviewed in 1). Because the intestinal epithelium is a frequent target of the inflammatory process in diseases such as Crohn's disease and ulcerative colitis, whether epithelial functions are modulated by cytokines has been examined. Indeed, many cytokines and growth factors have been shown to alter a spectrum of epithelial functions (Table 1). Another area of research receiving considerable attention is the possibility that the epithelium acts not only as a target of intestinal inflammation, but also as an active participant in the overall inflammatory response. In part, this participation may result

from the ability of epithelial cells to express adhesion and accessory molecules, and to synthesize inflammatory mediators such as eicosanoids. Both properties may be subject to cytokine regulation. Other recent data suggest that the epithelium can act as a source of some cytokines. The ability of the epithelium to produce both eicosanoids and proinflammatory cytokines may represent one segment of an autocrine loop whereby inflammatory dysfunction of the epithelium is amplified. Recent progress in the area of cytokine-epithelial interactions, with particular reference to the involvement of such interactions in intestinal inflammation, is reviewed. By drawing on the findings of a number of laboratories, an integrated overview of the epithelial functions that may be subject to regulation by cytokines and growth factors is provided.

Division of Gastroenterology, Department of Medicine, University of California and School of Medicine, San Diego, California

Correspondence: Dr Kim E Barrett, UCSD Medical Center, 8414, 200 West Arbor Drive, San Diego, CA 92103-8414, USA. Telephone 619-543-3726, fax 619-543-6969, e-mail kbarrett@ucsd.edu

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TABLE 1
Epithelial functions subject to regulation by cytokines and growth factors

Function	Implicated cytokines
Ion transport	IL-1, IL-3, TGF- β , EGF
Paracellular permeability	IFN- γ , IGF-1
Restitution and proliferation	IL-1, EGF, TGF- α , TGF- β
Viability	TNF- α , IFN- γ
Expression of adhesion and accessory molecules	IL-1, IL-6, TNF- α , IFN- γ
Production of cytokines and other inflammatory mediators	IL-1, IL-6, TGF- β , TNF- α , IFN- γ

EGF Epidermal growth factor; IFN Interferon; IGF Insulin-like growth factor; IL Interleukin; TNF Tumour necrosis factor

EPITHELIAL FUNCTIONS SUBJECT TO MODULATION BY CYTOKINES

Effects of cytokines on epithelial transport properties: A primary function of the intestinal epithelium is to control the movement of electrolytes and other solutes (2). This function, which is responsible for the control of luminal water content, is achieved via the regulation of two main pathways: transcellular transport, whereby electrolytes and nutrients are actively transported across cells, and the paracellular pathway, controlled by intercellular tight junctions. A classical view of the regulation of active ion transport across the intestinal epithelium recognized three main regulatory systems: paracrine regulation by adjacent endocrine cells located within the epithelium; endocrine regulation involving bloodborne hormones from distant sites; and neurocrine regulation via the release of stimulatory and inhibitory neurotransmitters by nerves within the enteric nervous system. However, over the past 10 years it has become apparent that a fourth regulatory system should be added to this list, that of the intestinal immune system (3). Studies – both in vivo and in vitro – in humans and experimental animals have revealed that the release of inflammatory and immune mediators can be a prominent stimulus leading to transepithelial chloride secretion in the mammalian gastrointestinal tract. Because active secretion of chloride is the primary driving force for secretory diarrhea, the hypothesis has arisen that the ability of various immune and inflammatory mediators to evoke chloride secretion, perhaps in concert with agonists from other regulatory systems (such as the enteric nervous system [3]), is the primary pathophysiological mechanism underlying diarrhea associated with intestinal inflammation. In this context, a number of investigators have examined the ability of various cytokines to modify chloride secretory responses of the epithelium.

There is evidence that chloride transport may be stimulated by various cytokines. However, in contrast to the secretory effects of various other inflammatory mediators (including histamine, adenosine, prostaglandins and certain reactive oxygen species), the stimulatory effects of cytokines on chloride secretion appear to be primarily indirect and to require the participation of secondary mediators released

from nonepithelial cell types. This conclusion is based on the fact that cytokines examined to date do not appear to evoke chloride secretion directly when added acutely to intestinal epithelial cell lines. Secretory effects have been noted, however, when certain cytokines are added to intact intestinal preparations. Addition of interleukin-1 (IL-1) or IL-3 to segments of chicken intestine mounted in Ussing chambers led to a rapid increase in chloride secretion (4). This effect, however, was blocked by a cyclo-oxygenase inhibitor, suggesting that it involved the secondary generation of prostaglandins, which then acted as the final stimulus for chloride secretion acting at the level of the secretory epithelial cells.

Similarly, the stimulatory effects of cytokines on chloride secretion may not be acute, but may involve delayed up-regulation of responsiveness to other neurohormonal stimuli. This was found to be the case for a stimulatory effect of transforming growth factor-beta (TGF- β) on chloride secretion by the T₈₄ intestinal epithelial cell line, where the effect of the cytokine was to potentiate responses to vasoactive intestinal polypeptide (VIP) after 24 h of preincubation (5). Further, IL-1 can chronically up-regulate the ability of fibroblasts to deliver a paracrine signal for the stimulation of chloride secretion by the epithelium (6).

Cytokines and growth factors may also have negative effects on chloride secretion, positive effects on absorptive mechanisms or both. In the case of TGF- β , an inhibitory effect of chronic exposure on responses to the cAMP-dependent agonist VIP or direct elevation of intracellular cAMP levels with a cell-permeant cAMP analogue was noted in some T₈₄ cell monolayers, which contrasts with the stimulatory effect of this cytokine described above (5). Whether a stimulatory or an inhibitory effect was observed appeared to depend, at least to some extent, on the overall level of responsiveness of the monolayers. Thus, when cells displayed an inhibition of chloride secretion after TGF- β treatment, other monolayers examined in parallel were more likely to have a higher level of responsiveness to VIP under control conditions. These findings indicate that factors intrinsic to the epithelium may quantitatively or even qualitatively define the response of the epithelium to a given cytokine. Another cytokine capable of acting as an antisecretagogue is epidermal growth factor (EGF). This factor has been shown to enhance nutrient absorptive mechanisms in the small intestine (7), apparently by rapidly increasing the surface area of absorptive cells via an effect directed to the microvilli (8). EGF also specifically down-regulates calcium-dependent chloride secretion, an action that may be related to the prolonged generation of a putative second messenger for this process, inositol (3-6) tetrakisphosphate (9). Overall, these antisecretory effects of TGF- β and EGF may represent an adaptive response of the epithelium. Conversely, diarrhea may result if a normal inhibitory tone, provided by the influence of agonists such as EGF, is lost in the setting of disease.

In addition to the regulation of active transport mechanisms in the intestinal epithelium, intestinal fluid and electrolyte balance are modulated by the dynamic regulation of

paracellular permeability pathways, via the regulation of intercellular tight junctions. Cytokines may also regulate these paracellular transport pathways. Interferon-gamma (IFN- γ), insulin and insulin-like growth factors significantly reduce transepithelial resistance and thus enhance permeability to small solutes (10-14). The effect of these substances on epithelial resistance is slow in onset, and appears to require the synthesis of new proteins within the epithelial cell. In general, the effects of these agents appear to be limited to increasing epithelial permeability to small solutes and electrolytes. No evidence to suggest that cytokines such as IFN- γ provide the mechanism whereby epithelial macromolecular permeability is up-regulated in intestinal inflammation has been found (15).

Effects of cytokines on epithelial damage, restitution and proliferation: Intestinal inflammation is frequently characterized by frank damage to the epithelium. This effect can partially result from the actions of cytokines. Supernatants from activated mucosal T lymphocytes were shown to be cytotoxic for HT29 intestinal epithelial cells grown in culture (16). This effect has been ascribed to the synergistic action of the cytokines tumour necrosis factor- α (TNF- α) and IFN- γ . While almost all cytotoxicity of the supernatants appeared to be due to the presence of TNF- α , when the effects of recombinant TNF- α on cell viability were assessed, the cytokine was capable of causing significant cell death only when given simultaneously with IFN- γ . Overall, these results point to the potential for cytokine release from activated lymphocytes and other inflammatory cells in the lamina propria to contribute to the epithelial damage seen in inflammatory bowel disease (IBD).

The epithelium can respond to inflammatory damage in two ways. The first is a rapid repair mechanism and involves a process referred to as restitution. In this process, epithelial cells adjacent to damaged areas flatten and migrate to seal epithelial discontinuities. There is evidence that cytokines and growth factors may be regulators of this process. For example, IL-1 has been shown to induce ornithine decarboxylase activity in intestinal epithelial cells (17). Ornithine decarboxylase is a key initial enzyme involved in both restitution and epithelial proliferation (18). Likewise, both EGF and TGF- β stimulate migration of epithelial cells over extracellular matrix components (19,20). The effect of EGF appears attributable, in part, to the up-regulation of epithelial integrins (19).

The second way by which the epithelium can respond to damage is by increasing its rate of proliferation. Ultimately this may lead to crypt hyperplasia, a common feature of IBD, because the rate at which enterocytes differentiate may not be able to keep pace with a larger increase in epithelial proliferative capacity.

It is beyond the scope of this article to review in detail the complex networks thought to be responsible for the control of epithelial dynamics in both the normal and diseased intestine (for review see 21). However, it is pertinent to make a few remarks concerning the peptide growth factors that are thought to be primarily responsible for control of

Figure 1) Example of a potential eicosanoid synthetic pathway, involving transcellular cooperation between the epithelium and inflammatory cell types, that may be subject to up-regulation by cytokines. Inflammatory cells can supply leukotriene A_4 (LTA_4) to the epithelium for conversion to the chemotactic lipid LTB_4 , which would then stimulate further inflammatory cell migration and activation. Inflammatory cells can also supply cytokines capable of specifically up-regulating enzyme (eg, LTA_4 hydrolase) expression, thereby amplifying the loop and allowing a vicious cycle of inflammation

this process. The overall rate of proliferation of the intestinal epithelium appears to reflect a balance between the growth stimulatory factor TGF- α and the growth inhibitory TGF- β (21). EGF may also play a stimulatory role in the control of epithelial proliferation, although the importance of this growth factor relative to that of the TGF is not clearly defined. This is because the majority of EGF is secreted into the intestinal lumen where it is subject to significant proteolytic cleavage; moreover, EGF receptors on intestinal epithelial cells appear to be confined to the basolateral membrane domain (22).

Effects of cytokines on the ability of the epithelium to express immune accessory and adhesion molecules: The intestinal epithelium is becoming increasingly recognized as a constituent of the mucosal immune system (23). Intestinal epithelial cells have the capability to present antigen to helper lymphocytes, a property that appears to be specifically up-regulated during inflammation (24). Conversely, epithelial cells from inflamed tissues fail to present antigen effectively to antigen nonspecific suppressor T cells (24). Stimulated intestinal lymphocytes release a cytokine, identified as IFN- γ , that can induce major histocompatibility class II molecule (HLA-DR) expression on HT29 cultured intestinal epithelial cells (25). Similarly, recombinant IFN- γ induces HLA-DR on the surface of the T₈₄ epithelial cell line (26). These findings may relate to the changes in antigen presentation seen in IBD because it was shown that lamina propria lymphocytes from patients with either Crohn's disease or ulcerative colitis displayed significantly higher rates of IFN- γ secretion upon stimulation (27).

Cytokines may also be responsible for the regulation of adhesion molecule expression on intestinal epithelial cells. For example, intercellular adhesion molecule-1 (ICAM-1)

Figure 2) The ability of the epithelium to secrete chemokines and other proinflammatory cytokines may provide a mechanism whereby phagocytes are recruited to a specific mucosal location. The epithelium acts as a source of cytokines. In response to luminal stimuli, such as invasive microorganisms or endotoxin (or possibly epidermal growth factor [EGF]), or in response to mucosal cytokines, intestinal epithelial cells can synthesize the chemotactic cytokine interleukin (IL)-8. This likely results in the recruitment of inflammatory cell types to the site of initial injury or insult, and their subsequent activation. TNF Tumour necrosis factor

expression can be induced on cultured epithelial cells by IFN- γ , IL-1, TNF- α and IL-6 (28,29). This may have implications for the ability of epithelial cells to orchestrate mucosal immune responses, in that increased ICAM-1 expression promotes the adhesion of activated T cells via the leukocyte function-associated antigen-1 ligand for this molecule (30). The expression of adhesion molecules on the epithelial surface may also be important for their interaction with other inflammatory cell types. Neutrophils have been shown to adhere to and migrate through T84 epithelial cell monolayers when driven by a chemotactic gradient (31). Neutrophil migration across epithelial monolayers is subject to modulation by IFN- γ , although the effects seen are qualitatively different depending on the direction of cell migration examined. Thus, IFN- γ pretreatment markedly up-regulated transmigration of neutrophils in the apical to basolateral direction (32). However, in the physiologically more relevant basolateral to apical direction for migration, IFN- γ actually reduced transmigration (32); the cytokine appeared to up-regulate an adhesive interaction between the neutrophils and the basolateral surface of the epithelial cells that enhanced the retention of the inflammatory cell type in the subepithelial space. Colgan and associates (32) speculated that this may result in the accumulation of neutrophils in a location where they would be poised to participate in host defence responses.

Effect of cytokines on the production of inflammatory mediators by the epithelium: Finally, the ability of the epithelium to synthesize proinflammatory mediators and, indeed, cytokines has recently been recognized and is the subject of much active research. These abilities may also be subject to regulation by the cytokine milieu. The epithelium has, for

example, been recognized as a potential supplier of proinflammatory eicosanoids. In some cases, synthesis may involve a transcellular metabolic route, where infiltrating inflammatory cells supply the intermediate substrate, leukotriene A₄, for conversion to the proinflammatory leukotriene B₄ by the intestinal epithelial leukotriene A₄ hydrolase (unpublished data). This ability of the epithelium can contribute to a vicious cycle of inflammation, contributing to tissue damage by amplifying inflammatory cell migration (Figure 1). In other cases, the complete enzymatic machinery for the generation of an eicosanoid product may be present within the epithelial cell. It has been shown that the enzyme 12-lipoxygenase is specifically induced in the epithelium of tissue specimens from IBD patients (33). Similarly, epithelial cells express phospholipase A₂ enzymes responsible for the initial release of arachidonic acid from membrane phospholipids, which then supplies downstream eicosanoid synthetic pathways (34). Arachidonic acid metabolites have also been implicated as second messengers for chloride secretion (35), and an increase in their synthesis may contribute to inflammatory diarrhea. By analogy with other epithelial and nonepithelial systems, it seems reasonable to predict that these various eicosanoid metabolic enzymes may be subject to regulation by cytokines and growth factors. However, with the exception of the observation that TNF- α appears to up-regulate phospholipase A₂ activity in the cultured human intestinal cell line INT 407 (34), the precise cytokine signals responsible for modulating arachidonic acid metabolism in the epithelium, *in vivo* or *in vitro*, remain to be established.

The intestinal epithelium may also serve as a local source of complement components. *In vitro* analyses of Caco-2 cells showed that these cells were capable of synthesizing biologically active C3, C4 and factor B under control conditions (36). Moreover, the synthesis of each of these molecules was selectively up-regulated by cytokines. C3 production was enhanced by IL-1 and TNF- α , C4 by IL-6 and IFN- γ , and factor B by IL-1, IL-6 and, to a small extent, IFN- γ (36). Given the numerical significance of epithelial cells in the intestine, the findings suggest that the epithelium may act as the primary source for complement components involved in mucosal host defence and/or local inflammation.

Epithelial cells have also been shown, at least in *in vitro* models, to act as a source of proinflammatory and chemotactic cytokines, such as IL-1, IL-6 and IL-8. IL-8 secretion may represent a primitive immune response to a cellular insult, such as that provided by bacterial colonization with invasive bacteria such as *Salmonella* species (37). Similarly, mucosal cytokines derived from lamina propria mononuclear cells may also signal the epithelium to produce additional cytokines. In the rat intestinal epithelial cell line IEC-6, TGF- β and IL-1 have been shown to promote the secretion of IL-6 synergistically (38,39). Likewise, in four human intestinal epithelial cell lines, TNF- α , IL-1 and bacterial lipopolysaccharide all serve to up-regulate the synthesis of IL-8 (40). In sum, the ability of the epithelium to secrete chemokines and other proinflammatory cytokines may provide a mechanism whereby phagocytes are recruited to a specific mucosal loca-

tion (Figure 2). This may be a highly appropriate response if evoked in response to bacterial invasion. However, inappropriate triggering of cytokine secretion may lead to an uncontrolled inflammatory response, perhaps also involving some of the other cytokine regulatory loops described above.

SUMMARY AND CONCLUSIONS

The intestinal epithelium appears to act as both a target and a supplier of cytokines, properties that may be of particular relevance in the setting of inflammation. In some cases, the precise response displayed by the epithelium to a given cytokine may depend on the intrinsic functional properties of the epithelial cell. Thus, significant information remains to be elucidated regarding the exact details of the highly in-

tegrated and redundant network of cytokine-epithelial interactions. Similarly, despite considerable progress in identifying the cytokines that are elevated in the inflamed tissue of IBD patients (1), details of the precise cytokine milieu (both qualitatively and quantitatively) at different stages of the disease process, or in patients who are being treated with various therapeutic modalities, remain to be determined. Nevertheless, information obtained to date regarding the interaction of cytokines with epithelial cells suggests that increased knowledge in these areas may have clinical implications for IBD management. Elucidation of the precise regulatory loops involved may aid our ability to modulate processes such as secretory diarrhea, epithelial restitution and mucosal immunity.

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