Intestinal inflammation: a complex interplay of immune and nonimmune cell interactions

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Fiocchi, Claudio. Intestinal inflammation: a complex interplay of immune and nonimmune cell interactions. Am. J. Physiol. 273 (Gastrointest. Liver Physiol. 36): G769–G775, 1997.—Intestinal inflammation has traditionally been viewed as a process in which effector immune cells cause the destruction of other mucosal cells that behave as passive bystander targets. Progress in understanding the process of intestinal inflammation has led to a much broader and more integrated picture of the various mucosal components, a picture in which cytokines, growth factors, adhesion molecules, and the process of apoptosis act as functional mediators. Essentially all cellular and acellular components can exert immunelike activities, modifying the classical concept of selected immune cells acting on all other cells that has been the dogma of immunologically mediated tissue damage for decades. The existence of specialized communication pathways between epithelial cells and T cells is well documented, including abnormal epithelial cell-mediated T cell activation during inflammation. Mesenchymal cells contribute to fibrosis in the inflamed gut but are also responsible for retention and survival of leukocytes in the mucosa. In chronically inflamed intestine the local microvasculature displays leukocyte hyperadhesiveness, a phenomenon that probably contributes to persistence of inflammation. The extracellular matrix regulates the number, location, and activation of leukocytes, while metalloproteinases regulate the quantity and type of deposited matrix proteins. This evidence from the intestinal system, consolidated with the use of data from other organs and systems, reveals a rich network of reciprocal and finely orchestrated interactions among immune, epithelial, endothelial, mesenchymal, and nerve cells and the extracellular matrix. Although these interactions occur under normal conditions, the dysfunction of any component of this highly integrated mucosal system may lead to a disruption in communication and result in pathological inflammation.

epithelial cells; mesenchymal cells; endothelial cells; extracellular matrix
and eventually die at the hands of an all powerful army of effector immune cells (Fig. 1). This simple unidirectional model is intuitive, answers the plea for one cause-one effect relationship, and is convenient, since it is merely necessary to understand how mucosal immunity works to explain most types of intestinal inflammation. Unfortunately, this view is also likely to be too restrictive, naive, and incorrect. The unidirectional model is increasingly challenged by emerging evidence showing that all cell types populating the mucosa have an active role in intestinal immunity and inflammation. Epithelial, endothelial, mesenchymal, and nerve cells display broad and previously unsuspected effector and regulatory functions, including immunelike functions, and interact intimately with lymphoid cells. Even acellular components appear to play an active and surprisingly broad role, typically exemplified by the immunoregulatory activity of the extracellular matrix under both normal and inflammatory conditions (58, 64). As a consequence of this multiplicity and reciprocity of cellular actions in the mucosa, a multidirectional model of interactions between effector cells and target cells in normal and inflamed mucosa makes practical sense and probably more closely reflects reality (Fig. 2). Furthermore, a multidirectional model may be especially appropriate to investigate the mechanisms of chronic intestinal inflammation, as in inflammatory bowel disease (IBD), in which reactive behavior by nonimmune cells underlies the symptoms and structural changes observed in patients, such as pain, dismotility, fibrosis, stricture, and fistula formation, obstruction, and neoplastic transformation.

The concept of an integrated and tightly regulated multicellular response in pathological processes in general, and inflammation in particular, has been applied to several organs and tissues, but only very

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**Fig. 1.** Unidirectional model of cell-cell interactions in intestinal inflammation. In this model, activated immune cells (effector cells) interact with, attack, and destroy all other types of mucosal cells and the extracellular matrix (targets), which behave as simple bystanders.

**Fig. 2.** Bidirectional or multidirectional model of cell-cell interactions in intestinal inflammation. In this model, all cells and the extracellular matrix (effectors) reciprocally interact with and respond to all cell types and the extracellular matrix (targets) in the mucosa. Interactions are mediated by cell surface (adhesion molecules) and secreted (cytokines and growth factors) molecules, as well as by whole cell responses (apoptosis and proliferation).
recently has this concept been considered in the gut (19). Thus it is not surprising that there is a remarkable paucity of information on cellular interactions in complex inflammatory diseases, such as Crohn's disease and ulcerative colitis, and there are essentially no data derived from animal models of IBD. This makes it difficult to understand the cellular and molecular mechanisms underlying gut inflammation in humans. Therefore, some of the discussion of this review refers to cellular systems and organs outside of the gastrointestinal tract and to data, often of a preliminary nature, generated from a limited number of laboratories. Three specific aspects are addressed within the scope of this review: the types of immune-nonimmune cell interactions, the molecular (cytokines, growth factors, adhesion molecules) and functional (activation, proliferation, and apoptosis) bases for interaction, and the integration of cell interactions.

Among the various immune-nonimmune cell interactions occurring in the gut, the functional communication existing between epithelial cells and lymphocytes has been studied extensively. The concept of an immunological regulation of epithelial function is over a decade old (10) and was consolidated only after the demonstration of a well-defined antigen-presenting activity by rodent and human epithelial cells for T cells (6, 47). More recent work showing that human intestinal epithelial cells produce cytokines regulating the proliferation of intestinal lamina propria mononuclear cells (71) and express functional cytokine receptors for several T cell-derived cytokines (60) has further strengthened the concept of an exchange of regulatory signals between the epithelial and immune compartments of the mucosa. This reciprocal exchange of regulatory signals is probably altered during intestinal inflammation, as epithelial cells express de novo or upregulate expression of activation and cell adhesion molecules, such as HLA-DR antigens (63) and intercellular adhesion molecule-1 (32), and secrete a variety of proinflammatory cytokines affecting leukocyte activity (37). Another way in which epithelial cells may participate in or even induce intestinal inflammation is through defects of their basic function. This could be an explanation for the well-documented increase in intestinal permeability in Crohn's disease and intestinal infections (5) or the defective induction of suppressor T cells in patients with IBD (46).

Of the many types of nonimmune cells, those of mesenchymal origin, such as fibroblasts, myofibroblasts, and muscle cells, have traditionally been viewed as purely structural, designed to fill the space around other more functionally important cells or to perform mundane activities such as collagen deposition (44). This unsophisticated view no longer fits with evidence derived from studies indicating a far broader and more refined function for mesenchymal cells (69). For instance, intestinal electrolyte transport occurring in response to inflammatory mediators is modulated by fibroblastic cells (2). These likely represent a group of cells that are highly heterogeneous and selectively distributed throughout the mucosa, as suggested by the subepithelial localization of stellate myofibroblasts, a strategic location where they can receive, regulate, and transmit immune cell-derived signals to adjacent epithelial cells (30). Evidence for the heterogeneity of phenotype and function of mucosal mesenchymal cells is still limited, since these cells have only recently received attention, but information from other organs and systems is quite convincing (74). Mesenchymal cells from normal and inflamed tissues produce various cytokines (9, 14, 41), express cytokine receptors (28), and physically interact with immune cells (40), an activity that is in turn modulated by cytokines (54). Similar results have been obtained from murine and human studies using intestinal mesenchymal cells (31, 38, 52). Another aspect directly relevant to cell-cell interactions during inflammation is the ability of mesenchymal cells to produce proinflammatory cytokines, raises a provocative question. Which cells are actually responsible for the chronicity of inflammation, immune cells activated by an unknown primary antigen or byproducts of surrounding nonimmune cells, mesenchymal cells activated by immune cell- or self-derived cytokines, or perhaps both cell types stimulating one another in a perpetuating unregulated loop? This critical question waits for answers from ongoing studies.

A cell-cell interaction of great importance to the maintenance of mucosal immune homeostasis and sine qua non for the initiation of pathological gut inflammation is that between leukocytes and the local microvascular endothelium (55). Each vascular bed displays unique characteristics, with cell heterogeneity within different vessels of the same organ and between segments of the same vessel (75). Consequently, information derived from large vascular structures does not apply to the intestinal microvasculature, which displays specific features in response to inflammation (26). The key elements that regulate endothelial-leukocyte interactions are fairly well defined and include the state of differentiation and activation of endothelial cells (1), expression of cell adhesion molecules by both cell types (21), and the spectrum of cytokines they produce (43). Leukocyte migration to specific tissues, including the mucosal microcirculation, occurs through high endothelial venules (HEV), specialized endothelial cells that are probably involved in inflammatory diseases (23). A key cell adhesion molecule expressed by gut HEV is the mucosal vascular addressin MadCAM-1, a receptor for the α4β7-integrin present on circulating lymphocytes and proposed to mediate their selective migration to the gut (15). A large body of evidence supports the view that reciprocal signaling between endothelial cells and leukocytes also involves cytokines produced by and acting on both cells. T cellderived cytokines induce phenotypic and functional changes in endothelial cells (20), and monocyte/
macrophage-derived tumor necrosis factor-α induces them to produce interleukin-1 (50). Cytokines selectively increase leukocyte adhesiveness to vascular endothelium, as interleukin-1 does for polymorphonuclear cells and monocytes (3) and interleukin-4 does for T cells, but not for neutrophils (68). All of these interactions are relevant to inflammation and contribute to tissue damage (73).

Until recently, evidence that the above phenomena actually take place in the intestine was lacking due to a lack of experimental systems to directly evaluate relevant cell types. In the last two years methods have been established allowing the isolation and study of human intestinal microvascular endothelial cells (HIMEC) (4, 29, 33). Particularly exciting are data showing that HIMEC derived from IBD mucosa display enhanced adhesiveness for leukocytes compared with microvascular endothelium from normal mucosa (4). It is particularly significant that enhanced leukocyte adhesiveness persists regardless of whether IBD HIMEC are kept in culture, suggesting the existence of permanent functional alterations of the microvasculature in chronically inflamed gut mucosa. Knowledge derived from leukocyte endothelial interaction in the gut is fundamental not only to the understanding of the cellular and molecular mechanisms controlling vascular permeability and angiogenesis (12) but also to the development of novel forms of therapy for intestinal inflammation (51, 57, 70).

The above discussion shows how the misconception that immune cells alone control immunity and inflammation is being gradually modified by evidence that other cell types actively participate in those responses. An acellular component, the extracellular matrix (ECM), must be added to the growing list of nonimmune cellular elements involved in immunity and inflammation. All immune-nonimmune cell interactions mentioned so far occur in the midst of a complex mixture of proteins including fibronectin, collagen, laminin, thrombospondin, tenascin, enactin, proteoglycans, and others (58). In the gut mucosa these proteins occupy distinct domains that can be roughly divided into a compact laminar structure represented by the basement membrane and a diffuse network surrounding lymphoid, mesenchymal, vascular, and nerve cells. To a large extent, the composition of the ECM determines what cell surface receptors are expressed, which in turn controls the number and types of cells locally retained. This is especially important during inflammation, when the ECM plays a major role in regulating the number, location, and state of activation of leukocytes (13, 22). These interactive events are mediated through specific mononuclear cell surface receptors represented by integrins, CD44, CD26, and CD37 (64). Further interaction between the ECM and immune cells occurs through the action of matrix metalloproteinases (MMP), a family of zinc-containing endoproteinases produced by macrophages and T cells and capable of degrading connective tissue, enhancing chemotaxis and cell adhesion, aiding extravascular tissue access, and facilitating secretion of membrane-anchored cytokines (24). There is preliminary evidence suggesting that MMP are involved in intestinal inflammation. Granulation tissue next to IBD ulcers contains MMP1 and MMP3 mRNA (61), and activation of lamina propria T cells can lead to proteolytic degradation of mucosal ECM (53).

Extremely limited information exists on the amount, composition, and function of ECM in intestinal inflammation. In situ studies using Crohn’s disease and ulcerative colitis tissue sections show that in both forms of IBD there are significantly increased levels of procollagen mRNA, but the patterns of collagen deposition differ between the two diseases (45). Fibroblasts from strictured segments of Crohn’s disease-affected bowel produce significantly elevated amounts of collagen type III and display a heightened response to transforming growth factor-β induction (65). Only preliminary data are available on the function of mucosal

Fig. 3. Model of intestinal homeostasis in which all mucosal cell types interact with each other and the extracellular matrix to achieve and maintain a state of physiological inflammation. In this model, the dysfunction of one or more components can trigger or perpetuate pathological inflammation.
ECM in inflammation. Using matrix proteins deposited by cultured mucosal fibroblasts, Musso et al. (48) have shown that adhesion of T cells to this ECM is significantly greater with fibroblasts derived from IBD and that T cell adhesion can be augmented by pretreating the fibroblasts with proinflammatory cytokines. The cause and mechanisms of these provocative observations remain to be elucidated, but they suggest that considerable attention should be paid to the communication and exchanges between immune cells and ECM in intestinal inflammation.

The participation of the ECM expands the dimension of biological interactions in intestinal immunity and inflammation, which, in addition to traditional interactions between immune cells, now consists of interactions between immune and nonimmune cells, immune cells and ECM, and nonimmune cells and ECM. When these interactions occur in the normal mucosa, the result is intestinal homeostasis, which is seen as physiological inflammation (Fig. 3). Consequently, pathological inflammation can be viewed as the product of abnormal or disrupted interactions between two or more of the immune or nonimmune mucosal components. In cases of chronic intestinal inflammation such as IBD, multiple components are probably involved in anomalous communications among themselves. Accepting this hypothesis, a new challenge is to determine what precise elements mediate the actual communication and integrate exchanges among the various cellular and acellular constituents of the mucosa under both physiological and pathological conditions. These elements are multiple and different in nature: some are elaborated by the cells themselves, such as cytokines, growth factors, and adhesion molecules (Fig. 2); others are events triggered by cell interactions, such as migration, activation, proliferation, and apoptosis; and others are preexisting elements of the mucosa, such as the enteric nervous system. Because the focus of this review is on the importance of interactions to intestinal inflammation rather than the specific mechanisms of interaction during inflammation, only a few comments are made with regard to the above regulatory elements. The crucial role of cytokines and growth factors in intestinal inflammation is firmly established (17), and mounting evidence predicts a similarly crucial role for other regulatory elements. In cases of chronic intestinal inflammation such as IBD, multiple components are probably involved in anomalous communications among themselves. Accepting this hypothesis, a new challenge is to determine what precise elements mediate the actual communication and integrate exchanges among the various cellular and acellular constituents of the mucosa under both physiological and pathological conditions. These elements are multiple and different in nature: some are elaborated by the cells themselves, such as cytokines, growth factors, and adhesion molecules (Fig. 2); others are events triggered by cell interactions, such as migration, activation, proliferation, and apoptosis; and others are preexisting elements of the mucosa, such as the enteric nervous system. Because the focus of this review is on the importance of interactions to intestinal inflammation rather than the specific mechanisms of interaction during inflammation, only a few comments are made with regard to the above regulatory elements. The crucial role of cytokines and growth factors in intestinal inflammation is firmly established (17), and mounting evidence predicts a similarly crucial role for other regulatory elements.

In a recent review, Podolsky (56) indicated that there are many questions, but few answers, concerning our understanding of the regulation of intestinal epithelial cell proliferation. If a single biological phenomenon is so complex and challenging, the reader may wonder how one can possibly study all mucosal cell types and hope to fully understand their functions and interactions, not to mention the countless abnormalities sure to be found in intestinal inflammation. These concerns are legitimate, but a Cartesian approach to split, divide, and pick the simplest problem first, combined with the careful choice of an integrated experimental system, will duly reward the dedicated investigator.

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