Perspectives Series: Host/Pathogen Interactions

Epithelial Cells as Sensors for Microbial Infection

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Mucosal surfaces of the intestinal, respiratory, and genitourinary tracts are the most important route of entry of microbial pathogens into the host, and are important sites of microbially induced disease. Mucosal infections with microbial pathogens can result in a spectrum of disease manifestations that range from mild and self-limited to fulminant and lethal, or can be chronic and debilitating. The latter may occur in response to repetitive infections and eventually lead to organ dysfunction. The variability in outcome is determined by differences in the virulence of the infecting pathogens, and the effectiveness of the host response.

Epithelial cells that line mucosal surfaces are an important mechanical barrier that separates the host's internal milieu from the external environment, as most microbes found in the environment, including commensals in the large bowel, do not enter epithelial cells. In addition to barrier functions, epithelial cells at different mucosal sites (e.g., urinary, bladder, and small intestine) and at different locations within a given organ system (e.g., stomach and colon) have specialized host adaptive functions. In the gastrointestinal tract, for example, epithelial cells have an important role in ion transport and fluid absorption and secretion. For pathogens that invade the host, epithelial cells are the first site of contact with the host, which is relevant for this article.

Studies over the past several years have clearly indicated the integral role that epithelial cells at mucosal surfaces play in generating and transmitting signals between both invasive and noninvasive microbial pathogens, and adjacent and underlying cells in the mucosa. This led to the concept of epithelial cells as an integral component of a communications network that involves interactions between epithelial cells, luminal microbes, and host immune and inflammatory cells. This article focuses on the role epithelial cells play in this communication network as sensors of the intestinal microflora and providers of signals to the host that can affect the growth, development, and function of cells in the adjacent and underlying mucosa, and activate mucosal inflammatory and immune responses. This subject is divided into a section covering the repertoire of intestinal epithelial responses relevant for initiating and regulating the mucosal inflammatory and immune response (the host perspective), and a section on the pathophysiologic conditions under which these epithelial responses occur (the pathogen perspective). The reader is alerted to other important studies that have examined the expression of proinflammatory genes in epithelial cells of the respiratory and urinary tract (1, 2).

Repertoire of intestinal epithelial responses

Studies to elucidate the potential of intestinal epithelial cells to activate or regulate mucosal functions have mostly used conditions, e.g., stimulation with TNFα and IL-1, or infection with invasive bacteria such as *Salmonella*, designed to maximally stimulate a set of epithelial cell responses that are related to initiating and sustaining mucosal inflammation. In addition, intestinal epithelial cells can produce signals that do not directly regulate mucosal inflammation and immune responses and whose expression is controlled by stimuli different from those above. Such signals are more important, for example, in controlling functions like epithelial growth and differentiation.

Secreted epithelial products. Stimulation of human intestinal epithelial cells with TNFα, IL-1, or infection with enteroinvasive bacteria such as *Salmonella*, causes the increased expression and secretion of a number of cytokines with chemoattractant and proinflammatory functions. Thus, stimulated epithelial cells express and secrete relatively high levels of the chemoattractant cytokines IL-8, GROα, GROβ, GROγ, and ENA-78 (3–6a). These cytokines belong to the C-X-C family of chemokines and are characterized by their ability to chemoattract and activate polymorphonuclear leukocytes (PMN),[1] suggesting that an important function of intestinal epithelial cells is to initiate the mucosal influx of PMN. The latter is a hallmark of the initial acute inflammatory response that often results from infection of the intestinal tract with pathogenic bacteria. Activated epithelial cells also secrete, albeit at lower levels, a range of C-C chemokines, including MCP-1, MIP-1β, MIP-1α, and RANTES (6–7), which variably can act as chemoattractants of monocytes/macrophages, eosinophils, and subpopulations of T cells. Although speculative at this point, this suggests that activated intestinal epithelial cells, in addition to inducing an acute influx of PMN, may play an important role in orchestrating the initiation of mucosal inflammatory and immune responses in which a number of different cell types participate.

In addition to chemokines, agonist stimulated or bacteria-infected human intestinal epithelial cells express and secrete

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1. *Abbreviations used in this paper:* ICAM-1, intercellular adhesion molecule-1; NO, nitric oxide; NOS, NO synthase; PGHS-2, prostaglandin H synthase-2; PMN, polymorphonuclear leukocytes.

other proinflammatory cytokines, including TNFα, GM-CSF, IL-1α, and IL-1β, although expression of these cytokines is generally much lower than that observed for the chemokines (6, 8). In contrast to the differential and regulated expression of proinflammatory cytokines, intestinal epithelial cells do not appear to express a number of cytokines such as IL-2, IL-4, IL-5, IL-12 p40, or IFN-γ that are more commonly associated with antigen-specific acquired immune responses (6). This indicates that products secreted by intestinal epithelial cells are likely to play a more important role in initiating and regulating the innate mucosal inflammatory response rather than antigen-specific mucosal immune responses.

Upregulated expression of proinflammatory cytokines in human intestinal epithelial cells occurs rapidly after stimulation with agonists such as TNFα or IL-1, or after infection with invasive bacteria, since, for most of the cytokines, increased expression is seen within 90 min after infection, peaks by 3 h and returns towards baseline by 6 h postinfection (3, 4, 6a, 7). Increased secretion of proinflammatory cytokines by intestinal epithelial cells follows a parallel but delayed course with maximal secretion usually seen within 4–6 h after stimulation with return to baseline by 12 h (4, 6a). Thus, proinflammatory signals provided by intestinal epithelial cells are rapidly upregulated but transient in nature, suggesting an important role in signaling the onset of the inflammatory response in the early period after infection. Later during the course of the inflammatory response, we envision that signals important for maintaining immune and inflammatory reactions are mediated predominantly by monocytes/macrophages and other cells within the intestinal mucosa.

Although intestinal epithelial cells likely play their major role in signaling inflammatory responses very early after bacterial infection, the kinetics of expression of ENA-78 is delayed for several hours after bacterial infection or agonist stimulation of human colon epithelial cells. Moreover, the upregulated expression and secretion of this chemokine continues for a more prolonged period both in cell lines and in freshly isolated colon epithelial cells (6a). Although produced at relatively low levels, the T cell and eosinophil chemoattractant RANTES also is expressed with delayed kinetics by intestinal epithelial cells. Differences in the kinetics of production of these chemokines, coupled with quantitative differences in their production, suggest that epithelial cells may play a more complex role in the regulation of mucosal inflammation than initially appreciated by influencing both the temporal and spatial migration patterns of leukocytes within the intestinal mucosa (6a). Finally, it will be important in the future to define the signaling pathways within epithelial cells that both upregulate and downregulate proinflammatory cytokines and to focus on the possible role epithelial cells can play in downregulating mucosal immune and inflammatory responses through the production of other cytokines such as TGFβ1 and IL-10.

Epithelial gene products expressed at the cell membrane. The repertoire of products secreted by human intestinal epithelial cells suggests an important function in orchestrating the innate mucosal inflammatory response. In an interesting contrast, the spectrum of membrane-expressed products suggests that these cells also contribute to antigen-specific mucosal immune responses. Thus, intestinal epithelial cells constitutively express or can be induced to express MHC class II molecules, can present protein antigens to T lymphocytes in vitro, and express classical MHC class I molecules and nonclassical MHC-related molecules (9). Furthermore, intestinal epithelial cells also respond to a range of signals from the underlying mucosa, as suggested by the expression of receptors for several cytokines including IFN-γ, IL-1, TNFα, TGFβ1, as well as IL-2, IL-4, IL-7, and IL-9 (10).

Another important class of membrane molecules are adhesion molecules, which play a central role in regulating the flux of immune and inflammatory cells through tissues. Intercellular adhesion molecule-1 (ICAM-1) is a cell surface glycoprotein that serves as a counter receptor for β2 integrins expressed on PMN and lymphocytes. Intestinal epithelial cells upregulate ICAM-1 expression in response to coculture with invasive bacteria or after agonist stimulation (11, 12). Using an in vitro model of polarized monolayers of human intestinal epithelial cells and an in vivo model (13) in which human intestinal xenografts in SCID mice are infected with invasive bacteria, ICAM-1 was shown to be expressed in a polarized distribution on the apical surface of intestinal epithelial cells after bacterial infection, with its density being greatest in the area of the intercellular junctions (11). Recently, others have shown increased ICAM-1 expression on intestinal epithelial cells in chronically inflamed areas of intestinal mucosa (14). Although colon epithelial cells expressing increased ICAM-1 bind PMN and lymphocytes in vitro (11, 12), a physiologic role for increased ICAM-1 expression on epithelial cells after microbial infection in vivo has not yet been demonstrated. The possibility exists, however, that ICAM-1 expression on the apical surface of intestinal epithelial cells functions to maintain PMN that have transmigrated across the epithelium into the intestinal crypts within that site, thereby reducing further invasion of the mucosa by the enteric pathogen (11, 14, 15).

Gene products expressed inside epithelial cells. Increased fluid secretion is initiated rapidly after infection of the intestinal tract with invasive bacteria. After infection with enteroinvasive bacteria, human epithelial cells upregulate PGE_2 and $PGF_{2\alpha}$ production and the expression of one of the crucial rate-limiting enzymes for prostaglandin formation, prostaglandin H synthase (PGHS)-2, as shown in recent studies using colon epithelial cell lines or human intestinal xenografts in SCID mice (16). These findings may explain the pathophysiology of the acute diarrhea associated with enteroinvasive bacterial infection, since PGE_2 produced by infected intestinal epithelial cell lines can directly stimulate uninfected epithelial cells to increase chloride secretion (16), and can act indirectly by stimulating enteric nerves to release neurotransmitters that activate epithelial ion transport processes (17). This shows that, in addition to proinflammatory cytokines, epithelial cells can produce additional physiologic mediators that may act in an autocrine/paracrine function on neighboring intestinal epithelial cells or other mucosal cells.

Nitric oxide (NO) is produced by NO synthases and affects multiple gastrointestinal functions, including blood flow and mucosal inflammation. Increased expression of inducible NO synthase (NOS2) is found in intestinal epithelial cells during the course of intestinal inflammation (18) and in response to stimulation of epithelial cells with a combination of cytokines. Ongoing studies in our laboratory indicate that enteroinvasive bacteria are potent inducers of NOS gene expression and nitric oxide production in intestinal epithelial cells. Moreover, studies using NO donors and NOS inhibitors suggest that increased NO production by intestinal epithelial cells, in response to bacterial infection, contributes to a striking increase in apoptosis

we have noted in epithelial cells cocultured with enteroinvasive bacteria.

Interaction of intestinal epithelial cells with enteric pathogens

A number of in vitro and in vivo model systems have been used to characterize host epithelial cell responses to mucosal infections, with bacterial and protozoan pathogens that range from highly invasive to minimally invasive to noninvasive, as well as to colonization with commensal bacteria.

Interactions with invasive bacterial and protozoan pathogens that penetrate the epithelium and invade the mucosa. The mechanisms used by *Salmonella*, *Yersinia*, *Shigella*, and *Listeria* to invade host epithelial cells have been studied extensively. Although these bacteria all induce their own uptake into epithelial cells, the uptake processes involve different host receptors and cell signaling pathways (19). Moreover, these organisms have different intracellular localizations (e.g., after entry, *Salmonella* and *Yersinia* reside in membrane-bound vesicles, whereas *Listeria* and *Shigella* rapidly lyse such vesicles and move freely within the cytoplasm). Nonetheless, entry of these bacteria requires rearrangement of the epithelial cell actin cytoskeleton, and is impaired by inhibitors of actin polymerization (e.g., cytochalasin D). Infection with each of these organisms results in a qualitatively similar host response in regard to the upregulated expression of immunoregulatory genes in epithelial cells. This includes increased production of proinflammatory cytokines (3, 5, 6), PGHS-2 and prostaglandins (16), NOS2 and NO, and ICAM-1 (11). These studies suggest that intestinal epithelial cells have evolved a set of conserved functions that are activated in response to a broad array of different invasive bacterial pathogens, irrespective of the particular bacterial invasion strategy, and are likely to be important for host survival. The mechanisms and pathways underlying this uniform epithelial response are poorly understood at this time.

Trophozoites of the protozoan parasite *Entamoeba histolytica* invade the intestinal mucosa through focal areas of epithelium where they result in extensive lysis of epithelial cells and cells in the underlying mucosa. Acute mucosal lesions in *E. histolytica* infection, in striking contrast to chronic infections with this parasite, are characterized by an infiltration with inflammatory cells, particularly PMN. A partial explanation for this host response is provided by the observation that coculture of human intestinal epithelial cells with trophozoites results in a rapid increase in the expression and secretion of chemoattractant and proinflammatory cytokines (8). This cytokine response involves two major mechanisms. First, lytic damage of cells by *E. histolytica* results in the release of preformed IL-1α which, together with new IL-1α production, upregulates proinflammatory chemokine production by uninfected neighboring cells. Second, trophozoites induce increased cytokine production after trophozoite–epithelial cell contact via a galactose inhibitable amebic adherence protein, a mechanism that is probably related to increased intracellular calcium levels (8). Recent studies in which human intestinal xenografts in SCID mice were infected with *E. histolytica* trophozoites suggest similar mechanisms are operative in vivo (20).

Interactions with minimally invasive pathogens that invade epithelial cells but not the underlying mucosa. Chlamydia species infect epithelial cells at all major mucosal surfaces and are important causes of sexually transmitted disease. Infection is characterized by acute inflammation that is exacerbated upon re-infection, ultimately leading to tissue damage and scarring. Although *Chlamydia* resides within epithelial cells and does not invade deeper layers of the mucosa, the infection initiates an inflammatory response that is key for the development of disease. Infection of cervical and intestinal epithelial cell lines and primary cultures of cervical epithelial cells with *Chlamydia* upregulates epithelial cell expression and secretion of IL-8, GROα, GM-CSF, and IL-6 (21). Unlike the rapid, but transient, upregulation of cytokine production after infection with enteroinvasive bacteria, the epithelial cell cytokine response after *Chlamydia* infection is delayed for 20–24 h postinfection, persists throughout the chlamydial growth cycle, and requires bacterial protein synthesis (21). Similar to the findings with *E. histolytica*, IL-1α released from cervical epithelial cells after *Chlamydia*-induced cell lysis can amplify the inflammatory response by stimulating additional cytokine production by noninfected neighboring cells (21). These studies suggest that the acute response to *Chlamydia* at mucosal surfaces is primarily initiated and sustained by epithelial cells, which are the first and major targets of *Chlamydia* infection.

Cryptosporidium parvum is a protozoan parasite that invades intestinal epithelial cells and cells of the biliary tract and, in the case of severe infections, is associated with an inflammatory response in the underlying mucosa. In the biliary tract, the inflammatory response can result in biliary duct scarring and bile duct obstruction. Like *Chlamydia*, *C. parvum* undergoes a life cycle that results in lysis of epithelial cells within 3–5 d after infection. This results in the release of infective life stages of *C. parvum* that can infect previously uninfected neighboring cells. Coculture of *C. parvum* with human colon epithelial cell lines results in upregulation of epithelial cell proinflammatory cytokines, including IL-8 and GROα, which appear to be derived directly from infected cells (Laurent, F., L. Eckmann, C. Theodos, M. Naciri, and M.F. Kagnoff, manuscript submitted for publication). Moreover, like intraepithelial infection with *Chlamydia*, cytokine gene expression by epithelial cells in response to *C. parvum* is delayed for 18–24 h postinfection, and increased levels of proinflammatory cytokine production persist for at least 72 h postinfection. Although *Cryptosporidia* ultimately lyse intestinal epithelial cells at the apical surface, proinflammatory cytokine secretion occurs predominantly from the basolateral surface (Laurent, F., L. Eckmann, C. Theodos, M. Naciri, and M.F. Kagnoff, manuscript submitted for publication), further underlining that the relevant target cells are located in the underlying mucosa.

The studies using minimally invasive mucosal pathogens that invade epithelial cells but not deeper layers of the mucosa provide new insights into the mechanisms by which intestinal epithelial cells may orchestrate a more prolonged mucosal inflammatory response, than that seen after acute infection with enteroinvasive bacteria, by directly activating proinflammatory cytokine production in infected cells. Although the life span of the infected intestinal epithelial cells is limited because of their turnover every 3–5 d, these intracellular pathogens can maintain an ongoing inflammatory response in the host by virtue of their ability to lyse host epithelial cells and repeatedly infect newly generated healthy epithelial cells.

Interactions with noninvasive pathogens. Proinflammatory cytokine genes can be activated in uroepithelial cells after interactions of the cells with uropathogenic *Escherichia coli* that bind to and interact with cell surface molecules, but neither appear to enter the epithelial cell nor activate it by extracellular

lipopolysaccharide (2). Thus, uroepithelial cells, which normally reside in a sterile environment, and colon epithelial cells, which normally are exposed to an abundant bacterial flora, respond to different aspects of the bacteria/host interaction. Like the urinary tract, epithelial cells within the human stomach reside in a relatively sterile environment and, here too, interaction with a noninvasive bacterial pathogen, *Helicobacter pylori*, upregulates IL-8 gene expression in the apparent absence of bacterial entry (22). Finally, we note that enteropathogenic *E. coli*, which bind to the epithelial cell surface and induce actin reorganization and membrane pedestal formation, also can stimulate low level epithelial cell IL-8 responses (23). Whether this reflects the fact that this microorganism is minimally invasive or whether other membrane signaling events are involved is not known.

Interactions with resident commensal flora. Recent studies using models in which germ-free mice are associated with a single bacterial species indicate that commensal luminal bacteria, which are components of the conventional flora, can influence epithelial cell gene expression (24). Moreover, mechanisms putatively involved in epithelial cell communication with the host's commensal flora can be studied in such models using wild type and mutant isogenic bacterial strains. Such studies may be particularly important in determining how commensals can signal mucosal inflammation (25).

Conclusions

In summary, epithelial cells that line mucosal surfaces are a critical component of a communications network that links signals provided by luminal and invasive bacteria to immune and inflammatory cells in the underlying mucosa. The epithelial cell has evolved a series of conserved early and late responses by which it interacts with invasive and minimally invasive mucosal microbial pathogens. We have termed the most extensively studied of these the epithelial cell inflammatory gene program. This program includes, but likely is not limited to the regulated expression and production of proinflammatory cytokines, PGHS-2 and prostaglandins, NOS2 and nitric oxide, and increased cell surface expression of ICAM-1. Each of the rapidly upregulated genes is a target gene of the transcription factor NF-κB and each of the products encoded or produced as a result of upregulated expression of these genes likely plays a role in the host's resistance to the invading microbe and host mucosal defense. For example, chemokines produced by epithelial cells in response to microbial infection may provide signals essential for the initiation and, in the case of intraepithelial pathogens, the maintenance of the mucosal inflammatory response. PGHS-2, on the other hand, is responsible for increased epithelial prostaglandin production, thereby contributing to the infection related diarrhea, and may also directly influence epithelial cell growth and apoptosis. Recent studies also suggest that epithelial cells in the intestinal tract can sense the conventional microbial flora. Thus, it is tempting to speculate that communication between the normal resident microbial flora and intestinal epithelial cells may play a role in regulating normal epithelial cell growth and development as well as lymphoid cell development and physiologic inflammation in the intestine. It now also seems clear that intestinal epithelial cells maintain a dialogue with immune cells in the adjacent and underlying mucosa through the production of growth factors (e.g., IL-7 and stem cell factor) and perhaps also through local hormone networks, as recently reported for thyroid stimulating hormone (26), although the influence of pathogenic microbes and commensal bacteria on the expression of these factors is not yet known. Definition of the signal transduction and regulatory mechanisms that govern interactions between epithelial cells, mucosal microbes, and inflammatory and immune cells in the adjacent mucosa may lead to new therapeutic approaches for manipulating and regulating inflammatory and immune responses at the mucosal surfaces of the gastrointestinal tract, respiratory tract, and genitourinary tract, as well as for regulating the growth and development of epithelial cells and other cell types in these tissues.

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"Host/Pathogen Interactions: Understanding the Strategies of Microbial Virulence and Host Defense"

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