Understanding the Dialogue:
the Microbial–Host Interaction

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Introduction

The intestinal epithelium is the largest mucosal surface, providing an interface between the external environment and the mammalian host. Its exquisite anatomical and functional arrangements and the finely tuned coordination of digestive, absorptive, motility, neuroendocrine and immunological functions are testimony to the complexity of the gastrointestinal (GI) system.

Another important, yet often overlooked function of the GI tract is its selective regulation of cells, microorganisms, and macromolecules trafficking between the intestinal lumen and the submucosa. This function requires sophisticated sensor systems to be responsive to a wide variety of stimuli and to modulate proper responses to the complex climax community of microbial partners that populate the GI tract. Under physiological circumstances, the GI epithelial layer forms a tight, but selective barrier: microbes and most antigens are held at bay, but nutrients are actively absorbed. Moreover, the tightness of the epithelial barrier is itself dynamic, though the mechanisms governing and effecting dynamic permeability are poorly understood. What is becoming increasingly clear is that some microorganisms have developed tools to twist the host–microbial interaction to their own advantage, so triggering host pathophysiological changes leading to local and even systemic disorders.

Key Words
Intestine · Pattern recognition receptors · Inflammation · Intestinal permeability · Autoimmunity · Irritable bowel syndrome · Antigen trafficking

Abstract
The mammalian gastrointestinal tract is much more complex than previously appreciated. A single layer of epithelial cells covers the entire gastrointestinal tract, so providing the largest interface with the environment. The gut epithelium is a sensor of the luminal environment, not only controlling digestive, absorptive, and secretory functions, but also relaying information to the mucosal immune, vascular and nervous systems. These functions involve a complex array of pattern recognition receptors (PRRs) and cell types that elaborate growth factors, cytokines, and extracellular matrix proteins. Moreover, enteric microbes may hijack PRR-activated pathways as part of their pathogenic arsenal through ‘host mimicry’. Understanding the cross-talk between enteric microbiota and the host under both physiological and pathological circumstances may provide key information on the pathogenesis of local as well as systemic diseases. This knowledge may potentially lead to the identification of novel therapeutic strategies for the treatment of these disorders.

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Principles of GI Physiology

Structural Characteristics of the GI Tract

Each region of the gut provides a distinct contribution to the digestion of a meal, which is supported by unique morphology and function. At every level, the wall can be divided into four basic layers: serosa, muscularis externa, submucosa and mucosa. There are variations in the type and distribution of mucosal cells present along the length of the GI tract that reflect the specialized function of a particular region. The mucosal layer of the small intestine is designed to provide a large surface area for exposure of luminal contents to absorptive cells. Three anatomic factors contribute to the amplification of the absorptive surface beyond that of a simple cylinder. The circular folds of the intestinal mucosa, called plicae circulares, valvulae conniventes, or Kerckring folds, increase the surface area by 3-fold. The mucosal surface is further extended 10-fold by the presence of villi and crypts along the surface. The apical aspect of the enterocytes is covered with microvilli, further increasing the absorptive surface some 600-fold.

There are several types of epithelial cells lining the villi and crypts of the small intestine and this variety allows the intestine to perform its varied functions. The most common epithelial cells are columnar cells, which can be divided further on the basis of their proliferative activity. Cells in the crypt region have the highest activity, while the surface cells are less active. Functionally, crypt cells are thought to be primarily secretory, while enterocytes are primarily absorptive cells, with the apical brush border containing hydrolases and other enzymes critical in the terminal digestion of carbohydrates and proteins. Recent studies in the colon challenge this classical compartmentalization of crypt secretion and surface cell absorption by showing that epithelial cells have both secretory and absorptive abilities in this region [1, 2]. Goblet cells are present all along the GI tract, especially in the terminal jejunum and ileum, and the mucus they secrete acts as a lubricant as well as protecting the ciliated cells, and hormones like cholecystokinin, glucagon-like peptide-1, peptide YY and ghrelin are important in the regulation of appetite and satiety [4]. The GALT is composed of several specialized cells, including Peyer’s patches, M cells, and intraepithelial lymphocytes, which play key roles in host defense [5]. It is well documented that bacterial colonization is required for the structural and functional development of the GALT. One of the most important functions of the GALT is to discriminate between commensal versus pathogenic microorganisms [6]. Microflora derived from the mother at birth initiates microbial–epithelial crosstalk that serves as a defense against enteric pathogens. Epithelial cells become active participants in mucosal immunity through expression of Toll-like receptors (TLRs) that induce transcription of immune and inflammatory responses [7]. Processing of these bacterial antigens promotes the development of memory T cells that make up most of the T cells in gut lymphoid tissues. The structural arrangement of intestinal epithelial and immune cells just underneath the epithelial mucosa is a testimony to their coordinated complex series of responses to microorganisms and macromolecules present in the intestinal lumen.

Functional Features of the GI Tract Involved in the Microbiome–Host Interaction

Water and Electolyte Transport

One of the most important functions of the GI tract is absorption of water and electrolytes. Fluid absorption is passive and dependent on rate of solute transport and is, therefore, isotonic. The energy-dependent 3Na⁺-2K⁺ pump in the basolateral plasma membrane provides the energy-requiring step for driving the transcellular and paracellular flow of water across the epithelium. Other factors that influence fluid absorption are luminal osmolality and the region of the gut. There is a cephalocaudal increase in transepithelial resistance, which is regulated largely by intercellular tight junctions, along the intestine that underlies the greater paracellular flow of water in the small intestine compared to the colon. The transcellular flow of water is intimately coupled to solute transport, with the greatest flux occurring in the small intestine because of sodium-linked solute transporters [8]. The role of aquaporins, integral membrane proteins with high water selectivity [9], must also be considered in transcellular fluid transport. These water channels are located at both the apical and basolateral aspects of the epithelial cell in the small intestine and colon. Shifts in the location of aquaporins 7 and 8 from the apical to the basolateral membrane of enterocytes in inflammatory bowel disease patients support a role for these channels in the defective fluid transport in these patients [10]. Non-solute-coupled...
sodium transport is attributed to neutral NaCl absorption that is predominant during the interdigestive period. The sodium/hydrogen exchangers, NHE-2 and NHE-3, are present in the apical membrane of surface epithelial cells in both the small intestine and colon. Of interest, elevation in cyclic nucleotides induced by either endogenous signals or bacterial toxins, such as Vibrio cholerae-derived cholera toxin or heat-stable enterotoxin elaborated by entelorotoxigenic Escherichia coli, inhibits neutral sodium chloride absorption and NHE-3 activity [8].

While sodium transport provides the driving force for absorption, intestinal secretion is linked to movement of chloride through the cystic fibrosis transmembrane regulator (CFTR) located in the apical plasma membrane. Cyclic nucleotide-dependent phosphorylation increases the conductance of the CFTR channel. Excessive CFTR activity causes secretory diarrhea that occurs in response to the bacterial toxins such as choleragen, which elevates cyclic nucleotide production in the gut. In addition to the CFTR channel, there are also two other classes of Cl⁻ channels in the intestine, the CLC family and a calcium-activated chloride channel [11]. The CLC gene family are broadly expressed chloride channels, the most prominent in the intestine being CLC-2 [12]. These channels can be activated by hyperpolarization, cell swelling and extracellular acidification [11]. The precise physiological function of this channel remains to be elucidated; however, it is proposed to play a role in cholinergic mediated secretion in the colon [13].

Intestinal Barrier Function
The paracellular route is the dominant pathway for passive solute flow across the intestinal epithelial barrier, and its functional state depends on the regulation of the intercellular tight junction, also known as the zonula occludens (ZO) [4]. The tight junction is one of the hallmarks of absorptive and secretory epithelia. As a barrier between the apical and basolateral compartments, it selectively regulates the passive diffusion of ions and small water-soluble solutes through the paracellular pathway, thereby compensating for any gradients generated by transcellular pathways [14]. Due to the high resistance of the enterocyte plasma membrane, variations in transepithelial conductance have been ascribed to changes in the paracellular pathway [15]. The tight junction represents the major barrier in this paracellular pathway with electrical resistance of epithelial tissues dependent on the number and complexity of transmembrane protein strands within the tight junction, as observed by freeze-fracture electron microscopy [16]. Evidence now exists that the tight junctions, once regarded as static structures, are in fact dynamic, and readily adapt to a variety of developmental [17–19], physiological [20–23] and pathological [24–26] circumstances.

To meet the diverse physiological challenges to which the intestinal epithelial barrier is subjected, tight junctions must be capable of rapid and coordinated responses. This requires the presence of a complex regulatory system that orchestrates the state of assembly of the tight junction multiprotein network. While knowledge about tight junction ultrastructure and intracellular signaling events has progressed significantly during the past decade, relatively little is known about their pathophysiological regulation secondary to extracellular stimuli. The discovery of zonulin, a molecule that reversibly modulates tight junction permeability, sheds light on how the intestinal barrier function is regulated in health and disease [27] (fig. 1). The physiological role of the zonulin system remains to be established. However, it is likely that this pathway is involved in several functions, including tight junction regulation responsible for the movement of fluid, macromolecules, and leukocytes between the bloodstream and the intestinal lumen, and vice versa. Another physiological role of intestinal zonulin is protection against colonization by microorganisms of the proximal intestine (that is innate immunity) [15]. Given the complexity of both cell signaling events and the intracellular structures involved in the zonulin system, it is not surprising that its activation by small intestinal bacterial contamination can be the trigger of several immune-mediated disorders, including autoimmune diseases [28, 29].

GI Mucosal Immunology

Gut-Associated Lymphoid Tissue
Paracellular passage of macromolecules, under either physiological or pathological circumstances, is safeguarded by the GALT. GALT serves as a containment system preventing potentially harmful intestinal antigens from reaching the systemic circulation and induces systemic tolerance against luminal antigens by a process that involves polymeric IgA secretion and the induction of regulatory T cells. GALT is composed of both inductive (Peyer’s patches) and effector sites (intraepithelial cells and lamina propria). Recent studies also include isolated lymphoid follicles, which are tertiary lymphoid structures formed in autoimmune diseases as well as in a number of inflammatory pathologies of the gut [14]. Mature
isolated lymphoid follicles bear a resemblance to Peyer’s patches in cellular composition and localization in the distal intestine, as well as a dependence on the lympho-toxin interaction lymphotoxin $\beta$ receptor for formation of these structures [16]. Another important factor for the intestinal immunological responsiveness is the major histocompatibility complex. HLA class I and II genes are located in the major histocompatibility complex on chromosome 6. These genes code for glycoproteins, which bind peptides, and this HLA-peptide complex is recognized by certain T-cell receptors in the intestinal mucosa [30, 31]. Susceptibility to at least 50 diseases is associated with specific HLA class I or class II alleles.

The balance between immunity and tolerance is essential for a healthy intestine, and abnormal or inappropriate immune responses may result in inflammatory pathologies. Antigen-presenting M cells efficiently take up and transport a variety of microorganisms and present antigen [32]; therefore, isolated lymphoid follicles are proposed to be local sites for lymphocytic, antigen and antigen-presenting cell interactions. In addition to M cells, dendritic cells also capture antigens present in the intestinal lumen by sending dendrites through tight junctions between epithelial cells while maintaining barrier integrity [17, 18] and then rapidly migrating to other areas, such as mesenteric lymph nodes [19]. There is evidence that antigen-presenting dendritic cells are educated by memory T cells and subsequently induce naïve T cells [20], thereby supporting the role of dendritic cells in coupling innate and adaptive immune responses that affect intestinal permeability.

Innate and Adaptive Immunity and Their Interactions

Recognition of antigens by dendritic cells triggers a family of pattern recognition receptors, TLRs, which change dendritic cell phenotype and function. TLRs are the major receptors involved in the discrimination between self and non-self based on the recognition of con-
served bacterial molecular patterns (fig. 2). In intestinal epithelial cells, TLRs play a role in normal mucosal homeostasis and are particularly important in the interaction between the mucosa and the luminal flora [22]. There are a number of TLRs, all of which are present in the gut and respond to different stimuli resulting in different adaptive immune responses [21, 23, 25]. There is now evidence for a differential response to stimuli arising from TLRs located at the basolateral versus the apical surface [33].

TLRs direct immune responses by activating signaling events leading to elevated expression of factors, such as cytokines and chemokines that recruit and regulate the immune and inflammatory cells, which then either initiate or enhance host immune responses [34]. The peripheral memory T-cell response is a critical outcome of adaptive immunity and TLRs likely are required for the generation and maintenance of memory T cells [26]. TLRs are implicated in chronic diseases such as enteric inflammation and may have both proinflammatory and protective roles. Of interest, commensal flora acting through TLR4 positively influences the susceptibility to food antigens [24] and implicates TLRs in the regulation of intestinal permeability. This concept is supported by recent in vitro studies using intestinal epithelial cell cultures, which show that TLR2 enhances epithelial integrity by a rearrangement of the tight junction protein, ZO-1 [21]. In addition, TLR signaling is important in the anti-inflammatory effects of probiotics [35]. These data show the critical role of bacteria in shaping the immune response and underscore the current interest in probiotic effects on permeability [36–38] that may act to limit polarization to Th1 or Th2 responses and, thereby, maintain intestinal barrier function.

The Intestinal Neuroendocrine Network

Intestinal homeostasis is coordinated by responses of different cell types, including both immune and non-immune cells. The interaction between immune and non-immune cells is amplified by the influx of inflammatory and immune cells, increasing the exposure of non-immune cells to soluble mediators, such as cytokines, that are released from immune cells. Macrophages, leukocytes and mucosal mast cells all elaborate a number of
mediators that alter gut function. Of interest, mucosal mast cells appear to play a role in both Th1- and Th2-driven adaptive immune responses, release a number of preformed mediators (such as histamine and serotonin), as well as newly synthesized mediators, including leukotrienes, prostaglandins, platelet-activating factor, and IL-4 and TNF-α, many of which have an effect on epithelial permeability [39–43]. This may explain, at least in part, the increased permeability that is a feature of both Th1- and Th2-driven pathologies.

The Microbial–Host Interaction

Intestinal Microbiota

The human gut is host to a large and diverse population of microbiota that are known to play a critical role in the development of the GALT. The collective bacterial genome of the human microbiota encodes an estimated 2–4 million genes, surpassing the human genome by a staggering 140-fold [44]. Intestinal bacteria carry thousands of enzymatic reactions not catalyzed by the mammalian host, and thus act as an ‘organ within an organ’. Therefore, acquisition of the intestinal microbiota at birth from the mother’s microbiota can be considered as the inheritance of a parallel genome. One of the most important functions of the mucosal epithelium is the ability to discern commensal from pathogenic bacteria to maintain tolerance. The epithelium recognizes specific microbiota and responds with increased production of chemokine and cytokines that serve to promote an antigen-specific immune response [45]. The mechanisms that govern this recognition of bacterial species are of interest, particularly with respect to the mechanisms of the beneficial effect of probiotics on autoimmune diseases that are associated with an impaired mucosal barrier function such as type 1 diabetes [46]. The nucleotide oligomerization domain (NOD) proteins are another set of recognition receptors that function in the innate immune response. Genetic polymorphisms in NOD-2 are linked to an increased susceptibility to Crohn’s disease in certain populations [47, 48]. Recent studies show that DNA derived from the combination probiotic VSL3 improved inflammation in IL-10-deficient mice [49], suggesting a novel mechanism by which bacteria are recognized by epithelial cells. Recent studies showed increased expression of surface TLR9 expression on cell cultures in response to pathogenic bacteria [50], evidence that can negate inflammatory signals initiated by activation of basolateral TLR [33].

Enteric Pathogens

The distinguishing characteristics of bacteria (small size, concise deployment of genetic information, and the ability to survive in highly varied circumstances) contribute to their acclaimed virtuosic ability to adapt and learn fast in order to survive. To be a successful enteric pathogen, a bacterium must be a good colonizer, must compete for nutrients, and must be able to interact with the target eukaryotic cell to induce changes in gut homeostasis advantageous for its species. Because the basic metabolism of enteric pathogens and commensals is the same, it follows that pathogens must possess highly specialized attributes that enable them to activate one of the eukaryotic intracellular pathways leading to intestinal secretion. This cross-communication between enteric bacteria and the intestinal host is typically activated by the elaboration of enterotoxins that subvert host–cell signal transduction pathways, leading to changes in gut homeostasis, including increased water and electrolytes secretion (i.e., diarrhea) and changes in intestinal permeability.

Microbial–Host Interaction and Human Diseases

The focus of the clinical outcome of the microbial–host interaction has been traditionally limited to enteric infections. However, research during the past few years has clearly shown that this interaction goes well beyond infectious diseases, causing both local and systemic functional, inflammatory, metabolic, and immune-mediated diseases. Some of these conditions (specifically, inflammatory bowel diseases, allergies, and obesity) are more specifically addressed by other articles in this issue. Here we focus on other conditions, i.e.; irritable bowel syndrome and autoimmune diseases, in which the microbiota–host interaction has been involved in their pathogenesis.

Irritable Bowel Syndrome

Several studies have established that the prevalence of post-infective (PI) irritable bowel syndrome (PI-IBS) can affect as much as 20–25% of patients [51, 52]. However, little is known of the pathogenesis of PI-IBS. The fact that only 25% of patients who have had infectious diarrhea develop IBS-like symptoms suggests other risk factors, including age, sex, and prolonged enteric infection, and the involvement of the nervous and immune systems is necessary for IBS symptoms to develop among patients suffering from bacterial enteritis [51, 53]. Brain–gut interactions are believed to play an key role in IBS pathogenesis. Possible connections exist between enteric nerves and immune cellular components, with mast cells repre-
senting the possible connecting factor between the local immune response and the neurohormonal system during acute intestinal infection. The higher incidence of PI inflammatory bowel disease among patients who had a longer duration of infective enteritis may be explained by a more severe inflammation which causes a more severe impairment of the underlying nerve fibers. The notion that PI-IBS results from an enhanced inflammatory response is further supported by Wang et al. [53] who showed a higher expression of IL-1β mRNA in the intestinal mucosa in PI-IBS patients. The same authors also detected an increase in the number of mast cells within the lamina propria in the terminal ileum of the IBS patients studied. The increase in number and activation of mast cells in the intestinal mucosa and release of its mediators (i.e. IL-1β) could reflect enhancement of the immune response to previous inflammation in PI-IBS patients. Release of IL-1β may cause inhibition of intestinal transport of water, electrolytes and, ultimately, diarrhea [53]. Also, IL-1β is a potent hyperalgesic agent which may be responsible for hypersensitivity to rectal stimulation in IBS [54]. An increased number of T lymphocytes in the colorectal mucosa of IBS patients has also been reported [55], indicating persistence of the immune response in these patients. Combined, these observations suggest that activation of the mucosal immune system as an inflammatory response may play an important role in the pathogenesis of PI-IBS.

Autoimmune Diseases: Old Theories

Autoimmune diseases are the third most common category of diseases in the United States after cancer and heart disease, affecting up to 8% of the population or 14–22 million persons [56]. They can affect virtually every site in the body, including the GI tract. At least 15 diseases are the direct result of an autoimmune response, while circumstantial evidence links >80 conditions with autoimmunity [57].

Soon after autoimmune diseases were first recognized more than a century ago, researchers began to associate them with viral and bacterial infections. A mechanism often called on to explain the association of infection with autoimmune disease is ‘molecular mimicry’, where antigens (or, more properly, epitopes) of the microorganism are postulated to closely resemble self-antigens [58]. The induction of an immune response to the microbial antigen then results in a cross-reaction with self-antigens and the induction of autoimmunity. Once the process is activated, the autoimmune response becomes independent of continuous exposure to the environmental trigger and, therefore, the process is self-perpetuating and irreversible. Epitope-specific cross-reactivity between microbes and self-tissues has been shown in some animal models [59]. Conversely, molecular mimicry in most human autoimmune diseases seems to be a factor in the progression of a preexisting subclinical autoimmune response, rather than in the initiation of autoimmunity by breaking tolerance [60].

Another theory suggests that microorganisms expose self-antigens to the immune system by directly damaging tissues during active infection. This mechanism has been referred to as the ‘bystander effect’ and occurs when the new antigen is presented with the originally fed antigen [61]. Whether pathogens mimic self-antigens, release sequestered self-antigens, or both, remains to be elucidated.

Recently, increased hygiene and a lack of exposure to various microorganisms has been proposed to be responsible for the ‘epidemic’ of autoimmune diseases that has occurred over the past 30–40 years in industrialized countries, including the US [62]. The essence of the ‘hygiene hypothesis’ argues that the rising incidence of immune-mediated (including autoimmune) diseases is due, at least in part, to lifestyle and environmental changes that have made us too ‘clean’. This hypothesis is supported by immunological data showing that the response to microbial antigens induces Th1 cytokine expression that offsets the Th2-polarized cytokine production in neonates. In the absence of microbes, the gut may be conducive to an exaggerated IgE production, atopy and atopic diseases. Alternately, the absence of helminth infections eliminates the normal upregulation of Th2 in childhood, culminating in a more Th1-prone immune environment that is characteristic of autoimmune and inflammatory diseases [63]. Regardless of whether autoimmune diseases are due to too much or too little exposure to microorganisms, it is now generally considered that adaptive immunity and imbalance among Th1, Th2, Th17 and T regulatory cell responses are key elements in the pathogenesis of the autoimmune process [64].

Autoimmune Diseases: New Theories

A common denominator of autoimmune diseases is the presence of several preexisting conditions leading to an autoimmune process. The first is a genetic susceptibility for the host immune system to recognize, and potentially misinterpret, an environmental antigen presented within the GI tract. Second, the host must be exposed to the antigen. Finally, the antigen must be presented to the GI mucosal immune system following its paracellular
passage (normally prevented by tight junction competency) from the intestinal lumen to the gut submucosa [65]. In many cases, increased permeability appears to precede disease and causes an abnormality in antigen delivery that triggers the multi-organ process leading to the autoimmune response [66].

Therefore, the following hypothesis can be formulated to explain the pathogenesis of autoimmune diseases that encompasses the following three key points:

1. Autoimmune diseases involve a miscommunication between innate and adaptive immunity.
2. Molecular mimicry or bystander effects alone may not explain entirely the complex events involved in the pathogenesis of autoimmune diseases. Rather, continuous stimulation by non-self antigens (environmental triggers) appears necessary to perpetuate the process. This concept implies that the autoimmune response can theoretically be stopped and, perhaps, reversed if the interplay between autoimmune predisposing genes and trigger(s) is either prevented or eliminated.
3. In addition to genetic predisposition and the exposure to the triggering non-self antigen, the third key element necessary to develop autoimmunity is the loss of the protective function of mucosal barriers (mainly the GI and lung mucosa) that interface with the environment.

Conclusions

The GI tract has been extensively studied for its digestive and absorptive functions. A more attentive analysis of its anatomo-functional characteristics, however, clearly indicates that its functions go well beyond the handling of nutrients and electrolytes. The exquisite regional-specific anatomical arrangements of cell subtypes and the finely regulated cross-talk between epithelial, neuroendocrine and immune cells highlights other less studied, yet extremely important functions of the GI tract. Of particular interest is the regulation of antigen trafficking and intestinal mucosa–microbiota interactions. These functions dictate the switch from tolerance to immunity, and are likely integral mechanisms involved in the pathogenesis of both local GI inflammatory processes and systemic diseases.

The classical paradigm of autoimmune pathogenesis involving specific genetic makeup and exposure to environmental triggers has been challenged recently by the addition of a third element, the loss of intestinal barrier function. Genetic predisposition, miscommunication between innate and adaptive immunity, exposure to a specific microbiota, and loss of intestinal barrier function secondary to a dysfunction of the intercellular tight junction, all seem to be key ingredients involved in the pathogenesis of inflammatory and autoimmune diseases. This new theory implies that once the autoimmune process is activated, it is not auto-perpetuating. Rather, it can be modulated or even reversed by preventing the continuous interplay between genes and the environment. Since changes in microbiota causing tight junction dysfunction seem to allow such interactions, new therapeutic strategies aimed at reestablishing a ‘healthy’ cross-talk between intestinal microorganisms and the host, including the use of prebiotics and probiotics, offer innovative approaches for the management of these chronic diseases.

References

Intestinal Microbial–Host Interaction