Immunity, Inflammation, and Allergy in the Gut

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REVIEW

Immunity, Inflammation, and Allergy in the Gut

Thomas T. MacDonald[1]*† and Giovanni Monteleone[2]

The gut immune system has the challenge of responding to pathogens while remaining relatively unresponsive to food antigens and the commensal microflora. In the developed world, this ability appears to be breaking down, with chronic inflammatory diseases of the gut commonplace in the apparent absence of overt infections. In both mouse and man, mutations in genes that control innate immune recognition, adaptive immunity, and epithelial permeability are all associated with gut inflammation. This suggests that perturbing homeostasis between gut antigens and host immunity represents a critical determinant in the development of gut inflammation and allergy.

The gastrointestinal tract is the site where the divergent needs of nutrient absorption and host defense collide: The former requires a large surface area and a thin epithelium that has the potential to compromise host defense. Many infectious diseases involve the gut, and the investment by the gut in protecting itself is evident in the abundant lymphoid tissue and immune cells it harbors. In westernized countries, most infectious diseases of the gut are largely under control, yet gastrointestinal food allergies and idiopathic inflammatory conditions have dramatically increased; in other words, we now have inflammation without infection. Although the reason for this remains unknown, a prevailing notion is that the absence of overt gut infection has upset the balance between the normal bacteria that colonize the healthy gut and the mucosal immune system.

The Gut Epithelial Barrier

The primary cellular barrier of the gut in preventing antigens encountering the immune system is the single layer of gut epithelium, the surface area of which is expanded to the order of 400 m^2, largely because it is formed into millions of fingerlike villi in the small bowel. Each epithelial cell maintains intimate association with its neighbors and seals the surface of the gut with tight junctions. In the upper bowel, the bulk of the antigen exposure comes from diet, whereas in the ileum and colon, the additional antigenic load of an abundant and highly complex commensal microflora exists.

Nevertheless, the gut epithelial barrier does not completely prevent lumenal antigens from entering the tissues. Thus, intact food proteins can be detected in plasma (*1*), and a few gut bacteria can be detected in the mesenteric lymph nodes draining the gut of healthy animals (*2*). Antigens can cross the epithelial surface through breaks in tight junctions, perhaps at villus tips where epithelial cells are shed, or through the follicle-associated epithelium (FAE) that overlies the organized lymphoid tissues of the intestinal wall (*3*). Peyer's patches (PP) in the small bowel are aggregates of lymphoid tissue numbering ~200 in the average adult, although tens of thousands of much smaller individual follicles also line the small bowel and colon. FAE contains specialized epithelial cells termed M cells whose function is to transport lumenal antigens into the dome area of the follicle (*3*) (Fig. 1). Antigen-presenting dendritic cells (DC) also send processes between gut epithelial cells without disturbing tight junction integrity and sample commensal and pathogenic gut bacteria (*4*, *5*). The gut epithelial barrier therefore represents a highly dynamic structure that limits, but does not exclude, antigens from entering the tissues, whereas the immune system constantly samples gut antigens through the FAE and DC processes.

Commensal Bacteria in Epithelial/Immune Cell Function in the Gut

Interaction of commensals with gut epithelium. The gut epithelium itself can also directly sense commensal bacteria and pathogens; integral to this are the mammalian pattern recognition receptors (PRRs), which recognize conserved structures of bacteria and viruses and generally activate pro-inflammatory pathways alerting the host to infection (*6*). Two different classes of PRRs are involved. The Toll-like receptors (TLRs) are usually associated with cell membranes and have an external leucine-rich repeat (LRR) recognition domain and an intracellular interleukin-1 receptor (IL-1R)–like signaling domain (*7*). The nucleotide-binding oligomerization domain (Nod) molecules, Nod1 and Nod2 [also known as CARD4 and CARD15 (caspase activation and recruitment domain)], are present in the cytosol of epithelial cells and immune cells. These proteins also have LRRs at the C terminus, a Nod domain, and CARD domains at the N terminus (*8*). There is abundant evidence that signaling through Nod or TLR activates transcription factor NF-κB, leading to pro-inflammatory gene expression (*7*, *8*)

TLR1 to TLR9 and Nod1 and Nod2 are each expressed by gut epithelial cells (*6*, *9*). Nod1 and Nod2 recognize slightly different muropeptide motifs derived from bacterial peptidoglycans (*6*), which suggests that they sense intracellular infection or attempted bacterial subversion of epithelial cells (*10*). TLRs recognize many different components of bacteria and viruses. For example, TLR4 recognizes

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lipopolysaccharide from the Gram-negative bacterial cell wall, and TLR5 recognizes bacterial flagellin (*6*, *7*). An unresolved question is how the gut distinguishes between pathogens and commensal bacteria. One means by which inappropriate responses to innate signals from commensals may be achieved is through the compartmentalization of TLRs to the basolateral aspects of epithelial cells or inside epithelial cells (*11*, *12*).

Mutualism also appears to exist between the commensal flora and the gut epithelium to maintain epithelial integrity. For example, recognition of TLR2 or TLR9 ligands by epithelial cells increases gut barrier function (*13*, *14*). The normal flora also induces cytoprotective proteins hsp25 and hsp72 in colonic epithelial cells (*15*). Mice deficient in MyD88, the adapter molecule essential for TLR signaling, fail to express epithelial hsp25 and hsp72 (*16*) and are highly susceptible to experimental inflammatory bowel disease (IBD) initiated by dextran sodium sulfate, which suggests that through TLR signaling, the bacterial flora may help protect the gut epithelium from nonspecific damage. Nonpathogenic microorganisms in the gut have also been shown to regulate inflammation negatively in other ways (*17*, *18*). For example, avirulent Salmonella inhibits activation of NF-κB in epithelial cells by blocking polyubiquitination of phosphorylated IκBα (*17*).

Overall, there is good evidence that the normal commensal flora exerts an anti-inflammatory influence and protects epithelial cells from toxic insult. Epithelial pro-inflammatory responses to the commensal flora exist in vitro (*19*, *20*), but most individuals maintain an abundant intestinal flora without incurring disease.

Interactions of commensals with the mucosal immune system. Healthy individuals possess an abundant and highly active gut immune system that is tightly regulated to prevent excessive immune responses to foods and gut bacteria (Fig. 1) (*21*, *22*). A major difference between the systemic and mucosal immune system is the anatomical separation of the inductive sites of mucosal immunity in the organized lymphoid tissue, such as PP, from the effector sites in the lamina propria (LP) and epithelium (Fig. 1) (*22*).

When T and B cells are activated in PP, they express the α4β7 integrin and migrate to the blood (*23*). Gut-specific homing is achieved by expression of the ligand for α4β7, MADCAM-1, on gut endothelial cells, which allows PP-derived cells to migrate through blood vessels into the LP (*23*). Chemokines produced by either colon or small bowel epithelial cells fine-tune the localization of lymphocytes to these tissues (*23*).

The LP is filled with antibody-producing plasma cells that secrete between 3 and 5 g of the IgA immunoglobulin isotype into the gut lumen each day (*22*). Numerous other immune cells also reside in the gut LP, including large numbers of CD4$^+$ T cells (*24*), macrophages, DC, mast cells, and eosinophils (*21*). The gut epithelium also contains abundant intraepithelial lymphocytes (IEL) (*25*), an intriguing population made up mostly of CD8$^+$ T cells. Compared with other tissues, IEL are enriched in T cells expressing the γδ T cell receptor and often express the homodimeric form of the CD8α coreceptor (*26*). The exact function of IEL is not known, although it has been suggested that they may play a role in epithelial tumor surveillance, protection against epithelial pathogens, or promotion of healing of the gut after injury (*25*, *26*).

The presence of an extensive and activated intestinal immune system depends on the commensal flora. Thus, mice bred under germ-free conditions possess small, underdeveloped PP lacking germinal centers, few IgA plasma cells and CD4 cells in the LP, and reduced numbers of IEL. Furthermore, reconstitution of germ-free mice with a microbial flora is sufficient to restore the mucosal immune system (*27*, *28*).

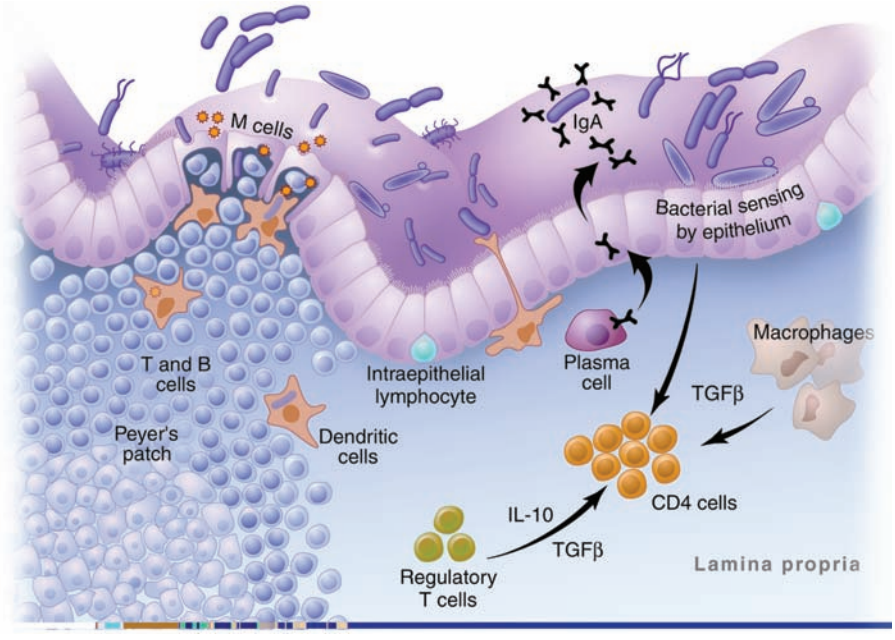

Fig. 1. The gut makes a huge investment in maintaining an extensive and highly active immune system. The epithelium overlying organized gut-associated lymphoid tissue (GALT) contains specialized M cells that constantly transport gut bacteria and antigens from the gut lumen into the lymphoid tissue. DC in the LP reach through epithelial cells and also sample gut bacteria. The epithelium is filled with CD8$^+$ T cells, and the LP contains many CD4 T cells, macrophages, and IgA antibody–producing plasma cells. Potentially tissue-damaging T cell responses may be inhibited by immunosuppressive cytokines and regulatory T cells.

The Commensal Flora as the Antigenic Stimulus for Gut Inflammation

The relationship between the immune system and the commensal flora is a precarious one, and perturbations in immune or epithelial homeostasis can lead to gut inflammation. In this situation, the commensal flora appears to act as a surrogate bacterial pathogen, and it is thought that lifelong inflammation ensues because the host response is incapable of eliminating the flora.

Chronic inflammatory bowel disease in humans. Two main types of IBD exist: Crohn's disease and ulcerative colitis (UC) (*29*) (Table 1). Patients suffer from chronic diarrhea and weight loss, abdominal pain, fever, and fatigue. Extra-intestinal manifestations can also occur, including skin ulcers, arthritis, and bile-duct inflammation, the last especially in UC. Both UC and Crohn's disease are characterized by mucosal ulceration, which is patchy in Crohn's disease but continuous in UC (Fig. 2). In Crohn's disease, ulcers penetrate into the gut wall, and fistulous tracts may develop between loops of bowel or to the skin. The downstream effector pathways that drive tissue injury are similar to those in immune-mediated diseases in other organs. Thus, excess immune activation leads to an influx of inflammatory cells from the blood and to increased concentrations of cytokines, free radicals, and lipid mediators (*30*). There is also massive overexpression of matrix-degrading enzymes, the matrix metalloproteinases, by fibroblasts, which are ultimately responsible for ulceration and fistulae (*30*).

Crohn's disease bears the immunological stigmata of an exaggerated CD4 T helper cell type I response. Thus, intestinal CD4 T

cells isolated from Crohn's patients produce large amounts of the Th1 signature cytokine interferon-γ (*31*) and display marked overexpression of the Th1 cell–specific transcription factor, T-bet (*32*). Mucosal macrophages from Crohn's patients also produce large amounts of the Th1-inducing cytokines IL-12 (*33*) and IL-18 (*34*). Th1 cell resistance to apoptosis and increased cell cycling in Crohn's disease inflammation appear to be sustained by cytokines (*35*, *36*). Blocking the pathways that confer resistance of Th1 cells to apoptotic stimuli and the use of drugs that enhance mucosal T cell death, such as the immunosuppressive agent azathioprine or the antibody to TNFα, Infliximab, are effective in down-modulating intestinal inflammation (*37*–*39*).

Identifying the particular antigen(s) that drive the Th1 inflammatory response in the face of the myriad of potential antigens in the gut has proven difficult. Nevertheless, the likelihood is that bacterial antigens are involved, because stimulation of mucosal CD4 cells from Crohn's disease patients with extracts of their own commensal flora can induce interferon-γ production (*40*), and in murine colitis, flagellin from commensal bacteria also activates mesenteric lymph node CD4 cells (*41*). Clinical observations also support a role for antigens derived from the commensal flora. Thus, for example, the antibiotic metronidazole is of therapeutic benefit in Crohn's disease of the distal colon (*42*).

Gut inflammation induced by the commensal flora: Evidence from animal models. The more than 30 models of IBD in rodents fall into four major groups: colitis that develops spontaneously, chemically induced colitis, colitis that develops from defects in epithelial barrier function, and colitis in mice in which the immune system has been genetically manipulated or regulatory cell function has been disrupted (*43*).

In a number of these models, the absence of commensal bacteria under germ-free conditions leads to an absence of or reduction in disease (*44*). Consistent with evidence from human IBD, there is evidence in some models that CD4 T cell lines reactive to enteric bacterial antigens can cause colitis (*45*), although no individual component of the flora has been yet identified as being specifically important. Nevertheless, in some models, particular bacteria species have been shown to cause disease (*45*). For example, in human leukocyte antigen–B27 (HLA-B27) transgenic rats, monoassociation with *Bacteroides vulgatus* induces colitis, while *Escherichia coli* elicit no lesions. In IL-10–deficient mice, although *B. vulgatus* does not induce colitis, commensal *E. coli* can induce disease (*45*). These models have been enormously important in demonstrating that immune responses to the flora can cause IBD, as well as the numerous pathways that can lead to chronic gut inflammation (*43*).

Crohn's disease susceptibility genes and their relation to innate immunity and intestinal permeability. Crohn's disease and UC represent complex genetic diseases but also tend to run in families. Genome-wide mapping has identified Crohn's disease susceptibility loci on chromosomes 1, 5, 6, 12, 14, 16, and 19 (*46*). In 2001, two groups mapped the locus on chromosome 16 to Nod2 (*47*, *48*). Three major polymorphisms have been specifically associated with ~15% of Crohn's disease cases (Arg702Trp, Gly908Arg, and Leu1007fsinsC), and all are in, or around, the LRR region of the protein required for recognition of bacterial muramyl dipeptide (MDP). Individuals who carry two copies of the risk alleles have a 20- to 40-fold increase in their risk of developing Crohn's disease. About 8 to 17% of Crohn's patients carry two copies of the major risk-associated alleles, compared with 1% of the general population. Interestingly, Nod2 has not been found to be associated with Crohn's disease in Japan (*49*), again highlighting the complex nature of this disease

Nod2 is expressed in the cytosol of gut epithelial cells, macrophages, and DC (*8*). After ligand binding, Nod2 oligomerizes and recruits RICK/RIP, which leads to phosphorylation and degradation of IκB and activation of NF-κB (*50*). A consequence of mutations in Nod2 may therefore be a decreased ability to kill gut bacteria (*51*). Consistent with this, monocytes from patients with common Crohn's disease mutations show defective activation of NF-κB and IL-8 secretion when stimulated with MDP (*52*).

Interestingly, Nod2-deficient mice do not develop spontaneous gut inflammation (*53*, *54*), and their macrophages show normal NF-κB activation and pro-inflammatory cytokine production to ligands for TLR3, 4, and 9. However, they secrete large amounts of IL-12 in response to TLR2 ligands (*55*). Concomitant activation through Nod2 inhibits TLR2 induction of IL-12 in cells from wild-type mice but has no effect in Nod2-deficient mice, suggesting that enhanced IL-12 production in Crohn's disease may be due to a failure of Nod2 to negatively regulate TLR2 signaling, which then facilitates a Th1 response through IL-12. It is not known whether Nod2-mediated negative regulation of TLR2 signaling occurs in Crohn's patients bearing the common mutations. In other studies, macrophages from mice engineered to express the *3020insC* Nod2 mutation show increased activation of NF-κB and increased IL-1β and IL-6 production when activated with MDP, which suggests that Nod2 mutations may, in some situations, lead to a gain of function and increased pro-inflammatory cytokine production (*56*).

Nod2-deficient mice are also unusually susceptible to intestinal infection with the pathogen *Listeria monocytogenes* (*54*) and have been found to be deficient in cryptdin 4 and 10, bacteriacidal defensins produced by Paneth cells found in small intestinal crypts (*57*). In the human gut, Nod2 is highly expressed in Paneth cells (*58*), and reduced defensin expression has been reported in Crohn's patients with Nod2 mutations (*59*). Nod2 mutations may thus also predispose to Crohn's disease indirectly by reducing defensin-mediated innate antimicrobial immunity.

Two other genes associated with Crohn's disease have been identified. The first of these, located on 5q31, encodes the organic cation transporter (OCTN) genes, and mutations at these loci affect the ability of the transporters to pump xenobotics and amino acids across cell membranes (*60*). In the gut, these genes are expressed in epithelial cells, macrophages, and T cells, correlating closely with their potential function in IBD. The second gene is located on 10q23 and encodes the guanylate kinase DLG5 (*61*). The mutation in this gene involves a single amino acid substitution that is thought to impair the ability of DLG5 to maintain epithelial polarity. Both genes may be important in epithelial permeability, and disruption of this function could

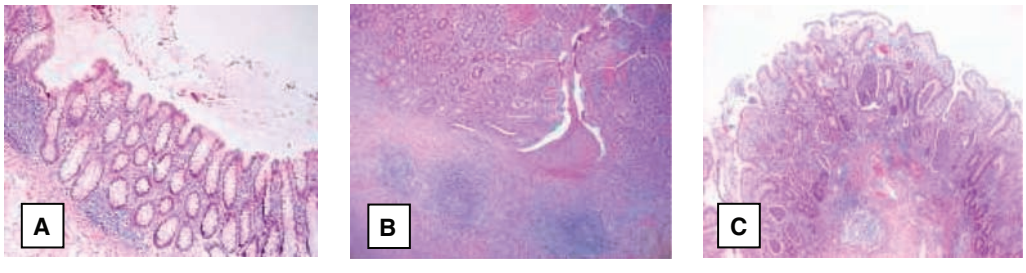

Fig. 2. Histological appearance of (**A**) normal colon, (**B**) Crohn's disease, and (**C**) ulcerative colitis. The normal colon contains glands filled with mucus-producing goblet cells. The image contains a small lymphoid follicle with FAE on the left. In the low-power image of Crohn's disease, the massive mucosal thickening and distortion of the glands is evident, there is a massive lymphoid infiltrate, and an ulcer penetrates through the mucosa from the lumen into the submucosa. In ulcerative colitis, the mucosa is also massively thickened and filled with inflammatory cells. Numerous neutrophil-filled crypt abscesses are present.

Table 1. Inflammatory diseases of the intestine.

	Crohn's disease	Ulcerative colitis	Celiac disease
Incidence	Presently 10–200/100,000 per year. Increased 8 to 10-fold since 1960s.	10–20/100,000 per year. Incidence stable since 1960s.	Around 0.5% of the European and North American population.
Distribution	A disease of westernized societies, with the highest incidence in northern Europe. Excess of cases in urban compared with rural environments.	UC is seen world-wide and appears to show no relation with western-ization or affluence.	Restricted to regions of the world where wheat, barley, and rye are a major part of the diet.
Cause	Probably an excessive cell-mediated immune response to antigens of the normal bacterial flora.	Unknown, but perhaps an organ-specific autoimmune disease.	An excessive cell-mediated immune response to the storage proteins of wheat, barley, and rye (gluten) in individuals with HLA-DQ2 or HLA-DQ8 haplotypes.
Site of disease	Can affect any part of the gut from mouth to anus, but most commonly occurs in the ileum and colon. The lesions are characteristically patchy, with areas of normal mucosa between ulcers (skip lesions). Some extra-intestinal involvement.	UC first occurs in the rectum and, as disease progresses, lesions become more proximal. Inflammation is continuous and is restricted to colon.	Upper small intestine—the duodenum and jejunum.
Inflammatory response	Inflammation consists mainly of T cells and macrophages. Granulomas are seen in just over half the cases. Inflammatory cells are present throughout the gut wall, and deep fissuring ulcers can lead to fistulae. Fibrosis of the external muscle layers frequently occurs.	Inflammation is restricted to the mucosa. Neutrophils are the major infiltrating inflammatory cells. These form crypt abscesses and damage the epithelium. There is loss of mucus-secreting goblet cells.	Inflammation restricted to the mucosa. There is a marked mononuclear infiltrate into the lamina propria and an increase in the density of intraepithelial lymphocytes, which results in a transformation of mucosal structure from a situation of long villi and short crypts to the flat mucosa, with short or absent villi.
Other features	Smoking is a risk factor for Crohn's disease.	Smoking appears to protect against the development of UC, as does appendectomy.	Celiac patients show an increased prevalence of autoimmune diseases.
Treatment	Corticosteroids, azathioprine, antibody to TNFα.	Corticosteroids, azathioprine, aminosalicylates.	Gluten-free diet.

lead to inappropriate exposure of the mucosal immune system to bacterial products.

Inflammatory Immune Responses to Food Antigens

The other major antigenic challenge facing the gut derives from ingested food antigens. Under normal circumstances, oral administration of protein antigens induces systemic unresponsiveness when the same antigen is given parenterally (a phenomenon known as oral tolerance). In animal models, oral tolerance appears to be a specific consequence of the immune environment in the gut, which favors the generation of T regulatory cells (*62*). In recent years, food allergy has become increasingly common, and although there has been little progress in understanding host mechanisms involved at the molecular level, there has been great progress in clinical management (*63*).

Celiac disease. In contrast to the lack of progress in understanding food allergy, huge progress has been made in understanding celiac disease. This condition occurs in some genetically susceptible individuals after the ingestion of cereal products, including those from wheat, barley, or rye, and the disease is treated by adherence to a gluten-free diet (Table 1). Many celiacs are undiagnosed (silent celiacs); the disease may affect as many as 0.5 to 1% of the European and North American population. Celiac disease shows classical morphological changes to the mucosa of the upper bowel, with long crypts and partial or complete atrophy of villi.

Celiac disease involves four components: gluten; T cells; the major histocompatability complex locus HLA-DQ; and the endogenous enzyme, tissue transglutaminase (tTG). The past 10 years have seen a huge increase in our understanding of the immunology of celiac disease and how the interplay among these four components produces enteropathy. The original gluten-specific T cell clones isolated from intestinal biopsies of celiac patients were found to respond to a peptic/tryptic digest of gluten restricted by HLA-DQ2 (*64*). The peptide anchor positions of HLA-DQ2 preferentially bind negatively charged amino acids (*65*), yet gluten, which is very proline and glutamine rich, has very few such residues. A key observation in helping resolve this was that tTG, which is expressed ubiquitously in the gut, can deamidate glutamine to glutamic acid, producing the negatively charged residues necessary for efficient binding to DQ2 and for T cell activation (*66*).

In theory, the identification of the immunogenic peptides in gluten would allow the derivation of genetically modified cultivars of wheat that would not cause disease. A polypeptide of α2 gliadin (residues 57 to 89) appears to survive digestion in the gut (*67*). Interestingly, this polypeptide contains three concatemerized epitopes that are recognized by T cells from celiac patients and can be deamidated by tTG; removing this polypeptide could, theoretically, make gluten much less able to activate T cells. However, the in vivo situation is complex because T cell clones have been identified, especially from celiac children, which recognize epitopes of high molecular weight glutenins and diverse gliadin epitopes (*68*, *69*). It may therefore not be possible to remove all disease-inducing T cell epitopes from wheat. An alternative approach may be to modify gluten epitopes so that they tolerize T cells (*70*).

A polypeptide of A-gliadin (residues 31 to 49) produces rapid villus atrophy when infused into the gut of celiac patients (*71*), but of the many T cell lines and clones made against gluten peptides, only a single T cell line clone has been identified that recognizes peptide 31-49 (*72*). However, if a similar peptide, 31-43, is added to ex vivo cultured biopsies

from celiac patients, within hours there is a rapid increase in HLA-DR mRNA, an increase in the number of macrophages making IL-15, and phosphorylation of p38 MAP kinase (*73*), which suggests T cell–independent innate immune activation by gluten.

A number of potential pathways exist to explain the effector mechanisms that cause the pathology in celiac disease (*74*). One of the primary pathways is thought to involve the major histocompatibility complex class I chain–related gene (MICA), which is a dominant ligand for the NKG2D-activating receptor on human NK cells and CD8 T cells. The addition of peptide 31-49 to biopsies of treated celiac disease patients increases MICA on epithelial cells, which can be blocked by antibody to IL-15 and recapitulated by recombinant IL-15 (*75*). NKG2D is expressed on the majority of IEL, and MICA+ epithelial cells have been shown to be killed by NKG2D + IEL (*75*, *76*). It is possible therefore that some peptides of gliadin may activate gut macrophages to produce IL-15, which then increases MICA on epithelial cells and arms IEL to kill MICA+ epithelial cells. Celiac disease is also marked by a significant increase in the numbers of γδ cells, yet their possible role in this condition is not established.

Control of Inflammation in the Gut

Recent years have seen the identification and characterization of dedicated regulatory T cells, in both mice and humans, that have the ability to profoundly suppress a variety of immune responses (*77*, *78*). These regulatory T cells have been shown to be able to significantly control gut inflammation in mouse models of IBD (*79*) and appear to mediate their effects through the cytokines IL-10 and transforming growth factor–β1 (TGFβ1) (*79*). Other work has shown that such cells with specificity for gut bacteria can also inhibit colitis (*80*). It is still not clear whether there is active suppression of T cell responses to the flora in normal mice, because systemic injection of antigens cloned from commensal flora results in a vigorous T cell response, suggesting ignorance rather than specific immune tolerance (*81*).

Compared with their characterization in the mouse, relatively little is known about regulatory T cells in the human gut (*82*). However, the potential for regulatory T cells to suppress IBD in humans through the production of immunosuppressive TGFβ is theoretically limited, because inflammatory cells in IBD lesions express high levels of Smad7, which prevents TGFβ signaling and immune down-regulation (*83*). Nevertheless, the possible role of T regulatory cells in controlling immune responses to bacterial flora in both mice and humans is a question that needs further investigation.

An understanding of how the gut remains disease free in the face of constant immune challenge may involve the separation of the inductive sites in the PP from the effector sites in the rest of the mucosa (Fig. 3) (*22*). Because T cells in the PP may potentially respond to all gut antigens, the problem of activated cells accumulating in the PP is solved by T cells leaving and migrating to the LP. If the T cell has specificity for a pathogen invading the mucosal tissues, antigen-driven cell-mediated immunity in the LP would ensue. However, if the T cell had responded to an antigen from a commensal or a food antigen, in a healthy individual, the epithelial barrier would help prevent the antigen from entering the LP. The few commensal organisms that do cross the barrier will be phagocytosed and killed by macrophages without provoking pro-inflammatory cytokine production (*84*), and in the absence of reactivation the T cells would die by apoptosis.

If this notion is correct, then situations in which the normal flora either enters in increased numbers or persists in the LP should lead to T cell activation and Crohn's-like disease. To support this notion, children with genetic defects that lead to impaired killing of commensal bacteria by phagocytes can develop a condition virtually indistinguishable from Crohn's disease (*85*, *86*). Furthermore, some healthy relatives of Crohn's patients have increased intestinal permeability (*87*), which suggests that genetically determined epithelial permeability is an important contributing factor in the development of disease. Chimeric mice with patchy increases in small intestinal epithelial permeability also develop spontaneous transmural Crohn's-like inflammation (*88*). Considered together, such data suggest that a major determinant in the initiation of mucosal inflammation is the ability of antigen to enter into the LP and trigger T cell activation.

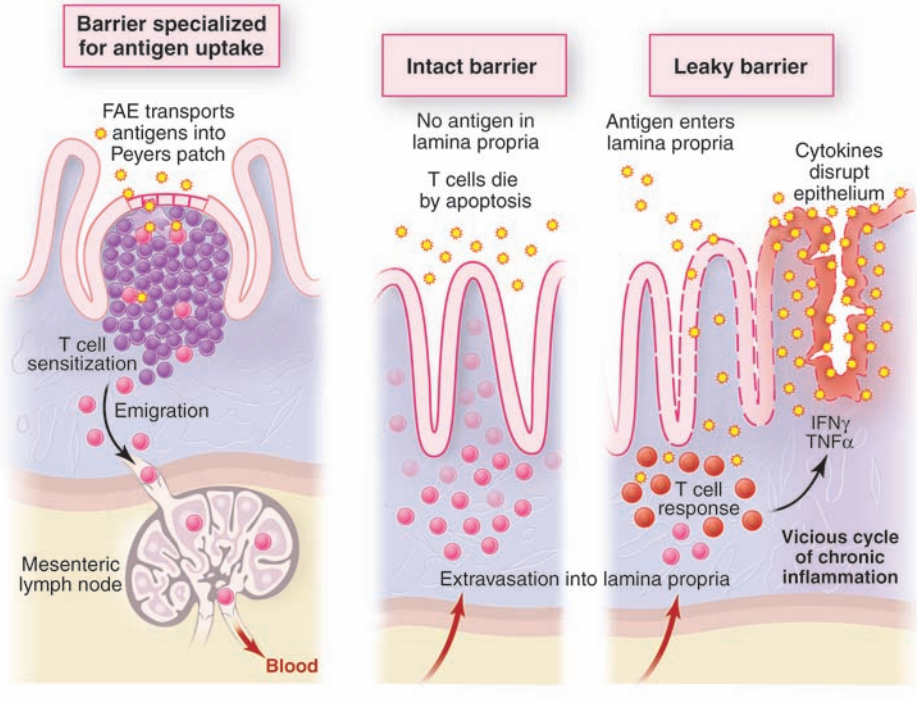

Fig. 3. Increased epithelial permeability may be important in the development of chronic gut T cell–mediated inflammation. CD4 T cells activated by gut antigens in Peyer's patches migrate to the LP. In healthy individuals, these cells die by apoptosis. Increased epithelial permeability may allow sufficient antigen to enter the LP to trigger T cell activation, breaking tolerance mediated by immunosuppressive cytokines and perhaps T regulatory cells. Pro-inflammatory cytokines then further increase epithelial permeability, setting up a vicious cycle of chronic inflammation.

Conclusions

In the evolutionary battle against infectious disease, the immune system cannot afford to err on the side of caution, because failure to mount effective and vigorous immune responses will be exploited by pathogens. This is best exemplified by celiac disease, in which the high prevalence of HLA-DQ2 in the general population suggests an evolutionary advantage of this allele against infection, even in the face of the negative effects of the coincidental affinity of gluten peptides for HLA-DQ2 to cause celiac disease.

With this in mind, it is probably unrealistic to prevent chronic inflammatory diseases, especially in the gut, so attention has to be paid to new treatments based on understanding disease at the molecular level. Great advances have already been made, with the best to date being the therapeutic antibody to TNFα, Infliximab, in Crohn's disease. At the same time, in the gut there is a silent partner

whose influence on the host immune response is only beginning to be appreciated, namely the commensal flora. There are clear indications that the flora is beneficial but also has the potential to be harmful, and increasing knowledge of how the flora interacts with the immune system should allow exploitation of the former and minimization of the latter.

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