A role for *Campylobacter jejuni*-induced enteritis in inflammatory bowel disease?

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**Kalischuk LD, Buret AG.** A role for *Campylobacter jejuni*-induced enteritis in inflammatory bowel disease? *Am J Physiol Gastrointest Liver Physiol* 298: G1–G9, 2010. First published October 29, 2009; doi:10.1152/ajpgi.00193.2009.—The inflammatory bowel diseases (IBD), Crohn’s disease and ulcerative colitis, are T cell-mediated diseases that are characterized by chronic, relapsing inflammation of the intestinal tract. The pathogenesis of IBD involves the complex interaction between the intestinal microflora, host genetic and immune factors, and environmental stimuli. Epidemiological analyses have implicated acute bacterial enteritis as one of the factors that may incite or exacerbate IBD in susceptible individuals. In this review, we examine how interactions between the common enteric pathogen *Campylobacter jejuni* (*C. jejuni*), the host intestinal epithelium, and resident intestinal microflora may contribute to the pathogenesis of IBD. Recent experimental evidence indicates that *C. jejuni* may permit the translocation of normal, noninvasive microflora via novel processes that implicate epithelial lipid rafts. This breach in intestinal barrier function may, in turn, prime the intestine for chronic inflammatory responses in susceptible individuals. Insights into the interactions between enteric pathogens, the host epithelia, and intestinal microflora will improve our understanding of disease processes that may initiate and/or exacerbate intestinal inflammation in patients with IBD and provide impetus for the development of new therapeutic approaches for the treatment of IBD.

Crohn’s disease; intestinal; epithelial; inflammation

MORE THAN 1 IN 1,000 PEOPLE in developed countries are affected by the inflammatory bowel diseases (IBD), Crohn’s disease (CD) and ulcerative colitis (UC) (22, 109). These diseases are characterized by chronic, relapsing inflammation of the intestinal tract and the presence of activated T lymphocytes. In CD, these activated T cells are primarily of the Th1 and Th17 subsets (35, 96, 111), whereas Th2 and natural killer T cells predominate in UC (36, 47). IBD causes lifetime morbidity and, in Canada alone, accounts for a financial burden exceeding $1.8 billion per year in economic costs (including >$700 million in direct medical costs) (22). At present, there is no cure, and therapeutics are primarily aimed at suppressing inflammatory responses. Treatment with anti-TNF-α antibodies has met with some success; however, its therapeutic limitations, elevated cost, and the side effects of other conventional immunosuppressive drugs underscore the need for novel therapeutic strategies (22).

As is the case for many chronic diseases, the pathogenesis of IBD involves the cumulative interaction of many variables; these include host immunity and genetic susceptibility, the intestinal microflora, and environmental factors (8, 66, 74, 131). The complexity of these interactions is consistent with the heterogeneous clinical manifestations of IBD and the nonuniversal efficacy of currently available therapeutics. This underscores the tremendous challenges faced by clinicians and researchers in identifying the causes of IBD. Notwithstanding its multifactorial origin, accumulating evidence consistently implicates intestinal microorganisms across the global distribution of IBD.

The Role of Intestinal Microorganisms in IBD

An ever increasing number of studies indicate that chronic inflammation in IBD is driven by inappropriate and excessive mucosal immune responses toward the intestinal microflora, but the mechanisms involved remain obscure. Early reports had indicated that typical IBD may develop in a small number of people following an episode of acute dysentery (98, 127). In IBD model systems, animals develop less severe disease when raised in germ-free conditions (93, 107). Inflammation occurs more frequently in regions of the intestine that are colonized by the highest density of bacteria, and diversion of the fecal stream (27, 106) or treatment with antibiotics (63, 110, 114) may attenuate inflammation in some patients with IBD. These patients also exhibit exaggerated immune responses to their own intestinal bacterial antigens, indicating a loss of immunological tolerance toward the intestinal microflora (28, 68, 91). In addition, the association of Crohn’s disease with polymorphism of the NOD2/CARD15 gene, which acts as an intracellular sensor of bacteria-derived muramyl dipeptide (a component of Gram-positive and Gram-negative bacterial cell walls), as well as the more recently recognized role of IL23/Th17, further supports that derangements of the delicate equilibrium...
between microbial flora and host immunity are at the core of the etiopathogenesis of IBD (25, 46). Although it is generally accepted that intestinal bacteria (i.e., including normal resident or "commensal" bacteria, which are comprised of taxa that can be beneficial or detrimental to varying degrees, and/or bona fide pathogens) play a role in the pathogenesis of IBD, the specific mechanisms by which these bacteria may cause intestinal inflammation remain obscure.

At least three nonexclusive hypotheses have been proposed for the involvement of luminal bacteria in IBD, namely 1) the dysbiosis hypothesis, 2) the persistent infection hypothesis, and 3) the luminal antigen translocation hypothesis (Table 1).

The dysbiosis hypothesis suggests that an imbalance between “beneficial” vs. “detrimental” resident intestinal bacterial species may incite chronic inflammatory responses. Endogenous microbial communities seem to differ between healthy subjects and patients with IBD (32). Evidence also indicates that the biodiversity of fecal microorganisms in patients with CD is globally diminished (72, 90), and, in particular, there is a marked decrease in the prevalence of butyrate-producing Firmicutes, which exhibit anti-inflammatory activity within the intestine (119). The intestinal microflora of patients with CD also has a higher prominence of potentially detrimental bacteria such as Bacteroides vulgatus (41, 104, 124), which have been shown to induce intestinal inflammation in animal models of IBD (88, 101, 102).

The persistent infection hypothesis suggests that IBD may arise as a result of persistent infection with enteric pathogens. Mycobacterium avium subspecies paratuberculosis is one of the pathogens that has been most commonly implicated in the etiopathogenesis of IBD (4). This intracellular pathogen causes chronic granulomatous colitis in cattle (i.e., Johne’s disease) that bears similar pathohistological characteristics to that of CD in humans (14). However, a direct etiologic role for Mycobacterium avium paratuberculosis in IBD remains controversial (66). Clostridium difficile (21, 33, 80, 130) and Yersinia enterocolitica (57, 108) have also been cited as putative IBD-causing pathogens. Here again, no direct cause-to-effect relationship has yet been established between these enteric microbes and development of IBD. Studies also have implicated Escherichia coli (E. coli), particularly adherent and invasive E. coli strains, which are able to invade epithelial cells and replicate within macrophages, in IBD patients, as well as in murine models of colitis, via mechanisms that remain obscure (9, 24, 75, 112). High prevalence of E. coli belonging to the B2+D phylogenetic group was recently reported in patients with CD (61). Presently, supporting data for the dysbiosis and persistent pathogen hypotheses have yet to conclusively demonstrate whether the microorganisms involved are causative in nature or whether their occurrence in patients with IBD is coincidental because the disease state allows these bacteria to readily colonize the intestine. One argument possibly weighing against these hypotheses is that immunosuppressive agents (which would be expected to favor the pathogen and exacerbate disease) are often used successfully to treat IBD.

The luminal antigen translocation hypothesis suggests that defects in the intestinal barrier function and/or impaired mucosal clearance facilitates increased translocation of luminal antigens, including resident intestinal bacteria, across the intestinal barrier where they may prime mucosal immune responses that lead to the loss of immunological tolerance toward the luminal antigens (115). In susceptible hosts, failure to downregulate these inflammatory responses promotes chronic inflammation because the host is unable to eliminate the luminal microflora. In some experimental studies, it has been observed that epithelial barrier dysfunction may precede the onset of inflammation in IBD (69, 87, 103). Moreover, mice that express epithelial cell-specific, dominant-negative E-cadherin, a pivotal element of the adherens junction, spontaneously develop histological features typical of IBD at 3 mo of age (48). Although these studies suggest that a loss of epithelial barrier integrity can induce inflammation in susceptible hosts, the mechanisms implicated have yet to be fully elucidated (3, 20, 65). Moreover, evidence unequivocally supporting an initiating role for loss of intestinal barrier function in IBD is still lacking.

Many of the inflammatory mediators implicated in IBD, such as TNF-α, are upregulated in response to activation of the transcriptional regulator, NF-κB (77, 125). Consistent with a prominent role for microorganisms in the pathogenesis of IBD, several bacterial products, including LPS, peptidoglycan, and flagellin, are potent activators of the NF-κB pathway through their activation of microbial-associated molecular pattern recognition receptors, such as Toll-like receptors (TLRs) and NOD2 (77, 125). Altered expression of these receptors may play a fundamental role in IBD pathogenesis by affecting microbial recognition and subsequent activation of NF-κB-mediated inflammation. Polymorphic mutation of the bacterial LPS receptor, TLR4, is associated with CD and UC (31), and increased TLR4 expression has been observed in the intestinal epithelium of many patients with IBD (13). It has also been recently reported that peripheral blood monocytes from patients with IBD exhibit increased TLR2 expression, and this is correlated with a marked increase of TLR2-mediated TNF-α production (12). Furthermore, defects in the NOD2/CARD15 gene significantly increase susceptibility to CD (50, 85, 25). It

### Table 1. Summary of hypotheses through which intestinal bacteria may be implicated in IBD pathogenesis

<table>
<thead>
<tr>
<th>Hypotheses</th>
<th>Descriptions</th>
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<tbody>
<tr>
<td>Dysbiosis Hypothesis</td>
<td>Proposes that an imbalance between “beneficial” vs. “detrimental” resident intestinal bacterial species may incite chronic inflammatory responses (41, 72, 90, 104, 119, 124).</td>
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<tr>
<td>Persistent Infection Hypothesis</td>
<td>Proposes that IBD may arise as a result of persistent infection with enteric pathogens (4, 9, 21, 24, 33, 57, 80, 108, 112, 130).</td>
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<tr>
<td>Luminal Antigen Translocation Hypothesis</td>
<td>Proposes that defects in the intestinal barrier function and/or impaired mucosal clearance facilitates increased translocation of luminal antigens, including resident intestinal bacteria, across the intestinal barrier where they may prime mucosal immune responses that lead to the loss of immunological tolerance toward the luminal antigens (3, 20, 69, 87, 103, 115).</td>
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IBD, inflammatory bowel disease.
is thought that polymorphic mutations in NOD2, which are commonly observed in patients with CD, may result in the loss or gain of NOD2 function and could lead to either a lack of bacterial detection and elimination or hyperactivation of immune responses upon detection (29, 70, 84, 92, 129). In both cases, this may result in excessive inflammatory responses against bacterial residents of the intestinal tract. Thus intestinal inflammation in patients with IBD may result from deregulated bacterial recognition in combination with increased bacterial translocation or higher mucosal densities of certain bacterial taxa.

**IBD Following Acute Pathogen-Induced Enteritis**

Consistent with a pathogenic consequence from disruptions in the homeostatic balance between microbial flora and host intestine, acute microbial infections may directly be responsible for relapse in IBD (130). Because this aspect of IBD seems to be conserved across the global distribution of the disease, the possible pathogenic role for ubiquitous microbial products in IBD needs to be investigated.

Early reports indicated that IBD develops in a small number of people following an episode of acute bacterial enteritis (45, 57, 80, 83, 121, 130). Similar processes of postinfectious intestinal inflammation and symptoms of irritable bowel syndrome have also been reported after various enteric viral infections (39, 59, 60) or after parasitic infection with *Entamoeba histolytica* (15, 98, 100) or the globally distributed protozoan enteropathogen *Giardia duodenalis* (11, 23). Table 2 summarizes specific bacterial, parasitic, and viral pathogens that have been implicated in IBD and the proposed mechanisms by which they may contribute to IBD pathogenesis.

Among the pathogens recently implicated in IBD pathogenesis are *Campylobacter* and *Salmonella* (38), which are the two most common causes of human bacterial enteritis (99). A more recent study using cohorts of over 13,000 infected and 26,000 control patients even more convincingly established a role for *Campylobacter* or *Salmonella* acute gastroenteritis in the development and relapse of IBD (44). Results from another study also indicate that upon *Salmonella* infection, early transepithelial bacterial sampling and migration of dendritic cells into the gut lumen may represent early mechanisms whereby acute enteritis by common pathogens may contribute to the development of symptoms in IBD (2). Together, and consistent with a recent editorial article in *Gastroenterology* (58), these observations demonstrate that research is needed to better understand how, in susceptible patients, acute infection with common and ubiquitous microorganisms such as *Campylobacter* spp. or *Salmonella* spp. may represent a pivotal event that sets the IBD process of inappropriate intestinal immune response in motion. Human infections with these pathogens are typically self-limiting, and, as such, the host generally eliminates the offending pathogen from the intestine. However, these infectious agents, although not acting as the etiological chronic inflammatory stimulus in IBD, appear to initiate and/or exacerbate inflammation in patients with the IBD genetic background. In the following paragraphs, this review examines mechanisms whereby the common enteric pathogen, *Campylobacter jejuni* (*C. jejuni*), disrupts intestinal epithelial structure and function, thereby permitting the translocation of luminal material, including resident intestinal bacteria, into the subepithelial compartment. This, in turn, may prime the intestine for subsequent chronic inflammatory responses in susceptible hosts. A better understanding of these processes will help identify novel therapeutic targets in IBD.

**Campylobacter jejuni and Inflammatory Disorders of the Bowel**

*C jejuni* is the most prevalent cause of human bacterial enteritis in North America (99). Chickens (43) and livestock animals such as cattle (52–54) and pigs (89) serve as reservoirs for *C. jejuni*, which may be transmitted to humans via contaminated food or water (34, 62). Infected humans exhibit a range of symptoms varying from mild to severe diarrhea, and histological examination of affected intestinal tissues commonly reveals infiltration of neutrophils into the lamina propria (128).

Although distinct from IBD, irritable bowel syndrome (IBS) is another poorly understood chronic disorder of the intestine that was recently linked to postinfectious events. Indeed, campylobacteriosis has been recognized as one of the most common risk factors for postinfectious IBS. In May 2000, the municipal water supply of Walkerton, Ontario (Canada) was contaminated with livestock waste containing *E. coli* O157:H7 and *Campylobacter* species. Subsequent waterborne infections caused acute enteritis in more than 2,300 people, of whom

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**Table 2. Summary of specific bacterial, parasitic, and viral pathogens that have been implicated in the development of IBD and the proposed mechanisms by which they may contribute to IBD pathogenesis**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Proposed Mechanism(s) of IBD Pathogenesis</th>
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<tr>
<td><em>Campylobacter</em> (38, 44, 83)</td>
<td>Increased translocation of intestinal microflora because of loss of intestinal epithelial barrier function as a result of tight junctional disruption (64) or increased lipid raft-mediated transcytosis (56) (i.e., consistent with Luminal Antigen Translocation Hypothesis)</td>
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<tr>
<td><em>Salmonella</em> (38, 44)</td>
<td>Unknown</td>
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<tr>
<td><em>Mycobacterium avium</em> subspecies <em>paratuberculosis</em> (4); <em>Clostridium difficile</em> (21, 33, 80, 130); <em>Yersinia enterocolitica</em> (57, 108); adherent and invasive <em>Escherichia coli</em> (9, 24, 112)</td>
<td>Chronic inflammation attributable to persistent pathogenic infection (i.e., consistent with Persistent Infection Hypothesis)</td>
</tr>
<tr>
<td><em>Giardia duodenalis</em> (11, 23)</td>
<td>Loss of intestinal epithelial barrier function as a result of <em>Giardia</em>-induced enterocyte apoptosis (17) (i.e., consistent with Luminal Antigen Translocation Hypothesis)</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em> (15, 98, 100)</td>
<td>Depletion of colonic mucus (15) (i.e., consistent with Luminal Antigen Translocation Hypothesis’)</td>
</tr>
<tr>
<td><em>Rotavirus</em>, <em>Norwalk virus</em>, <em>adenovirus</em> (39); <em>Rubella virus</em>, <em>Epstein-Barr virus</em>, and <em>adenovirus</em> (59); <em>Norovirus</em> (60)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
more that 36% subsequently developed postinfectious IBS (compared with 10% of subjects without gastroenteritis) (73). As mentioned previously, a small number of people may also develop IBD following an episode of acute campylobacteriosis (38, 44). The mechanisms by which this pathogen incites inflammatory disorders in the bowel remain obscure; however, there is a purported link between postinfectious IBS and IBD that is centered on the loss of intestinal epithelial barrier function and failure to downregulate inflammation following intestinal epithelial injury (120).

Effects of Campylobacter jejuni on Epithelial Cells

Enteric pathogens can damage the epithelium and disrupt intestinal barrier function via a number of pathological mechanisms that include inducing host cell death, targeting epithelial tight and adherens junctions, and causing inflammation-mediated damage (86). With respect to *C. jejuni*, cellular damage appears to be largely attributable to cytotoxic effects and/or host-cell invasion (105, 128). According to genome sequence analysis, the only known toxin produced by *C. jejuni* is cytolethal distending toxin (CDT), a DNase-like toxin produced by several species of bacteria. This toxin causes cell cycle arrest (132) and ultimately apoptotic death of lymphocytes and monocytes (49) and nonapoptotic death of endothelial cells (7). Recent evidence indicates that *C. jejuni* causes nonapoptotic death (i.e., oncosis) of human intestinal epithelial cells, in a CDT-independent manner (55).

Invasion of the mucosa appears to be one of the primary mechanisms through which *C. jejuni* causes intestinal injury. The invasive ability of *C. jejuni* is strain dependent and host cell-type dependent (55, 133), and invasion is associated with nonapoptotic death of human colonic epithelial cells (6, 55). In many cases, cell death (as a result of microbial or inflammatory stimulation or exposure to drugs) may result in a loss of intestinal barrier function (1, 17, 18, 42, 122). Some studies have shown that invasion of epithelia by certain strains of *C. jejuni* is associated with increased epithelial permeability (6, 64, 133). However, it has yet to be conclusively determined whether barrier dysfunction is a consequence of epithelial damage associated with increased cell death or is attributable to the targeting of the epithelial tight junctions, as has been recently observed for this pathogen (16, 64, 67).

Campylobacter jejuni Promotes Intestinal Translocation of Commensal Bacteria: Potential Implications for IBD

Two recent studies have demonstrated that *C. jejuni*-mediated disruption of the intestinal epithelial structure and function results in the translocation of noninvasive bacteria across the epithelium. These two studies utilized different *C. jejuni* strains to assess *C. jejuni*-mediated translocation of noninvasive *E. coli*. Consistent with the ability of *C. jejuni* to interact with epithelial cells in a strain-dependent fashion, two distinct mechanisms of bacterial translocation were observed. Namely, *C. jejuni* RM1221 induced translocation of noninvasive bacteria across the epithelium via a paracellular pathway (64), whereas *C. jejuni* 81–176 induced bacterial translocation through a transcellular mechanism (56).

In the first study, *C. jejuni* RM1221, a strain isolated from chickens, caused increased epithelial permeability, disruption of the tight junctional protein, claudin-4, and translocation of noninvasive *E. coli*, in vivo as well as in vitro (64) (Fig. 1A). This is in agreement with other recent studies demonstrating that *C. jejuni* targets the tight junctions to subvert the epithelial barrier (16, 67). In such a manner, *C. jejuni* while facilitating its own dissemination by disrupting tight junctional integrity, may inadvertently “open the gate” for resident intestinal bacteria to translocate across the intestinal epithelial barrier via a paracellular route. *C. jejuni* RM1221-mediated *E. coli* translocation was prevented by epidermal growth factor (EGF) (64), a gastrointestinal peptide that is well known for its broad mitogenic bioactivities and its ability to promote epithelial differentiation (5, 94, 95). EGF also upregulates the key tight junctional proteins claudin-4 and zonula occludens-1 and restores tight junctional integrity (10, 117). Thus it is plausible that EGF treatment prevented *C. jejuni*-mediated *E. coli* translocation by regulating paracellular permeability.

Although tight junctions serve to restrict paracellular translocation of luminal bacteria, they also maintain cellular polarity by confining the distribution of membrane proteins between the apical and basolateral cell membranes (116). Cellular polarity plays a central role in allowing the host to discriminate between pathogens and commensal bacteria. For example, TLR5, a pattern-recognition receptor for bacterial flagellin, is generally localized to the basolateral side of enterocytes so that only bacteria that translocate across the epithelium (i.e., primarily pathogens) are detected (40). More research is needed to clearly determine whether disruption of epithelial tight junctions by enteric pathogens, such as *C. jejuni*, may promote relocation of pathogen-recognition receptors to the apical surface and thereby permit luminal material, including commensal bacteria and/or their products, to activate the receptors. Indeed, enteric pathogens that disrupt tight junctions such as enteropathogenic *E. coli* and *Yersinia pseudotuberculosis* also utilize this mechanism to relocate basolateral bacterial adhesion receptors to the apical membrane to facilitate their own epithelial adhesion and invasion (76, 79).

Another study demonstrating that translocation of noninvasive bacteria is increased in *C. jejuni*-infected human intestinal epithelia used the well-characterized human clinical *C. jejuni* isolate 81–176 (56). In this study, *C. jejuni* induced rapid translocation of noninvasive *E. coli* across human colonic epithelial monolayers via a transcellular pathway. Indeed, *E. coli* translocation occurred across an intact barrier in the absence of increased paracellular permeability, and evidence indicated that this involved a novel lipid raft-dependent endocytic mechanism (56). Although invasive pathogens can “shuttle” other, noninvasive bacteria into epithelial cells (39), *C. jejuni* invasion was not required, as an invasion-defective mutant of *C. jejuni* 81–176 and other noninvasive clinical isolates of *C. jejuni* and *Campylobacter fetus* also induced *E. coli* translocation. Figure 1 summarizes hypothetical pathways through which acute *C. jejuni* enteritis may contribute to the development and/or exacerbation of symptoms in IBD.

Other studies have observed that commensal bacteria are internalized and translocate across the intestinal epithelium via a transcellular route during periods of inflammatory and metabolic stress (19, 81). *C. jejuni*-infected epithelial cells also exhibit swollen mitochondria, loss of mitochondrial transmembrane potential, and ATP depletion, all indicative of metabolic stress (26, 37, 51, 55, 82). Consistent with a role for cellular stress in IBD, it has also been observed that enterocytes of IBD
patients display elevated transcellular antigen transport (97, 113, 118) and occasionally contain intracellular bacteria (124). This evidence suggests that C. jejuni may play a role in the pathogenesis of IBD by promoting the internalization and translocation of commensal bacteria, at least in part, via stress-related pathways that have yet to be identified.

Normally, recognition of internalized commensal bacteria by cytosolic receptors such as NOD2 would lead to appropriate effector immune responses and effective elimination of the bacteria (71, 126). Future research will assess whether, in intestinal epithelial cells containing a loss-of-function NOD2 protein, such as might occur in people that carry certain NOD2 polymorphisms, defective elimination of intracellular bacteria may allow for increased proliferation, which, in turn, would provide a powerful antigenic stimulus that would promote activation of commensal-specific T cells (Fig. 1D). It also remains to be established whether detection of intracellular bacteria in epithelial cells containing a gain-of-function NOD2 protein would result in excessive NF-kB activation and inflammation. C. jejuni itself acts as a strong inflammatory stimulus (78), as do host cells ruptured during C. jejuni-induced non-apoptotic cell death. Studies need to determine whether this combination may, in adjuvant fashion, create a costimulatory milieu that is conducive to T cell activation and subsequent inflammation.

Conclusion

IBD is a multifaceted disease in which intestinal microflora, host genetics and immunity, and environmental factors all play significant roles in pathogenesis. Prominent among these factors is the multitude of bacterial species that comprise the intestinal microflora, which act as the antigenic stimulus for T cell activation and effector responses. Some studies implicate the involvement of an “unbalanced” microflora (dysbiosis) or specific pathogens such as adherent-invasive E. coli. However,
at present, no single species of pathogenic or detrimental, intestinal bacteria has been identified as “The” etiological antigenic stimulus in IBD. Rather, immune responses may be targeted toward members of the normal resident intestinal microflora. Regardless of the nature of the microbial stimulus, IBD is a T cell-mediated disease, and, therefore, a mechanism must exist by which these intestinal antigens can interact with the mucosal immune system and activate T cells and perpetuate effector responses.

Increased translocation of bacteria across the epithelium may occur as a result of a primary barrier defect, which remains controversial, or be the consequence of epithelial damage attributable to microbes or inflammatory injury. Enteric pathogens can damage the epithelial barrier by directly targeting tight and adherens junctions or by causing cellular destruction. Evidence suggests that C. jejuni disrupts intestinal epithelial structure and function and thereby permits the translocation of luminal material, including resident intestinal bacteria, into the subepithelial compartment. This, in turn, may prime the intestine for subsequent inflammation in susceptible hosts. Recent findings indicate that C. jejuni causes translocation of noninvasive E. coli via two distinct mechanisms, one that involves the disruption of epithelial tight junctions and increased paracellular trafficking of bacteria (64), and the other that involves increased transcellular trafficking via epithelial lipid rafts (56). Although these studies suggest hypothetical mechanisms by which C. jejuni may contribute to the pathogenesis of IBD, many unanswered questions remain. Regardless, an ever-increasing body of evidence on the basis of large human cohort studies indicates that acute C. jejuni gastroenteritis promotes the development and/or exacerbation of symptoms in patients with IBD. Improving our understanding of epithelial responses to C. jejuni may shed new light on the mechanisms responsible for the initiation and/or relapse of intestinal inflammation in patients with IBD. In turn, uncovering the mechanisms whereby these responses may disrupt microbial-host intestinal homeostasis will help identify novel therapeutic targets in IBD.

GRANTS

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DISCLOSURES

No conflicts of interest are declared by the author(s).

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