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Microbial Translocation Across the GI Tract*

Jason M. Brenchley[1] and **Daniel C. Douek**[2]

Jason M. Brenchley: jbrenchl@mail.nih.gov; Daniel C. Douek: ddouek@mail.nih.gov

[1]Program in Barrier Immunity and Repair and Immunopathogenesis Unit, Lab of Molecular Microbiology, NIAID, NIH, Bethesda, Maryland [2]Human Immunology Section, Vaccine Research Center, NIAID, NIH, Bethesda, Maryland

Abstract

The lumen of the gastrointestinal (GI) tract is home to an enormous quantity of different bacterial species, our microbiota, that thrive in an often symbiotic relationship with the host. Given that the healthy host must regulate contact between the microbiota and its immune system to avoid overwhelming systemic immune activation, humans have evolved several mechanisms to attenuate systemic microbial translocation (MT) and its consequences. However, several diseases are associated with the failure of one or more of these mechanisms, with consequent immune activation and deleterious effects on health. Here, we discuss the mechanisms underlying MT, diseases associated with MT, and therapeutic interventions that aim to decrease it.

Keywords

intestinal permeability; innate immunity; inflammation

INTRODUCTION

The microbiota of the gastrointestinal (GI) tract comprises a large population of diverse bacterial species. The colon alone contains approximately 10^{14} microorganisms with approximately 10^{12} microorganisms per gram of colonic content. Thus, within an adult human the bacteria within the colon outnumber host cell numbers by up to two orders of magnitude, with a frequency of bacterial genes at least 100 times greater compared with those within the human genome. This microbiota is composed of approximately 1,000 species of predominantly unculturable bacteria that belong to two main phyla: the Firmicutes and the Bacteroidetes. Although the mechanistic details of the relationships between the microbiota and the host remain unclear, this relationship is undoubtedly complex and involves interactions among the individual members of the microbiota itself, the mucus layer of the GI tract, the local and systemic innate and adaptive immune systems, and the enterocytes.

Here, we discuss both beneficial and pathological interactions between the host and its microbiota, diseases that are characterized by unphysiological translocation of microbial products into peripheral circulation (microbial translocation, MT), mechanisms underlying MT, and therapeutic interventions that have been proposed to decrease pathologic MT.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

INFLUENCES OF THE GI TRACT MICROBIOTA ON THE HOST

Local Relationships

Humans and the normal microbiota of the GI tract have evolved a symbiotic relationship. These beneficial interactions are highlighted by the finding that germ-free animals are more susceptible to infections and have reduced vascularity, digestive enzyme activity, muscle wall thickness, and serum immunoglobulin levels as well as smaller Peyer's patches and fewer intraepithelial lymphocytes (reviewed in 1). Furthermore, these abnormalities appear to be enhanced in germ-free mice that were fed elemental diets containing no complex food antigens or bacterial products, and such animals also have lower numbers of circulating lymphocytes (2). The critical role of the microbiota is revealed by the finding that colonization of germ-free mice with a single species of bacterium is sufficient to enhance the mucosal immune system, including increased numbers of intraepithelial lymphocytes and increased activity of local antigen-presenting cells (APCs) (3). The beneficial roles that the GI microbiota play are multifactorial and may be separated into immunological, structural, and metabolic functions (4).

Being present in such high numbers, the organisms of the microbiota serve as competitors for potentially pathogenic bacterial species. This likely involves competition for limited sources of nutrition and limited sites of adherence to the epithelial barrier. The microbiota also protects against pathogenic infection by producing antimicrobial factors such as lactic acid, short chain fatty acids, and bacteriocins. Finally, the microbiota is capable of attenuating mucosal immune responses to pathogenic bacterial species. Indeed, certain microbiota species can promote nuclear export of the p65 segment of nuclear factor κB (NF-κB) through the peroxisome proliferator-activated receptor, thus limiting NF-κB-mediated transcription (5, 6).

The microbiota also leads to enhanced integrity of the structural barrier of the GI tract by metabolizing dietary carbohydrates into short-chain fatty acids, which are a major nutritional source for the colonic epithelia (7). Enterocytes also express Toll-like receptors (TLRs) through which signaling is thought to contribute to epithelial cell homeostasis (reviewed in 8). Consistent with this premise, decreased epithelial cell proliferation is observed in TLR-deficient mice (9). In addition to aiding in epithelial cell turnover, the microbiota is also involved in maintenance of the mucus layer. Indeed, the absence of the intestinal microbiota in germ-free mice is associated with a decrease in goblet cells, which are also smaller in size, and the thickness of the mucus layer is decreased (10).

In addition to the important role of the microbiota in maintaining the epithelial barrier and mucus layer, it also has a significant impact on production of luminal IgA. In the intestinal tract and other mucosal sites, most plasma cells secrete dimeric or oligomeric IgA that can transcytose directly into the lumen. That these antibodies are specific for luminal bacteria and viruses suggests that the microbiota shapes the specificity of luminal IgA (11). The corollary of this is exemplified in $AID^{-/-}$ mice, which do not produce sIgA and have a 100-fold increase in the number of small intestinal anaerobic bacteria (12). Secretory IgA thus serves as a line of defense against MT by limiting adhesion and entry into the epithelium, thereby facilitating clearance via the fecal stream (13, 14). Taken together, it is clear that the microbiota provides invaluable functions to the host locally within the GI tract.

Distal Relationships

In addition to the local effects that the microbiota has on the GI tract of the host, the microbiota also provides significant and beneficial functions for the host systems distal to the GI tract. Specifically, the microbiota metabolizes toxic and potentially carcinogenic compounds such as pyrolysates (15), thus reducing their bioavailability to the host. The

microbiota also produces biotin, folate, and vitamin K from dietary precursors, which are then absorbed by the GI tract and circulated. That germ-free animals fed elemental diets have fewer systemic lymphocytes compared with conventional mice suggests a tonic stimulation of the systemic immune system by gut-derived microbial antigens (2).

Dysbiosis

Although the microbiota provides metabolites and beneficial immunological stimuli to the host, the actual composition of the microbiota also appears to have a significant impact on the host. Previous studies have implicated an altered balance in the composition of the microbiota (dysbiosis) in many diseases, such as obesity (16, 17), celiac disease (18), type 2 diabetes (19), atopic eczema (20, 21), asthma (22), inflammatory bowel disease (IBD) (23, 24), and chronic diarrhea (25).

Given the specific roles that the microbiota fulfills, it is reasonable to propose that its specific composition influences the capacity of the host to regulate its many functions. Indeed, only certain species of the microbiota, predominantly those belonging to a small subset of the Firmicutes, can metabolize complex carbohydrates into short-chain fatty acids (butyrate in particular) that can serve as growth factors for enterocytes (7). Along these lines, one study compared the composition of the microbiota in inflamed tissue and uninflamed tissue of individuals with IBD and tissue from healthy individuals and found fewer Firmicutes present in inflamed tissue from IBD patients (24). The same reduction in levels of Firmicutes was also observed within individuals diagnosed with type 2 diabetes, and the degree to which the microbiota was abnormal was correlated with plasma levels of glucose, suggesting that the dysbiotic microbiota may have a direct role in the pathogenesis of type 2 diabetes (19).

Additionally, in children diagnosed with atopic eczema and in non-breast-fed children, the microorganism *Bifidobacterium pseudocatenulatum* is more commonly identified than in healthy, breast-fed children, even though there are no correlations between severity of atopic eczema and levels of *B. pseudocatenulatum* (20).

Although low levels of Firmicutes can be associated with inflammatory conditions, their overgrowth is also associated with detrimental consequences. Increased levels of Firmicutes appear to alter the metabolic capacity of the microbiota, resulting in an increased ability to transfer carbohydrates, which results in host obesity (17).

In such correlative types of studies, it is difficult to conclude that an altered microbiota is causing disease rather than that the disease is affecting the composition of the microbiota. Indeed, among infants, factors such as geographical location, breast-feeding, mode of delivery, and antibiotic use can clearly alter the composition of the microbiota (26). Hence, alterations of the microbiota observed in disease states may be the result rather than the cause of disease. Comparative studies of culturable microbiota in human immunodeficiency virus (HIV)-infected and uninfected individuals have shown significant differences between the two, suggesting that the altered microbiota may contribute to HIV disease progression (27). Yet this finding could certainly be attributed to demographic differences between the two groups of individuals.

However, certain experimental approaches may distinguish between the two scenarios. For example, germ-free mice can be colonized with microbiota from diseased tissues or with microbiota of individuals suffering from diseases associated with altered microbiota. This approach has shown, for example, that microbiota from obese mice, transferred to germ-free animals, appears to cause the germ-free animals to gain significant weight (28).

Alternatively, alterations in disease-associated microbiota through the use of probiotics and/or prebiotics could ameliorate symptoms of disease, as discussed in more detail below.

HOW THE MICROBIOTA IS EXCLUDED FROM SYSTEMIC CIRCULATION

The health of the host depends on the tight regulation of interactions between the host and microbiota. Translocation of microorganisms, or microorganism components, from the lumen of the GI tract into the systemic circulation can certainly have detrimental consequences, including activation of the immune system. In extreme cases of MT, septic shock ensues, where patient mortality can approach 70% (29) and is characterized by clinical manifestations including thermal dysregulation (hypothermia or hyperthermia), tachycardia, tachypnea, and altered white blood cell count (leukocytopenia or leukocytosis). Underlying these phenomena is an overwhelming production of inflammatory cytokines including tumor necrosis factor (TNF) and interleukin (IL)-1, and high motility group 1 protein (HMGB1) and nitric oxide. Although these trigger beneficial inflammatory responses to confine the infection and tissue damage, their excessive production results in elevated systemic inflammatory responses that may be more lethal than the bacterial infection itself (30). The importance of this phenomenon is of particular relevance in severe sepsis, where excessive production of proinflammatory mediators causes capillary leakage, tissue injury, and multiple organ failure (30). These proinflammatory mediators are predominantly produced by innate immune cells after stimulation through pattern-recognition receptors specific for bacterial products. Indeed, administration of bacterial lipopolysaccharide (LPS) in high doses is sufficient to recapitulate the physiologic abnormalities of septic shock (31). Thus, given the tremendous luminal bacterial burden, protecting against excessive MT may be regarded as essential to life.

Defense Against MT at the Gastrointestinal Surface

The first line of defense against MT is mediated by macromolecules within the lumen of the GI tract, including the constituents of the mucus layer: proteins, phospholipids, electrolytes, and water. The unique capacity of the mucus to protect the underlying epithelial surfaces is due primarily to the gel-forming properties of its glycoprotein mucins. Furthermore, luminal IgA and antimicrobial defensins can bind to and kill bacteria, thus limiting their ability to translocate.

Secondly, the epithelial barrier of the GI tract itself represents a significant obstacle against MT. There are four major types of GI tract epithelial cells (32): absorptive enterocytes; mucin-producing goblet cells; enteroendocrine cells, which produce peptide hormones (33); and Paneth cells, which secrete antimicrobial defensins, digestive enzymes, and growth factors (34). Enterocytes are short-lived cells, and the entire mouse GI epithelium is renewed every 3–4 days (35). Enterocytes are adjoined to one another via a complex of transmembrane and peripheral proteins that are tethered to the cytoskeleton of the adjacent enterocytes. These intercellular tight junctions are formed by interactions with claudin proteins, which form selective pores between enterocytes to promote specific ion permeability.

Should microbial products traverse the mucus and epithelial barriers, they are met by a large number of specialized resident macrophages that prevent such products from accessing the systemic circulation (36). The GI tract is a major reservoir of macrophages in the body (37) and have a very distinct phenotype and functional capacity. Although intestinal macrophages express high levels of HLA-DR and the myeloid marker aminopeptidase (CD13), similar to blood monocytes and other tissue macrophages (38), these cells are distinct in that they do not express the LPS coreceptor (CD14), the Fc receptors (CD89, CD16, CD32, and CD64), or receptors for IL-2 (CD25) and IL-3 (CD123) (39). The

functional consequence of the absence of such receptors on intestinal macrophages is an inability to respond to many ligands that directly stimulate blood monocytes and other tissue macrophages. Indeed, GI macrophages do not produce proinflammatory cytokines such as IL-1 and TNF after stimulation with LPS (39). However, these cells can express various other pattern-recognition receptors including TLR4, TLR2, TLR5, and TLR9 and are capable of recognizing and phagocytosing bacterial antigens (38, 39). Hence, intestinal macrophages are specialized in their ability to clear antigens from the lamina propria without production of an inflammatory response to those antigens. This specialized role of intestinal macrophages is likely critically important to the maintenance of a noninflammatory state within the lamina propria of the GI tract.

Defense Against MT in the Liver

GI tract macrophages represent the first line of defense against translocated microbial products. However, should the GI tract macrophages fail to contain all such products, these are then drained by the portal vein into the liver. Thus, one of the many functions performed by the liver is the clearance of foreign and potentially harmful substances that drain from the GI tract. Indeed, concentrations of LPS in the portal vein are higher than in either the hepatic or peripheral veins (40), and bacteria can be cultured from healthy liver explants (41).

Besides the parenchymal hepatocytes, the liver contains other cell populations including liver sinusoidal endothelial cells (LSECs), tissue macrophages (Kupffer cells) and liver-associated lymphocytes. LSECs constitute the wall of the liver sinusoids, whereas Kupffer cells are located predominantly in the periportal area (42). Kupffer cells are therefore well situated for the phagocytosis of particulate antigens and organisms within the portal venous circulation. Both Kupffer cells and LSECs are responsive to direct stimulation with bacterial products (43), with measurably distinct responses compared with those of other tissue macrophages or monocytes in peripheral blood. Kupffer cells and LSECs constitutively express prostranoids and upregulate their expression concomitant with upregulation of IL-10 following LPS stimulation, which results in downregulation of antigen presentation by the APC within the liver (44, 45). Thus LPS-mediated stimulation of LSECs and Kupffer cells does not result in the release of proinflammatory mediators, and, similar to the response of GI tract macrophages, these cells are specialized in their ability to clear but not to respond immunologically to microbial antigens.

Defense Against MT in the Systemic Circulation

As discussed above, in order to access the systemic circulation, microbial antigens that originate in the GI tract must pass through the luminal mucus and IgA, traverse the tight epithelial barrier, escape uptake by GI tract lamina propria macrophages, and then avoid liver-mediated clearance by LSECs and Kupffer cells. Once in the circulation, microbial products are met with a further host-mediated response regulated by cell-surface receptors that sense and circulating factors that bind to and clear these products.

For example, healthy humans have high titers of circulating IgM, IgA, and IgG antibodies directed against the LPS core antigen that neutralize LPS activity (46, 47). When microbial products gain access to the circulation, such as during sepsis, these antibodies, termed EndoCAb, bind to and clear LPS from the circulation, and as a result their titers decrease (46). In contrast, in conditions when microbial products are found in the systemic circulation chronically, such as in IBD (discussed below), EndoCAb levels are increased (48), presumably as part of the normal humoral response to antigenic stimulation.

Additionally, the innate immune system produces soluble factors such as soluble CD14 (sCD14) and LPS-binding protein (LBP). CD14 is an LPS coreceptor expressed by

peripheral blood monocytes and tissue macrophages. Following LPS stimulation, $CD14^+$ monocytes/macrophages secrete sCD14 and shed surface CD14, which binds to LPS (49, 50). LBP, in contrast, is an acute phase reactant produced by hepatocytes (51). In healthy humans these proteins circulate at high concentrations in plasma, reaching the milligram/liter levels (50, 52). sCD14 and LBP both bind LPS and can, at given relative concentrations to one another and LPS, transfer LPS either to high-density lipoproteins (HDLs) to decrease the bioactivity of LPS or to the TLR4/MD-2/CD14 complex on monocytes/macrophages, leading to LPS-mediated stimulation (50). Indeed, the biological activities of different levels of sCD14 and LBP vis-à-vis LPS activity in vitro and in vivo are not completely understood, with experimental observations and interpretations varying considerably (50, 53). However, therapeutically increased levels of circulating LBP can be protective against gram-negative septicemia (54). Taken together, it is clear that several circulating factors, including EndoCAb, sCD14, LBP, and HDL, act as fundamental lines of defense against systemic stimulation of the immune system by translocated microbial antigens.

With approximately 10^{14} potential microorganisms residing within the GI tract at any given time, it is no surprise that humans allocate tremendous resources in corralling the microbes within the lumen of the GI tract and in controlling them should they enter the systemic circulation. Despite having these multiple mechanisms in place, the system could fail at any one of these checkpoints, and increased systemic MT would ensue.

MECHANISMS UNDERLYING MT

Low Levels of IgA

IgA is the most abundant antibody isotype in the body and is the second most dominant isotype in the peripheral circulation after IgG (55). IgA deficiency is the most common primary immunodeficiency (affecting between 1:300 and 1:3000 individuals) and has many genetic causes, including heavy chain gene deletions, T cell dysfunction, and alterations in cytokine signaling (56). Although many individuals with selective IgA deficiency are apparently asymptomatic, IgA-deficient individuals have a tendency to develop infections and disorders of the GI tract (57). Giardiasis, mal-absorption, lactose intolerance, celiac disease, ulcerative colitis (UC), nodular lymphoid hyperplasia, and increased epithelial cell proliferation are among the associated diseases (57, 58). Because the protective barrier of the GI system is impaired in IgA deficiency, protozoa such as *Giardia lamblia* can adhere to the epithelium, proliferate, and more easily cause infection (59). Even in the absence of infection, some GI tract luminal contents may enter the lamina propria and submucosal tissue. Indeed, individuals with IgA deficiency tend to mount large systemic IgG and IgM antibody responses to GI tract luminal antigens, including food and bacteria (60). Hence, low levels of IgA, with or without GI tract symptoms, can lead to increased MT; however, the degree to which MT occurs in IgA deficiency with subsequent systemic immune activation is unclear and warrants further study.

Alterations of the Structural Integrity of the GI Barrier

Pathogens—The tight epithelial barrier of the GI tract is clearly a major hurdle that must be breached in order for microbial antigens to traverse from the lumen of the intestine to the lamina propria of the GI tract. Consistent with this, many enterotoxins, which are expressed by pathogenic bacteria, target tight junction proteins of the GI tract. Enteropathogenic species of *Vibrio*, *Escherichia*, *Salmonella*, *Helicobacter*, and *Clostridia* all express such enterotoxins (61–63). Moreover, it is thought that the ability of these bacteria to cause systemic infections is entirely dependent on enterotoxin expression. Thus, one could conclude that the disruption of tight junctions alone may cause increased MT. The importance of the tight epithelial barrier in protecting against MT is also highlighted by viral

infections, which are associated with diarrheal diseases and subsequent increased intestinal permeability. Rotavirus, reovirus, norovirus, adenovirus, and coxsackievirus infections are all associated with disruption of the structural barrier of the GI tract and subsequent increased MT (64, 65).

Inflammation—In addition, alteration to the regulation of tight junction protein expression can lead to increased MT. Interferon (IFN)-γ expression increases claudin endocytosis with subsequent increase in paracellular permeability, whereas TNF and IL-13 lead to decreased expression of claudins (66, 67). Moreover, inflammatory conditions can be associated with upregulation of specific channel-forming claudins such as claudin 2 (66, 68). Indeed, it has been suggested that the ability of inflammatory cytokines to increase paracellular permeability allows neutrophil migration across epithelial barriers to combat invasive pathogens directly (69).

Not only can inflammatory cytokine production modulate claudin expression, but it can also influence the turnover of epithelial cells. Indeed, exposure to TNF or IL-1 can induce apoptosis in epithelial cells in vitro (70). Moreover, in vivo studies also suggest that excess production of TNF plays a deleterious role in perturbing the tight epithelial barrier, in part by induction of enterocyte apoptosis (reviewed in 71). Although inflammation may have multiple deleterious effects on GI tract integrity, it is important to note that therapeutic interventions aimed solely at decreasing TNF levels in vivo result in improved integrity of the structural barrier of the GI tract in individuals with CD (discussed below) (72).

TNF stimulation of enterocytes also leads to phosphorylation of the myosin light chain by myosin light chain kinase (MLCK) (73), which in turn leads to intestinal permeability via cytoskeleton rearrangement and modulation of tight junction protein expression. Consistent with this observation, inhibition of MLCK restores barrier function after TNF treatment and suggests that therapeutic interventions aimed at decreasing MLCK activity may be a promising approach in the treatment of TNF-mediated dysfunction of the structural barrier, as discussed below (74).

The propensity for chronic TNF signaling to induce GI tract structural damage via the mechanisms described above is highlighted by the finding that GI epithelial cells constitutively produce factors to extinguish TNF signaling. One such factor is A20, an NF-κB target gene that encodes a ubiquitin-editing enzyme essential for the termination of NF-κB activation after TNF or microbial product stimulation. Mice lacking A20 succumb to inflammation in several organs including the GI tract, and A20 mutations have been associated with CD (75). Moreover, tissue-specific disruption of A20 expression within GI tract enterocytes renders them exquisitely sensitive to TNF-induced toxicity and experimental colitis (75). Taken together, it is clear that inflammation may cause increased intestinal permeability and consequent MT.

Modulation of RORγt$^+$ cells—Repair of the structural barrier of the GI tract after damage is also critically dependent on the local immune system. Certain lymphoid cells within the GI tract express the nuclear hormone receptor retinoic acid orphan receptor (ROR)γt and are involved in maintenance of the structural barrier of the GI tract and in defense against pathogens through the production of cytokines such as IL-17 and IL-22. IL-17 and IL-22 function in vivo to promote recruitment of neutrophils to areas of bacterial infection, to induce proliferation of enterocytes, and to produce defensins (76–80). Although most data regarding IL-17-producing cells are derived from experiments in mice, several studies have shown that IL-17-producing cells can be identified in the blood of humans, can be characterized phenotypically based on expression patterns of certain chemokine and cytokine receptors, and appear to have specificity for bacterial and fungal antigens (81–84).

RORγt$^+$ cells that produce IL-17 and IL-22 include CD4$^+$ and CD8$^+$ T cells and innate lymphoid cells (iLCs) such as lymphoid tissue–inducer cells and IL-22-producing NKp46$^+$ cells (85).

Consistent with the notion that RORγt$^+$ cells are important for maintenance of the structural barrier of the GI tract, mice lacking the transcription factor RORγt are significantly more prone to MT than wild-type mice (86). In these mice, containment of the luminal microbiota requires the generation of abnormally large numbers of tertiary lymphoid tissues (86). Although at steady state these animals tend to maintain the integrity of their GI tract, upon epithelial damage these mice have decreased regeneration of enterocytes and develop severe intestinal inflammation due to MT.

IL-17 production is also thought to play an important role in maintaining the appropriate immunological environment within the GI tract. A recent study described an accelerated wasting disease following induced colitis in mice incapable of IL-17 production (87). Moreover, in this model lack of IL-17 among responding T cells was sufficient to cause the effect. The mechanisms underlying this protective effect are likely multifaceted and include decreased neutrophil recruitment, decreased antibacterial defensin production, decreased regeneration of GI tract enterocytes, and increased frequencies of Th1-type CD4$^+$ T cells, which produce high levels of tissue-damaging cytokines such as IFN-γ.

IL-22 is also thought to be critical for repair of the GI tract barrier. IL-22 belongs to the IL-10 family of cytokines (88), and its receptor is expressed on various epithelial tissues (89) and is believed to mediate epithelial innate immunity (90). The importance of IL-22 in repairing damage to the structural barrier of the GI tract is highlighted by studies of IL-22 knockout mice and by administration of IL-22-depleting antibodies. In these studies, mice that lack IL-22 are significantly more susceptible to chemically induced colitis (91).

IL-22 is clearly of lymphocyte origin with specific subsets of T cells (especially CD4 T cells) and iLCs capable of its production (92). However, the timing of IL-22 production may play an important role in the repair of the GI tract structural barrier, as is highlighted by experimental mouse infections with *Citrobacter rodentium*, which is characterized by damage to the structural barrier of the GI tract and MT. It was recently observed that rapid IL-22 production is critical for survival in this model, and it was suggested that IL-22 was produced by iLCs (93) in an IL-23-dependent manner. Therefore, though such studies suggest that IL-22 production by iLCs is critical for innate immunity in the intestine, the role of these cells in maintenance of the GI tract in the absence of infections is unclear given the relatively healthy structural barrier observed in IL-22-deficient mice (91) and the apparent overall GI tract health of uninfected mice selectively depleted of iLCs (93).

Decreased Microbial Clearance

In addition to mechanisms related to decreased ability to maintain the microbiota within the lumen of the GI tract leading to systemic MT, the inability to clear microbial products that cross the GI tract at steady state can also lead to systemic MT. The best studied mechanism related to decreased microbial product clearance is liver failure (discussed below). Consistent with this, there are several liver-associated diseases that are characterized by increased levels of microbial products in the peripheral circulation. Additionally, given that HDLs can clear LPS from the circulation, recent data suggest that the protective nature of high HDL levels against cardiovascular disease can be, at least partially, attributed to HDL's ability to clear LPS from circulation, thus decreasing LPS-induced inflammation, which can accelerate atherogenesis (94). Consistent with a role for inflammation and decreased LPS clearance in cardiovascular disease, polymorphisms in the *CD14* gene are associated with altered expression of sCD14 (95) and increased incidence of myocardial infarction (96).

Although the levels of MT occurring at any given time in individuals without overt disease, but harboring mutations in CD14, LBP, and IgA or having low HDL levels, are currently unknown, the data clearly demonstrate that decreased clearance of microbial products from systemic circulation is associated with disease states.

DISEASES ASSOCIATED WITH SYSTEMIC MT

Given the numerous mechanisms that underlie the inability to restrict the microbiota to the GI lumen and the evidence suggesting that microbial products translocate frequently even at steady state, it comes as no surprise that there are multiple disease states that can be associated with translocation of microbial products into the peripheral circulation with consequent host responses.

Inflammatory Bowel Disease

MT has been most widely recognized as playing a major role in the pathogenesis of IBD. UC involves inflammation of the large bowel, whereas CD may involve inflammation of the entire GI tract. The etiology of IBD remains largely unknown, although mutations in genes encoding proteins involved in immunological responses through pattern-recognition receptors, genes involved in IL-17 production, and tight junction proteins are associated with IBD (97, 98). Additionally, altered composition of the GI tract microbiota has also been suggested to play a role in IBD pathogenesis (99, 100), as revealed by mouse models of IBD in which inflammation is significantly reduced when the mice are housed in germ-free conditions (101, 102).

Individuals with IBD also have elevated levels of circulating proinflammatory mediators (103–105), and this systemic inflammation has been suggested to be due to MT (106–108) because elevated serum levels of LPS (108–113), bacterial DNA (114), EndoCAb (108, 112), and LBP (109, 112, 115) can be detected. In individuals with active disease, high levels of circulating bacterial products are associated with increased levels of proinflammatory cytokines (108, 112–114), and granulocyte phagocytic activity is decreased, presumably due to recent bacterial phagocytosis in vivo (111). Finally, increased proinflammatory cytokine production by B cells has been suggested to be due to increased MT in individuals with IBD (113). That individuals with IBD have significantly higher intestinal permeability compared with healthy controls suggests that one of the mechanisms underlying disease pathogenesis in IBD is damage to the structural barrier of the GI tract (107). Taken together, it is clear that systemic MT occurs in IBD, and it follows that MT-induced immune activation may be at the heart of disease pathogenesis.

Human Immunodeficiency Virus Infection

During the acute phase of HIV infection, there is a significant insult to the immunological and structural components of the GI tract. Massive depletion of GI tract CD4 T cells (116–120), low frequencies of IL-17-producing CD4 T cells (121–123) and CD8 T cells (124), apoptosis of enterocytes (125), with subsequent damage to the structural barrier of the GI tract (126) and increased intestinal permeability (127–130), are all manifestations of progressive HIV infection in humans and simian immunodeficiency virus (SIV) infection in Asian macaques. Moreover, generalized systemic activation of the immune system is a hallmark of the chronic phase of progressive HIV/SIV infection, and the degree to which the immune system is activated is the best predictor of the rate of disease progression (131–135). Indeed, one cause of immune activation is increased MT due to damage to the GI tract, as elevated levels of LPS were found in the plasma of chronically HIV-infected individuals compared with either acutely HIV-infected or HIV-uninfected individuals (52, 136). Consistent with a proinflammatory role for LPS in the systemic circulation, levels of plasma

LPS were associated with markers of immune activation of both the innate and adaptive arms of the immune system (52). Moreover, in patients with AIDS-associated dementia the activation status of monocytes in vivo was associated with levels of plasma LPS (137). Not only does MT occur during progressive HIV-1 infection, but increased levels of LPS are also observed in HIV-2-infected individuals (138).

Subsequently, using immunohistochemical analysis and the rhesus macaque/SIV model of HIV infection, investigators found that MT begins during the late acute phase of infection (~day 21–28 post infection), that microbial products colocalize with proinflammatory cytokines, and that one of the mechanisms underlying MT is damage to the structural barrier of the GI tract (126). The ability of the host to prevent microbial products from reaching circulation in the short term is highlighted by the normal plasma levels of LPS in acutely HIV-infected individuals, even though immunohistochemical analysis clearly demonstrates increased MT. Indeed, during the acute phase of infection EndoCAb titers decrease, sCD14 levels increase, and most microbial products found within the lamina propria of the GI tract are within the specialized tissue macrophages described above (52, 126, 139). In chronically infected individuals, GI tract macrophages fail to phagocytose all translocated bacterial products (126), EndoCAb titers remain low (52, 139, 140), and the number of Kupffer cells decreases (141). Hence, LPS clearance mechanisms are adversely affected during chronic HIV infection.

From these studies we can conclude that MT occurs in chronically HIV-infected individuals and that these microbial products can cause immune activation. It has also been proposed that the virus itself is a direct cause of immune activation in HIV infection (142, 143). However, there are certain cohorts of HIV-infected individuals in which viral replication is reduced to a minimum, yet immune activation remains pathologically elevated: elite controllers (ECs) and highly active antiretroviral therapy (HAART)–treated individuals. ECs are a rare group of individuals who spontaneously control viral replication to levels below the detection limit of conventional analyses (144, 145). Although these individuals have a significantly improved prognosis compared with viremic HIV-infected individuals, ECs tend to have higher levels of immune activation compared with HIV-uninfected individuals; many of these individuals nevertheless lose peripheral blood CD4 T cells, and some even progress to AIDS (133). In these individuals, elevated levels of LPS were detected and the frequency of activated phenotype $CD38^+$ $HLA\text{-}DR^+$ CD8 T cells correlated with MT (133). Moreover, there was a significant negative correlation between the levels of plasma LPS and the peripheral blood CD4 T cell count (133).

Additionally, recent studies have shown clearly that even though HAART can suppress plasma viral loads to undetectable levels, HAART-treated individuals nevertheless have increased mortality and morbidity compared with HIV-uninfected individuals, which are associated with inflammation and consequent cardiovascular disease (146, 147), osteopenia, (148), and cognitive decline (149). Given the long-term HAART-mediated control of viral replication in this group, it is unlikely that the residual inflammation is directly attributable to ongoing viral replication. Instead, a recent study suggests that elevated plasma levels of sCD14 independently predict increased mortality in HAART-treated, HIV-infected individuals (147). This is consistent with reports that, although chronic immune activation and levels of LPS in plasma decrease after initiating HAART, they remain elevated for years (52, 150–152) and that GI tract CD4 T cells do not return to healthy levels even after long-term HAART (153–155). In individuals with limited recovery of peripheral blood CD4 T cells after HAART, several studies have pointed to increased MT and immune activation as playing a causative role (52, 150–152, 156–158). Given recent data demonstrating increased mortality of HIV-infected individuals despite suppressed viral replication in HAART-treated individuals, and given the clear associations between mortality and inflammation and the

associations with persistent MT, investigators have proposed (147) that adjunctive therapies aimed at reducing MT and/or its inflammatory consequences could improve the long-term prognosis of HIV-infected individuals.

Hepatitis B and C Virus Infection

Infection with hepatitis B (HBV) or C (HCV) virus can also be associated with increased systemic MT and immune activation. Infection with these hepatocytetropic viruses often leads to significant liver damage, increased systemic inflammation, and ultimately, liver fibrosis (159, 160). Consistent with decreased clearing of microbial products, Caradonna et al. (159) described increased plasma LPS levels in HCV-infected individuals that decreased after IFN-α treatment. That IFN-α treatment is associated with decreased MT and inflammation in chronically HCV-infected individuals suggests that IFN-α itself is unlikely to lead to damage to the structural barrier of the GI tract. Moreover, in patients with late-stage HCV-related cirrhosis, investigators found a concomitant increase in intestinal permeability and bacterial DNA within plasma (161). Finally, another study showed increased levels of plasma LPS, damage to the GI tract epithelial barrier, and increased sCD14 in patients with HBV or HCV infection (162). The levels of sCD14 in these patients correlated with markers of hepatic inflammation and fibrosis and predicted clinical outcome (162). The precise interplay between decreased microbial product clearing, systemic inflammation, intestinal permeability, and liver fibrosis in HCV-infected individuals is unclear, and further studies are certainly warranted.

Alcohol Use

Chronic alcohol use is also associated with significant inflammation and MT. There are two broad sources of alcohol-related inducers of inflammation: those derived from alcohol-damaged cells and those derived from the microbiota. Hypoxia, which results from alcohol metabolism, is known to induce an inflammatory response, but the underlying mechanisms remain unclear (163). However, MT has been extensively studied as a key inducer of inflammation in alcohol-related conditions. Alcoholics are known to have significantly elevated plasma LPS levels compared with healthy controls (164, 165). Indeed, heavy alcohol consumption is associated with an increase in gut permeability and MT independent of liver disease, and these effects are long lasting, with a two-week period of abstinence required for intestinal permeability to return to healthy levels (166). Moreover, acute heavy alcohol consumption is associated with a transient increase in plasma LPS in otherwise healthy human subjects (167), and animal models show that acute enteral alcohol administration to mice increases MT approximately fivefold within 30–90 min (168), whereas daily binge feeding of alcohol in rats for four weeks induces MT 15-fold compared with control animals (169).

The mechanisms underlying alcohol-induced MT are likely multifactorial. Recent studies have demonstrated that alcohol and/or acetaldehyde can directly increase gut permeability by induction of inducible nitric oxide synthase and NF-κB signaling, which, in turn, modulates a differential expression of tight junction proteins (170). Furthermore, damage to the liver could lead to decreased clearance of microbial products that translocate at steady state. Finally, chronic alcohol exposure also alters the composition of the microbiota, which results in bacterial overgrowth (171, 172). Consistent with MT playing a deleterious role in inflammation associated with chronic alcoholism, treatment with probiotics in alcoholic patients and animals with alcoholic liver disease resulted in decreased intestinal permeability and reduced liver tissue injury (173).

Fatty Liver Disease

A third liver-associated disease in which MT has been suggested to have a role is fatty liver disease (FLD) (174). Nonalcoholic FLD develops in the setting of obesity, insulin resistance, and high dietary carbohydrate intake (175). Although the specific etiology of FLD remains somewhat obscure, some have suggested that fatty livers are less capable of performing their normal functions (176). The decreased ability of the fatty liver to clear antigens and harmful substances from the circulation eventually leads to the death of hepatocytes, increased liver fibrosis, the accumulation of inflammatory cells within the liver, and systemic MT (177). Subsequently, MT then leads to increased inflammation and further liver damage, which perpetuates the cycle. Consistent with MT playing an important role in FLD, treatment of ob^{-}/ob^{-} mice (a model of FLD) with the nonorally absorbed antibiotic neomycin improves biological outcome (178).

Given the increased incidence of FLD in the setting of high dietary carbohydrate intake, it follows that the microbiota might be altered in individuals with FLD. Indeed, in a rat model of FLD, associated with total parenteral nutrition, the proliferation and overgrowth of certain gram-negative enteric organisms ensues (179). Hence, dysbiosis may play a role in MT, inflammation, decreased hepatic clearance, and increased liver fibrosis, which are associated with FLD. Consistent with MT and dysbiosis playing a role in FLD, treatment of a mouse model of FLD with probiotics leads to reduced hepatic fatty acid oxidation (180).

Pancreatitis

Acute pancreatitis has a mortality rate of approximately 10% with between 40% and 80% of the mortality due to sepsis (181, 182). Given that most bacteria associated with sepsis in pancreatitis are gram-negative enteric bacteria, it has been proposed that a series of events occurs in which, due to the proximity of the pancreas to the GI tract, local inflammation associated with acute pancreatitis results in damage to the structural barrier of the GI tract, increased intestinal permeability, and MT (182). Increased intestinal permeability as soon as 72 h after the onset of symptoms and the degree of intestinal permeability is directly associated with levels of LPS in the circulation (182). Moreover, increased MT has been observed in mouse models of acute pancreatitis (183). A subsequent study described increased intestinal permeability in individuals with severe compared with mild pancreatitis (184). In those individuals with severe pancreatitis, increased damage to the structural barrier of the GI tract is associated with increased plasma LPS and increased levels of circulating proinflammatory cytokines (184). Thus, many have suggested that therapeutic interventions for acute pancreatitis should also aim to decrease MT in affected individuals (181–185).

Graft-versus-Host Disease

Given the rapid turnover of GI tract enterocytes, therapeutic interventions that aim to decrease proliferation of rapidly dividing cells result in damage to the structural barrier of the GI tract and systemic MT. Such is the case during the treatment of cancer with chemotherapeutic agents. Indeed, the MT that results from the conditioning regimen used for myeloablation before allogenic hematopoetic stem cell transplantation is thought to contribute to graft-versus-host disease (GVHD) (186). A role for LPS in the graft-versus-host response has been suggested by clinical studies aimed at decontamination of gram-negative bacteria from the GI tract during allogeneic stem cell transplantation, which has been shown to reduce GVHD (187), and the extent of such decontamination has been demonstrated to be an important predictor of GVHD severity (188). Notably, mutations in TLR4, which are associated with macrophage hyporesponsiveness to LPS within either the host or the donor, are associated with decreased incidence of GVHD (189). Similar results were seen in mouse models of GVHD when lymphocyte-depleted mice were reconstituted

with allogenic stem cells from mice with mutations in TLR4 (190) or from CD14 knockout mice (191). Given the transient nature of damage to the GI tract after myeloablative chemotherapy, the role for MT in driving GVHD may be circumvented therapeutically, and antibiotics are one of several options. An alternative approach to limiting MT-induced immune activation is the administration of antibodies directed against microbial products. Indeed, infusion of a polyclonal antiserum against *Escherichia coli* as prophylaxis for acute GVHD in a prospective, placebo-controlled trial reduced overall GVHD from 63% to 42% and was found to be particularly efficacious in the subset of patients with severe GVHD (192).

THERAPEUTIC INTERVENTIONS TO DECREASE MT

As discussed, there are many levels at which both the host and microbiota minimize systemic immune activation from MT. Therefore, therapeutic interventions can be targeted against individual mechanisms underlying systemic MT. Such therapeutic interventions can be divided into four general classes: alteration of the composition of the microbiota, enhanced clearance of translocated microbial products, repair of the enterocyte barrier, and reduction of local inflammation.

Antibiotics

Possibly the most obvious therapeutic approach that might curb the deleterious effects of MT is nonabsorbed oral antibiotics. Indeed, use of a gut-sterilizing antibiotic regimen prior to abdominal surgery significantly decreases the incidence of subsequent wound infection and septicemia (193). The unique properties of rifaximin, a broad spectrum antibiotic that has low systemic absorption and high fecal concentrations, might, therefore, make it an ideal agent for the treatment of diseases associated with MT. Indeed, although rifaximin appears promising as a treatment for IBD, clinical trials to date have lacked sufficient power to assess its efficacy. In one multicenter, randomized, double-blind, placebo-controlled clinical trial, fewer treatment failures were seen in patients treated with rifaximin ($n = 83$). However, in a separate study there were no significant differences in clinical remission or improvement in active CD in patients receiving rifaximin compared with placebo (194).

Additionally, rifaximin may serve as a steroid-sparing agent for UC. In an open-label study of 30 patients receiving maintenance mesalamine in which rifaximin was used in lieu of steroids, approximately 77% of patients experienced clinical resolution (195). However, in another trial no significant clinical improvement with rifaximin compared with placebo was shown for patients with moderate-to-severe steroid-refractory UC (196). The disparate results from these clinical trials may have several explanations: nonoptimal rifaximin doses were used, the GI tract was unable to be sterilized for long periods of time, or there were differences in rifaximin-mediated alterations in the composition of the microbiota.

However, although decreasing the GI tract bacterial burden may improve the prognosis of individuals suffering from diseases associated with MT, as discussed above, the microbiota generally survives in a symbiotic relationship with the host. Although antibiotic use may decrease immune activation and improve some of the symptoms associated with MT-related diseases, long-term antibiotic use may not be the best therapeutic approach, as it results in outgrowth of antibiotic-resistant bacteria, decreased integrity of the structural barrier of the GI tract, and decreased bioavailability of microbiota-derived nutrients.

Probiotics

Given the ample data demonstrating that alterations to the composition of the microbiota often accompany diseases that are characterized by systemic MT and the described effects of probiotic organisms in maintaining the structural barrier of the GI tract, several studies have

investigated the potential therapeutic benefit of promoting the growth of probiotic organisms. This goal has been pursued via direct oral administration of live probiotic organisms. Initially, studies were aimed at demonstrating proof of concept that orally administered live bacteria could survive transit through the length of the GI tract (197, 198). Although many bacterial species have been classified as probiotic, clinical trials showing any benefit to patients have been restricted to two mixtures of probiotic bacterial species: VSL#3 and *Lactobacillus rhamnosus* GG (207–210). VSL#3—a combination of four strains of *Lactobacilli*, three strains of *Bifidobacteria,* and one strain of *Streptococcus thermophillus* —was shown to induce remission in 53% of treated individuals with UC (199). Moreover, a recent study demonstrated the safety and efficacy of VSL#3 in reducing symptoms of mild to moderate colitis with improved integrity of the structural barrier of the GI tract (200). The administration of *Lactobacillus rhamnosus* GG has shown clinical benefit in individuals with IBD (201, 202). Furthermore, a recent study described significantly increased reconstitution of peripheral blood CD4 T cells in chronically HIV-infected individuals treated with conventional antiretroviral therapy and *L. rhamnosus* (203). However, the potential effects of probiotics on improvement of the GI tract or on decreased immune activation were not studied. Finally, in animal models of FLD, probiotic supplementation reduced hepatic fatty acid oxidation (180). However, though large-scale placebo-controlled human trials are lacking, two small-scale human trials of probiotics for liver disease have been completed, and levels of liver enzymes were decreased among patients receiving probiotics (173, 204).

Antibodies Against Microbial Products

A second therapeutic approach to decreasing systemic MT is the administration of agents that clear microbial products from the circulation. Such compounds are generally monoclonal or polyclonal antibodies directed against microbial products. Historically, design of antimicrobial antigen immunoglobulin therapy was based upon preliminary data suggesting that mortality associated with sepsis was reduced by passive immunization with sera from individuals vaccinated with a mutant strain of *Escherichia coli* (205). Based on these findings, researchers developed several monoclonal antibodies directed against LPS for clinical trials of sepsis. The first were HA-1A and E5. These monoclonal antibodies and subsequently developed anti-LPS monoclonals have had only limited success in reducing mortality (reviewed in 206, 207). Because of the limited benefit afforded to septic individuals by administration of antibodies against microbial products, investigators have given little effort to studying such therapeutic approaches in settings of systemic MT. However, oral administration of a spray-dried, purified immunoglobulin protein isolate has been shown to decrease systemic inflammatory effects associated with MT in certain animal models (208–210).

IL-22

Several therapeutic interventions aim to improve enterocyte homeostasis by the administration of cytokines such as IL-22, which is critical for maintenance of the structural barrier, particularly in the event of tissue damage (77, 85, 90, 211). Using a gene therapy approach, Sugimoto found that IL-22 administration could ameliorate intestinal inflammation in a mouse model of UC (212). This improvement was thought to be secondary to IL-22-enhanced mucus production and goblet cell replacement and restitution of the epithelial surface (212). Importantly, IL-22 receptor is also expressed by other epithelial cells, including those in the liver, and recombinant IL-22 administration resulted in decreased liver damage in a mouse model of hepatitis (213).

Glucagon-Like Peptide

Another epithelial cell growth factor which has been suggested as a therapeutic intervention to improve the structural integrity of the GI tract is glucagon-like peptide (GLP). GLP-2 is a

33 amino acid peptide produced with GLP-1 from the proglucagon gene, which encodes glucagon in the pancreas but undergoes specific posttranslational processing in the enteroendocrine L cells of the small intestine to produce the small GLP molecules. GLP-1 and -2 are released by L cells primarily in response to direct contact with luminal nutrients, especially long-chain fatty acids in the terminal ileum (214). Therapeutically, GLP-2 has been used extensively for treatment of short bowel syndrome with some success (reviewed in 215). Subsequently, certain GLP-2 analogs were developed and have been used to enhance the structural barrier of the GI tract in individuals with severe UC who were more likely to enter remission compared with placebo-treated individuals (216). Finally, GLP-2-treated individuals with CD had significantly improved enterocyte function compared with placebo-treated individuals (216).

CONCLUDING REMARKS

When considering the possible ramifications of harboring such an enormous bacterial burden within the GI tract, it seems reasonable to propose a few conclusions: (*a*) the interactions between the microbiota and host are generally symbiotic; (*b*) dysbiosis can both cause and result from systemic disease; (*c*) although humans have evolved multiple mechanisms to restrict the microbiota to the lumen of the GI tract, varying degrees of MT are a consistent feature in healthy humans; and (*d*) chronic MT and consequent immune activation are a feature of many diseases. Indeed, multiple lines of evidence are consistent with each of these conclusions. Given the increasingly large number of studies that have demonstrated or proposed a role for MT in many pathologic processes in humans, it is clear that therapeutic interventions that mitigate MT and its effects on systemic immune activation could be of great clinical benefit to many individuals. However, it is also clear that multiple mechanisms can underlie an inability to contain microbial products completely within the lumen of the GI tract. Thus, the development of novel interventions that target MT will require a more detailed understanding of the molecular mechanisms that damage the integrity of the GI tract barrier, activate local immune responses, decrease clearance of translocated microbial products, activate systemic MT and immune responses, and perturb the composition of the microbiota.

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