MINI-REVIEW | Microbiome and Host Interactions

Gut-liver axis at the frontier of host-microbial interactions

Katharina Brandl,1 Vipin Kumar,2 and Lars Eckmann2

1Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, California; and 2Department of Medicine, School of Medicine, University of California, San Diego, La Jolla, California

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Brandl K, Kumar V, Eckmann L. Gut-liver axis at the frontier of host-microbial interactions. Am J Physiol Gastrointest Liver Physiol 312: G413–G419, 2017. First published February 23, 2017; doi:10.1152/ajpgi.00361.2016.—Liver and intestine are tightly linked through the venous system of the portal circulation. Consequently, the liver is the primary recipient of gut-derived products, most prominently dietary nutrients and microbial components. It functions as a secondary “firewall” and protects the body from intestinal pathogens and other microbial products that have crossed the primary barrier of the intestinal tract. Disruption of the intestinal barrier enhances microbial exposure of the liver, which can have detrimental or beneficial effects in the organ depending on the specific circumstances. Conversely, the liver also exerts influence over intestinal microbial communities via secretion of bile acids and IgA antibodies. This mini-review highlights key findings and concepts in the area of host-microbial interactions as pertinent to the bilaterally communicating liver and gut and highlights the concept of the gut-liver axis.

A connection between intestine and liver was already postulated two millennia ago by Galen (129—c. 216 CE) in ancient Greece. He held that blood was continually formed by the liver from digested food, brought to it via the portal vein, and was subsequently passed through systemic veins to the periphery where it was consumed as nutrient or transformed into flesh. Seminal discoveries in the 16th and 17th century by Harvey (1578–1657 CE) and others demonstrated that blood is, in fact, not generated in the adult liver but continuously circulates in a stable volume through the systemic and pulmonary vascular systems. However, the ancient concept that nutrients travel from the gut through the portal vein to the liver where they are consumed for metabolic purposes has remained remarkably intact in modern times. Harvey also described the essential elements of the portal blood circulation as a parallel venous system that is fed by mesenteric arteries and drains through the liver directly into the vena cava (13). It is now well established that the liver receives ~70% of its blood supply from the portal vein, the direct outflow of the intestine. Therefore, the liver is the first and principal organ outside the intestine that is exposed to gut-derived products, i.e., ingested nutrients and the products of bacterial metabolism.

The close functional and vascular association between gut and liver has been termed the “gut-liver axis.” This now fashionable term has been applied to many functional connections between different organs and systems, such as the gut-brain axis, liver-lung axis, hypothalamic-pituitary-adrenal axis, and so on, and could be readily expanded to all organs, raising the question whether the underlying axis concepts are physiologically meaningful or simply used to elevate the importance of any particular observation. Nonetheless, the connections between gut and liver are indeed more intimate, direct, and extensive than those found in most other reported organ axes. A special association between these two digestive organs is also underlined by the common developmental origin of hepatocytes and intestinal epithelium from the ventral foregut endoderm (74).

In addition to being the primary recipient of gut-derived products, most prominently dietary nutrients, the liver also modulates intestinal functions by producing bile for release into the small intestine. Bile acids, the primary component of bile, have an important role in the absorption of lipids and lipid-soluble vitamins (56). In addition, bile acids, as well as liver-derived IgA transported in the bile, affect the intestinal microbiota and help to defend the intestine against microbial pathogens (31). Together, these bidirectional interactions of gut and liver can be viewed as centered around two major entities, nutrients and microbes. While nutrient absorption has been extensively studied for many decades, explorations of the interactions between host and intestinal microbiota are an emerging field of research. This mini-review highlights key findings and concepts in the area of host-microbial interactions as pertinent to the gut-liver axis.

Intestinal Integrity and Microbial Exposure of the Liver

The direct venous connection of gut and liver permits the rapid appearance of passively absorbed or actively translocated bacteria and their products from gut to liver. As a consequence, the quantity and composition of the intestinal microbiota influence the microbial exposure of the liver. In healthy individ-
through the cannabinoid receptor 1 (CB1) (50), while 2-AG is
inhibiting their ability to form tight junctions and secrete protective mucus (26) (Fig. 1). Host factors are also involved in mediating dietary effects on epithelial permeability. For example, a high-fat diet promotes the production of endocannabinoids, bioactive lipids such as arachidonoylglycerol (2-AG), and \(N\)-arachidonoyl ethanolamine (AEA) that are derived from host membrane precursors or dietary fatty acids. AEA can diminish epithelial barrier functions in vitro and in vivo through the cannabinoid receptor 1 (CB1) (50), while 2-AG is thought to be barrier protective (1), indicating that the balance of different endocannabinoids is likely to determine their overall impact on intestinal barrier permeability and translocation of microbial products into the portal and systemic circulation (9).

While dietary factors can alter epithelial permeability to bacterial products, extensive physical or functional disruption of the intestinal barrier allows whole bacteria to enter the portal vein and liver in greatly increased numbers (Fig. 1). In illustration, when mice are fed with the irritant dextran sulfate sodium, a sulfated polysaccharide that disrupts the epithelium and leads to mucosal inflammation, live bacteria are readily detected in the liver (2). Similarly, patients with Crohn’s disease, which is characterized by chronic remitting-relapsing intestinal inflammation and epithelial barrier disruption, display increased levels of bacterial colonization in portal blood, liver, and peritoneum (38), further underlining that intestinal barrier loss intensifies liver exposure to intestinal microbes. The physical integrity of the intestinal barrier is also actively regulated, so its dysregulation can lead to bacterial translocation into the liver (11). As one example, TNF is a major regulator of tight junctions in the intestine (Fig. 1). Elevated TNF levels, secondary to alcohol administration to mice and men, lead to tight junction disruption and increased LPS levels in plasma and presumably liver (4). Deficiency in two critical signaling mediators of this effect, TNF receptor 1 and myosin light chain kinase, in gene-targeted mice reverses the TNF effects and is consequently associated with reduced plasma LPS levels (11).

Beyond constituting a physical barrier, the intestinal surface is protected by functional defenses. One of these is the mucus layer overlying the epithelium. It is composed of an inner and an outer layer of highly glycosylated mucin molecules. Whereas the outer layer is rich in bacteria, the inner layer is largely devoid of bacteria (34). The most abundant mucus molecule is mucin-2 (Muc-2), which is selectively secreted by goblet cells in the intestine but not found in the liver. Loss of Muc-2 in gene-targeted mice leads to loss of the mucus barrier and can cause spontaneous colitis depending on the genetic

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**Fig. 1. Importance of intestinal barrier in preventing liver exposure to intestinal microbes and their products.** The intestinal epithelium serves as a physical and functional barrier that protects the liver from exposure to intestinal bacteria and their products. Multiple mechanisms are involved in protection, including a thick mucus layer (e.g., Muc-2), antimicrobial molecules (e.g., Reg3b) and tight junction molecules (e.g., JAM-A). These protective mechanisms can be compromised by dietary factors, injurious agents, and endogenous factors such as TNF or endocannabinoids. As a consequence, intestinal bacteria and their products can translocate into the portal vein and reach the liver.

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**Intact**

- Bacterial products
- Dietary factors (e.g., high fats)

**Disturbed**

- Injurious agents (e.g., DSS)
- Endogenous factors (e.g., TNF, endocannabinoids)

- J Mucin
- J Tight junctions
- J Antimicrobial molecules

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**Portal vein**

- Inner mucus layer
- Outer mucus layer

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**References:**

1. Host-microbial interactions and the gut-liver axis

2. AJP-Gastrointest Liver Physiol • doi:10.1152/ajpgi.00361.2016 • www.ajpgi.org

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background (63, 66). Importantly, upon oral challenge of these mice with intestinal pathogens, such as *Citrobacter rodentium* (3) and *Salmonella enterica* serovar Typhimurium (72), bacterial loads increase in intestine and liver, indicating that the Muc-2-dependent mucus barrier prevents intestinal pathogen expansion and dissemination to the liver.

Another active defense of the intestinal epithelium is production of antimicrobial molecules. Paneth cells at the bottom of the small intestinal crypts secrete several antimicrobial molecules including defensins (termed cryptdins in mice), cathelicidin, lysozyme, and C-type lectins (53). Other epithelial cells also produce antimicrobial peptides in the intestine (22, 30). These defense proteins target bacteria by attacking common surface molecules such as peptidoglycan of Gram-positive bacteria and the outer membrane of Gram-negative bacteria (51). For example, deficiency in Reg3b, a C-type lectin primarily expressed in intestine and pancreas but not the liver, leads to increased bacterial burden in colon and liver upon oral infection of knockout mice with *S. Typhimurium*, indicating that loss of a single antimicrobial molecule in the intestine can increase bacterial translocation into the liver (62). Further disruption of the epithelial barrier in these mice by alcohol feeding increases the number of mucosa-associated and liver bacteria, and this increase could be reversed by transgenic overexpression of Reg3b in intestinal epithelial cells, emphasizing the importance of intestinal epithelial defenses for protecting the liver against bacterial colonization (67).

Taken together, these findings clearly demonstrate that disturbance of the intestinal barrier results in increased influx of whole bacteria and their products into the portal system and liver, where they can impact a range of normal and pathological processes.

**Fate of Enteric Microbes and Their Products in the Liver**

The liver not only is a passive recipient of intestinal bacteria and their products that arrive through the portal system but also actively controls their numbers in the organ and their access to the systemic circulation. Kupffer cells, the resident macrophages of the liver, play a prominent role in the clearance of whole bacteria (57). Similarly, hepatic neutrophils, whose numbers in the liver are low under physiological conditions but can increase dramatically during acute inflammation, are effective pathogen killers in the liver (14, 33).

Kupffer cells, in particular, have been most extensively investigated for their importance and mechanisms of bacterial capture. For example, LPS has been detected in Kupffer cell vacuoles, suggesting that these cells contribute to endotoxin clearance (23), although the underlying mechanisms are poorly understood. In mouse models of *Listeria monocytogenes* infection, Kupffer cells efficiently phagocytose the bacteria (6), and cell depletion dramatically increases mortality after infection (18). This so-called “fast track” route of bacterial capture and killing in the liver is mediated in part by scavenger receptors on Kupffer cells (6). Nonopsonized, unbound bacteria can be removed via this rapid route, suggesting that this innate organ defense is active immediately after bacterial exposure without a need for antibacterial antibodies. In addition to scavenger receptors, which recognize both Gram-positive and Gram-negative bacteria, another innate receptor, the complement receptor of the immunoglobulin superfamily, contributes to the capture of Gram-positive bacteria, including *L. monocytogenes* and *Staphylococcus aureus* (73). Surprisingly, the interaction between lipoteichoic acid on Gram-positive bacteria and the complement receptor is independent of complement proteins and opsonization (73). The combination of these different receptors for bacterial capture might help to explain the ability of Kupffer cells to capture bacteria under flow conditions resembling sinusoidal blood movement, which is in contrast to other tissue macrophages that can only take up bacteria under static conditions with minimal shear forces (33, 43).

Despite the importance of clearing bacteria and their products rapidly and effectively from the liver to minimize organ damage, a need also exists to retain some fraction of bacteria to initiate adaptive immune responses. In this context, the liver has evolved a “slow track” of bacterial handling, which allows a small percentage of opsonized and platelet-bound bacteria to induce antibacterial, T-cell-mediated immunity via activation of CD8α dendritic cells (6). This is of particular importance for developing lasting immunity, as illustrated in listeriosis by the observation that reinfection can only be prevented by *Listeria*-specific CD8 T cells (25).

**Functional Impact of Microbial Exposure of the Liver**

Bacteria and their products in the liver have multi-faceted effects, which can be detrimental or beneficial depending on the circumstances (Fig. 2). LPS, the best-studied bacterial product in regard to liver impact (57), first binds to soluble LPS-binding protein in the serum, and this complex subsequently attaches to myeloid differentiation factor 2 (MD2) and

![Fig. 2. Beneficial and detrimental effects of bacterial products on liver function. Bacterial products reaching the liver can have beneficial or detrimental functions depending on the physiological circumstances. Stimulation of Kupffer and other liver cells via TLR-Md88 leads to production of proinflammatory cytokines and chemokines, resulting in the recruitment of inflammatory cells and injury and death of hepatocytes. Md88-dependent mechanisms can also alter the bile acid (BA) profile and together with other factors (e.g., IgA) modulate microbial composition in the intestine. Cytokines (e.g., IL-6) released by bacterially stimulated Kupffer cells activate cytoprotective mechanisms and promote liver regeneration.](Image)
despite, and perhaps because of, their increased bacterial ex-
products in the liver, hepatocyte-specific deletion of the com-
products in the liver but also have beneficial effects. Mice treated with broad-
Bacteria and their products are not only detrimental in the liver but also have beneficial effects. Mice treated with broad-
Bile acids, the primary component of bile, are synthesized in the liver from cholesterol. As amphipathic detergent-like molecules, they can exert direct effects on intestinal bacteria by causing membrane damage and disrupting protein and DNA functions, particularly in Gram-positive bacteria. In addition, bile acids are metabolized in the intestine by the gut microbiota to form secondary bile acids that can activate specific host receptors, particularly the nuclear farnesoid X receptor (FXR) and the G-protein-coupled bile acid receptor, Gpbar1 (also termed TGR5). These receptors regulate numerous immunological and metabolic pathways in the host, which can indirectly impact the intestinal microbiota. Bile acid composition may also be regulated indirectly by the microbiota, since deletion of the TLR signaling adaptor, Myd88, in hepatocytes altered the bile acid profile (17). Whether by direct or indirect mechanisms, feeding of bile acids or changes in bile acid composition can impact microbial composition in the intestine, such as reduction of Bacteroidetes and Actinobacteria, and expansion of Firmicutes at the phylum level (32), or decreases of Sutterella and Allobaculum at a lower taxonomic level (17). In another example, specific secondary bile acids can inhibit germination of Clostridium difficile, an opportunistic pathogen associated with antibiotics use (68). During infection, secondary bile acids are reduced, but successful fecal matter transplantation for treatment of C. difficile infection led to normalization of secondary bile acids, possibly providing a partial explanation for the efficacy of this intervention (68).

The liver is an important source of IgA, which is by far the most abundant immunoglobulin isotype in the intestinal lumen. In the intestine, IgA is produced by B cells and plasma cells in the lamina propria, and transported across intestinal epithelial cells via the polymeric immunoglobulin receptor (pIgR). In the liver, IgA producing plasma cells, originating from the Peyer’s patches, colonize portal regions and the submucosa of the biliary tract, and locally produce IgA, which together with serum IgA is transported across biliary epithelial cells (and

Although the mechanisms underlying liver protection and regeneration are not fully understood, production of IL-6 by liver macrophages promotes growth factor production and hepatoprotection, and has been proposed as a central cytokine responsible for liver regeneration (65). Consistent with this notion, mice deficient in MyD88 and TLR4 show impaired IL-6 production after partial hepatectomy (64). However, in spite of decreased IL-6 levels, complete liver restitution was observed in mice lacking one or more TLRs or MyD88 (59), suggesting that TLR- and MyD88-independent pathways exist that contribute to liver regeneration, possibly by mechanisms other than LPS recognition. Besides IL-6, production of IL-12 and IL-18 by hepatic natural killer cells in response to microbial ligands can induce IFN-γ, a cytokine that can also contribute to hepatic healing (57).

Role of the Liver in Controlling Intestinal Microbes

As the “distal” organ in the gut-liver axis, the liver receives microbial input from the intestine. However, the liver also exerts influence over intestinal microbes, commensurate with the two-way communication that is implied by the axis concept. Most importantly, the liver shapes microbial communities in the intestine via production and release of bile and IgA antibodies.

Bile acids, the primary component of bile, are synthesized in the liver from cholesterol. As amphipathic detergent-like molecules, they can exert direct effects on intestinal bacteria by causing membrane damage and disrupting protein and DNA functions, particularly in Gram-positive bacteria. In addition, bile acids are metabolized in the intestine by the gut microbiota to form secondary bile acids that can activate specific host receptors, particularly the nuclear farnesoid X receptor (FXR) and the G-protein-coupled bile acid receptor, Gpbar1 (also termed TGR5). These receptors regulate numerous immunological and metabolic pathways in the host, which can indirectly impact the intestinal microbiota. Bile acid composition may also be regulated indirectly by the microbiota, since deletion of the TLR signaling adaptor, Myd88, in hepatocytes altered the bile acid profile (17). Whether by direct or indirect mechanisms, feeding of bile acids or changes in bile acid composition can impact microbial composition in the intestine, such as reduction of Bacteroidetes and Actinobacteria, and expansion of Firmicutes at the phylum level (32), or decreases of Sutterella and Allobaculum at a lower taxonomic level (17). In another example, specific secondary bile acids can inhibit germination of Clostridium difficile, an opportunistic pathogen associated with antibiotics use (68). During infection, secondary bile acids are reduced, but successful fecal matter transplantation for treatment of C. difficile infection led to normalization of secondary bile acids, possibly providing a partial explanation for the efficacy of this intervention (68).

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possibly hepatocytes in some species but probably not humans) and secreted into the bile (49). The relative contributions of intestinal and hepatic production to luminal IgA levels varies by species, ranging from 5 to 10% in humans to >50% in some rodents (41). Furthermore, these contributions are presumably affected by the specific location in the gut and by meal status.

IgA production in the intestine and liver is largely dependent on the normal microbiota, as it is nearly absent in germ-free mice (45). Conversely, IgA is important for controlling intestinal microbial loads and protection of the mucosal-luminal interface. For example, an inability to class switch the immunoglobulin heavy chain to IgA, as observed in mice lacking activation-induced cytidine kinase, leads to a significant increase in the biomass of anaerobic microbes in the small intestine (21). In plgR-deficient mice, the diversity of the cecal microbiota was also altered compared with wild-type mice, which might be responsible for the increased susceptibility of these mice to DSS-induced colitis because treatment with antibiotics attenuated weight loss and mortality (55). Similarly, IgA-deficient mice show increased susceptibility to intestinal injury in this model (48). The transition from the neonatal to the adult microbiota is also controlled by IgA. Thus, mice lacking IgA show persistent colonization with γ-proteobacteria, which are normally present in newborns but lost in adults.

The continued presence of these bacteria can induce proinflammatory cytokines in the colon and enhance intestinal inflammation (48). These observations correlate with those in humans, as IgA-deficient individuals are more prone to developing inflammatory and autoimmune gastrointestinal disorders including ulcerative colitis and Crohn’s disease (71).

**Outlook**

Although the importance of the microbiota in the bidirectional communication between intestinal tract and liver is becoming ever more evident, much remains to be learned about the details and consequences of these interactions. What is the spectrum of intestinal bacteria that enter and persist in the liver under physiological and different disease conditions? How does it differ from the composition in different sites of the intestine? Does the microenvironment of the liver permit selective survival of some bacteria, but not others, and what are the functional consequences of this bacterial selection for liver functions? Are other bacterial products and metabolic functions beyond LPS important? For instance, flagellin is recognized by TLR5, whose potential role in the liver is only established. Finally, the mechanisms that determine the balance of liver destruction versus protection by microbial products will be an important topic of future research.

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