Mini-Review

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

Running title: Host-microbial interactions and the gut-liver axis

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ABSTRACT

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 bilateral communication between liver and gut, and 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 approximately 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 individuals, intact bacteria are rarely detectable in the liver (2), presumably because the intestinal barrier is normally sufficient
to prevent live bacteria from entering the portal system. Although the liver is devoid of intact bacteria under physiological conditions, bacterial mRNA and LPS are readily detectable in trace amounts in the liver (7, 20) and peripheral blood (19), suggesting that the liver and other organs are constantly exposed to and functionally influenced by bacterial products even under healthy conditions. Other important bacterial products such as lipoteichoic acid or flagellin have not yet been carefully investigated in the liver, probably due to the lack of sensitive assays, but it would not come as a surprise if these and other bacterial products will also be found at low levels in the liver under physiological conditions.

Absorption of bacterial products from the intestine into the portal and systemic circulation is influenced by dietary factors. For example, a high-fat diet was shown to increase plasma LPS concentrations in mice by a moderate but functionally relevant degree that attenuates insulin actions, leading to the concept of “metabolic endotoxemia” for this condition (8). Similarly, diets rich in saturated fats cause postprandial endotoxemia in humans (19, 39, 44). In vitro studies have confirmed that fatty acids can promote transepithelial LPS absorption (39), perhaps by inducing endoplasmic reticulum stress in epithelial cells, and 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-arachidonylethanolamine (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 overlaying 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 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 knock-out 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 pathologic processes.

**Fate of enteric microbes and their products in the liver**

The liver is not only a passive recipient of intestinal bacteria and their products that arrive through the portal system, but 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). Non-opsonized, 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 anti-bacterial 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 *Listeria 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 anti-bacterial, 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 CD14 on the cell surface of responsive cells. Together they activate Toll-like receptor (TLR) 4, resulting in the production of pro-inflammatory cytokines and chemokines. Consequently, high levels of LPS in the liver under disease conditions can activate the recruitment of inflammatory cells, which can potentially destroy the liver parenchyma (27). Interestingly, recognition of LPS and other microbial molecules may not only occur in Kupffer cells (61), but possibly also directly in hepatocytes, as suggested by the expression of functional TLR2 in these cells (46).

LPS can synergize with other noxious stimuli in the liver. In alcoholic liver disease, increased levels of bacterial products such as LPS and peptidoglycan, which are presumably derived from the intestine, are found in the liver and blood (5, 24, 52). Activation of the respective TLRs on Kupffer and other liver cells promotes a cascade of events leading to the production and release of inflammatory cytokines (i.e. TNF-α, IL-1β) and subsequently injury, inflammation, and hepatocyte death (37). In another example, mice with a deletion of the tight junction molecule, JAM-A, in intestinal epithelial cells, display increased intestinal permeability and bacterial translocation to the liver (40). These mice develop more severe steatohepatitis when fed a diet high in
saturated fat, fructose or cholesterol (54). Interestingly, colon biopsies from patients non-
alcoholic fatty liver disease show decreased levels of JAM-A and increased mucosal
inflammation in the colon, suggesting that defects that primarily impact the intestine may
contribute to liver disease (54).

Despite the ability of microbial products to induce or exacerbate liver disease, and the
constant presence of at least low levels of LPS in the liver, the organ does not display
overt inflammatory reactions under physiological conditions (33), suggesting that a
threshold of activation exists for inflammatory responses to bacterial products. For
instance, Kupffer cells are generally responsive to LPS, but possess mechanisms that
attenuate the pro-inflammatory actions of LPS. The cells express lower levels of CD14
compared to peripheral blood monocytes, and exhibit decreased (but not absent) LPS
responses (42). In addition, LPS-stimulated Kupffer cells secrete the anti-inflammatory
cytokine IL-10, which down-regulates pro-inflammatory cytokine responses (36).

Bacteria and their products are not only detrimental in the liver but also have beneficial
effects. Mice treated with broad-spectrum antibiotics that markedly diminish the
intestinal microbiota show impaired liver regeneration after partial hepatectomy (69).
This and earlier work with LPS-hyporesponsive mice suggested that LPS is responsible
for promoting liver regeneration after partial hepatectomy (15, 16). Studies in models of
alcoholic liver disease and liver fibrosis also demonstrated a beneficial role of the
commensal microbiota in protection against these diseases under specific circumstances
(10, 47). Consistent with such beneficial effects of bacterial products in the liver,
hepatocyte-specific deletion of the common TLR signaling adaptor, Myd88, predisposes to liver inflammation, steatosis, and insulin resistance (17). Another example of the liver-protective impact of intestinal microbes are Muc2 deficient mice, as these mice are protected from the development of fatty liver disease and alcoholic liver disease despite, and perhaps because of, their increased bacterial exposure in the liver (28, 29).

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).
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 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 5-10% in humans to >50% in some rodents (41). Furthermore, these contributions are presumably affected by gut location and 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 pIgR deficient mice, the diversity of the cecal microbiota was altered compared to 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 pro-
inflammatory 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 disorder 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 beginning to be appreciated (60, 70). Production of saturated long-chain fatty 
acids by the microbiota is diminished in alcoholic liver disease, and their dietary 
supplementation attenuated alcoholic liver injury (12). Surely, other bacterial metabolites 
exist with selective effects on the liver and other host organs. Another poorly understood 
aspect of the gut-liver axis and its role in controlling host-microbial interactions is the
differentiation and migration of immune cells. For example, in conditions of extra-
intestinal inflammation associated with inflammatory bowel disease such as primary
sclerosing cholangitis, CD8 T cells are primed by dendritic cells in the intestine and
subsequently migrate into the liver where they promote cholangitis (58). Recognition of
bacterial ligands from enteric bacteria by TLR4 appears to be important in mediating this
recruitment of CD8 T cells into the liver (35), but the importance of specific bacteria and
their products in these processes and, more broadly, for different liver diseases remains to
be 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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**FIGURE LEGENDS**

**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 expand locally in the intestine and translocate into the portal vein and reach the liver.

**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 physiologic circumstances. Stimulation of Kupffer and other liver cells via TLR-Myd88 leads to production of pro-inflammatory cytokines and chemokines, resulting in the recruitment of inflammatory cells and injury and death of hepatocytes. MyD88-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.
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**Intact**

- Bacterial products
- Bacteria

**Disturbed**

- Injurious agents (e.g. DSS)
- Endogenous factors (e.g. TNF, endocannabinoids)
- Dietary factors (e.g. high fats)
- ↓Mucin
- ↓Tight junctions
- ↓Antimicrobial molecules

- Outer mucus layer
- Inner mucus layer

Portal vein to liver
Inflammation and cell death

Cytoprotection and regeneration

TNF
IL-6 other mediators

portal vein

Liver

IgA

Hepatocyte

Biliary epithelial cells

Neutrophil

Kupffer cell

MyD88

TLR complex

Microbiota

Intestine

IgA