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Linking intestinal homeostasis and liver disease

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Abstract

Purpose of review—Interactions of the gut microbiome with the host are important in health and disease. Microbial translocation releases bacterial products that play a key role in progression of chronic liver disease by promoting hepatic injury and inflammation. Although this has long been recognized, we are just beginning to understand the circumstances under which the gut becomes leaky and to discover bacterial metabolites that promote liver disease. In this review we will summarize recent findings from the last two years.

Recent findings—Chronic liver disease is associated with an altered microbiome with both qualitative (dysbiosis) and quantitative (overgrowth) differences. This can be viewed as a loss of the symbiotic relationship between the microflora and the host. An imbalanced intestinal homeostasis results in a breach of the gut barrier and subsequent microbial translocation. However, the contribution of the intestinal microflora is beyond simple microbial translocation as pathogenic factor. Bacterial metabolites resulting from an imbalanced homeostasis and dysbiosis play also a crucial role in liver disease.

Summary—A combination between an initiating liver insult and a disturbance of the gut – host symbiosis synergize in progression of liver disease.

Keywords

bacterial translocation; bacterial dysbiosis; microbiota composition; microbiome; intestinal inflammation; intestinal bacterial overgrowth

Introduction

The intestinal microbiome and the host share a very close symbiotic relationship. This symbiosis requires a tight control, because the close proximity of a large amount of intestinal bacteria with host intestinal tissue poses a serious risk. The host immune system controls the composition of the microbiome and translocation of bacteria across the mucosal barrier and prevents host damage, e.g. inflammation, while the microbiome itself is important for the proper development and functioning of the immune system [1, 2]. A disruption of this delicate homeostasis between the gut microflora and the immune system can result in disease. A classic example for such a disease process is inflammatory bowel

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disease. A subset of patients with ulcerative colitis develops primary sclerosing cholangitis, a chronic liver disease characterized by a destruction of mostly large bile ducts.

Chronic liver disease has long been associated with changes in the intestine. Microbial translocation defined as the penetration of viable commensal microbes or their products (also called pathogen associated molecular patterns or PAMPs) across the intestinal gut barrier to mesenteric lymph nodes and extraintestinal sites is common in patients with liver cirrhosis. The rate of bacterial infections is as high as 34% per year in patients with advanced cirrhosis [3]. However, bacterial translocation is not only prevalent in advanced stages of chronic liver disease causing spontaneous infections, but a leaky gut and translocation of microbial products occur early in disease. Patients with liver disease show a disruption of the gut barrier and levels of bacterial products are elevated in the systemic circulation, which correlate with liver disease severity. Microbial translocation releases bacterial products that reach the liver via the portal vein or the lymphatic ducts, where they activate numerous hepatic receptors of the innate immune system. Although activation of these receptors might be beneficial and protective against acute infections in health, persistent activation contributes to liver injury and disease progression. Reducing the intestinal bacterial burden using non-absorbable antibiotics decreases bacterial translocation and prevents liver disease in experimental animal models, and improves clinical parameters in patients. Genetic deletion or mutation of receptors for bacterial ligands or signaling molecules downstream from these activated pathways convincingly proves the involvement of microbial molecules in experimental liver injury and disease progression. We have recently summarized all of these findings in several reviews [4–6].

We would like to take the opportunity to highlight new findings from the recent literature important to the gut-liver axis. We will emphasize findings under this novel aspect of an unbalanced homeostasis between the microbiome and the host resulting in liver disease.

Changes in the gut microbiome associated with liver disease

Culture-independent technologies have identified microbial, metagenomic and metabolomic changes of the enteric microflora contributing to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Advances over the last decade have been summarized in an excellent review article [7].

Several recent studies reported qualitative changes (dysbiosis) in the intestinal microbiome associated with chronic liver disease of different etiologies in humans. Patients with chronic hepatitis or decompensated cirrhosis secondary to hepatitis B infection show reduced numbers of probiotic *Bifidobacteria* and lactic acid producing bacteria (*Lactobacillus*, *Pediococcus*, *Leuconostoc*, and *Weissella*) in the feces, while *Enterococcus faecalis* and Enterobacteriaceae were increased as compared to asymptomatic carriers and healthy controls [8]. No change was observed between chronic hepatitis B carriers with normal biochemical liver function tests and healthy controls, suggesting that hepatitis B infection itself does not cause microbiome changes. Using deep pyrosequencing of the common 16S rRNA region of bacteria, fecal microbial communities from patients with alcoholic or hepatitis B related cirrhosis could clearly be distinguished from healthy controls [9]. An

increase of *Streptococcaceae*, *Veillonellaceae*, and *Enterobacteriaceae* with a decrease of *Lachnospiraceae* characterizes the gut microbiota in cirrhosis. The relative abundance of the *Lachnospiraceae* and the *Streptococcaceae* family was negatively and positively, respectively, related with the Child-Pugh score in cirrhotic patients [9]. The mucosa-associated microbiome was evaluated in patients with alcoholic cirrhosis or in alcoholics without liver disease. Surprisingly, only minor changes were seen between the alcohol groups and normal controls. The abundance of *Bacteroidaceae* was decreased in the alcoholic groups as compared to healthy individuals [10]. A comparison of the mucosa-associated microbiome showed a lower abundance of autochthonous genera (*Dorea*, *Incertae Sedis other*) and a higher abundance of potentially pathogenic ones (*Proteus*) in non-encephalopathic cirrhotics as compared to controls [11]. Interestingly, the microbial composition of the colonic mucosa differed from the corresponding stool.

We are now starting to understand the factors that shape the microbiome composition in patients with chronic liver disease. Based on the above studies, the presence of a liver noxious agent such as hepatitis B virus without evidence of liver disease does not cause significant changes in the gut microbiome. Since the microbiome does not differ between alcoholic and hepatitis B cirrhosis, other, liver disease etiology-independent factors play a more important role in shaping the intestinal microbiome. Such a condition might be end-stage liver disease itself, which is associated with reduced intestinal motility, portal hypertension and reduced bile flow. Total fecal bile acids are reduced in patients with chronic hepatitis or decompensated cirrhosis secondary to hepatitis B infection as compared to asymptomatic carriers and healthy controls [8]. The influence of bile acids on microbiome composition will be discussed later in this review.

Dietary factors and changes are strong determinants of the microbiome composition. Diet correlates with enterotypes in humans. Enterotypes are strongly associated with long-term diets, particularly protein and animal fat (*Bacteroides*) versus carbohydrates (*Prevotella*) [12]. Alcohol intake or a Western-style diet are similarly important dietary determinants for shaping microbiome composition. Diet might be more important to determine the microbiome composition in early stages of liver disease, while late stages are more influenced by consequences of end stage liver disease such as a decrease in bile flow.

Although human studies are extremely important to study the changes in the microbiome, experimental animal models provide several advantages to detect differences in the microbiota that are characteristic of disease states. Experimental animal studies allow controlling for factors that greatly affect the microbiome composition such as age, gender, diet, geography and ethnic background. Animal experiments further provide the advantage to compare littermates. Newborns are colonized by the microbes they first encounter, typically from their mother. Littermates from the same parents carry a similar gut microbial diversity. Subjecting these littermates to a liver injury model, allows monitoring microbiome changes in a temporal fashion. As such, experimental alcoholic steatohepatitis showed a reduction of commensal probiotic bacteria in mice, a similar trend as seen in human microbiome studies. Mice with early stages of alcoholic liver disease had significantly reduced members of the phylum Firmicutes, namely *Lactococcus*, *Pediococcus*, *Lactobacillus* and the *Leuconostoc* genera [13]. When the intestinal microbiome was

compared in early stages of toxic (carbon tetrachloride), cholestatic (bile duct ligation), alcoholic and fatty liver disease in *ob/ob* mice with a mutation in the satiety-promoting hormone leptin, there was no unique and common bacterial species dominating the microbiome associated with four different liver diseases [14]. Most changes were seen in mice fed alcohol, again supporting the concept that dietary factors are likely more important in shaping the intestinal microbiome in early stages of liver disease.

Differences in the microbiome composition associated with liver disease are not only of a qualitative nature (dysbiosis), but quantitative differences are commonly found in patients with chronic liver disease. Quantitative PCR or traditional culture techniques detected intestinal bacterial overgrowth in the small bowel mostly in patients with chronic liver disease or cirrhosis [4]. Animal studies again have the advantage of providing temporal assessment of quantitative microflora changes. Early stages of alcoholic, toxic and cholestatic liver disease are associated with intestinal bacterial overgrowth in mice [13, 14]. It will be important to determine whether intestinal bacterial overgrowth is a common feature of early stage of liver disease in humans, too. Ideally such studies should obtain luminal aspirates from the jejunum as gold standard to assess quantitative changes. In contrast, in patients with decompensated cirrhosis a small observational study demonstrated the clinical importance of intestinal bacterial overgrowth. Intestinal decontamination with the non-absorbable antibiotics rifaximin reduced endotoxemia and improved liver disease severity [15]. Randomized placebo-controlled trials obviously will need to confirm these preliminary data. It will also be interesting to see whether reducing the intestinal bacterial overgrowth slows the progression of fibrosis in patients with chronic liver disease.

Taken together, microbiome changes that are either induced by diet or liver disease might represent an early starting point for the loss of intestinal homeostasis. It is likely that disease is not caused by a single bacterial species, but rather through global changes in the intestinal microbiome, metagenome and/or metabolome.

Disruption of the gut barrier and microbial translocation is an early event in liver disease

Traditionally, research has focused on a leaky gut and bacterial translocation as one of the major interactions between the intestine and the liver. The intestinal microflora is a source for several hepatotoxins and PAMPs including lipopolysaccharide (LPS). Disruption of the mucosal barrier facilitates the translocation of these molecules from the intestinal lumen to the liver. The concept of bacterial translocation is well established in patients with end-stage liver disease and has been associated with infections such as spontaneous bacterial peritonitis. Intestinal permeability as assessed by urinary excretion of polyethylene-glycol after oral administration is higher in cirrhotics than in healthy controls [16]. Increased intestinal permeability often involves a disruption of the tight junction barrier. Expression of duodenal tight junction proteins occludin and claudin-1 is lower in patients with cirrhosis as compared to healthy controls and it is inversely correlated with systemic endotoxin levels [17]. Plasma markers of enterocyte necrosis (intestinal fatty acid binding protein), microbial translocation (LPS), and monocyte activation (sCD14) are increased in subjects with chronic hepatitis B or C infection; the degree of the host response to LPS, as reflected by the level of

sCD14, correlates with hepatic inflammation (IL-6), distinguishes subjects with severe fibrosis (cirrhosis) and is associated with liver disease progression. Activation of the host's immune system by translocated microbial molecules accelerates fibrogenesis and the clinical progression of viral liver disease [18].

Experimental animal models can determine the temporal correlation between liver injury and changes in the gut barrier. Acute liver injury due to various etiologies including alcohol, hepatotoxin and cholestasis is associated with an early onset of increased intestinal permeability and microbial translocation [13, 14]. As emphasized above, the same models demonstrated intestinal bacterial overgrowth. A leaky gut and an increased intestinal bacterial burden synergize in increasing systemic levels of bacterial products. Microbial translocation is therefore an early event in experimental animal models and does not exclusively occur in late stages of liver disease such as bridging fibrosis or cirrhosis. Reducing the intestinal bacterial load by means of intestinal decontamination slows liver disease progression in animal models. Genetically modified mice that are resistant to sensing bacterial products or to propagating signal transduction are similarly resistant to experimental liver disease [6]. Taken together, bacterial translocation is an early event liver disease and it causes not only infectious complications in cirrhotics, but it also contributes to liver disease progression.

Dysbiosis can trigger intestinal inflammation and microbial translocation

The intestinal immune system has the delicate function of regulating luminal bacteria and preventing the invasion into host tissues. Chronic liver disease can be viewed as a failure of this immune system control function. Detailed molecular mechanisms that lead to a failure and disruption of the gut barrier in early stages of liver disease are poorly understood, although some factors have been identified that are associated with bacterial translocation in late stages of liver disease and cirrhosis. Identification of a molecular mechanism implies potential new targets not only for preventing microbial translocation, but also for the prevention and treatment of liver disease.

Intestinal injury and inflammation is an important determinant of mediating a gut barrier dysfunction in experimental liver disease. Three recent studies support this novel concept:

Inflammasomes are cytoplasmic multi-protein complexes composed of nucleotide-binding domain and leucine-rich repeat containing proteins (NLRP). Inflammasomes are sensors of endogenous or exogenous PAMPs or damage-associated molecular patterns (DAMPs) that govern cleavage of effector proinflammatory cytokines such as pro-interleukin (IL)-1 β and pro-IL-18. The loss of NLRP3 and NLRP6 inflammasomes in mice is associated with intestinal dysbiosis and results in inflammation of the colon, which requires the chemokine CCL5. Subsequent microbial translocation then leads to increased accumulation of bacterial products such as LPS and bacterial DNA in the portal vein. These bacterial products stimulate Toll-like receptor (TLR)4 and TLR9, respectively, leading to enhanced liver expression of the pro-inflammatory cytokine tumor-necrosis factor (TNF), which in turn drives progression of NAFLD to NASH. Importantly, wild-type mice co-housed with NASH-prone apoptosis-associated speck-like protein containing a CARD (Asc) deficient

mice develop NASH [19]. Thus, an altered microbiome triggering colonic inflammation and bacterial translocation causes simple hepatic steatosis to turn into NASH. Dysbiosis contributes to liver disease and cannot be considered as an innocent bystander.

Intestinal inflammation and colitis can be simply induced by oral administration of a chemical toxin such as dextran sodium sulfate (DSS). After experimental induction of mild colitis and disruption of the gut barrier, mice fed a high fat diet and DSS showed increased endotoxin levels in the portal vein, more hepatic steatosis, inflammation and fibrogenesis. Mice on a high fat diet alone showed fatty liver disease only, suggesting that mild intestinal inflammation is a critical factor for its progression to NASH [20]. Taken together, high fat diet feeding is associated with increased intestinal permeability in animals and humans. A leaky gut is apparently not sufficient to induce NASH, because high fat diet alone does not cause significant liver inflammation and fibrosis that is characteristic of NASH. An additional component is likely necessary to move NAFLD beyond the tipping point towards NASH. One could speculate that more bacterial products might translocate in a “super” leaky gut, alternatively toxic or metabolic products other than LPS and bacterial DNA migrate to the liver and cause NASH.

Intestinal inflammation is also one of the factors contributing to a leaky gut following cholestatic liver injury. An accumulation of TLR2⁺ monocytes in the intestinal lamina propria mediates intestinal barrier disruption by production of TNF in mice. Subsequent binding of TNF to TNF-receptor-I (TNFRI) on enterocytes mediates tight junction disruption in the colon by activation of the RhoA/myosin II regulatory light chain (MLC) pathway. While TNFRI mutant mice are protected from cholestatic liver fibrosis, mice with a reactivation of TNFRI on intestinal epithelial cells partially lose this protection [21]. The cause for the intestinal inflammation is currently not known, although based on the above studies, microbiome changes might cause the intestinal inflammatory infiltrate. Interestingly, mice with cholestasis show no significant dysbiosis, but a rapid onset of intestinal bacterial overgrowth [14]. An increased amount of luminal bacterial ligands might be sensed by intestinal dendritic cells or bacterial ligands might directly activate mucosal innate immune cells triggering intestinal inflammation.

Taken together, dysbiosis might affect intestinal homeostasis by causing intestinal inflammation with subsequent microbial translocation and liver disease progression. On the other hand, there is also evidence that a compromised mucosal immune system contributes to dysbiosis and bacterial translocation.

Paneth cells, specialized cells in the crypts of the small intestine, are part of the mucosal innate immune system. Paneth cells secrete several antimicrobial molecules and contribute to host defense. Compromised Paneth cell antimicrobial host defense seems to predispose to bacterial translocation in experimental cirrhosis. Rats with cirrhosis and bacterial translocation had lower expression of cryptidin 5 and 7 along with a concomitant diminished antimicrobial activity against several commensal strains in the distal ileum, which might contribute to changes in the microbial composition and bacterial translocation [22]. Reg3g belongs to the family of c-type lectins and is an antibacterial molecule secreted by Paneth cells and enterocytes. Reg3g is essential for maintaining a zone that physically separates the

luminal bacteria from the small intestinal epithelial surface. Loss of Reg3g resulted in increased bacterial colonization of the intestinal epithelial surface [23]. Experimental alcohol feeding resulted in a suppression of small intestinal Reg3g expression in mice, while restoration of Reg3g levels with prebiotics ameliorated alcoholic steatohepatitis [13]. Reg3g protein expression was also significantly suppressed in duodenal biopsies from alcoholics as compared to healthy controls [13].

Thus, loss of the host – microbiome symbiosis as a consequence of microflora changes might not only activate the intestinal immune system, but might also suppress an appropriate immune response. On the other hand, intestinal inflammation induces dysbiosis that affects the progression of colorectal cancer in mice [24], although studies demonstrating a link to liver disease are currently lacking.

Microbial metabolites as communicator between the intestine and the liver

The microbiome is being shaped by various influences such as diet, diseases, medication use including antibiotics and the host immune system. The host immune system in turn is affecting the gut microbiome. Such complex interactions are not only simply guided by bacterial PAMPs, but rather through metabolites such as choline or bile acids.

Choline has been known for a long time to be important for the development of experimental fatty liver disease. Animal models have used a choline-deficient diet to induce fatty liver that progresses to a NASH like disease with hepatic fibrosis and inflammation. Conversion of choline into methylamines by microbiota in a susceptible mouse strain reduces the bioavailability of choline and mimics the effect of choline-deficient diets causing NAFLD [7]. This concept has now been verified in humans. When patients are placed on a choline-deficient diet, a *PEMT* promoter SNP rs12325817, which is important in the endogenous de novo synthesis of phosphatidylcholine, and the presence of certain bacterial species predicts the development of fatty liver disease [25]. These data indicate an active role for the intestinal microflora in the development of fatty liver disease.

The liver is communicating to the intestine via many ways, of which bile is a very important one. Bile acids are the primary solute in bile. Intestinal bacteria are known to participate in bile acid metabolism by generating secondary bile acids (deconjugation, dehydroxylation). Secondary bile acids are being taken up in the ileum to enter the enterohepatic circulation. Not surprisingly, germ-free rats showed an altered bile acid profile, which was characterized by predominately taurine-conjugated bile acids with relatively lower unconjugated and glycine-conjugated bile acids in germ-free animals [26]. Bile acids are not only important for absorption of dietary fats, but also as ligands for receptors such as farnesoid X receptor (FXR) and TGR5. Microbial modification of bile acids represents an excellent way through which the microbiome can talk to the host and impact not only liver disease, but also other organs and metabolic pathways. The liver releases high levels of retinol into the bile and bile induces retinoic acid receptor (RAR)-dependent retinol-metabolizing activity in small intestinal dendritic cells. Dendritic cells are imprinted with the ability to generate gut-tropic T cells thus representing a classic example how the liver can alter intestinal immune function [27].

Enterotypes for healthy controls, obese individuals and patients with biopsy proven NASH can be distinguished in a pediatric patient population. On the phylum level, while changes in Firmicutes and Bacteroidetes were similar in obese and NASH patients as compared to healthy controls, Proteobacteria distinguished NASH from obese patients and controls. *Escherichia* is the only abundant genus within the whole bacteria domain exhibiting a significant difference between the obese and the NASH group [28]. Interestingly, blood ethanol levels were significantly higher in NASH patients when compared to healthy subjects and obese patients. The authors speculate that the intestinal microbiome and perhaps *Escherichia* contribute to endogenous alcohol production [28]. Metagenomic, metatranscriptomic and metabolomic studies need to confirm a role for ethanol as a bacterial metabolite in the pathogenesis of NASH.

Conclusion and future directions

Qualitative and quantitative microbiome changes have been characterized in various etiologies of liver disease and represent an imbalanced intestinal homeostasis. The mechanisms of how microflora changes cause a disruption of the intestinal barrier and contribute to liver disease are starting to evolve. The mucosal immune system seems to play a major role in the onset of a leaky gut and in mediating bacterial translocation. An inappropriate activation results in intestinal inflammation with a subsequent disruption of the mucosal barrier, while a suppression of the immune system by means of lower antimicrobial molecules, also facilitates bacterial translocation. We need a better understanding of the mechanisms whereby microflora changes result in an alteration of the mucosal immune system in liver disease. Comparison between germ free and conventional wild type mice subjected to liver disease models will help to delineate its specific role. Alternatively, transplant experiments of the microbiota associated with liver disease, can further support the evidence that the intestinal microflora is the driving force in disease progression. For example, transfer of intestinal microbiota from lean donors increases insulin sensitivity in human recipients with metabolic syndrome [29].

It is general accepted that the microbiome affects host metabolism and contributes to liver disease. However, little is known about how dysbiosis with subsequent metabolic consequences affects liver disease. Metagenomic and metatranscriptomic approaches will determine microbial genes and factors contributing to liver disease pathogenesis. Metabolomic measurements will complement this approach and help identifying metabolites that might be causatively related to liver disease.

A better understanding of the microbiome – host interactions will identify targets for therapy and improve treatment for patients with liver disease. The ultimate goal is to restore eubiosis which might result in restoration of intestinal homeostasis and symbiosis. The microbiome represents a very attractive target for treatment as it is very easily accessible and changeable by dietary factors.

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Abbreviations

FXR	farnesoid X receptor
IL	interleukin
LPS	lipopolysaccharide
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NLRP	NLR family, pyrin domain containing
PAMPs	pathogen-associated molecular patterns
Reg3g	regenerating islet-derived 3 gamma
TLR	Toll-like receptor
TNF	tumor necrosis factor

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Key Points

- Liver disease is associated with an altered intestinal microbiome.
- An imbalanced intestinal homeostasis results in a breach of the gut barrier and subsequent microbial translocation.
- Microbial translocation is an important pathogenic factor in the progression of chronic liver disease.
- Bacterial metabolites play also a crucial role in liver disease.