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Microbiome in liver diseases

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Abstract: Understanding of the gut-microbiota-liver axis is still rudimentary. Over the past year, substantial progress has been made in understanding the complexity of host/microbial interactions in the context of liver disease. In this review, we provide an overview of studies which focus on liver and microbiota published between April 2018 and March 2019. The review includes novel insight in the role of microbiota in obesity, non-alcoholic fatty liver disease, autoimmune liver diseases, and liver cirrhosis. We summarize the impact on hepatocellular carcinogenesis and the influence of various microbiota factors in relation to liver disease and liver function. Finally, we included the new data on fecal microbiota transplantation (FMT) in liver disease.

Keywords: Liver, Microbiota, Microbiome, FMT, NAFLD, Liver cirrhosis, Probiotics.

OBESITY, NAFLD, AND NASH

The interrelation between gut microbiota and liver within the context of non-alcoholic fatty liver disease (NAFLD) and its progression from simple steatosis to the inflammatory form, non-alcoholic steatohepatitis (NASH) is not yet sufficiently elucidated. There are several co-factors that may affect the course of NAFLD, including obesity, but also diabetes, insulin resistance, or presence of liver fibrosis or cirrhosis. Microbiome analysis of 107 adolescent participants revealed an association between gut microbiota in subjects with livers steatosis defined by increased hepatic fat (based on magnetic resonance imaging) and lower alpha-diversity and alteration within microbial taxa including *Bilophila* and *Paraprevotella*[1]. Caussy et al[2] performed gut microbiome analysis of 203 subjects, including twin and family cohorts, encompassing the entire spectrum of NAFLD, including liver cirrhosis, and showed a strong familial correlation of gut-microbiome profiles strongly driven by housing. The authors proposed a panel of 30 features including 27 bacterial features with robust diagnostic accuracy to identify NAFLD-cirrhosis subjects.

Hoyles et al[3] performed a multi-level analysis combining shotgun sequencing of fecal metagenomes and hepatic transcriptomes and urine metabolomes in morbidly obese women from two well-characterized cohorts. Patients with hepatic steatosis had lower microbial gene richness but increased genetic potential for processing of dietary lipids and endotoxin biosynthesis (which associated with an increased representation of Proteobacteria), aromatic and branched-chain amino acids that are predicted to increase liver inflammation. FMT of the feces from subjects with steatosis hepatitis and phenylacetic acid, a microbial product of aromatic amino acid metabolism, was shown to trigger the steatosis phenotype. According to the study, the molecular and microbiome patterns are not only predictive for steatosis phenome but may be actionable for microbiome-based therapies.

Maternal obesity is one risk factor that may predispose to obesity and NALFD in offspring. Soderbourg et al[4] compared germ-free mice colonized with stool from infants born from obese or normal weight mothers and showed that FMT from infants from obese mothers led to an increased inflammatory pattern in the liver and signs of periportal inflammation. Furthermore, they showed that the inflammation was associated with an increased intestinal

permeability, reduced macrophages, and changes within the immune system in germ-free mice. Exposure to a Western-style diet promoted weight gain and accelerated NAFLD progression suggesting that maternal microbes are a crucial factor in establishing obesity-associated infant dysbiosis. Similarly, Wankhade et al[5] studied the influence of HFD-diet in an offspring murine model. They showed that male offspring of HFD treated mice have a hyper-responsive weight gain to postnatal HFD treatment with increases in *Lachnospiraceae* and *Clostridiaceae* families and *Adlercreutzia*, *Coprococcus*, and *Lactococcus* genera detected. Moreover, the mice developed worse hepatic pathology with raised pro-inflammatory cytokines, altered expression of bile acid regulators (Cyp7a1, Cyp8b1 and Cyp39a1) and serum bile acid concentrations. Paul et al[6] investigated NAFLD development in offspring from prebiotic oligofructose treated rats. The dams were fed with a high-fat/high-sucrose diet (HFSD) either with or without prebiotic oligofructose, while the offspring received a long-term HFSD diet without prebiotics. Maternal oligofructose intake was associated with improved glucose tolerance, insulin sensitivity, and hepatic steatosis in the HFSD treated offspring compared to the controls. Prebiotics led to an alteration in gut microbiota composition and inflammatory profile. Additionally, inflammatory and fatty-acid gene expression profiles were ameliorated. The data suggest a link between prebiotic intake and lower hepatic steatosis.

The mechanistic role of diet in NAFLD is primarily studied in animals' models and evidence from human studies is usually by association rather than direct causal evidence. The role of diet has been studied in the cohort of 52 adolescent obese participants 12-19 years old[7]. Dietary assessment was performed *via* 24 h diet recalls and were correlated with body composition and gut microbiome. The authors showed that high-dietary fructose intake was associated with lower abundance of the beneficial microbes *Eubacterium* and *Streptococcus*, which may be involved in carbohydrate metabolism.

High fat diet (HFD) is an established model to study obesity and NAFLD development. HFD is associated with hepatic steatosis, disruption of intestinal barrier, changes in fat and bile acid metabolism and gut microbiota alterations at various extent[8,9]. Mouries et al[10] studied the gut microbiota in a NASH mice model showing that intestinal barrier and gut vascular barrier dysfunction are early and crucial event in the progression of steatosis to NASH. FMT from HFD-fed mice into pathogen-free recipients induced barrier damage and promoted adipose tissue enlargement. Pharmacologic intervention with bile acid derivates and farnesoid x receptor agonists (FXR) obeticholic acid (OCA) protected against gut barrier disruption preventing NASH development[10]. In another elegant study, Thaiss et al[11] studied the role of hyperglycemia in intestinal barrier dysfunction. In mouse models of obesity and diabetes, hyperglycemia was associated with increased intestinal barrier permeability through a GLUT2-dependent transcriptional reprograming of intestinal epithelial cells. Treatment of hyperglycemia, reduction of glucose metabolism or deletion of intestinal epithelia GLUT2 restored the intestinal barrier function and bacterial containment providing a mechanistic link between intestinal barrier and hyperglycemia[11].

In a comprehensive multi-omics study (transcriptomics, proteomics, phosphoproteomics, lipidomics), Kindt et al[12] investigated the effect of intestinal microbial colonization on hepatic lipid metabolism. They demonstrate that microbial colonization affected host fatty acid metabolism. In particular, gut bacteria as a community induced generation of monounsaturated fatty acids leading to substantial alterations in glycerophospholipid acyl-chain profiles. Interestingly, the degradation of dietary fiber leads to synthesis of acetate which is a precursor for hepatic synthesis of C16 and C18 fatty acids and glycerophospholipid species which is released in the circulation. The authors concluded that alterations in the gut microbiota can generate nutritional precursors or intermediate molecules that can be used by other bacterial groups to generate fatty acids that promote inflammation and metabolic disorders. Besides intestinal permeability or gut barrier dysfunctions, direct interaction of the gut microbiota with intestinal cells may affect hepatic steatosis and inflammation. Whitt et al[13] showed that epithelial cells-derived histone deacetylase 3 (HDAC3) promotes the development of diet-induced obesity while bacteria-derived butyrate prevented the development. These findings indicate that the gut microbiota does not only interact with its host *via* the intestinal immune system or *via* bacterial derived components that reach the liver through the portal blood stream but also by a close direct interaction with the gut cells due to epigenetic regulatory factors.

Identification of strategies for prevention or therapy of microbiota-related disease including obesity, diabetes, and NAFLD remain a major challenge. A number of studies have reported the impact of therapeutics, exercise, and various dietary additives in terms of microbiota changes. Brandt et al[14] evaluated microbiota alterations in mice fed with fat-, fructose- and cholesterol-rich diet with a particular focus on the role of metformin in NAFLD development. Metformin treatment was strongly associated with attenuated hepatic inflammation and lipid peroxidation, reduced levels of bacterial endotoxins in portal plasma, and reduced loss of small intestinal tight junction proteins. The protective effect of metformin was additionally associated with changes in intestinal microbiota composition. The benefit of exercise was been studied in the juvenile rat HFD model[15]. Exercise effectively counteracted HFD-induced microbiome changes that were associated with preservation of intestinal barrier, improved bile acid homeostasis, and the NAFLD-phenotype. Microbiome analysis revealed increased *Parabacteroides*, *Bacteroides* and *Flavobacterium* genera and reduction of *Blautia*, *Dysgonomonas* and *Porphyromonas* as potential changes towards a more beneficial metabolomic profile. Camu camu (*Myrciaria dubia*) is a fruit with strong antioxidant and inflammatory potential. Anhe et al[16], using combined metabolic test and microbiome analysis, assessed the effect of camu camu in high fat/high sucrose fed mice (HFHS). Camu camu led to activation from brown adipose tissue and prevented visceral and liver fat deposition. In addition, camu camu-treated mice showed gut microbiota changes, including increased *Akkermansia muciniphila* and a reduction in *Lactobacillus*. The role of camu camu on microbiota was confirmed in FMT experiments in germ-free mice and furthermore linked to the bile acids.

AUTOIMMUNE LIVER DISEASES

The gut microbiota may also contribute to predisposition and progression of autoimmune liver diseases, including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). Manfredo Vieira et al[17] investigated the role of microbiota and autoimmunity. Full-length 16S rDNA sequencing of single colonies from aerobic and aerobic cultures from mesenteric lymph nodes and liver detected *Enterococcus gallinarum*, a gram positive pathobiont, which was also detectable in feces and mucosal tissues in mice. Translocation of *E. gallinarum* in various models to the liver or systemic tissue induced proinflammatory pathways and triggered autoimmune response which may predispose to autoimmunity. Antibiotic treatment suppressed the bacterial growth, ameliorated the Th17-immune response, and prevented mortality in mice model. In similar fashion, DNA of *Enterococcus gallinarum* was found in liver tissue from AIH patients further suggesting that certain microbiota may contribute to the development of autoimmune liver diseases[17].

Nakamoto et al[18] also examined the influence of pathobionts in the development of cholestatic liver disease. They first identified *Klebsiella pneumonia* in the gut microbiota of PSC patients and demonstrated its role in disruption of the epithelial barrier. *Klebsiella pneumonia* disrupted the epithelial barrier to trigger bacterial translocation and liver inflammatory reaction. Transfer of PSC-derived microbiota to a gnotobiotic murine model led to increased infiltration of T helper 17 cells in the liver and the mesenteric lymph nodes. *K. pneumoniae*, *Proteus mirabilis,* and *E. gallinarum* were isolated from lymph nodes and were associated with hepatobiliary injuries caused by TH17 cells and PSC development[18]. Antibiotic treatment ameliorated the immune response to PSC-derived microbiota.

Tedesco et al[19] investigated the role of ABCB4 and MDR2 receptors that are frequently associated with cholestatic liver diseases in the development of PSC. The authors used a Mdr2-/-mice model and studied liver samples from PSC and hepatitis C patients showing that Mdr2-/- mice develop collagen deposition around hepatic bile ducts and periportal-bridging fibrosis which is associated with increased infiltration of the inflammatory cells and high level of IL17. In this model, the development of the disease required *Lactobacillus gasseri* medicated activation of γδ TCR+ cells and production of IL17. The IL17 production was found in cells isolated from PSC patients but not from chronic Hepatitis C virus patients. Using a similar Mdr2-/- murine model, Fuchs et al[20] explored the effect of colesevelam, a bile acid sequestrant, in cholestatic liver disease. The mice received 8-week treatment with colesevelam to disrupt enterohepatic circulation which reduced serum liver enzymes, bile acids and lower proinflam-

matory and profibrogenenic markers which were associated with alterations in microbiota. The authors showed that the treatment was associated with expansion of δ-*Proteobacteria* phylum and a shift from *Clostridiales* to *Lactobacillus* in the *Firmicutes* phyla.

With the aim of characterizing microbial changes and identifying potential biomarkers of early-onset primary sclerosing cholangitis; Iwasawa et al[21] assessed microbial composition of saliva samples from PSC, UC, and healthy controls. Although, the bacterial richness was comparable between the groups, saliva samples form PSC patients showed less *Rothia* and *Haemophilus* in comparison to the control group and lower abundance of *Haemophilus* and more *Oribacterium* in comparison to UC patients. A cross-validation enabled a discrimination between PSC/healthy (AUC 0.742) and PSC/UC (AUC 0.876).

CIRRHOSIS AND LIVER INJURY

Iebba et al[22] performed combined microbiome sequencing and NMR-metabolomics analysis to evaluate the interrelationship between alterations in the gut microbiota and liver cirrhosis. They studied microbiota changes in liver biopsies and feces combined with studies of peripheral/portal blood and fecal metabolites in association with clinical parameters. The results supported the previously reported impaired short-chain fatty acid profiles and carbon/methane metabolic profiles reported in cirrhosis. Specifically, fecal Enterobacteriaceae and trimethylamine were positively associated with increased proinflammatory cytokine levels, while Ruminococcaceae were seen to be protective[22].

Bajaj et al[23] published a series of papers that provided a deeper view on microbial alterations in liver cirrhosis. They investigated liver cirrhosis patients with compensated/decompensated diseases and compared for effects of diet and hospitalization risk. For better comparison, the authors included patients from two geographic locations – US and Turkey. Overall, diet rich in fermented milk, vegetables, cereals and coffee/tea were associated with a higher microbial diversity which was associated with lower risk of hospitalization. Furthermore, the authors studied the link between bacterial and fungi "dysbiosis" in liver cirrhosis patients demonstrating that bacterial and fungal diversity are linked and patients on antibiotics or with culture-positive infection have the lowest diversities[24]. Overall, fungal and bacterial profiles were stable for up to 6 months, but antibiotic treatment significantly reduced the diversity with an increased *Candida* and lower autochthonous bacterial abundance. Increased Bacteroidetes/Ascomycota ratios were associated with lower 90-day hospitalization rates[24]. This role of "dysbiosis" in liver cirrhosis patients was also supported in another study where authors analyzed fecal specimen from hospitalized patients with liver cirrhosis. The "dysbiosis" of the intestinal microbiota on admission was associated with increased risk of extra-hepatic organ failure, acute on chronic liver failure, and death[25].

Alcohol remains one of the main causes of liver cirrhosis, as well as being implicated in alcoholic hepatitis. Puri et al[26] studied the circulating microbiota signature using functional metagenomics in patients with alcoholic hepatitis. They show that high alcohol consumption may be the primary driver in changes of the circulating microbiota. The authors observed an overall increase in 16S copies/ng DNA in the high alcohol group, but also a decreased abundance of Bacteroidetes and enrichment of Fusobacteria. Metagenomics analysis suggested increased isoprenoid synthesis *via* mevalonate and anthranilate degradation, which are linked to Gram-positive bacterial growth and production of biofilms. Alcoholic liver disease is also associated with a dysregulated immune response. Riva et al[27] studied the mucosa-associated invariant T cells (MAIT) in liver cirrhosis and severe alcoholic hepatitis and showed that MAIT cell dysregulation is common in patients with alcoholic liver disease, and the fecal bacteria and antigens contribute to the functional impairment of the MAIT cells.

Akkermansia muniphila has been frequently linked with liver disease. Grander et al[28] reported decreased abundance of *Akkermansia muniphila* in feces of patients with alcoholic liver disease, which was also correlated with hepatic disease severity. In mice experiments, alcohol feeding resulted in a decline in *Akkermansia muciniphila* levels that could be restored by oral supplementation. Surprisingly, in established alcoholic liver disease, *Akkermansia muniphila* showed also therapeutic benefit with reduced hepatic injury and neutrophil infiltration.

HEPATOCELLULAR CARCINOMA (HCC)

Several studies were published with the focus on microbiota changes in hepatocellular carcinoma. Ponziani et al[29] studied three patient groups (healthy, NAFLD with/without HCC) and showed that patients with HCC had higher fecal calprotectin levels but gut permeability was similar to liver cirrhosis patients without HCC. Plasma levels of various inflammatory markers, including IL-8, IL-13, CCL-3, CCL-4, and CCL-5 were elevated in HCC patients. In correlation to above mentioned data, liver cirrhosis patients had a higher abundance of *Enterobacteriaceae* and *Streptococcus* and less *Akkermansia*. In comparison, HCC patients harbored more *Bacteroides* and *Ruminococcaceae* and less *Bifidobacterium*. Interestingly, *Akkermansia* and *Bifidobacterium* were negatively correlated with fecal calprotectin values. Ren et al[30] investigated microbiota alterations in patients with HCC and compared the results with subjects without HCC, including controls and liver cirrhosis patients. Interestingly, the authors observed increased fecal microbial diversity from cirrhosis to early HCC with cirrhosis. Specifically, Phylum *Actinobacteria* and 13 genera, including *Gemmiger* and *Parabacteroides*, were increased in early HCC versus cirrhosis patients. As previously reported, patients with HCC had less butyrate-producing genera and increased lipopolysaccharide-producing genera compared to controls. With an aim to obtain a non-invasive biomarker panel for HCC the authors identified 30 microbial markers that could identify HCC patients in comparison to non-HCC samples with an area under the curve of 80.64%[30]. Ma et al[31] studied the interaction between the gut microbiota and liver carcinogenesis. Using several mouse HCC models they showed that an antibiotic cocktail consisting of vancomycin, neomycin, and primaxin was associated with fewer HCC tumors with the suppressive effect linked to an increase in hepatic CXCR6+ natural killer T cells, increased interferon-gamma production and increased antigen stimulation. Most importantly, microbiota-mediated primary to secondary bile-acid conversation for instance due to *Clostridium* species controlled NKT cell accumulation in the liver. The data provides a strong link between gut microbiota-related bile acid metabolism and immune alterations in the liver[31].

DIET, DRUGS AND ENVIRONMENTAL FACTORS

Gut microbiota composition is influenced by various factors, including host genetic and environmental factors. Rothshild at al[32] examined the genotype and microbiota composition from 1,046 healthy individuals from distinct ancestral origins but who share a common environment. While host genetics had no significant impact on the gut microbiota, individuals who shared a household had common microbiome patterns with 20% of inter-person microbiota variability was associated with factors related to diet, drugs and anthropometric measurements. Using microbiota data, the authors could significantly improve the prediction of human traits, including glucose and obesity measures, compared to alternative models based on genetic or environmental data.

Nutrition is known to play an important role in the development of the triggering microbiome in liver diseases. Xia et al[33] evaluated the effect of lycopene-rich tomato and tomato products in high-fat-diet (HFD) induced hepatocellular carcinogenesis in βCarotene-15, 15'-oxygenase (BCO1), and β-carotene-9', 10'-oxygenase (BCO2) knockout mice. They showed that intake of tomato products was associated with reduced liver inflammation and accordingly reduced rate of hepatocellular carcinoma, but also with increased microbial richness and diversity but decrease in abundance of *Clostridium* and *Mucispirillum*. Dietary soluble fibers are fermented by gut bacteria into short-chain fatty acids (SCFA) and are considered to have heath promoting benefits. Singh et al[34] performed in depth analysis of inulin fermentation and the consequences for the gut microbiota. They found that inulin-enriched high-fat diet but not diet with insoluble fibers induced icteric HCC. Development of HCC was microbiota-dependent and reproducible in multiple strains but not in germ-free nor antibiotic-treated mice. The HCC progression was related to the onset of cholestasis, hepatocyte death followed by neutrophilic inflammation in the liver. Therapeutic intervention using pharmacologic inhibition of fermentation of reabsorption of bile acids with cholestyramine prevented HCC development[34].

Besides the diet, drugs play an important role in the development of liver diseases and influence microbiota composition. Kim et al[35] studied the effect of ursodeoxycholic acid on liver function with a focus on microbiota alterations. Although the number of patients included in

the study was small (n=9), the authors showed that ursodeoxycholic acid was associated with improvement in liver function which was associated with marked decline in *Lactobacillus* and *Bifidobacterium*.

Proton pump inhibitors (PPI) are strongly linked to microbiome alteration in gut. Yamamoto et al[36] found significant differences between PPI treated and non-treated patients with chronic liver diseases. Amongst other things the Child-Turcotte-Pugh score, ascites, encephalopathy, and esophageal varices were significantly higher in patients under PPI treatment. The microbiota of these patients contained more *Lactobacillus*, *Streptococcus*, *Selenomonas*, *Veillonella*, *Campylobacter*, and *Haemophilus* compared to PPI negative patients. Moreover, bacteria like *Eggerthella*, *Paraprevotella*, *Turicibacter*, *Dorea*, *Anaerotruncus*, and *Ruminococcus* were less frequent in the stool samples of PPI treated patients. The authors suggested that PPI-related alterations including related metabolic pathways may enhance the risk for hepatic encephalopathy or spontaneous bacterial peritonitis.

Patients with chronic liver diseases like NASH have higher endotoxin levels in their blood and intestinal overgrowth and increased gut permeability. In this context, Sawada et al[37] investigated the impact of angiotensin-II type 1 receptor blocker (ARB) and probiotics in choline-deficient/L-amino acid-defined (CDAA) fed rats. It is suggested that ARB may suppress activated stellate cells (HSC) and hepatic fibrosis. The authors demonstrated an inhibition of liver fibrosis due to both treatments through different mechanisms, including the direct suppression of HSCs, liver-specific transforming growth factor-β, and TLR4 expression.

Rifaximin as considered as one of the non-classical antibiotics with potential to modulate gut microbiota. Kawaguchi et al[38] studied the effect of rifaximin therapy in patients with hepatic encephalopathy and analyzed the gut microbiome of these patients. The total bacterial load was comparable between before and after therapy (14 days), but *Streptococcus*, *Veillonella*, and *Lactobacillus* were decreased after RFX therapy. There was also an association between gut microbiota and liver/neuropsychological functions. For example, *Streptococcus* was more frequent in patients with portal-systemic shut or *Lactobacillus* was associated with higher blood cell count and impaired aspartate aminotransferase level.

As mentioned above, diet is among the most crucial factors in development of the liver disease. It has been previously shown that dietary lipids promote the growth of the pathobiont *Bilophila wadsworthia.* Natividad et al[39] demonstrated that *Bilophila wadsworthia* synergizes the effect of high-fat diet and promotes intestinal inflammation, dysfunction of intestinal barrier promoting hepatic steatosis, and metabolic dysfunction. Pharmacological suppression, as well as a probiotic treatment, with *Lactobacillus rhamnosus* was associated with inhibition of the *Bilophila wadsworthia*-induced immune and metabolic dysregulation leading to improvement of intestinal barrier and reduced inflammation and providing evidence for potential novel interventional options.

Since the role of probiotics increasingly evaluated in management of liver diseases it is important to mentioned two recent studies[40,41] that provide valuable clues to microbial stability and potential influence of probiotics on its physiology. The authors reliably confirmed that probiotics remain viable following oral supplementation; however, there is a microbiota-driven resistance to probiotic colonization in the murine gut. In contrast, in humans, there is high individual variability making colonization potentially possible. Based on the results of a placebo-controlled 11-strain probiotic trial for a 4-week period the authors identified two main groups that may be permissive or resistant for probiotic colonization which may be predictable by microbiome and host features[40]. In addition, antibiotics significantly enhanced probiotic colonization of human mucosa, while probiotics delayed gut microbiome and transcriptome constitution following antibiotic treatment[41].

FMT

The field of FMT is in its infancy in liver disease. Following the first randomized clinical proof-of-principle trial published in 2017, Bajaj et al[42] performed the first phase 1 study on FMT in patients with decompensated cirrhosis and also provided the extended follow-up data on those patients[43]. The primary outcome was FMT safety in patients with decompensated liver cirrhosis with hepatic encephalopathy (HE) and secondary outcome was an improvement

in short-term and long-term cognitive function and hospitalization. The study had several unique issues to be highlighted. Firstly, the authors performed rational donor selection based on the finding that HE patients showed a relative reduction of *Lachnospiraceae* and *Ruminococcaceae* species compared to controls subjects. Based on those results a single donor was selected to complement those differences and the samples were used for all FMT-assigned participants. Twenty subjects were 1:1 assigned to either FMT-Group (n=10) which consisted of 5-days of antibiotic treatment of broad-spectrum antibiotics (ciprofloxacin, amoxicillin, metronidazole) followed by 90 ml of FMT *via* enema or to standard of care (SOC) group (n=10). All subjects remained on lactulose and rifaximin throughout the study period. Combining the short-term and long-term results, the authors showed a lower number of HE episodes in the FMT-Group, significantly lower hospitalization numbers, improvement of psychometric HE-score (especially in the long-term follow-up) or encephalopathy performance. This clinical picture was associated with microbiota changes in both pre and post treatment analyses, as well increase in the relative abundance of *Burkholderiaceae* and decrease of *Acidaminococcaceae* species in the FMT-group compared to SOC. In another small non-randomized study from India[44], comparison of alcoholic hepatitis patient survival rates following treatment with corticosteroids and either receiving corticosteroids, nutrition, pentoxifylline or FMT were assessed. Although the results of the 30 days follow-up were relative heterogeneous, the data after 3 months showed better survival rates of subjects (n=16) who received FMT, which again correlated with beneficial microbial changes. The results of this study are too preliminary to make any valid conclusions, but further research in this field is warranted, as well as continuing to define the mechanistic basis of microbial manipulation strategies.

CONCLUDING REMARKS

Substantial progress has been made in understanding of contribution of the gut microbiota to liver diseases. Liver-microbiome-axis contributes to the development of metabolic liver diseases, is associated with liver decompensation and contributes to liver carcinogenesis. Deeper understanding of the microbiota may open new therapeutic options as suggested by several studies in mouse models. But also, the encouraging data from FMT-trails carry a hope for new landscape for intervention. Nevertheless, there is an increasing amount of data that requires caution. From one side the procarcinogenic effect of inulin-diet in mouse as well as interaction between pro- and antibiotics in regard to mucosal microbiome clearly highlight the importance of high-quality research needed not only in regard of FMT-studies but also in regard of probiotic trials.

Conflict of interest

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