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Gut-liver axis: Pathophysiological concepts and medical perspective in chronic liver diseases

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List abbreviations: AhR, Aryl hydrocarbon receptor; ASH, alcoholic steatohepatitis; ACLF, acute-on-chronic-liver-failure; ASBT, Apical Sodium-dependent BA Transporter; AUD, alcohol- use-disorder; ALD, alcohol-related liver disease; BA, bile acid; BSH, bile-salt-hydrolase; BT, bacterial translocation; CA, cholic acid; CDCA, chenodeoxy-cholic acid; CHB, chronic hepatitis B; CHC, chronic hepatitis C; DAMP, danger-associated molecular patterns; DCA, Deoxycholic acid; EUS, endoscopic-ultrasound; FABP, fatty-acid-binding-protein; FDA, Food and Drug Administration; FGF, fibroblast-growth-factor; FMO, flavin-monooxygenase; FMT, fecal microbial translocation; FOS, fructo-oligo-saccharide; FxR, farnesoid-x-receptor; GALT, gut-associated lymphatic tissue; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; IBD, inflammatory bowel disease; IL, interleukin; ILC, innate lymphoid cell; HE, hepatic encephalopathy; HFD, high-fat-diet; LBP, lipopolysaccharide-binding-protein; TIPS, transjugular-intrahepatic-portovenous stent; LCA, lithocholic acid; LPS, lipopolysaccharide; LTA, lipoteichoic acid; MASLD, metabolic dysfunction-associated steatotic liver disease; NASH, Non-alcoholic steatohepatitis; MAMPs, microbe-associated molecular patterns; MDR, multi-drug-resistance; NAS, non-alcoholic activity score; NLR, Nod-like-receptors; NK, natural killer cell; PAA, phenylaceticacid; PAGl, Phenylacetylglutamine; PAMPs, pathogen-associated molecular pattern; PBC, primary biliary cholangitis; PBT, pathological bacterial translocation; PPI, proton-pump-inhibitor; PSC, primary sclerosing cholangitis; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis; S/LCFA, short/long-chain fatty acids; TIME, tumor immune-micro-environment; TMA/O, Tri-methylamin-N-oxid; TNF, tumor-necrosis factor; TLR, toll-like-receptor; VH, variceal hemorrhage.

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1. Introduction

"A healthy liver stands on a healthy gut"with the gut and its barriers representing the roots that fuel the liver and expose it to an amazing diverse mixture of gut-derived material/agents, mediators, cells, solutes, gases…….Free title to logo from European Association for Studyof Liver Diseases (EASL)Adapted by Reiner Wiest.

"All diseases begin in the gut". This statement was coined many centuries ago (Hippocrates 370–460 before Christ) and just now over the last years experiences a renaissance with the gut and its involvement in gut-brain [1], -kidney [2], -heart [3,4], -lung [5], -muscle [6] and –"organ" [3] being in the focus of many basic and clinical scientific investigations. The gut-liver-axis has been addressed by multiple excellent reviews before [7–12]. This article provides our perspective as clinical scientists on the pathophysiological role of the gut-liver-axis for triggering and/or aggravating liver diseases. Chronic liver diseases are a major global health burden and account for approximately 2 million deaths per year worldwide[13]. Underlying etiologies in chronic liver disease comprise alcohol related steatohepatitis (ASH), non-alcoholic steatohepatitis (NASH, newly defined as metabolic dysfunction-associated steatotic liver disease=MASLD), viral (Hepatitis B; HBV and hepatitis C; HCV) related chronic liver disease as well as autoimmune and cholestatic diseases.

The liver as largest gland of the body is at the nexus of host-microbial interactions [14] and is perfectly equipped and trained for an amazing diversity of functions. It is tempting to speculate that any of its functions that are essential for metabolism, energy storage and detoxification, are modulated, regulated and/or influenced by the gut. For good reason, the liver hosts the largest population of macrophages shielding the host from dissemination of gut-derived material entering via the portal vein. In fact, a myriad of substances produced by intestinal microbes, nutrients absorbed through the intestine, and gut-derived molecules if traversing the muco-epithelial and gut-vascular barriers access the portal venous circulation and reach the liver "unfiltered". The liver is known, for long, to be central for body metabolism, first suggested by Jeff Gordon's group who showed its key role for energy harvest from the diet and impact on energy storage [15,16], also holds true for the microbiota. Hence, it is no surprise to see the gut and liver "talk" to each other and act in concert along the gut-liver-axis. The languages by which the gut and liver communicate are multiple. These include incoming (=afferent) microbe-associated molecular patterns (MAMPs), mainly gut-derived metabolites (e.g. short chain fatty acids (SCFA) trimethylamines, ammonia), pathogen-associated molecular patterns (PAMPs), gut-derived- hormones, -cytokines and -neurotransmitters which unequivocally modulate functional status and response pattern of the liver, as well as, feedback (=efferent) by the liver through the enterohepatic circulation (e.g. bile acids (BA)), but also immunoglobulin A.

The liver and gut have to be seen as one "orchestra" acting together in concert being responsible for energy homeostasis and generating the serum metabolome as one functional unit. Considering such vast physiological and hence, pathophysiological relevance of the "gut-liver-organ" requires some notes of caution, regarding evidence available in terms of clinical entities and liver diseases. In animal models, standardized housing, nutrition and genetic background, excellent molecular biology and sophisticated visualization tools, enable researchers to address specific questions under homogenous conditions by multiple precise approaches. However, even under such controlled conditions major seemingly robust findings are not reproduced, due to lack of exposure to "wild life background" conditions in animal vivarium around the world as has been elegantly introduced by the concept of "wildlings" [17,18].

In humans, not only "wild life" affects physiology, but also a myriad of add-on confounding factors from genetic host signature to nutrition and full exosome. This and the amazing complexity of interacting systems and mediators renders dissection of individual precise targets exclusively, difficult in humans. This most likely is the basis for frequent failures of promising logical therapeutic and/or preventive attempts in clinical trials. In fact, only 1 in 10 drugs being developed reach the market [19]. Finally, the lack of diagnostic tools to assess the gut-liver-axis hampers translational research and hinders dissecting individual pathways involved in liver and other disease states. Nonetheless, available data will be summarized and scrutinized, in the perspective of therapeutic approaches related to the gut-liver-axis.

2. Microbiota – complex diverse source of stimuli for the gut-liver axis

The liver harbours the largest reticuloendothelial system of the human body that is constantly exposed to gut-derived stimuli. Therefore, in healthy conditions, the liver has a highly tolerogenic environment with close immune regulation enabling efficient clearance of pathogenic organisms, while avoiding severe responses against non-pathogenic antigens. The microbiome has gained much attention particularly in terms of fueling and shaping the gut-liver axis. Microbiota includes prokaryotes (archea and bacteria) as well as eukaryotes (e.g. fungi) and viruses (actually outnumbering bacteria in the gut and mostly being bacteriophages that do infect bacteria). The function of microbiota is vastly more important than the taxonomic boundaries between them and thus, where possible, we do try to delineate the role of specific microbial products and metabolites within the gut-liver-axis, rather than discussing associations between bacterial species and disease states. Moreover, reduced microbial diversity (denominated alpha-diversity) and what is called "dysbiosis" is an almost generic finding in most liver diseases investigated and difficult to delineate in terms of specificity for individual disease types. However, it appears conceivable that such less diverse microbiota may represent an ecosystem with reduced resilience to cope with and eventually oppose disease development and/or complications.

Most human investigations on microbiome composition and changes associated with disease states and severity have been performed by sequencing parts of the bacterial 16 S ribosomal RNA (rRNA) gene which usually can define what bacteria are present only at genus level. In contrast, species-level resolution can be obtained from shot-gut sequencing of the whole metagenome, in which all microbial DNA is sequenced and abundance of various genes is analysed [20]. This method also delivers more accurate functional profiling and the possibility of discovery of previously unknown strains of bacteria [20]. In addition, the majority of human studies investigated feces and, to some degree, mucosal colorectal biopsies which in most instances have been taken after bowel preparation, but rarely at natural conditions. Bowel purging to prepare for endoscopy however, vastly affects bacterial load,

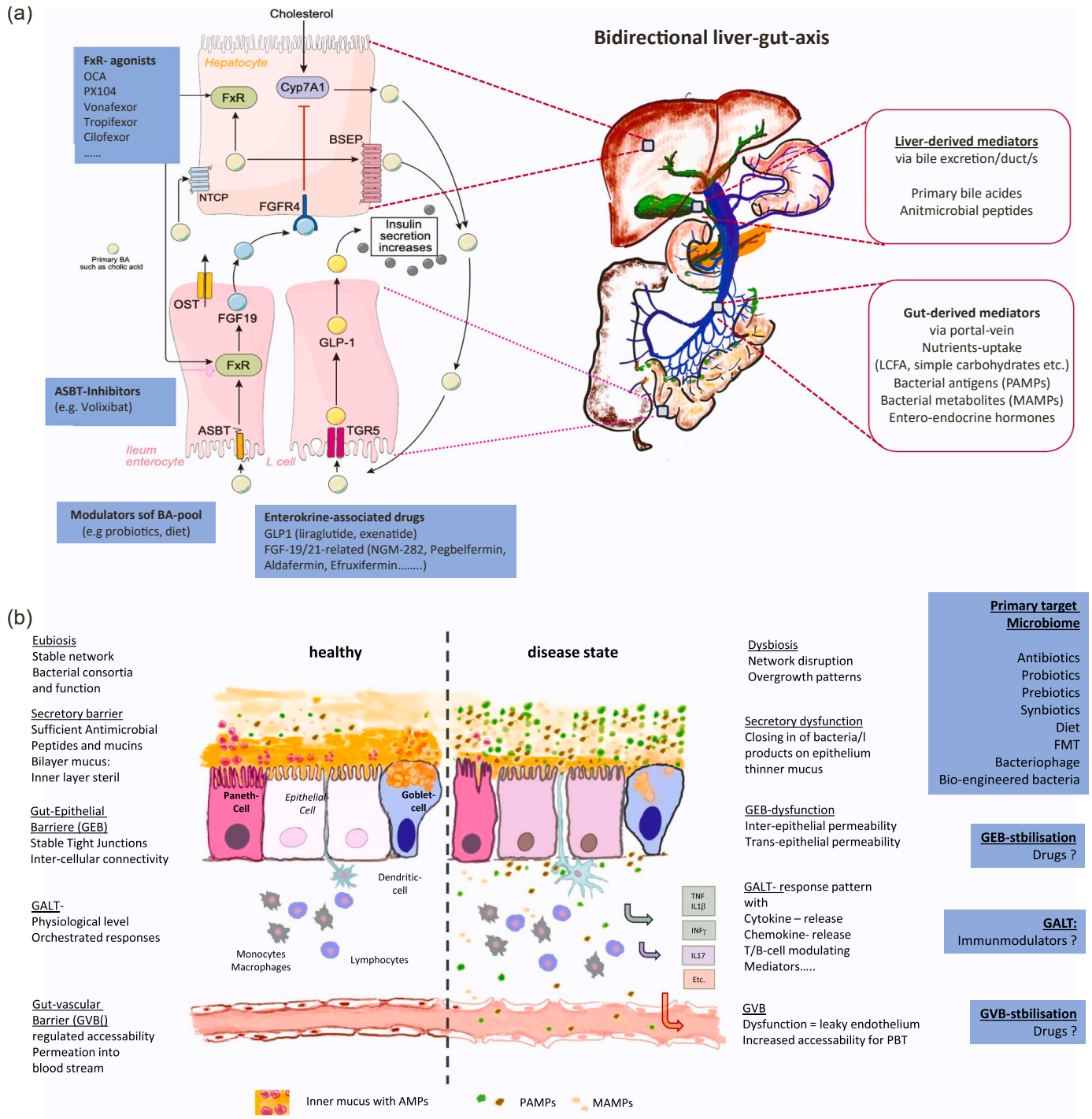

Fig. 1. A: Bile acid (BA) enterohepatic circulation, signalling and related drugs (Left). BAs secreted from hepatocytes (e.g primary BA) are undergoing enterohepatic circulation. They are absorbed in the terminal ileum by apical sodium-dependent bile acid transporter (ASBT), leading to fibroblast growth factor (FGF) 19-synthesis via farnesoid-X-receptor (FXR)-stimulation. FGF19 on hepatocytes leads to feedback inhibition of de novo synthesis of primary BA, via inhibition of the rate limiting enzyme Cyp7A1. The microbiota modulates the BA pool luminally by generating secondary BAs such as deoxycholic acid (DCA), which in the colon passively cross the epithelial barrier. **Bidirectional Gut-liver-axis (right):** with liver-derived mediators being excreted via bile and delivered through bile duct into the intestine including but not limited to primary bile acids and hepatic antimicrobial peptides. Gut-derived mediators include besides absorpted nutrients (e.g long-chain fatty acids/LCFA, simple carbohydrates, cholesterol, ethanol) also a myriad of bacterial metabolites/MAMPs (e.g. phenylaceticacid/PAA or Ahr-agonists, imidazoles, methylamines such as TMA etc.) antigens (PAMPs e.g lipopolysaccharide, peptidoglycans), FGF`s (15, 19) and entero-endocrine hormones (GLP-1, PYY etc.). Fig. 1**B: Intestinal hyperpermeability and response patterns.** Bacterial overgrowth and/or dysbiosis in presence of disruption of the gut mucosal barrier due to factors such as injury to the enterocytes or reductions in secretory barrier (e.g mucus or antimicrobial peptides) facilitate translocation of PAMPs (e.g LPS, LTA, Peptidoglycan, Flagellin) and MAMPs (e.g PAA, TMA, indole/-derivatives and kynurenine/-acid etc.) into the lamina propria and gut-associated lymphatic tissue (GALT). The response within the GALT depends on multiple factors and can include alterations in release of multiple cytokines (e.g TNF, IL8, IL17, IL22, IL33 etc.) affecting most likely itself the gut-epithelial (GEB) as well as gut-vascular barrier (GVB). Dysfunctional GVB finally permits and eases access of translocating agents into the portal-venous circulation.

(a) Modified from [62]. (b) Most likely many drugs do affect GEB, GALT and/or GVB but have not been assessed for this (due to limited diagnostic measures). Modified from [12].

as well as, microbiota composition [21]. Moreover, data on small intestinal microbiota are scarce, and those on the mucus-compartment at any site, absent. Mucus has been shown recently to harbor bacteria that are different from the luminal microbiome in terms of functions, behavior and replication [22]. The so-called autochthonous microbiome was proposed to be resident in the mucus (and/or associated to the mucosa). In more detail, recent animal data demonstrate that even the same bacterial species, in the same host, activates different metabolic pathways (transcriptomic assessment) depending on its site of living, namely in the lumen versus in the mucus [22]. More recently, a study showed that within-host evolution of bacteria may lead to niche colonization and mucosal adherence leading to host immune evasion [23]. In this study, acquired microbial mutations facilitated translocation and initiation of inflammation within bowel and liver. In fact, the same bacterial species within the same host diverged into independent lineages. One of which adapted to colonize mucus/mucosa-associated compartment, evading detection and clearance by the immune system, and concomitantly exhibiting increased translocation [23]. Thus, more high-quality trials utilizing shotgun sequencing and addressing the mucus/ mucosa-associated compartment, at natural conditions, in clinically well-phenotyped patients should be encouraged.

The list of microbiome- and gut-derived stimuli for the liver is extensive, most likely not yet completely unraveled and beyond the scope of this review. In brief, pathogen-associated molecular patterns (*PAMPs*) are a set of molecular motifs that are present on the surface of various classes of microbes recognized by pattern-recognition receptors (PRR) such as Toll-like-receptors (TLRs) or NOD-like receptors (NLRP3, NLRP6 etc.) to promote hepatic inflammation and tissue injury. A vast array of different types of molecules can serve as PAMPs, including glycans and glycoconjugates. Bacterial lipopolysaccharides (LPSs), endotoxins found on the cell membranes of gram-negative bacteria (recognized by TLR4), are considered to be the prototypical class of PAMPs. Other PAMPs include bacterial flagellin (recognized by TLR5), lipoteichoic acid (LTA) from gram-positive bacteria (recognized by TLR2), peptidoglycan (recognized by TLR2) or unmethylated CpG motifs from bacterial DNA, recognized by TLR9. However, not only microbiota, but also processed food, contain stimuli for TLRs potentially promoting liver inflammation [24]. In addition, danger-associated molecular patterns (*DAMPs*) are also known to stimulate TLRs involved as molecular triggers of sterile inflammation in the liver [25]; however, the gut-derived contribution of these DAMPs is largely unknown.

Finally, also microbe-associated molecular patterns (*MAMPs*), mainly microbe-derived metabolites have been shown to exert various metabolic [26] and immune-modulatory actions [27]. For instance, most prominently and early on, rapamycin (isolated from Streptomyces) was found to modulate liver injury to various insults [28,29]. Rapamycin complex 1 (mTORC1) is targeted also by microbially produced histidine- derived metabolite imidazole propionate which is present at higher concentrations in diabetes type 2 and mostly in the portal vein [30]. Increased activation of mTORC1 is observed in livers from subjects with type 2 diabetes, and imidazole propionate impairs glucose tolerance directly linking this MAMP to the liver and diabetes type 2 [30]. However, many further and more recent pathways have been delineated, such as derivatives of aromatic amino acids (phenylalanine, tryptophane), Phenylacetylglutamine (PAGln), phenylaceticacid (PAA) or Ahr-agonists, as well as, methylamines such as TMA/O deserve attention. Phenylacetylglutamine (PAGln) stems from phenylacetic acid (PAA) produced by microbiota from phenylalanine and conjugated to the amino acid glutamine (Gln) by liver enzymes [31,32]. PAGln has recently been shown to signal through adrenergic receptors effectively simulating catecholamine-like actions namely, associating with cardiovascular disease and incident major adverse cardiovascular events (myocardial infarction, stroke or death) [32] and heart failure [33]. In other words, besides the sympathetic nervous system [34] and mononuclear cells [35], well-known sources of catecholaminergic agents, the "gut-liver-organ" is a rich source as well. To what degree PAGln exerts adrenergic action intrahepatically is currently unknown, but deserves attention considering the well-known modulation of liver functions by adrenergic signalling [36–38]. Interestingly, PAA has been demonstrated to induce liver steatosis [39]. Two-week treatment in mice vastly increased hepatic triglycerides and plasma metabolic profiling in a large cohort of morbidly obese women revealed the strongest association with liver steatosis for PAA [39].

Metabolization of tryptophan by gut bacteria produces indole/-derivatives and kynurenine/-acid some of which bind the aryl hydrocarbon receptor (AhR) [40,41]. Experimental data strongly indicate AhR-signalling to be crucial for maintaining intestinal barrier integrity and intestinal immunity, at least partly via IL-22 pathway [42]. On the other hand, AhR-signaling exerts direct effects within the liver involved in dampening LPS-induced inflammation [43] as well as diet-induced lipogenesis [44]. Reduced microbiome-derived AhR-agonist production can attenuate IL-22-production and subsequent intestinal inflammation [45] and has been linked to metabolic syndrome, fatty liver and alcoholic hepatitis [46,47]. Although the statement "you AhR what you eat" [48] may overrate its relevance, recent progress indicates AhR signaling as a valid target for gut microbiota intervention in liver diseases [41,49].

Trimethylamine (TMA) is generated exclusively by the gut microbiota from dietary choline, betaine, and L-carnitine. TMA is absorbed in the intestines and delivered to the liver where it is converted to TMAO by hepatic flavin monooxygenases (FMO-1 and-3). High-fat exposure as well as TMA per se can stimulate hepatic FMOs [50]. TMAO increases expression of pro-inflammatory genes, adhesion molecules and chemokines in various models [51], can activate NLPR3 inflammasome and induces oxidative stress [52]. Thus, TMAO undoubtedly contributes to the occurrence of chronic inflammation, promotes platelet hyperreactivity and impairs vascular function inducing atherosclerosis and cardiovascular disease [53]. In terms of liver diseases, TMAO are involved in the pathophysiology of MASLD [54], alcohol-related liver disease [55], acetaminophen-induced liver injury [56] as well as gallstone formation [57].

Although quantitative and comparative measures are missing, it is tempting to speculate that the "gut-liver"-organ may well represent the largest source of stimuli for internal, nuclear, as well as, cell-surface receptors of any kind within the human body.

3. Intestinal barriers and communication within the "gut-liver-organ"

The gut-liver-organ consists of liver, stomach, small and large intestine being supplied by the splanchnic blood circulation [58] of which the portal venous system drains the gut exclusively into the liver. However, arterial blood supply to the liver completes sinusoidal perfusion and thus, gut-derived substances not only via portal-venous but also lymphatic [59] route and the systemic circulation enter into the liver.

3.1. Bile acids as common "language" for communication between liver and gut (Fig. 1A)

(Fig. 1) Bile is produced by hepatocytes, secreted into the duodenum and actively reabsorped by the intestinal epithelium in the terminal ileum and transported back through the portal vein to the liver as part of the enterohepatic circulation. The hepatocytes synthesize the primary bile acids (BA), which include cholic acid (CA) and chenodeoxycholic

acid (CDCA) being mainly secreted as conjugates of taurine (T) or glycine (G). BAs act as hormone-like signalling molecules that serve as ligands for various receptors among which farnesoid X receptor (FXR) and TGR5 (also known as GPBAR1) have gained most attention [60]. De novo BA synthesis is tightly regulated by a direct feedback inhibition by sensing the available pool of BAs in both the liver and the ileum. FXR activation by BA in the liver facilitates repression of CYP7A1 as the rate-limiting enzyme in BA synthesis. In addition, ileal BA-uptake by Apical Sodium-dependent BA Transporter (ASBT) leads to FXR activation and release of fibroblast growth factor (FGF) 15 (mice)/19 (humans) which also inhibits hepatic BA synthesis [60]. FGF15/19 acts through the FGFR4/Klotho-β receptor complexes in the liver to inhibit CYP7A1 [61].

3.1.1. BA and microbiome are heavily interacting and modulating each other

Enteric bacteria via i) exerting bile salt hydrolase (BSH) activity which deconjugates conjugated BA (removing glycine and/or taurine) and ii) 7-alpha-dehydroxylation which forms the secondary BA deoxycholic-acid (DCA) from CA and lithocholic acid (LCA) from CDCA. In addition, BA do undergo other extensive bio-transformations such as dehydrogenation and epimerization executed likewise at least partly by the microbiome generating multiple diverse BA/-metabolites [63,64]. Mono-colonization of germ-free mice with E. coli increases total serum BA pool evidencing that the microbiota substantially influences bile metabolism [29].

Overexpression of cloned bacterial BSH in the gastrointestinal tract of mice reduced total BA pool via reduction of taurine- conjugated murine CA which are known potent FXR antagonists and hence, impact the hepatic feedback inhibition of de-novo BA-synthesis. On the other hand, BA actively influence microbial composition [65–67]. Feeding CA to rats or GCA/TCDCA to mice induces changes in coecal/fecal microbial consortia similar to those observed in HFD-induced obesity [68,69]. These important synergistic and interdependent effects of BA-composition and microbial diversity do have profound consequences for the gut-liver axis. The BA-microbiome-network is setting the stage for translating dietary input to the gut into a common language namely BA/-metabolites delivering messages to the liver, the gut and most likely to any other organ.

3.1.2. BA-effects and gut-liver-immune traffic

BA/-metabolites regulate host specific metabolic pathways, modulate inflammation and shape the host's immune landscape [12,70]. Particularly secondary BA, being highly hydrophobic and toxic, in increased concentrations in the liver have been linked to inflammation, cholestasis and carcinogenesis [71]. Recent years have seen mounting evidence underscoring the role of BA for lipid, glucose and energy metabolism [60,72].

Enhanced bacterial BSH- activity in the gut reduced weight gain, serum cholesterol and liver triglyceride in response to normal as well as HFD in mice [73,74]. This represents one possible mechanism through which the microbiota (via BSH-activity) modulates bile and hence, host metabolism. BA^s are also important direct and indirect regulators for secretion of appetite and metabolism-regulating *gut-derived hormones* [75] e.g as inducer of glucagon-like-peptide-1 (GLP-1) [32]. In addition, BA induce thermogenesis increasing energy expenditure by promoting thyroid hormone activation [33]. These systemic effects of clear basic physiological and thus, pathophysiological relevance underline the far reaching and potent effects of BA/metabolites within but also beyond the gut-liver-axis. Finally, BA/metabolites influence innate [76] and adaptive immunity [77]. Most recent elegant investigations demonstrate that BA-metabolites control Th17/Treg-cell differentiation [78,79], modulate gut RORγ+ regulatory T cell homeostasis [80] and regulate dendritic cells attenuating autoimmune phenomena [81]. Data on effects of BA on B-cells are scarce but has been shown to potentially influence vaccination results negatively [82]. Important to realize is the bi-directional interaction since vice versa infiltrating T-cell in the liver can control bile acid metabolism as shown in a murine model of cholangitis [83].

3.1.3. FxR as example of multi-level effector within the gut-liver-axis

FxR is highly expressed in hepatocytes, intestinal cells as well as to some extend in monocytes and lymphocytes [84,85]. It serves as a sensor of intestinal BA's and protects hepatocytes during cholestasis [86]. Moreover, FxR strongly modulates intrahepatic metabolic signalling [87] and liver inflammation [88] as well as liver regeneration [89]. In more detail, hepatocellular FxR-stimulation increases hepatic glycogen synthesis and fatty-acid oxidation, reduces gluconeogenesis, lowers insulin resistance as well as triglyceride-synthesis and VLDL-export [87]. These clinically beneficial effects come along with undesired effects such as a pro-atherogenic lipid profile, pruritus and hepatocellular toxicity under certain conditions [90]. The hepatic effect of FxR-stimuation on cholesterol ester transfer protein increases serum LDL cholesterol levels and decreases HDL cholesterol [91] both known to act pro-atherogenic. An under-appreciated function of FXR is its effect on the gut where it has been shown to exert multiple actions preserving the intestinal epithelial as well as gut-vascular barrier [76,92,93]. In fact, FxR-activation has been shown to prevent dysfunction and/or breakdown of barrier integrity in animal models of sepsis [94], liver cirrhosis [93], cholestasis [95] as well as colitis [92]. This protection of gut barrier function most likely is at least partly attributable to the anti-inflammatory effects of FxR reflected in the baseline pro-inflammatory profile as well as increased suscepatibility for pro-inflammatory insults in FxR-knock-out animals [96], [97]. Accordingly, FxR-activation has been demonstrated to decrease bacterial and endotoxin-translocation and/or FITC-dextran leakage from the gut [93, 98]. Thus, FxR exerts multiple diverse different actions within the liver and the gut.

Other examples of communication within the gut-liver-axis illustrating clearly the close interaction with consequences on the liver emerging from a cascade of events not being apparent on first sight relates to cytokines IL22 and IL33. IL-22 can be produced by a wide variety of innate and adaptive immune cells, of which the gut-associated lymphatic tissue is the largest reservoir in the human body. In conditions of impaired intestinal barrier function, such as MUC2 deletion and deteriorated mucus layer plasma IL22 levels increase multi-fold [99]. IL22 exerts multiple protective effects within the liver including enhancement of innate immune response to pathogens, suppression of fibrogenesis, stimulation of antimicrobial proteins and induction of hepatocyte regeneration and proliferation [100]. IL33 is released by macrophages, dendritic cells and modulates serotonin-release by entero-chromaffine cells [101] with hepato-protective effects promoting liver regeneration in response to injury, attenuating fibrosis and modulating immune responses [102].

3.2. Intestinal permeability and concept of "leaky gut" challenging the liver (Fig. 1B)

3.2.1. Site of permeability changes

The gut barriers in healthy conditions protect the host from potentially harmful metabolites, bacteria and their antigens. Although ill-defined intestinal hyperpermeability is thus, considered an important pre-requisite for increased namely, pathological translocation of these agents. In general, intestinal hyperpermeability should be specified for the type of agent with its permeation being para- or transcellular and site of its occurrence [103]. In fact, hyperpermeability for one agent does not necessarily unequivocally translate into increased translocation for other molecules. Moreover, the small bowel appears to have a greater potential to promote pathological translocation for bacteria and/or bacterial products (BT). Indeed, with equivalent concentrations of E. coli, significantly higher rates of BT have been observed from the small bowel compared with the large bowel [104,105]. This is well in

accordance with the proposed essential role of MAMPs/metabolites and BA/derivatives which mostly permeate and/or are absorbed within the small intestine [106]. In contrast to the colon, being mainly a fluid absorbing organ preparing condens feces the small intestine is prepared for food digestion and absorption [107,108]. For this function the small intestine presents with lower electrical epithelial resistance, higher permeability (e.g. for solutes, ions) [109] and is equipped with diverse sets of enterochromaffin cells and specialized gut-associated lymphatic tissue, e.g. inter-epithelial lymphocytes orchestrating intestinal homeostasis.

3.2.2. The principal mechanisms

involved in promoting bacterial translocation (BT) are (a) an alteration of the microbiome, resulting in bacterial overgrowth and/or dysbiosis; (b) disruption of the gut mucosal barrier, for example, by injury to the enterocytes or factors limiting the secretory barrier (e.g. mucus or antimicrobial peptides) and (c) an impaired host defence, mainly within the gut-associated lymphatic tissue. Particularly the microbiome and its multiple diverse functions emerged in recent years as a key rheostat within the gut-liver-axis. Microbes that can maximize energy production in a specific environment will overgrow and because respiration yields more energy than fermentation (usual bacterial action in colon) availability of luminal oxygen is decisive. Therefore, weakened host control over microbial growth via increased luminal oxygen availability e.g. induced by western diet have been proposed as one potential underlying mechanism [110]. In addition, during inflammation, the intestinal epithelium produces antimicrobial products to impede bacterial growth, of which reactive oxygen species do allow *E. coli* to respire in an otherwise anaerobic environment and thus, also promotes the outgrowth of *E. coli* [111]. This at least partly can explain the frequently observed increased abundance of *Proteobacteria* (of which *E. coli* as *Enterobacteriaceae* is a typical genus) in many liver diseases with presence of any level of intestinal inflammation.

3.2.3. Physical and biological functions of intestinal epithelial cells

maintain the gut barriers e.g via secretion of mucus, IgA and antimicrobial peptides and expression of inter-cellular junctions (e.g. tight-junctions) [112]. Importantly, BA/derivatives [113], PAMPs (e.g. LPS) [114], MAMPs [115] and most pro-inflammatory cytokines (e.g. TNF) [112] each do impact on epithelial inter-cellular junctions underlining the complexity in regulating this line of defence against pathological BT.

Commensal bacteria contribute to maintenance of the muco-epithelial barrier by various mechanisms such as stimulation of mucus and antimicrobial peptides as well as the production of short-chain-fatty acids (SCFAs) [116]. SCFAs are produced by microbial fermentation of non-digestible carbohydrates, mucin-associated glycans or protein fermentation [117]. Bacterial degradation of dietary fibres leads to large amount of acetate (C2), propionate (C3) and butyrate (C4) the three main SCFA (60:20:20 mM/kg reaching up to a combined concentration of 50–150 mM in human colon) [118]. SCFA^s are efficiently taken up by intestinal epithelial cells representing the main energy source for colonocytes (mainly butyrate), contributing to epithelial proliferation and differentiation as well as gut endocrine function [117]. Butyrate also increases VO2 by coloncytes via stabilizing transcription factor HIF favoring physiologic hypoxia in the colon [119]. In addition, butyrate directly reinforces epithelial tight-junctions, increasing in-vitro trans--epithelial resistance and reducing intestinal permeability [120]. Besides barrier functions SCFAs affect a broad range of other intestinal functions such as motility [121], gut macrophage phenotyp/function [122] as well as host and specifically liver metabolism [117] but also is involved in regulation of satiety [123]. As for the latter, butyrate and propionate in contrast to acetate are almost completely extracted by the liver [124] underlining their relevance within the gut-liver-axis. Finally, proprionate and butyrate can inhibit proliferation of lymphocytes opposing inflammation [125]. As for more details on each of the components determining intestinal barrier function the reader is referred to excellent recent reviews [126].

3.2.4. Diet and intestinal hyperpermeability

The diet has emerged as one of the most potent triggers impairing gut barriers and linking dietary stress and related microbial dysbiosis to low-grade inflammation [127]. High-fat-diet (HFD) within several days induces dysbiosis, impairs gut barriers and triggers endotoxinemia in healthy volunteers [128,129]. This “metabolic endotoxinemia” seems very attractive explaining multiple aspects of the pathophysiology of MAFLD and experimental data utilizing antibiotics in mouse models [130] support its application but clinical evidence so far is less clear. This may well reflect the vast complexity of interacting systems influencing each other and hence, shall be exemplified for LPS-translocation and -effects within the gut-liver-axis. Besides goblet cell-associated and chylomicron-pathways [131] the bulk of LPS have been shown recently to be taken up from the gut lumen via lipid-raft mediated mechanisms [132] directly delivered to the portal vein. Most interestingly, in presence of fat increased uptake of LPS seems to occur [132] reflected in dietary lipid facilitating LPS absorption and corresponding observations of high-fat meal acutely increasing circulating LPS levels in human healthy volunteers [133]. Intestine-derived HDL-subtype HDL3 by interacting with LPS-binding-protein (LBP) sequesters LPS in the portal venous blood stream forming the HDL3-LBP-LPS complex which is not recognized by liver macrophages, thus preventing LPS binding to and activation of liver macrophages [134]. Loss of intestine-derived HDL worsened liver injury in response to alcoholic or dietary insults underlining the importance of gut-derived substances for protection of the liver and keeping the gut-liver-axis in balance. Finally, effects of LPS within the liver affect any cell typ, do occur via TLR4 but also TLR4-independent and depend not only on concentration, receptor-affinity but also priming, timing, clearance and susceptibility. For instance, LPS clearance through liver sinusoidal endothelial cells involves endocytosis and lysosomal inactivation via Stabilin-1 and 2 (Stab1 and Stab2) but does not involve TLR4 [135]. Thus, the rate, severity of LPS-translocation as well as LPS effect on various cells depends on a large variety of influencing factors creating vast heterogeneity in the human pathophysiology of liver diseases.

4. Diagnostics assessing gut-liver-axis in humans

4.1. Non-invasive assessment of microbial gut function

has been shown to be feasible by utilization of novel methods like transcriptional recording by CRISPR spacer acquisition from RNA endowing engineered *E. coli* with synthetic memory that through Record-seq can deliver transcriptome-scale records [136]. These *E. coli* after oral gavage and passage through the intestine capture non-invasively interactions with diet, host and other microbes, which can be dissected from feces. Besides multiple advantages, this method archives information of gut function along the length of the intestine which so far has been refractory to studies due to its rather inaccessible location. Application of such sentinel cells has already been used in mice as noninvasive living diagnostics for gastrointestinal diseases [136–138]. Although not yet available and no trials registered simply reflecting the potential use of this method in translational medicine seems outstanding.

4.2. Sugar tests

In humans, intestinal permeability can be assessed by a variety of techniques [139,140]. Most commonly used is the assessment of the differential urinary excretion of orally administered non- metabolizable sugars, which are known to pass paracellularly or transcellularly through the epithelium. This provides a specific index of intestinal permeability and by using different sugar probes (sucrose, lactulose, L-rhamnose, erythriol and sucralose) gastro-duodenal and colonic

permeability can be assessed individually [139]. The use of sugar-tests for intestinal permeability measurements has shown to detect hyper-permeability in various disease states including but not limited to inflammatory bowel disease (IBD) [141], MASLD [142,143] or liver cirrhosis [144]. The diagnostic add-on value of these sugar-tests in IBD can be appreciated by reflecting disease activity [141] predicting disease flares [142,143] and even the development of Crohn's disease [145]. Thus, these tests should be used more widely. However, potential confounders affecting the read-out like intestinal transit time, -dilution, blood flow, renal function and bacterial degradation do limit the applicability in certain circumstances [146]. Finally, practical issues like the necessity of overnight fast and several hours of urine collection are responsible for the lack of acceptance and limitation of its use to mostly academic tertiary referral hospitals.

4.3. Biomarkers

in serum reflecting increased intestinal permeability and/or bacterial translocation include among others zonulin, fatty-acid-binding-protein (FABP), LPS and LBP [147]. Zonulin (47 kDA), an endogenous human analogue of the bacterial enterotoxin zonula occludens toxin has emerged as popular serological marker of intestinal barrier function. However, the assays available have been reported not to detect zonulin (prehaptoglobin-2) but the levels of haptoglobin and complement factor C3 [148]. Intestinal fatty-acid binding protein (I-FABP) is a cytosolic protein in epithelial cells of the mucosal layer of the small intestine tissue involved in cellular uptake and metabolism of fatty acids. When intestinal mucosal damage occurs, I-FABP is released into the circulation and its plasma concentration increases [149]. Increased serum I-FABP has been identified as marker of disrupted gut permeability in intestinal ischemia-reperfusion [150], necrotizing enterocolitis [151] typ-2-diabetes [152] as well as liver cirrhosis [153]. In contrast to other intestinal inflammatory diseases, plasma I-FABP levels were decreased in experimental models of HFD [154] shedding some doubt on its universal usage. Endotoxins like LPS, present in the outer membrane of most gram-negative bacteria, have been implicated as marker of BT. Small amounts of LPS (< 5 pg) have been detected in the blood stream of healthy individuals without side effects (134). Moreover,during HFD otherwise healthy individuals did present with temporarily increased serum LPS levels (135). However, methodologies used for LPS-measurement have been criticized for being imprecise and results being contradicting (130). In fact, levels of LPS in blood stream vary considerable between methods and individuals (136. In addition, it is not evident whether the LPS detected by the assays is biologically active. This and available methodology has recently been reviewed by Munford [155]. Lipopolysaccharide-binding-protein (LBP) is a soluble acute-phase protein that binds to bacterial lipopolysaccharide (or LPS) to elicit immune responses by presenting the LPS to important cell surface pattern recognition receptors called CD14 and TLR4y[156]. LBP is synthesized by the liver, adipose tissue, and intestinal cells and has been proposed to be the better biomarker of plasma LPS than LPS itself due to the above-mentioned reasons as well as the short half-life of LPS. Moreover, LBP shows very low intraindividual variation over time indicating its use as robust surrogate marker of intestinal permeability [157]. Increased serum LBP has been demonstrated in patients suffering alcoholic liver disease [158,159], NASH [160], liver cirrhosis [161] and PSC [162]. However, bacterial infections can also increase LBP and it reflects only translocation of gram-negative bacteria, which may explain controversial results [163]. In summary, although holding some promise for clinical use, particularly I-FABP and LBP, serum biomarkers are currently not broadly used in clinical practice due to lack of sufficient standardization, precision and/or validation as well as high-quality longitudinal studies evidencing their use for monitoring purposes. Finally, bile acids and -derivates known to be involved in the pathophysiology of intestinal barrier disruption are measurable but in systemic concentrations not reflecting the site of action within the gut-liver axis. In contrast, harvesting bile from the liver although feasible requires an endoscopic-retrograde-cholangio-pancreaticography (ERCP) and assessment from intestinal juice and/or biopsies to our knowledge has not been achieved in standardized manner.

The *portal vein* being the inflow "highway" to the liver does represent the best target for diagnostics. In mice, a special surgical method for continuous intraportal infusion of gut microbial metabolites has been developed [164]. However, only few clinical studies investigate/d portal venous blood as for translocating bacteria/l products and/or metabolites fueling into the liver [30,165,166]. Portal venous access in these investigations was either intra-operatively during surgery (for obesity) or via transjugular-intrahepatic-portovenous stent (TIPS for portal-hypertension associated complications). These procedures are invasive and performed only in a minority of selected patients. More recently, an endoscopic-ultrasound (EUS)-based method has been proposed to safely access the portal and hepatic venous circulation [167–169]. EUS holds the potential of broader applicability given the wide accessibility of EUS in everyday GI practice, its technique relies on an already assimilated skillset of using puncture needles and it may largely overcome most of the mentioned shortcomings. This EUS-approach has been utilized to diagnose malignancy [170–175] and assess portal hypertension [176]. The latter is determined by directly puncturing and measuring hepatic venous and portal pressure (via 25 G FNA needle coupled to a digital pressure transducer). By subtracting the hepatic venous pressure from the portal pressure, the EUS-portal-hepatic-pressure-gradient is determined. The ENCOUNTER study (NCT04987034) is currently evaluating the diagnostic accuracy of this method in a prospective manner. Moreover, and most importantly during EUS-access to the portal and hepatic vein blood can be withdrawn enabling analysis of the metabolomic signature and characterization of the type and load of gut-derived P-/M-/DAMPs. Finally, EUS-based liver biopsy is now a routine procedure with meta-analysis demonstrating at least the same quality of diagnostics as transcutaneous liver biopsy [177]. This EUS-liver biopsy is performed under sedation and hence, a lower perceived apprehension of discomfort, lower postprocedural tenderness and markedly faster recovery after EUS-liver biopsy in comparison to conventional percutaneous biopsy is reported [177]. Liver biopsy by any route can be used to assess for presence of bacterial DNA by PCR directly evidencing bacterial translocation to the liver. This has to our knowledge for the first time be implemented in patients undergoing liver transplantation delivering detailed insights also into the associated hepatic immune environment [178]. A current clinical pilot trial is assessing the use of EUS-blood sampling (portal and hepatic venous) plus liver biopsy in morbidly obese patients since those do face more technical difficulties in undergoing transcutaneous liver biopsy and are most prone for pathological changes in their gut-derived metabolome (personal note). Therefore, *EUS-derived portal venous blood and liver tissue-acquisition could provide vast add-on value in terms of mechanistic insights into pathophysiology as well as diagnostic accuracy for optimal characterization and thus, stratification of patients suffering multiple different liver diseases.*

5. Measures to modulate the gut-liver-axis

5.1. Microbiome as target

The strongest inprint on microbiome composition in each individual human being is the host itself due to at least partly genetic determination of innate and adaptive immune responses and mutualistic co-evolution from birth to adolescence (Human Microbiome Project Consortium, 2012). The microbiome is a very individual, personal "fingerprint" within each of us. Nonetheless, multiple factors influence the microbiome and thus, can be used for therapeutic modulations. For more in-depth insights in to the promise of microbiome-based therapies, please be referred to Bajaj and Schnabl et al. [179] For planning, as well as judging, any investigation on modulating the microbiome one needs to

Table 1
Type of interventions and concepts utilized to target the gut microbiome (modified from Krag et al. [182]).

Intervention	Example	Concept
Antibiotics	Rifaximin	Kill the bug
Prebiotics	Dietary fibers	Feed the bug
Probiotics	Akkermansia mucinophila	Compete with the bug
Synbiotics	Pre- and Probiotics	Feed and compete
Postbiotics	SCFA	Skip the bug
Diet [183]	Keto-diet	Control substrate
FMT	Colonoscopic FMT	Substitute the bug
Bacteriophage	Target cytolytic E.faecalis	Bug the bug
Bio-engineered bacteria	Genetically modified E. Nissle 1917	Cheat the bug
Drugs	Metformin	Drug the bug

be aware also of the very individual personal response to food. This has been elegantly shown by ultra-dense longitudinal sampling of feces along with complete daily 24-h dietary records in parallel. Microbiome response to similar food is personalized namely having different effects on different people [180]. The goal of restoration and reconstitution of stable eubiosis has been proposed as the ultimate goal in chronic inflammatory diseases increasing chances to the most to sustain a healthy intestine and barrier function [181]. However, this may proof difficult in ongoing disease states particularly if underlying etiology is not eradicated. (Table 1).

5.1.1. Diet and exercise

Diet in the sense of healthy nutrition has emerged as most appealing attractive strategy to modulate the microbiome, bile acid composition and stabilize intestinal barriers. Healthy food stands for "Mediterranean diet" including vegetables, fruits, non-refined sugars, low-fat and unprocessed food [184]. This has been summarized nicely as "anti-inflammatory" diet contrasting "inflammatory" diet representing what is also known as "western diet" containing refined sugars, high-fat-content and processed food [12]. In more detail, simple carbohydrates such as fructose (frequently enriched in western diet) can trigger duodenal barrier dysfunction, leading to endotoxemia and MASLD [185]. Moreover, dietary emulsifiers have been observed to induce low-grade inflammation and gut dysbiosis in mice impairing intestinal barriers [186,187]. In addition, serum glucose concentration per se does affect intestinal permeability since treatment of hyperglycemia, intestinal epithelial–specific GLUT2 deletion, or inhibition of glucose metabolism in mouse models of obesity and diabetes did restore barrier function and bacterial containment [188]. This finding was supported by the observed correlation in humans between glycated hemoglobin (an indicator of hyperglycemia) and serum levels of pathogen recognition receptor ligands [188]. However, important to consider besides composition of diet is the caloric state with overnutrition also boosting at least temporarily hyperglycemia and causing dysbiosis [184]. Finally, beneficial effects of exercise have been evidenced on gut microbiota functionality, barrier integrity and gut-liver crosstalk in early obesity [189]. *Therefore, a healthy life-style combining physical activity and anti-inflammatory Mediterranean diet thus appears most sensible to be recommended to favour a healthy balanced microbiome and intestinal barriers. However, what is the most difficult in life namely, to change habits, behaviour and preferences such as switching from inflammatory to anti-inflammatory diet and low/no to high/real exercise. In contrast, the easiest in life is swallowing a pill.*

5.1.2. Anti-, pre-, probiotics

Antibiotics are effective in eradicating at least temporarily many different bacterial species and lowering bacterial load but are least favorable since consequences of long-term use are unknown or unfavorable. Moreover, antibiotics do promote multiple difficulties such as increased risk of multi-drug-resistance bacteria and clostridium difficile infections [190].

Pre-biotics are defined as substrates selectively utilized by host microorganisms that confer a health benefit [191,192]. Prebiotics are mostly non-absorbable carbohydrates, fibers, which are fermented by luminal bacteria, producing SCFAs which reduce pH in the lumen, stimulating beneficial taxa and by that reduce available nutrients for invading pathogens [193]. Moreover, pre-biotics have been reported to improve intestinal barrier function via stimulating mucus-producing goblet cells, augmenting TJ assembly and mitigating inflammation [194] as well as improving intestinal peristalsis and preventing colonization of pathogenic bacteria [195,196]. Most frequently studied pre-biotics are inulin-type fructans such as fructo-oligosaccharides (FOS), inulin or oligofructose. Dietary sources of prebiotic oligosaccharides are various types of vegetables, fruits, grains and legumes. Depending on their water solubility, dietary fibers are classed as insoluble (e.g., hemicellulose, cellulose, and lignin) and soluble (e.g., fructans, gums, and pectins). Only soluble fibers can be metabolized by the microbiota and have "prebiotic" functions. Currently more than 1300 ongoing active trials in clinical.trials.gov investigating fiber and its value in a vast variety of clinical entities and 23 investigations including liver diseases and/or endpoints.

Pro-biotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host which must extend beyond any nutritional benefit of the food matrix [197]. Evidence of a strain-specific benefit from a well-controlled intervention study is required together with proven safety and confirmation of sufficient numbers of that strain in the final product to confer the claimed benefit [197]. Multiple beneficial effects of probiotics improve intestinal barriers [196] and gut immune function [198] including, but not limited to, increases in mucus-secretion, stimulation of anti-microbial peptide synthesis/secretion, regulation of epithelial tight junction proteins, modulation of gut microbiome composition and microbial metabolites, reducing LPS- and TMAO-production, stimulation of anti-inflammatory cytokines (e.g. IL10) and impacting on immune cells such as dendritic cells, macrophages as well as B and T lymphocytes ameliorating innate and adaptive immune responses and related anti-pathogenic/inflammatory activities. One prominent example of next generation probiotic is *Akkermansia mucinophila*, for which detailed information has recently been reviewed [199,200]. *Akkermansia mucinophila* is an exclusive mucin-degrading specialist, the only representative of *Verrucomicrobiota* in humans and has proven experimental efficacy to improve hepatic steatosis, intestinal inflammation as well as obesity and diabetes. Besides exogenous oral supplementation using the pasteurized form each of us can stimulate its abundance by exercise [201], caloric restriction/starvation [202] and intake of polyphenol-rich foods [203].

Despite the substantial number of published studies and the huge efforts reflected by the number of active ongoing clinical trials testing probiotics (currently 467 on clinical.trials.gov) an extreme variation in outcomes but also differences in the strain of microbes used, dose, route of administration and duration do exist [204]. Thus, most recent guidelines on the use of probiotics in gastrointestinal disorders mainly state the knowledge gap or give no recommendation or only conditional at low evidence level for e.g pouchitis [205]. However, this huge heterogeneity in data can easily be explained by the most recent elegant investigation by the Elinav-group demonstrating that humans feature a person-specific gut mucosal colonization resistance to probiotics [206]. The probiotic colonization capacity however, is predictable by pre-treatment microbiome and host features [206]. The lower the abundance of a specific probiotic strain at baseline in the individual to be treated the more likely colonization is achieved by that probiotic strain [206]. Finally, optimal probiotic colonization has been proposed to be supported by the according diet delivering the corresponding best energy source most suitable for this probiotic strain (Prof. Schnabl, personal communication). Hence, individualization of probiotic strategy to the patient, underlying disease and provided diet e.g engineering new

probiotic strains based on metagenomic identification of individual specific deficits and thus, personalized approach may be key for success.

Symbiotics represent the co-administration of prebiotics that can enhance the proliferation of probiotic bacteria and certain bacterial genera can be stimulated selectively by these compounds.

5.1.3. Fecal microbiota transplantation (FMT)

represents the most direct form to manipulate the microbiome and refers to the transfer of processed stool from a healthy donor to a recipient. This has delivered promising results as therapeutic measure for many disease states with a growing list of indications including liver diseases and currently roughly 40 ongoing registered clinical trials (clinicaltrials.gov – accessed April 2023). Thus, consensus conferences try to provide guidance and general criteria required to promote FMT as a recognised treatment strategy [207]. However, caveats still include adverse events [208] such as transmission of resistant bacterial strains as has been reported in single cases in the literature despite following FDA-approved donor screening [209,210]. Other safety concerns relate to compositional uncertainties of donor feces and risk of potential transmissible effects on metabolism and immune-surveillance. The most practical limitation is optimal donor selection since analysis of microbiota function and not only composition may be of key relevance in treatment of liver diseases. This is most likely different from applying FMT to Clostridium difficile infections being characterized by most severe reduction in species richness giving "space and place" for any type of "healthy" microbiota lacking within the diseased gut.

5.1.4. Other strategies modulating microbiome

Bacteriophages are viruses that specifically target and infect bacteria without entering or harming human cells but regulating physiology through their effects [211]. Moreover, by replicating within the infected bacteria they kill them. However, concerns in terms of public health risks if bacteriophages would be used widespread on broader scale have been raised [212]. *Engineered bacteria* have been classified as next-generation microbiome therapeutics [213]. These bacteria are precisely designed to either produce a beneficial metabolite or metabolize/ consume toxic products [214]. Pharmacological modification of bacterial metabolism without eradicating the responsible microbe holds much promise as targeted specific approach. In the same line small molecules with specific enzymatic action are developed. For instance, inhibitors targeting microbial CutC choline trimethylamine-lyase that cleaves choline to produce trimethylamine (TMA) [215]. *Post-biotics* have previously termed microbial metabolites as bioactive products of beneficial bacteria. This has recently been changed defining postbiotics as "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" [216]. Thus, BA-modulators and SCFAs are postbiotics.

5.2. Modulation of BA-pool-/composition and/or -signaling (Fig. 1A)

also represents a strategy to target the microbiome since BA strongly interact with gut microflora (see above) but can exert many other FxR and/or TGR5-mediated effects. *Bile sequestrants* are a group of resins used to bind certain components of bile in the gastrointestinal tract. They disrupt the enterohepatic circulation of bile acids by combining with bile constituents and preventing their reabsorption from the gut. The majority of conjugated BA are absorbed in the terminal ileum for which the apical sodium-dependent bile salt transporter (ASBT, IBAT, gene symbol SLC10A2) is the first step at the brush-border [217]. *ASBT-inhibitors* have been developed leading to increased BA synthesis by the liver since feedback inhibition on the liver is reduced and more BA are reaching and lost via colorectal passage. This treatment approach is high-level evidenced by phase 3 trials in progressive-familial intrahepatic cholestasis (PFIC) [218] but comes with side effects such as diarrhoe. Finally, *direct FxR-agonists* available and tested in humans include Obeticholic acid (OCA), EDP-305, Tropifexor, Vonafexor and

Table 2
Current interventions targeting the gut liver axis in human chronic liver disease-selected (examplatory) trials/benefits reported and ongoing trials. Not intended to be complete.

Microbiome	
ArLD	
Antibiotics	Discordant effects on bacterial translocation,
Rifaximin alone or in combined treatment, Amoxicillin-clavulanic acid combined with steroids	hepatic and systemic inflammatory response and liver-related events [223] Paromomycin treatment had no significant effect on endotoxin concentration or liver function tests during the 4-week period [224] AntibioCor trial Amoxicillin-clavulanate in AH: Less infections, but no evidence for prognostic improvement in AH (2-month survival) [225] Pilot study (RIFA-AH) (21 vs. 42 patients, RIF vs. control) testing the effect of rifaximin on infections, acute-on-chronic liver failure and mortality in alcoholic hepatitis: safe in severe AH with a significant reduction in clinical complications. A lower number of infections and a trend towards a lower ACLF and mortality favours its use [223] Meta-analysis Rifaximin in AH: associated with a lower rate of infection rate. Additional research is needed to determine whether this efect is more pronounced in steroid treated patients, no improvement of 90-day survival [226] GALA-RIF Phase 2 trial rifaximin-α might reduce progression of liver fibrosis [227]
Prebiotics	Liver tests are not improved by inulin
Inulin etc.	supplementation in alcohol use disorder patients - pilot randomized, double blind, placebo-controlled study [228]
Probiotics	Significantly lower ALT levels in patients with mild AH [229] Significantly improved cytokine levels (TNF-α, IL-6, and IL-10), and improved liver function in patients with alcohol-related cirrhosis [230] *Ongoing:Profermin®: Prevention of Progression in Alcoholic Liver Disease by Modulating Dysbiotic Microbiota (SYN-ALD) Phase II NCT03863730; Bovine Colostrum: NCT01968382. NCT02473341; Others: NCT05830708, NCT05178069, NCT05007470*
Synbiotics	Synbiotic treatment was associated with significant improvement in ALT and GGT levels in alcohol-related cirrhosis[231]
FMT	Improvement of liver-related events in ArLD cirrhosis and AH [232,233] Improvement in 90-day survival reduction in infections in severe AH [234] FMT is safe and associated with short-term reduction in alcohol craving and consumption [235] *Ongoing: NCT04758806, NCT05285592, NCT02473341, NCT05548452, NCT05006430*
MASLD	
Antibiotics	6 months of rifaximin resulted in a significant
Rifaximin	reduction in ALT, AST, GGT, endotoxin, toll-like receptor-4, IL-6, TNF-α, CK-18, and NAFLD-liver fat score [236]
Prebiotics	Probiotics, prebiotics, and synbiotics
Inulin etc.	supplementation can potentially improve liver enzymes, lipid profiles, and liver steatosis in patients with NAFLD [237] Addition of inulin-type fructans such as oligofructose (OFS) in the diet decreases triacylglycerol accumulation in the liver tissue [238] Prebiotic supplementation improved liver steatosis relative to placebo and improved overall non-alcoholic fatty liver [239] *Ongoing:Prebiotics in MASLD: Inulin/OFS-NCT02642172, SimO1 - NCT05885373*
Probiotics	NAFLD patients were found to have improved liver function after VSL #3 [230]

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Table 2 (*continued*)

Microbiome	
	Probiotics had beneficial effects on BMI, ALT, AST, GGT, insulin, HOMA-IR, total cholesterol [240]
	3-month *A. muciniphila* administration reduced the levels of the relevant blood markers for liver dysfunction and inflammation [241]
	Meta-analysis on probiotics shows significant improvement in liver transaminases and varying effects on fibrosis in patients diagnosed with NAFLD [242]
	Meta-analysis on probiotics shows slight improvement on the degree of liverfat, liver tests [243]
	Ongoing: NCT05402449, NCT04671186, NCT05804422, NCT05635474, NCT05523024, NCT04781933
Synbiotics	Synbiotic treatment was associated with significant improvement in ALT and GGT levels in the NASH group [231]
	Ultrasound-detected steatosis improved significantly with synbiotic supplementation compared to baseline [244]
	Synbiotics improved AST, ALT, liver stiffness, but not BMI [245]
	Meta-analysis shows significant improvement in liver transaminases and fibrosis in patients diagnosed with NAFLD [242]
	Ongoing: NCT05821010 (+/- FMT)
Postbiotics	Meta-analysis shows significant improvement in liver transaminases and fibrosis in patients diagnosed with NAFLD [242]
FMT	Obese subjects with diabetes mellitus: Repeated duodenal FMT infusion every 4 weeks for up to week 12 lowered liver stiffness [246]
	FMT could successfully improve the liver tests in patients with NAFLD, and its clinical efficacy was higher in lean NAFLD than in obese [247]
	Ongoing: NCT02496390, NCT03803540, NCT05607745, NCT05622526, NCT05821010
Fibrosis/Cirrhosis Subsets/ conditions	
Antibiotics	In Phase 2-RCT (GALA-RIF) Rifaximin reduced
Rifaximin	progression of liver fibrosis with a number
Norfloxacin	needed to treat of six [227]
Vancomycin	Treatment with rifaximin maintained remission
Gentamicin,	from hepatic encephalopathy more effectively
Meropenem,	than did placebo[248]
Ciprofloxacin	Norfloxaxin reduces the incidence of
Ceftriaxone	spontaneous bacterial peritonitis, delays the develop- ment of hepatorenal syndrome, and improves survival [249]
	Intravenous ceftriaxone is more effective than oral norfloxacin in the prophylaxis of bacterial infections in patients with advanced cirrhosis and hemorrhage [250]
	Ongoing: Rifaximin in cirrhotics with severe HE NCT01846663
Prebiotics	Meta-analysis shows Lactulose to be most effective for reversal of minimal HE and prevention of overt HE in patients with cirrhosis [251]
FMT	Capsular FMT improves inflammation and cognition in cirrhosis [252]
	FMT was associated with improved duodenal mucosal diversity, dysbiosis, and antimicrobial-peptide expression, reduced LBP, and improved EncephalApp performance (A Phase 1, Randomized, Placebo-Controlled Trial) [253]
	Cognition improved in the FMT, but not the standard-of-care group:A randomized clinical trial [254]
	Ongoing: NCT04932577, NCT03420482, NCT03796598, NCT05229289
Bacteriophages	*Ongoing-recruiting observational study (NCT05618418) (BATTLE)*

Table 2 (*continued*)

Microbiome	
HCC	
FMT	*Ongoing: FMT in IT-refractory HCC - FAB-HCC Pilot Study (NCT05750030)*
	FMT and post-operative liver function in HCC (NCT04303286)
Autoimmune/ Cholangiopathies/ PSC	
Antibiotics	Vancomycin use has delivered controversial
Vancomycin	results but most likely as recently shown is of no clinical benefit [255]
	Ongoing: NCT058761829
FMT	FMT induced increases in bacterial diversity and engraftment may correlate with an improvement in ALP among patients with PSC [256]
Diet	
MASLD	
Mediterranean	Effectiveness on surrogate markers of NAFLD (liver fat content, non-invasive markers of liver fibrosis, and liver tests); impact on liver histological features as well as clinical outcomes unclear [257]
Other dietary modulations	*Ongoing: NCT03897218, NCT05960396, NCT05866744, NCT05968378, NCT05332613*
HCC	
Mediterranean	"Mediterranean" diet, associated with reduced risk for HCC in meta-analysis of 30 observational studies[258]
Bile acid-associated	
ArLD	
Farsenoid X receptor (FxR)-agonists	*Ongoing Phase IIa Trial:FXR Effect on Severe Alcohol-Associated Hepatitis (FRESH) (NCT05639543)*
MASLD	
Bile sequestrants	Colesevelam increases liver fat in patients with NASH as assessed by MRI without significant histological changes [259]
ASBT-inhibitors	Volixibat in NASH: 24-week interim analysis from a randomized, phase II study; did not elicit a liver-related therapeutic benefit [260]
Farsenoid X receptor (FxR)-agonists	Reduced markers of liver inflammation and fibrosis in patients with type 2 diabetes mellitus and NAFLD[261]
	Obeticholic acid (OCA) over 72 weeks significantly improves liver histology in patients with NASH (FLINT trial Phase 2b) [262]
	In noncirrhotic NASH (F2 or F3) OCA significantly improved fibrosis by >1 stage, but not NASH (REGENERATE Phase III) [263]
	Vonafexor was safe and induced potent liver fat reduction, improvement in liver enzymes, weight loss (LIVIFY trial) [264]
	Tropifexor for nonalcoholic steatohepatitis: FLIGHT-FXR phase IIa/b trial: Decreases in ALT and hepatic fat were sustained up to week 48 and significant reductions of collagen proportional area [265]
	Cilofexor for 24 weeks was well-tolerated and provided significant reductions in hepatic steatosis, liver biochemistry, and serum bile acids in patients with NASH in Phase 2 trial [266]
	Cilofexor in advanced fibrosis (F3-F4) NASH (ATLAS Phase II); in combination with firsocostat had significantly higher proportions with a $\geq$ 2-point NAS reduction with improvements in steatosis, lobular inflammation and ballooning; significant improvements in ALT, AST,
	bilirubin, bile acids, CK18, insulin, and liver stiffness [267]
	Non-steroidal FXR agonist PX-104 improved insulin sensitivity and liver enzymes after 4 weeks of treatment in non-diabetic NAFLD patients [268]
	MET409 (phase 1b): 12 weeks of treatment improved hepatic fat content [269]

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Table 2 (*continued*)

Microbiome	
	Ongoing: NCT03439254, NCT04328077, NCT0541572
Fibroblast growth factor (FGF 19/21)	Pegbelfermin (Pegylated FGF 21): NASH with F1–3 (phase 2a)176: reduced hepatic fat content (MRI-PDFF) and liver transaminases after 16 weeks [270] Pegbelfermin in NASH with decrease in fibrosis-related biomarkers and correlation with histological response in the FALCON 1 trial [271] Pegbelfermin in compensated NASH Cirrhosis (FALCON 2 Phase IIb): did not meet its primary endpoint of 1 or more stages of improvement in the NASH [272] Efruxifermin in NASH with F1-F3 (phase II a) Over 16 weeks improved hepatic fat content, patients with $\geq$ 30% reduction in hepatic fat 85% had a $\geq$ 2-point reduction in NAS, 78% had a $\geq$ 2-point reduction in NAS without worsening of fibrosis, 48% had $\geq$ 1 stage improvement in fibrosis without NASH worsening, 28% had both NASH resolution and fibrosis improvement [273] Efruxifermin in a phase IIa trial for compensated NASH cirrhosis, with encouraging improvements in markers of liver injury, fibrosis, and glucose and lipid metabolism following 16 weeks of treatment [274] Engineered FGF19 analogue NGM282 over 12 weeks in NASH with F4 (phase IIa): 16 weeks with improved markers of liver fibrosis, glucose and lipid metabolism and reduction in absolute liver fat content and liver fibrosis and histology in human NASH [274] Aldafermin in NASH(ALPINE 2/3): a Phase IIb did not produce a significant dose response on fibrosis improvement of at least one stage with no worsening of NASH [275]
Ursodeoxycholic Acid (UDCA)	UDCA in NAFLD - Clinical Observation (URSO) Recruiting NCT05256979 Treatment with Vit. E, UDCA and PTX was both safe and effective in improving hepatic aminotransferases and inflammatory markers in Egyptian NASH patients. The superior effect of Vit. E compared to UDCA and PTX [276] Two years of treatment with UDCA in combination with vitamin E improved laboratory values and hepatic steatosis of patients with NASH [277]
Autoimmune/ Cholangiopathies/PSC	
ASBT-Inhibitors	*Ongoing: NCT05642468, NCT04168385, NCT05050136,* NCT04663308
Farsenoid X receptor (FxR)-agonists	Obeticholic acid reduced serum alkaline phosphatase (up to 2 years follow-up) [278] *Ongoing: NCT05450887*

ArLD, alcohol-related liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; ACLF, acute-on-chronic liver failure; AH, alcohol-related hepatitis; IL, interleukin; TNF, tumour necrosis factor; CK, cytokeratin; NAFLD, nonalcoholic fatty liver disease= MASLD, metabolic-dysfunction associated steatotic liver disease; HE, hepatic-encephalopathy, BMI, body mass index; NASH, nonalcoholic steatohepatitis; ASBT, apical sodium-dependent bile salt transporter; FXR, farsenoid X receptor; FGF, fibroblast growth factor; Listed only completed or actively recruiting studies (search periode 2022- current). Further information regarding the trials listed can be found on: www.clinicaltrials.gov/

Cilofexor [90]. In contrast, dual FxR-/TGR5-agonist INT-767 has demonstrated beneficial effects in experimental liver disease models [219,220] but no clinical trial is registered currently to our knowledge. Direct selective TGR5-agonists due to multiple clinical relevant side effects [221] are no more in development to our knowledge.

5.3. Overview on current interventions targeting the gut liver axis in chronic liver disease

For the main chronic liver diseases Table 2 summarizes current knowledge on interventions and their clinical benefit as well as ongoing trials (for more details see supplementary). Mechanisms of action for many interventions most likely are very complex and involving different compartments and cellular targets. For instance, probiotic treatment/s exert multi-layer effects: improving intestinal barrier functions (e.g epithelial TJ), modulating the GALT and regulating innate as well as adaptive immune response (via DC, B- and T-lymphocytes), producing/ stimulating anti-microbial agents, SCFA, mucins but also neurotransmitters through the gut-brain-axis [222].

6. Liver cirrhosis: the gut-liver-axis driving fibrosis and advanced liver disease

Multiple investigations, as reviewed elsewhere [11,279,280], indicate that microbe-host interactions play a key role in fibrogenesis and liver disease progression. Ultimately any chronic liver disease can lead to cirrhosis and the progression of fibrosis follows shared patterns across different etiologies. Likewise, chronic inflammation in most organs due to remodelling associates with fibrogenesis. Thus, correspondingly the gut-liver-axis in conditions of intestinal hyperpermeability and dysbiosis, exposes the liver to a complex diverse range of pro-inflammatory, -fibrogenic stimuli. The liver then is infiltrated by responsive immune cells and microbiota-derived products may provoke and/or exacerbate innate immune responses, hence perpetuating liver inflammation and fibrosis, and potentiating the risks of developing cirrhosis. Indeed, fecal microbiota from chronic liver disease patients but not from healthy donors into mice leads to increases in gut permeability, LPS serum levels and severe liver fibrosis [281]. However, also in germ-free conditions enhanced liver fibrogenesis has been observed in experimental models of liver injury [282]. This underlines the importance of a diverse balanced eubiotic microbiome for keeping the liver sufficiently tolerant within the gut-liver-axis [283]. Gut-derived stimuli promoting fibrogenesis in experimental models of liver injury include LPS (via TLR-4) [284,285], bacterial DNA (via TLR-9) [286] as well as conjugated 12-OH-secondary BA (via TGR-5) [287]. Correspondingly, antibiotics (most likely lowering translocation of LPS, bacterial DNA and reducing availability of secondary BA) substantially ameliorated liver inflammation and fibrogenesis in various mouse models [284,288]. However, human data are scarce but recently a phase 2 double blinded RCT from the GALAXY consortium was published. The authors studied the effect of rifaximin in 136 patients with alcohol related liver fibrosis and found rifaximin to be associated to less progression of fibrosis and improvement in markers of fibrosis [227]. Moreover, the experimental observation of intestinal inflammation in experimental NASH promoting LPS translocation, hepatic inflammation, and fibrogenesis [289] is reflected in the most recent human cross-sectional case-control study demonstrating that inflammatory bowel disease associates with more than 5-times increased risk for advanced liver fibrosis [290]. Nonetheless, still to date no Food and Drug Administration (FDA)-approved anti-fibrotic drugs exist and the only available curative treatment option for patients with advanced liver cirrhosis is liver transplantation.

Advanced liver disease in the stage of cirrhosis harbours a microbial signature of its own most likely less influenced by the cause of cirrhosis but rather induced by multiple patho-physiological consequences of liver cirrhosis. Changes in microbiota composition and dysbiosis have been delineated in detail in human cirrhosis with diminished diversity being most pronounced in decompensated stages of disease [279] and ACLF [291]. Moreover, cirrhosis-specific microbiota profiles have been depicted [292,293], which even have been proposed as tool to diagnose liver cirrhosis [294,295]. Fecal microbiota signature in cirrhosis appears to reflect susceptibility of the patient towards further decompensation and associates with elevated risk of extrahepatic organ failure, ACLF and

mortality independent of baseline clinical characteristics [291,296]. In the same line of support for the concept of dysbiosis and PBT being relevant for cirrhotic patients are i) the finding of bacterial overgrowth of those species being also responsible for the most frequent spontaneous infections, namely *Enterobacteriaceae (*belonging to the class of *Proteobacteria*) *and Enterococci* [297,298] ii) the observation that bacterial virulence factors for adherence and biofilm-formation particularly of those *Enterobacteriaceae* and *Enterococcus spp* associate with death and hospitalizations independent of clinical factors [299] iii) the fact that PBT causes the gut to become a cytokine-releasing organ with splanchnic levels exceeding peripheral concentrations as shown for TNF [300–302] iv) the observed link between worsening of clinical parameters of liver cirrhosis and species translocating through the dysfunctional barrier, particularly gram-negative members of the *Proteobacteria* phylum [300] v) which correlated with portal and systemic inflammation [300,303].

Liver cirrhosis has multiple detrimental effects on the gut and its barriers inducing a vitious circle that can aggravate and/or perpetuate disease state via the gut-liver-axis [304]. Liver cirrhosis leads to reduced BA production and thus, availability in the intestine which per se induces dysbiosis, enables bacterial overgrowth. Moreover, diminished microbiome-induced BA-biotransformation to secondary BA known as most potent stimulators of FxR in the ileum thus, results also in diminished FxR-signaling further promoting dysbiosis [305] and intestinal barrier dysfunction. The latter is additionally promoted by reduced levels of intestinal antimicrobial peptides [306] and mucins [93] as well as attenuated expression of epithelial intercellular junction proteins [307] all together increasing intestinal permeability [304]. Moreover, functional dysbiosis in patients with cirrhosis with impaired faecal bacterial metabolism of SCFA has been reported [300] which is tempting to speculate to further endanger epithelial cell functions.

Finally, cirrhosis-associated immune-dysfunction hampers defenses against PBT [308] which together with disruption of the gut-vascular barrier [93] is setting the stage for gut-derived P-/M-DAMPs fueling the gut-liver-axis. This in fact is the reason why liver cirrhosis is the prime example where liver-gut-axis has been evidenced early on to be fundamental for prognosis.

Direct evidence of increased bacterial translocation along the gut-liver axis in cirrhotic patients is sparse but has been delivered by the Trautwein lab [178]. Cirrhotic patients undergoing liver transplantation displayed higher 16 S rRNA gene copies/ng total liver DNA as compared to liver healthy surgical controls [178]. Moreover, this bacterial translocation strongly correlated with fibro-inflammatory transcriptional pathways in human cirrhotic livers implicating PBT as driver of liver disease in terms of inflammation and fibrosis [178]. Due to porto-systemic shunting and decreased hepatic clearance function of the cirrhotic liver, patients with cirrhosis present with increased peripheral plasma levels of LPS [309] and correspondingly, LBP [161] (as long-term marker of gram-negative BT) as well as bacterial DNA [310]. Indeed, LPS-serum levels increase progressively in relation to the severity of liver dysfunction (Child-Pugh-classification) e.g. < 3 pg/ml in healthy volunteers to 4.9 pg/ml, 7.9 pg/ml and 10.2 pg/ml in Child A, B and C, respectively [309]. Other P-/MAMPs, however, to our knowledge have not been investigated systematically in human cirrhosis. Moreover, whether cirrhotic patients with hepatofugal blood flow due to most severe portal hypertension and porto-systemic shunting behave differently in terms of systemic inflammation and/or liver injury driven by PBT has not been addressed but may well be worthwhile.

Advanced cirrhosis can be considered as multi-organ-dysfunction putting the patient at risk for developing life-threatening complications such as spontaneous bacterial peritonitis (SBP), variceal hemorrhage (VH), hepatic encephalopathy (HE), acute kidney injury/failure (hepato-renal syndrome) and/or acute-on-chronic-liver failure (ACLF). For all of these, PBT has been proposed to contribute to their development and/or aggravation/severity and available evidence is summarized in the following. In decompensated cirrhosis with ascites PBT is the pathophysiological hallmark for spontaneous infections caused by translocating gut-derived commensal bacteria such as in ***spontaneous bacterial peritonitis (SBP)*** [311]. Patients suffering SBP display the most severe disturbance in intestinal barrier function, with more pronounced intestinal hyperpermeability than in cirrhotics without SBP and/or severe infections [144,312] and thus, most likely upmost PBT entering to the portal-venous and systemic circulation. The peritoneal cavity in cirrhosis with ascites is a "locus resistenciae minoris" thus, bacteria/l products are more difficult to resolve by the immune system giving rise to SBP [313]. This entity is known to associate with amplified splanchnic release of pro-inflammatory cytokines and frequently leads to acute kidney failure and hepato-renal syndrome limiting prognosis of those patients. Antibiotic prophylaxis by inhibiting and lowering PBT in patients with cirrhosis at high risk for SBP not only prevents (re-)occurrence of SBP [314,315] but also hepato-renal syndrome improving survival [249] and hence, is recommended by current guidelines [316,317].

Variceal hemorrhage is a life-threating complication in cirrhosis carrying a high mortality up to 40% within 6-weeks if not treated according to modern standards, in which mortality is reduced to 15% [318,319]. Hemorrhage-associated gastrointestinal hypoperfusion increases risk and severity of PBT but has not been studied in patients with cirrhosis. PBT in those patients however, has been proposed to aggravate hyperdynamic circulation [320], portal hypertension and to impact on coagulation systems [321] which explains at least partly the increased risk of recurrent variceal bleeding in patients developing spontaneous bacterial infections [322]. Therefore, in any patient with cirrhosis and gastrointestinal bleeding antibiotic prophylaxis is very effective lowering all-cause mortality, bacterial infection rate, rebleeding events and hospitalisation length [323]. Thus, antibioitic prophylaxis is established and recommended by current guidelines for variceal hemorrhage and gastro-intestinal bleeding in liver cirrhosis [324]. Another corner stone in the treatment of patients with cirrhosis are non-selective betablocker known for more than 4 decades to lower rate of first and recurrent variceal bleeding in cirrhosis [325]. Lately, evidence accumulates indicating that non-selective beta-blocker besides their known hemodynamic effects may also reduce PBT and associated likelihood of infections [326] and outcome in ACLF [327] at least partly via improvements in intestinal permeability [328]. This examplifies that potentially many drugs used in internal medicine may affect the gut-liver-axis but have not been investigated for this action.

Hepatic Encephalopathy (HE) is the classic microbiome-related complication of the gut-liver-axis in cirrhosis with gut-derived neurotoxic substances, e.g. ammonia as product of bacterial urea and protein metabolism being key for pathophysiology. In healthy conditions, ammonia is detoxified via the urea cycle in the liver keeping circulating levels low. In liver cirrhosis however, enhanced translocation in conjunction with lack of detoxification due to portal-venous shunting and hepatocellular injury lead to systemic levels of neurotoxic agents reaching the brain and entering astroyctes [329]. Clinically this is characterized by neurocognitive impairments including lethargy, confusion as well as motor dysfunction. Systemic inflammation facilitates neurotoxic effects [330] for which likewise the microbiome as well has been shown to be essential in gnotobiotic mouse models [331]. Not surprisingly, the main stay in treatment of HE since a long time is lactulose and rifaximin both being poorly (almost non-) absorbed and hence, mainly act at the gut.

Lactulose is the best known pre-biotic routinely used in cirrhosis. It is metabolized by colonic bacteria acidifying the micromileu, expanding bifidobacterial and Lactobacillus populations with fermentation requiring bacterial amino acid synthesis using ammonia as substrate and thus, reducing its luminal concentration and absorption [332]. Such increased amino acid synthesis with lactulose is absent in germ-free rodents evidencing the key role of the microbiota in this process [333]. Efficacy of lactulose in treating HE is very robust [334] with the

latest meta-analysis concluding that lactulose was the only agent to meet all 3 endpoints namely, reverse minimal HE, prevent overt HE and improve quality of life [251].

Rifaximin is an orally administered, semi-synthetic, non-absorbable antibiotic derived from rifamycin with broad antibacterial activity, which markedly reduces and hence, is recommended in current guidelines to prevent, recurrency of overt HE [248,335]. Despite its clear clinical benefit its mechanism of action is less clear but most likely multifactorial and independent from microbial shifts [336,337]. Rifaximin only marginally affects microbial community composition [337] (again emphasizing the importance of bacterial function rather than composition), but has been proposed amongst others to lower serum LPS levels [337], reduce gut-derived inflammation [267], attenuate adherence of bacteria to the gut wall [338], decrease bacterial virulence and mucin degradation as well as alter bacterial metabolism in cirrhosis [265,339,340].

FMT: Pilot studies utilizing FMT either via enema or oral capsule indicated safety and efficacy in patients with HE [253,341]. Interestingly, FMT also did lower serum LBP as indirect evidence for improved intestinal permeability and thus, reduced PBT achieved by this approach in cirrhosis with HE [253]. An open-label randomized clinical trial applying FMT to cirrhotic patients with recurrent HE reduced hospitalizations, improved cognitive function and dysbiosis as compared to standard of care [254]. Important to mention that a single donor was selected from a donor database using Random Forrest analysis, to complement the relative deficiencies of the patient microbiota in HE and was applied after 5 days of broad-spectrum antibiotics. Interestingly, microbial functional changes induced by FMT namely increased production of secondary BA (with corresponding PiCRUST gene analysis) were observed to be linked to improved clinical outcome [252]. Safety and efficacy with less HE and hospitalization episodes for up to 1 year were reported in the extended follow-up [342]. A recent systematic review on available high-quality data concludes that FMT overall induces improvement in neurocognitive function and a reduction in severe adverse events in patients with HE [343]. Thus, FMT may well be implemented in treatment of selected cirrhotic patients with HE in the future. However, considering the complexity of chronic liver disease and advanced stage of disease in presence of cirrhosis long-lasting cure from FMT is highly unlikely. Rather as adjuvant to existing multi-faceted treatments than sole therapy, FMT may proof helpful in chronic liver disease. However, uncertainties as for dose, frequency, pre-conditioning antibiotic use as well as route of administration persist and may affect outcome. Reflecting the importance of small versus large intestine in terms of pathological bacterial translocation the PROspective, randomized placebo-controlled feasibility trial of Fecal mIcrobiota Transplanation (PROFIT) is currently ongoing delivering FMT directly to the small intestine targeting small intestinal bacterial overgrowth in compensated stable cirrhotic patients [344]. The CHIFT trial *Faecal Microbiota Transplantation for Liver Cirrhosis* (NCT04932577) is an on-going double blinded RCT with 220 patients with decompensated cirrhosis. The aim is to investigate the effect of FMT on complications, progression, and mortality of cirrhosis.

Sarcopenia is a progressive and generalised skeletal muscle disorder with low muscle mass, quality and strength which is commonly found in cirrhosis and associates with increased likelihood of adverse outcomes including falls, fractures, physical disability, mortality and post-transplantation-complications [345–347]. The gut microbiome and its metabolic products are involved in mechanisms that impact skeletal muscle mass, muscle composition, and physical function, which has been defined as the gut-muscle axis [6]. In germ-free as well as antibiotic-treated mice, muscle mass and physical function are reduced [348]. Gut- bacteria-derived metabolites affect muscle mass, muscle composition, and physical function mainly positive effects being known for SCFAs [6]. In experimental cirrhosis besides its hypermetabolic state, endotoxinemia/inflammation and frequent protein-energy malnutrition particularly reduced SCFA`s, hyperammonia and concomitant dysbiosis have been linked to sarcopenia [349,350]. Indeed, circulating levels of butyrate are inversely related to portal hypertension, endotoxemia, and systemic inflammation in patients with cirrhosis [351]. Moreover, within cirrhotic patients those with sarcopenia present with specific alterations in microbiome composition and biosynthetic function [352, 353]. Most importantly, among the observed dysbiosis depletion of Ruminoccus 2 and Anaerostipes were independent predictors for 1-year risk of complications (SBP, HE, acute kidney injury) [352]. Hyperammonemia due to at least partly impaired hepatic ureagenesis in cirrhosis results in increased uptake of ammonia by skeletal muscle contributing to development of sarcopenia at least partly via increased myostatin expression [354]. Considering the gut as main source for endotoxins, ammonia and SCFA the microbiome has been realized as one of the key targets in treatment strategies for cirrhosis-associated sarcopenia [350]. Thus, measures lowering ammonia such as rifaxmin have been reported to improve skeletal muscle proteostasis [355] but human data on other modulators of the gut-liver-axis are not available so far. **Acute-on-chronic liver failure (ACLF)** is characterised by presence of organ failure in hospitalised patients with acute decompensation of cirrhosis [356]. The 90-day mortality rates vary from 30% to 100% depending on the age, number of organ failures and the severity of systemic inflammation. ACLF develops without identifiable pre-cipitating event in up to 30% of cirrhotic patients which has been proposed to be due to pathological BT from the gut [357–359]. Responsiveness to gut-derived pro-inflammatory stimuli is enhanced in cirrhosis as has been shown examplatory for TLR-4-related sensitization to LPS and switch from apoptotic to necroptotic cell death [285]. Thus, inhibiting TLR4 signaling with an inhibitor (TAK-242) ameliorated organ injury and systemic inflammation in rodent models of acute and acute-on-chronic liver failure [285,360]. TLR4-inhibition by TAK242 inhibits however, hepatocyte regeneration [361] and thus, is currently evaluated in combination with G-CSF (which can promote liver regeneration) in patients suffering ACLF (TANGO H2020-SC1-BHC-2018–2020). Finally, a randomized-placebo controlled clinical trial is currently ongoing in decompensated patients with cirrhosis assessing the effect of FMT on time to death or re-admission due to episode of acute decompensation (including ACLF) (NCT04932577).

Use of proton-pump-inhibitors (PPI): Often overlooked but commonly prescribed are PPI which can alter the microbiome and worsen dysbiosis [362]. In terms of progression and/or initiation of chronic liver disease experimental data elegantly demonstrated that absence of gastric acid promotes bacterial overgrowth and translocation, particularly evidenced for *Enterococcus*, exacerbating alcohol-induced as well as HFD-induced metabolic liver disease [363]. In humans, PPI use increases the risk of liver disease in people with alcohol use disorder [363] supporting the role of bacterial overgrowth and PPI-induced shifts in microbiome for susceptibility and/or severity of liver injury caused by alcohol or high-fat-diet. In addition, patients with cirrhosis due to stated reasons appear particularly susceptible for associated deleterious effects. PPI users exhibit lower authochthonous taxa and higher hospital readmission rates at 30 and 90 days [362] as well as increased rates of severe infections/SBP [364] HE and decompensation [365,366]. Currently, the STOPPIT-investigation (Stop of proton-pump inhibitor treatment in patients with liver cirrhosis) addressed the effect of PPI withdrawal on relevant outcome variables in patients with complicated liver cirrhosis in a prospective multicenter, controlled, randomized, double-blind trial [367]. Nonetheless, until these data are awaited any use of PPI in cirrhosis should be restricted to clear indications.

7. Cholangiopathies (PBC, PSC)

The last few years renewed interest has been sparked regarding the role of bile, microbiome and the interplay between host immunity and bile constituents in the pathogenesis of PSC, PBC and auto-immune liver disease. A plethora of studies **report** changes in the intestinal

microbiome with cholestatic liver diseases [368,369]. Circumstantial evidence has long suggested inappropriate immunological responses to bacteria or viruses may be responsible for the development of PSC, to a lesser extend PBC and auto-immune hepatitis. Thus, it seems possible that translocation of certain gut bacteria and/or bacterial products to the liver and other systemic tissues may trigger autoimmune responses in genetically susceptible animals and humans [370,371].

PSC: More than two thirds of patients with PSC suffer from inflammatory bowel disease where the intestinal barrier is compromised by ulceration allowing bacterial product translocation and the recovery of bacterial 16 S ribosomal RNA in blood and bile [372]. This association with IBD makes PSC a prototypic gut-liver-axis-disease [373]. The convincing rational for the gut as pathophysiological driving force in PSC is based on following observations that i) small intestinal bacterial overgrowth induced by surgical blind loop causes liver injury and sclerosing cholangitis in susceptible rat strains [374] ii) microbiota in PSC patients differs from healthy individuals [375] as well as from IBD patients without PSC [376] iii) colectomy before diagnosis of PSC in CU reduces the risk of liver transplantation or death [377] iv) colectomy before liver transplantation in manifest PSC protects against recurrent PSC [378] and v) Vancomycin with bactericidial activity against gram-positive bacteria including various *Clostridium spp* known to be responsible for formation of secondary bile acids (see above) improves alkaline phosphatase level and liver histology in PSC [379] and vi) serum concentrations of lipopolysaccharide-binding protein (LBP) (marker of PBT) are increased in PSC, being associated with reduced liver-transplantation-free survival [380]. Finally, individual bacteria or "pathobionts" from human PSC microbiota have been shown to modify experimental biliary disease [381].

In experimental models, more detailed information on the pathophysiological mechanisms within the gut-liver-axis have been delineated. Besides the "leaky gut concept" (PAMPs from the inflamed "leaky" intestine draining into the portal vein) particularly the "gut homing hypothesis" on gut-derived T-cell trafficking/homing to the liver/biliary tree gained much attraction. The latter describes an aberrant expression of homing molecules (CCl25 and MadCAM-1) in PSC-livers leading to homing of α4β7 expressing memory T-cells into the liver [382,383]. This has been proposed to explain recurrence of PSC after liver transplantation if the gut (mainly colon) is left in place [378] and facilitated clinical trials on vedolizumab, which binds to α4β7 integrin on blood monocytes, thereby inhibiting their ability to enter the intestinal epithelium. Unfortunately, vedolizumab did not improve liver enzyme concentrations in PSC patients even after 1 year of treatment [384,385]. Reasons for these disappointing results are not completely clear but could relate to the long half-life of T-memory and naïve T cells known to extend up to 8 and one year, respectively [386].

Finally, the "dysbiosis-centered" view on PSC has been unraveled in more detail. In murine PSC models, e.g. Mdr2-/- mice, i) germ-free conditions or antibiotic-induced depletion of microbiota accelerated liver disease progression as compared to conventional mice [63,368,387] and ii) transfer of Mdr2-/- microbiota into healthy wild type control mice induced significant liver injury in recipient mice underlining the causal role of dysbiosis for PSC progression [388]. Aggressive subsets of bacteria potentiating liver inflammation and fibrosis (*E. faecalis* and *Enterobacteriaceae/ E.coli*) as well as protective genera (*Lachnospiraceae* being SCFA-producer) have been identified in experimental and human PSC [368]. Vancomycin is known to deplete *Lachnospiraceae* shedding light on the long-standing controversy about its use in PSC patients [389] which most recently has been shown to be of no clinical benefit [255]. Human PSC faecal samples revealed enrichment of *E. faecalis* and *Enterobacteriaceae* being most prominent in those who received antibiotcs within the last 6 months [368]. Thus, broad-spectrum antibiotics and/or vancomycin should be administered with caution in PSC patients due to potential for exacerbating disease and contributing to recurrent cholangitis by promoting enterohepatic bacterial translocation. In contrast, FMT appears an attractive measure considering the "dysbiosis-centered" view on PSC. FMT was performed in a small pilot trial consisting of 10 PSC patients describing an improvement in alkaline phosphatase levels, a measure of PSC severity, in 3/10 patients [256] in IBD trials it appears convincing that manipulation of microbiome can attenuate inflammation – and hence, appears worthwile to be further investigated in colitis ulcerosa - PSC-patients with repetitive applications achieving more long-term stabilization and potentially eubiosis. In that regard, timing of microbial therapeutic interventions might well turn out to be essential for success. FMT rescued the lethal phenotyp of germ-free MDR2-/- mice only when applied early (< 5 weeks) but not in later phases (> 6 weeks old) [368]. This should encourage new trials in PSC patients in the early phase of their disease addressing dysbiosis.

Several mechanisms have been unraveled linking dysbiosis to PSC progression which include IL17-, BA/FxR-signalling and microbial metabolites. Mice inoculated with faecal samples from humans with PSC and ulcerative colitis showed T-helper 17 cell responses, liver injury and positive mesenterial lymph node cultures which identified *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterococcus gallinarum* as culprit organisms. Moreover, treatment of these animals with an inhibitor of Th17 proliferation improved liver histology indicating that liver injury occurred through activation of this T-cell subset [381]. There has been a long interest in the role of γδ T-cells in the pathogenesis of PSC. These cells have been demonstrated in the peripheral blood of patients with PSC [390]. Recently using a MDR (-/-) knockout mice the authors showed that intrahepatic IL17A+ γδ-T cells in Mdr2-/- mice were the main cellular source of IL17. Blocking these cells or neutralizing serum IL-17 improved fibrosis in these animals. In addition, the presence of IL17A+ γδ-T-cells was confirmed in explanted PSC and HCV livers. Finally, only IL17A+ γδ-T-cells from PSC livers were capable of secreting IL-17 [391]. IL-17 pathway is now a key drug target in many autoimmune and chronic inflammatory disorders [392]; diverse therapeutic monoclonal antibodies are available but have not been tested but should be encouraged to be tested in PSC patients. An ongoing trial implements a multi-disciplinary integrative research approach to test the hypothesis that PSC develops as a consequence of a genetically driven aberrant immune response to commensal or pathogenic bacteria, and that unique genetic-immune-microbial associations may underlie development of distinct disease patterns (NCT04685200).

BA-pool and -metabolism is altered in PSC whereby suppressed BA synthesis associates with poor prognosis [63]. Thus, pharmacological substitution by obeticholic-acid, an FxR-agonist, demonstrated reduced serum alkaline phosphatase, as marker of disease severity, during an initial 24-week treatment period in a phase II, randomized, double-blind, placebo-controlled, study [278]. The result was sustained during the 2-year, long-term extension [278]. Modulation of BA-pool by ASBT-inhibitors is known to be of clinical benefit in humans with cholestatic liver disease reducing circulating bile acid concentrations and thus, pruritus [218,393–395]. Moreover, ASBT-inhibition attenuates hepatic BA pool size and hepatobiliary inflammation/cholestasis in antibiotic treated *mdr2* − /− mice [368]. Volixibat as ASBT-inhibitor is currently under investigation in human PSC (NCT04663308).

In terms of microbiota-derived metabolites and PSC high serum levels of TMAO were found to predict reduced liver transplantation-free survival [396]. Similarly to ALD, treatment with AhR-ligand Indole-2-aldehyde reduced inflammation and fibrosis in the mouse DDC diet model of sclerosing cholangitis [397]. Considering the pleiotropic effects of AhR on gut barriers and liver phenotyp indicate that the microbial indole pathway of tryptophan metabolismus should also be investigated in human PSC [398]. Exploiting the gut-liver-axis further hopefully will be rewarding to treat this devastating disease which often culminates in liver transplantation.

PBC: Lipoteichoic acid, a component of the bacterial cell wall has been identified in the bile ducts of PBC patients [399]. In addition, PBC is characterized by selective immune-mediated biliary injury due to the loss of immune tolerance against mitochondrial antigens [400]. Well

conducted epidemiological and case control studies have pointed to a crucial role of urinary tract infection and *Escherichia coli* in increasing the risk of PBC, probably through molecular mimicry between human and bacterial PDC-E2 [401]. Biliary epithelial cells have the unique capability to express TLR and antimicrobial peptides and to secrete cytokines. Cholangiocytes in PBC seem to acquire MHC class II and play an active role by changing their phenotype to attract inflammatory cells [400,402–404]. However, the contribution of the intestinal barrier to the development of PBC remains obscure.

8. Alcohol-related and Non-alcoholic fatty liver disease

Alcohol-related liver disease (ALD) is the leading cause of liver cirrhosis and liver-related death worldwide. Globally, ALD cirrhosis was responsible for 0.6% of disability adjusted life years, 0.9% of all deaths, and 47.9% of all liver cirrhosis-attributable deaths in 2010 [405]. Excessive alcohol use over a prolonged period can lead to ALD. It can range from hepatic steatosis, steatohepatitis, acute alcohol-related steatohepatitis, and alcohol-related fibrosis to cirrhosis. Liver steatosis and early stage steatohepatitis are reversible after a few weeks of abstinence [406]. Persistent alcohol consumption however, can progress to liver fibrosis and cirrhosis, which can lead to portal hypertension or liver failure [407]. It is estimated that one in ten heavy drinkers (over 60 g a day) will develop alcoholic liver cirrhosis [123]. In terms of therapeutic options, severe alcohol-associated hepatitis is most limited due to lack of efficient evidence-based treatment strategies. Survival rates in patients with severe alcohol related hepatitis are poor with mortality rates up to 30% and the majority of patients will need liver transplantation [408].

Multiple factors are involved in the development of ALD. Alcohol and its metabolites induce reactive oxygen species and hepatocyte injury, though mitochondrial damage and ER stress [409–413]. In addition to direct hepatocyte injury, patients with excessive alcohol consumption have an increase in systemically available bacterial products, compared to healthy subjects [292,414]. PBT detected in patients with ALD has been directly linked to an increase in infection-related mortality in patients with cirrhosis [415]. Intestinal dysbiosis is more common in ALD for several reasons including: environmental, dietary and metabolic factors [416–418], genetics [419], reduced intestinal motility [420], hypochloridia [421,422], altered immune response from Paneth cells and intestinal epithelial cells, and shifts in BA-production [423].

Alterations in gut microbiota can occur in patients with alcohol use disorder (AUD) even before there is evidence of liver disease [424]. Small and large bowel intestinal overgrowth and dysbiosis have been reported in humans and mouse models with chronic alcohol intake [425–428]. Metagenomic studies have demonstrated that the intestinal microbiome is markedly modified with a reduction in diversity and a greater abundance of *Proteobacteria* and *Enterobacteriaceae* species accompanied by a decrease in *Bacteroidetes* and *Firmicutes*, as well as of *Lactobacillus* species [427,429,430]. Interestingly, patients with AUD also displayed reduced fungal diversity and Candida overgrowth, as well as translocation of Candida β-D-glucan in the systemic circulation, indicating a role of the gut mycobiome (fungi and yeast) in pathogenesis of ALD [431]. In mouse models of ALD, intestinal fungal overgrowth was treated with antifungals, and subsequently β-glucan translocation decreased and ALD improved [431]. Severe alcohol-related steatohepatitis is the disease in the broad spectrum of ALD where specific microbiomal changes have been described, namely greater quantities of *Bifidobacteria* and *Streptococci* [432]. Moreover, the degree of susceptibility to alcohol-induced liver injury was observed to be transmissible from patients to mice by fecal microbiota transplantation [432]. Thus, the individual susceptibility to alcohol-induced liver injury at least partly is driven by differences in microbiome composition and metabolites [432].

Intestinal barrier dysfunction and thus, intestinal hyperpermeability has been detected in humans and animal models of chronic excessive alcohol intake [433,434]. In patients with chronic AUD and in mouse models fed alcohol, in addition to the direct effect of alcohol and metabolites on the intestinal mucosa [435], increased intestinal inflammation leads to a subsequent disruption of the intestinal barrier function and translocation of microbial products. Loss of epithelial tight junction proteins is mediated by inflammatory cytokines such as tumour-like necrosis factor-α (TNF-α) leading to increased permeability, bacterial translocation of bacterial products and liver inflammation. TNF receptor-1 (TNFR-1) expressed on intestinal epithelial cells was the specific target of TNF-α secreted from inflammatory cells in the lamina propria [436]. Moreover, in both humans and mice after acute and chronic alcohol consumption, there is an increment in the levels of endotoxins (LPS), bacterial DNA, particularly marked in chronic intake [437,438].

Beyond the role of dysbiosis and inflammatory changes observed in ALD, AUD can induce changes in many potentially bioactive metabolites. Mouse models fed alcohol have a reduced capacity to produce saturated long-chain fatty acids (LCFAs), with a consequently reduction on intestinal bacteria dependent on LCFAs, such as *Lactobacillus* [429]. Alcohol-induced intestinal dysbiosis can significantly alter BA metabolism, increasing secondary BA conversion, while diminishing primary BA reabsorption. This increase in secondary BA leads to inactivation of the farnesoid X receptor (FXR), with a subsequent reduction in antimicrobial peptides in the gut lumen. Thus, the intestinal milieu becomes more susceptible to bacterial overgrowth [439,440]. In that regard cytolysin-producing *Enterococcus faecalis* has been observed to be increased in alcohol related hepatitis and its presence correlating with liver disease severity and mortality patients suffering alcoholic hepatitis [441]. Bacteriophages specifically targeting cytolytic *Enterococcus faecalis* decreased cytolysin in the liver and abolished ethanol-induced liver injury in humanized mice colonized with bacteria from faeces of patients suffering alcoholic hepatitis [441]. This trial did present the first evidence that by targeting a single gut pathopiont can deliver benefits in treating liver diseases. A phase-I-trial by the authors is currently planned (personal communication Prof. B. Schnabl). Moreover, altered tryptophan metabolism by bacteria has been shown in experimental and human ALD [442]. In experimental ALD model engineered *Escherichia coli Nissle* overproducing tryptophan-metabolites indole-3-acetic acid and – lactic acid increased intestinal IL22-expressing type 3 ILC, up-regulated intestinal IL22- and Reg3b,3 g-expression, reducing bacterial translocation to the liver and ameliorating liver disease [443]. Corresponding results were reported utilizing engineered *Lactobacillus reuteri* producing IL22 in a mouse model of ALD [442]. To our knowledge, no clinical trial utilizing such engineered bacteria in ALD is ongoing currently, but IL22-agonist F-652 was tested in a phase-II trial in 18 patients with moderate/severe AA [444]. IL22 reduced markers of inflammation, augmented markers of liver regeneration being associated with high rate of improvement in scores used to rank severity of alcoholic hepatitis and liver insufficiency [444]. The same approach is tempting to speculate to be similarly beneficial to prevent post-surgical infections, particularly after liver surgery. Type 3 ILC has been shown to restrict dissemination of intestinal bacteria (else causing at least partly post-operative infections) via IL22 that controls the expression of antimicrobial peptides in hepatocytes [445]. In the same line of mechanisms related to microbiome-derived metabolites, gut microbial TMA is elevated in patients suffering alcohol-associated hepatitis and contributes to ethanol-induced liver injury in mice [55]. Indeed, reducing gut microbe-dependent TMA/O production by TMA lyase inhibitors protects from experimental ethanol-induced liver injury [55].

Currently, many avenues of therapy are under investigation for the treatment of ALD in humans focusing either on stabilizing the intestinal barrier and/or modulating the microbiome. Zinc deficiency leads to epithelial barrier dysfunction in the distal small intestine contributing to leaky gut in ALD mouse models. Supplementation with zinc restored intestinal barrier function [446]. FXR agonists could improve intestinal FXR signalling and thus, antibacterial peptide synthesis [447] and revert

vascular barrier damage in the gut. Until date, only one phase II trial (ClinicalTrials.gov number, NCT02039219) sought to explore the effect of obeticholic acid, semi-synthetic FXR agonist, in patients with moderate ASH. The trial was terminated early due to reports of hepatotoxicity associated with obeticholic acid. The much-awaited phase 3 RCT utilizing an antibiotic (amoxicillin-clavulanic acid) in combination with prednisolone compared to prednisolone alone showed no significant improvement in 2-month mortality, but reduction in infection rate (ANTIBIOCOR ClinicalTrials.gov number, NCT02281929) [448]. As for rifaximin its use has been shown to be safe even in severe alcohol-related hepatitis and associate with a reduction in clinical complications [223]. The reported lower number of infections and trend towards a lower rate of ACLF and mortality induced by rifaximin in these patients favours its use in alcohol-related hepatitis. In terms of probiotics, alcohol-induced dysbiosis in patients with mild alcohol-related hepatitis was partially improved by alcohol withdrawal and 5-day probiotic with oral supplementation of *Bifidobacterium bifidum* and *Lactobacillus plantarum* 8PA3 [229]. The GALAXY consortium currently tests Profermin®, an oat drink fermented by Lactobacillus plantarum, in a phase 2 RCT (NCT03863730) for its effect on progression in ALD. Two small studies investigating the role of faecal microbiota transplant (FMT) from healthy donors into patients with severe ASH showed reduced disease severity, reduced or resolved portal hypertension-related complications, and improved 1-year survival [232,449]. Importantly, co-existence of donor and recipient species was seen up to 12 months post-FMT [232]. More recently, the same authors presented data from their case-matched control study demonstrating that FMT improved survival rate and reduced liver-related complications compared with pentoxifylline [450]. A RCT comparing FMT vs. corticosteroid therapy in patients suffering severe alcoholic hepatitis is currently running (NCT03091010). Moreover, Bajaj's group assessed the effect of FMT by capsules containing freeze-dried microbiota from healthy donors on alcohol craving and drinking in ALD patients (IMPACT-trial; NCT05548422).

Metabolic dysfunction-associated steatotic liver disease (MASLD): MASLD prevalence is globally around 30% increasing and is the fastest growing cause of chronic liver disease worldwide. The prevalence of MASLD is increasing in parallel with the global rise in obesity and type 2 diabetes mellitus (T2DM) [451]. Almost 25% of individuals with liver steatosis progress to metabolic steatohepatitis (NASH). A high-fat and low-fibre diet, common among patients with MASLD, alters the microbiome, leading to intestinal barrier dysfunction and facilitates the portal influx of PAMP/MAMPs, worsening inflammation and metabolic abnormalities [452]. The microbiome composition of patients with MASLD is characterized by reduction in diversity and increase in *Bacteroidetes* and *Proteobacteria* and decrease in *Firmicutes* and *Prevotella* species [453–455]. The reduction in *Prevotella* and increase in gram-negative bacteria is associated with liver fibrosis progression [456,457]. The increased abundance of alcohol-producing bacteria in microbiomes of MASLD and NASH patients correlated with elevated blood ethanol concentration [458]. Butyrate-producing bacteria such as members of the Firmicutes phylum are decreased in patients with MASLD [459]. Indeed, one randomized clinical study of specifically designed isoenergetic diets, demonstrated that when SCFA-producing strains promoted by dietary fibres were in abundance the patients with type 2 diabetes mellitus presented with an improvement in hemoglobin A1c levels, partly through increased glucagon-like peptide-1 production [460]. Another recent randomised study compared isocaloric diets of low in carbohydrate high fats versus high carbohydrate low fats diets in type 2 diabetes and MASLD. Low carb high fat diet lead to better glycemic control, improved liver histology and weight loss despite an eucaloric diet [461], suggesting that changes in gut function and microbiome might play a role. These differences in carbohydrate and amino acid metabolism in gut microbiome are particularly present in patients with MASLD-associated advanced fibrosis. These substrates can reach the liver through the enterohepatic system and further worsen inflammation. Changes in gut microbiota promote also liver steatosis and inflammation through the entry of PAMPs, mainly shown for toll-like receptor-4 (TLR4) and TLR9 agonists in mice, leading to enhanced hepatic inflammation [462]. As for MAMPs and their role in MAFLD increased systemic trimethylamine n-oxide (TMAO) production [54] and hepatic bile-acid synthesis, with decreased production of phosphatidylcholine are well-accepted features. TMAO has been linked to hepatic steatosis and progression of MASLD in humans and mouse models [463–466] at least partly via its inhibitory effect on FxR-signalling [467]. Most importantly, increased systemic TMAO-levels associate with all-cause mortality in MASLD/MASH independently from traditional risk factors [468]. In other words, at the same serum TMAO-levels such association with mortality was not present in patients without fatty liver disease underlining the prognostic key role of the liver.

In addition to the intestinal dysbiosis, in patients with MASLD, recently, a link has been established between high-fat diet, gut microbiota abnormalities and increased bacterial penetrability. This is linked to reduced mucus layer, redistribution of tight junction proteins of the epithelial barrier and low-grade gut inflammation [469–472]. Again, BA play an essential role for these phenomena. In experimental animal models BA sequestrants have been demonstrated to attenuate liver and bile duct injury in Mdr2-/- mice [60], prevent hepatic steatosis, inflammation and fibrosis in murine models of NASH [473]) and even to reverse liver injury [474]. These beneficial effects were associated with changes in microbiome and BA composition being linked to improvement in insulin resistance. Patients with MASLD present with an upregulation in hepatic bile acid synthesis and an increase in abundance of bacteria producing secondary bile acids subsequently being associated with reduced FXR-mediated signalling in the intestine and the liver [464]. Such reduction in FXR-signalling can lead to disruption of the gut vascular barrier, decreases in mucin-production, and increases in bacterial permeability. Indeed, administration of FXR agonists such as obeticholic acid has been shown to re-establish the integrity of the gut barrier [475,476]. Moreover, FXR activation protects against MASLD via bile-acid-dependent reductions in lipid absorption. [477] Indeed, obeticholic acid 25 mg significantly improved fibrosis and key components of NASH disease activity among patients with NASH. The results show clinically significant histological improvement [263] and the FDA has assigned a Prescription Drug User Fee Act (PDUFA) target action date of June 22, 2023 for obeticholic acid and its use for treatment of NASH. Vonafexor, a second generation highly specific FxR-agonist with separate chemical composition has recently been shown in a phase IIa- RCT in patients with suspected fibrotic NASH to induce potent liver fat reduction, improvement in liver enzymes, weight loss, and a possible renal benefit [478]. ASBT-inhibition has been shown to exert multiple events relevant to the pathophysiology of MASLD such as i) increase cholesterol consumption since lack of feedback inhibition on de-novo BA-synthesis via CYP7A1 in the liver increases catalysis of cholesterol into BAs MASLD ii) increases GLP-1 secretion known to be induced by BA. Although mouse models indicated benefits by ASBT inhibition in MASLD [479,480] volixibat showed no effect on liver steatosis or liver injury in NASH patients [260]. Whether combination of ASBT-inhibition with FGF15/19 treatment improves the therapeutic efficacy in MASLD has been proposed in animal models [481] and needs further evaluation.

Finally, FGF19/21 analogs are being tested in MASLD reporting benefits in reducing steatosis [482] and to some extent on liver injury and fibrosis [483]. Mechanism of action for FGF19/21-analogs include besides the stated hepatocellular suppression of BA synthesis the promotion of beta-oxidation of fatty acids and inhbiting lipogenesis in the liver, improvement in insulin sensitivity (particularly in skeletal muscles and adipose tissue) as well as influences on gut microbial composition and function [484].

Besides modulation of BA-/signalling treatments for MASLD addressing the gut-liver-axis focus on altering the gut microbiome and include antibiotics, probiotics, prebiotics, synbiotics and FMT. As for

antibiotic use one phase II clinical trial involving potent next-generation macrolide, solithromycin, showed a decrease in ALT and non-alcoholic fatty liver disease activity score (NAS) in patients with steatohepatitis [485]. In principle by modulating the gut microbiome and gut barrier, pro-, pre- and synbiotics could potentially improve MASLD. In the clinical setting, several probiotics have been tested, particularly *Lactobacillus, Bifidobacterium*, and *Akkermansia muciniphila*. As for the latter, supplementation with pasteurized *Akkermansia muciniphila* in a double-blind RCT-pilot-study in overweight insulin-resistant volunteers, reduced plasma LPS-level, attenuated markers of liver injury (AST, yGT) and improved insulin-sensitivity while overall gut microbiome structure was unaffected [241]. This observation led to the recognition of pasteurized *Akkermansia muciniphila* as a novel food by the European Food Safety authorities in 2021. Two large-scale meta-analysis including 28 clinical studies [240] and 22 randomized-controlled trials [179] demonstrated that probiotics improve liver enzyme levels and attenuate inflammation, lower body mass index and improve diabetes and dyslipidemia. Common prebiotics such as oligosaccharides, inulin or lactulose, can increase the growth and activity of probiotics [486] and potentially protect from MAFLD through the production of SCFAs, such as butyrate [487]. Bomhof et al. demonstrated that the prebiotic oligofructose improved liver steatosis and NAFLD activity score in patients with steatohepatitis [239]. Food4Gut randomized placebo-controlled trial tested 3 months inulin-based prebiotic dietary fiber in obese patients with at least one obesity-related metabolic disorder and observed beneficial effects on blood pressure, insulinemia and calprotectin (marker of intestinal inflammation) [488,489]. A meta-analysis including studies with prebiotics reported improvement of metabolic and liver factors [490]. Considering the excellent safety profile of pre- and probiotics and the quality of evidence available both could be utilized as a common complementary therapeutic approach in MASLD.

FMT from a patient with MASH/MASLD and hosting ethanol-producing *Klebsiella pneumoniae* into germ-free mice likewise caused steatohepatitis [491]. Most interestingly, selective elimination of this ethanol producing strain by ex-vivo bacteriophage treatment prior to FMT into mice prevented development of steatohepatitis [491]. This exemplifies the potential use of bacteriophages for targeted microbiome-modulation in treating liver diseases. However, challenges of applying bacteriophages into clinical practice/trials are multiple. These include the host range of some bacteriophages (namely what bacterial genera, species it can lyse), the development of resistance by the host bacteria and kinetics of the digestive tract.

FMT appears as a promising therapeutic option in MASLD patients and has recently been reviewed [492]. At least seven clinical trials assessed the effect of FMT on insulin sensitivity in patients with various degree of metabolic derangement/ syndrome with or without obesity [493,494] [495–498] delivering controversial results. Two studies reported an improvement in insulin sensitivity at 6 weeks in patients with the metabolic syndrome receiving FMTs from lean donors compared to placebo [493,494]. Craven et al., however, found that FMT from slim donors to individuals with MASLD did not affect hepatic steatosis or insulin sensitivity, but improved gut permeability [495]. Finally, Moncanu et al. reported that FMT in severe obese patients with T2DM did lead to significant improvements in HOMA2-IR only when administered in conjunction with daily oral low-fermentable, but not high-fermentable, fiber supplementation [496]. Potential explanations for this heterogeneity in impact of FMT on MASLD and/or insulin resistance could be the presence or absence of obesity and most importantly the baseline microbiota composition in recipients. FMT has been reported to exert better clinical efficacy in lean MASLD as compared to obese MASLLD such as decreasing liver fat and being accompanied by a more marked restoration of gut eubiosis [247]. Baseline intestinal microbiota composition appears to be decisive for metabolic success of FMT and thus, drives response to lean donor fecal microbiota transplantation in as much as its impact on insulin sensitivity depends on a decreased fecal microbial diversity before treatment [499]. This highlights the necessity to individualize FMT and phenotype each recipient thoroughly before any fecal microbial therapy. Finally, benefits achieved by FMT have been reported to be transient and not durable [496,499]. Thus, it has been questioned whether FMT alone, without other treatments (e.g. diet and life-style interventions) can exert sufficient long-lasting effects considering the course of disease extending over years and being multifactorial in pathogenesis [500].

Oral therapy with non-absorbable carbons of controlled porosity (YAQ-001) selectively modulates stool microbiome and its function [501] and thus, safety and tolerability of Yaq-001 is currently under investigation (CARBALIVE-SAFETY, NCT 03202498). Another ongoing study aims to assess the feasibility and safety of endoscopic duodenal mucosal resurfacing in this population (NCT03536650). By targeting the duodenal surface, an abnormal signal to endogenous insulin-sensitive tissues is transmitted due to reduced nutrient exposure or contact with the duodenal mucosa leading to significant metabolic effects and improvement in liver parameters [502]. Other strategies aiming to improve insulin resistance and metabolic dysfunction by Glucagon-like peptide-1 analogues have shown positive results in terms of significant steatohepatitis resolution without differences in fibrosis regression [503–505]. Finally, large-scale international consortia are currently running collecting comprehensive genetic, epigenetic, transcriptomic, metabolomic, proteomic and metagenomic datasets. The goal is to understand the drivers of interpatient variation in disease pathophysiology and severity, to utilize this information to develop and validate biomarkers and to individualize therapy (NCT04442334).

9. Modulation of viral hepatitis

9.1. Chronic hepatitis B (CHB)

Compared to metabolic and alcohol-related liver disease, less attention has focused on the interactions between hepatitis B virus (HBV)-infected patients and human gut microbiota. The immune response against HBV mainly includes innate immunity and adaptive immunity. The gut has been proposed to exert a regulatory effect on the development of CHB infection. Indeed, sterilization of the gut by antibiotics increased tolerance to HBV exposure in adult mice preventing them from rapidly clearing HBV similar to their young counterparts [506]. Thus, age-related immune-clearance of HBV requires the establishment of gut microbiota and the maturation of gut bacteria might transmit signals to the liver to break liver tolerance, resulting in rapid HBV clearance.

On the other hand, HBV infection has been demonstrated to alter the composition of the microbiome in a mouse model by hydrodynamic injection to mimic either acute or chronic HBV infection [507]. Moreover, antiviral treatment by entecavir effectively corrected dysbiosis developed in persistent HBV-infected mice [508]. In humans, data are more heterogeneous but nonetheless, intestinal flora of chronic HBV carriers, CHB patients, and hepatitis B-induced cirrhosis patients present with notably decreased *Bifidobacteria* and *Lactobacillus* levels, while *Enterococcus* and *Enterobacteriaceae* levels are significantly increased compared to healthy subjects [509].

Chassaing et al. reported that the development of liver disease through HBV is partly mediated via gut microbiota [510]. In patients with HBV-cirrhosis functional gene arrays data showed that genes relevant to including amino acid metabolism, lipid metabolism, nucleotide metabolism, and isoprenoid biosynthesis were significantly decreased [511]. Zheng et al. identified dysbiosis from the faecal microbiota of patients with CHB, HBV-cirrhosis and hepatocellular carcinoma [512]. There was an increase in potentially pathogenic bacteria and a loss in potentially beneficial bacteria. The eight most abundant phyla were *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia*, *Cyanobacteria*, *Fusobacteria* and *TM7*, together accounting for 99.9% of total sequences [512].

In patients with chronic HBV liver failure, LPS may be related to the

severity of the disease [513], via activation of various signalling pathways, leading to a series of immune defence response [514,515]. Interestingly, one study found that mice, subjected to TLR4 silencing were able to clear HBV and produce antibodies in 8 weeks [506]. These studies may imply that targeting the gut microbiota or TLR4 could be an effective pathway to prevent and treat of HBV-induced liver disease. Furthermore, there is data showing increased intestinal barrier permeability in CHB patients. In one study, serum zonulin (a protein regulating intercellular tight junctions and intestinal permeability) and copeptin were both significantly reduced in CHB patients; these negatively correlated with viral load [516]. In this line, Wang et al. demonstrated significantly higher levels of zonulin in HBV-infected patients with HCC compared to this with HBV cirrhosis and CHB. The implication is that serum zonulin levels most likely reflect systemic circulatory dysfunction in cirrhosis [517].

Research for gut-based therapies in patients with CHB is scarce. A mouse model study showed that entecavir had significant effects on gut microbiota dysbiosis restoring the presence of *Akkermansia, Lacnospiracea* and *Marvinbryantia* [508]. A study involving patients with CHB showed that probiotics containing six strains of lactic acid bacteria once per day for 4 weeks led to a significant improvement in small intestinal bacterial overgrowth, with no amelioration of liver tests, Child-Pugh Scores and intestinal permeability. Patients with cirrhosis and minimal hepatic encephalopathy received *Clostridium butyicum* and B infantis probiotics three times daily for three months. Significant improvements in ALT, AST, bilirubin and albumin levels and psychometric tests were reported [518]. In a case series, five patients with HBeAg-positive CHB with ongoing antiviral therapy reported HBeAg clearance in a significant proportion of after receiving FMT [519]. Chauhan et al. reported on FMT in HBeAg positive patients under antivivral therapy for over a year. The 14 patients received six cycles of gastroscope FMT at four-week intervals. HBeAg seroclearance was not superior in the FMT arm [520]. Given the growing interest in this field, there are four trials are registered in the setting of CHB and FMT.

9.2. Chronic hepatitis C (CHC)

The presence of viruses in the gut, or gut virome, may interact with physiological gut microbiota leading to microflora changes. Hepatitis C virus (HCV) has been detected frequently in the stool of patients [521]. It is unclear how the virus interacts with local microbiota. In patients with advanced liver disease due to HCV, certain families of bacteria have been isolated namely, abundance of *Bacteroidetes*, *Prevotella* with *Acinetobacter*, *Veillonella*, *Phascolarctobacterium* and *Faecalibacterium* [522]. One study showed a slight shift in the microbiota following HCV eradication, although significant changes were not detected shortly sustained virological response [523]. Previous data supported this finding in patients treated with ribavirin and pegylated interferon demonstrating no direct impact on gut dysbiosis, and increase in bile acids [524]. Specifically, less *Akkermansia municiphila* was found in HCV infected patients with higher fibrosis grades. It is thought that this group of bacteria could have a major role in the progression of HCV infection and liver damage [525]. Microbiota also seems to vary according to the genotype [526]. Furthermore, bacterial translocation can be seen in earlier stages of the disease before the development of cirrhosis [527].

Data regarding therapies aimed at modulating the gut microbiota in patients with CHC are lacking. A heat-treated *Enterococcus faecalis strain FK-23* was administered to 39 HCV and significantly reduced transaminases at 3 and 36-months, without impacting viremia [528]. In HCV-infected patients with cirrhosis, probiotics showed a beneficial effect [529]. It was suggested that in HCV patients, supplements with *Lactobacillus acidophilus* could aid in antiviral and antibacterial activities [530] and that a healthy microbiome could enhance natural killer cell efficacy against the virus [531]. In the field of HCC, animal models infected with HCV, a probiotic mixture seemed to suppress HCC growth via Th-17 cells and interleukin-17 [532]. Another study revealed that a probiotics significantly increased the number of *Prevotella* and *Oscillobacter* bacteria, known to produce antinflammatory cytokines via Th-17 cells. These exposed mice had a slower tumoral progression [533]. Future investigation is required to demonstrate that microbiota targeted therapy can prevent disease progression.

10. Metabolism, efficacy and toxicity of drugs

The unique human microbiome is crucial not only for the innate maintenance of health, but also in processing exogenous compounds such as drugs and modulating response to them. For instance, the antidiabetic drug metformin has been evidenced as potent inducer of *Akkermansia muciniphila* which is known to improve insulin sensitivity and glucose homeostasis in type 2 and type 1 diabetes [534,535]. Hence, this effect on gut microbiome has been identified as major confounder in studies addressing type 2 diabetes [536]. This observation also raises the realistic suspicion that also other drugs could exert some of their beneficial effects via associated changes in microbiome composition and/or function. Moreover, microbiome-encoded enzymes may represent potential intermediate targets to alter one of the four phases of drug pharmacokinetics: absorption, distribution, metabolism, and excretion, thus intensifying the effect. Inter- and intra-individual temporal microbiota diversity or dysbiosis may have an important clinical significance because microbiota-induced bioactivation of prodrug formulations may fluctuate and vary. In fact, pharmaco-metabolomics and pharmaco-microbiomics have been growing fields of development to predict and/or evaluate drug metabolism, based on metabolic phenotypes. Certain drugs have previously been studies regarding a direct link between their efficacy and gut microbiota: levodopa [537], lactulose [538], irinotecan [539], and digoxin [540]. Any of the phases of drug kinetics can be altered. Lovastatin or sulfasalazine are directly activated by the gut microbiota [541]. The bioavailability and uptake of drugs including simvastatin and amiodarone are influenced by the microbiota or by co-administration of probiotics through unknown mechanisms [542,543]. Irinotecan toxicity can be increased by β-glucuronidase activity and selectively inhibited by antibiotics or specific microbial β-glucuronidase inhibitors [544]. Specific strains of *Eggerthella lenta* can inactivate digoxin [545]. Hepatic detoxification of paracetamol is competitively downregulated by the gut microbial metabolite *p*-Cresol [546]. In theory, probiotic supplementation could homogenize and increase patients' responses to drugs. Notwithstanding, there is also a risk to potentially generate bio-inactive or toxic metabolites. In germ-free mice, the activity of drug-metabolizing enzymes was different compared to conventional mice. Supplementation with probiotic VSL#3 (genera *Bifidobacterium, Lactobacillus*, and *Streptococcus*) modulated the mRNA and protein expression levels of many detoxifying enzymes in these mice increasing the activity of Alcohol dehydrogenase 1, whereas decreasing UDP glucuronosyltransferase family 1 [547].

Compelling evidence is accumulating demonstrating that the gut microbiome modulates responses to chemotherapy [548,549] and immunomodulatory therapy [550–555]. The latter has particularly gained much attention as for therapeutic efficacy of immune-check-point-inhibitors such as anti-PD1/PD-L1-therapy for the treatment of cancer [552–555]. Studies in germ-free mice revealed that FMT from PD1-blockade responsive patients, but not from non-responders, could restore enhanced anti-tumor immunity [552, 554]. Moreover, a correlation was found between clinical responses to PD1-blockade and the relative abundance of *A. muciniphila* [552]. In fact, oral supplementation with *Akkermansia muciniphilia* in germ-free mice humanized with faeces from patients not responding to the checkpoint inhibitors could restore the treatment efficacy [552]. Likewise, other bacteria have been reported to enhance efficacy of checkpoint-inhibitor therapy including *Bifidobacterium pseudolongum*, *Lactobacillus johnsonii*, and *Olsenella species* [555]. As driving mechanism, the bacterial metabolite, inosine has been demonstrated to achieve increased systemic translocation due to gut-barrier dysfunction

induced by immunotherapy and activates antitumor T cells in various mouse models of cancer [555]. Most convincingly, oral and systemic administration of inosine led to reduced tumor weights and increased antitumor immunity rendering its use for clinical applications highly attractive. A prospective randomized open label study has just been completed assessing the add-on benefit on overall survival exerted by oral inosine in combination with PD-1/PD-L1 inhibitor ± chemotherapy in patients with malignant advanced solid tumors (NCT05809336). As for the gut-liver-axis and liver cancer/HCC, the use of checkpoint-inhibitors are now integral part of systemic treatment [556, 557]. Nonetheless, a large proportion of patients unfortunately, do not respond and, thus, modulation of responsiveness via the microbiome seems promising. Hinting towards such clinical impact on the responses of hepatobiliary tumors treated with anti-PD-1/-PD-L1 immunotherapy are distinct microbiota profiles unravelled by fecal metagenomics showing enrichment of high-inosine producing species such as *Akkermansia* in responding patients [558].

A trial testing FMT to overcome resistance to Atezolimumab/Bevacizumab (FLORA NCT 05690048) is actively recruiting patients. Probiotics (*Lactobacillus rhamnosus* Probio-M9) are currently being studied to enhancetreatment efficacy of PD-1 Inhibitors in HCC patients (NCT05032014). Vice versa, many experimental pre-clinical data demonstrated reductions of anti-tumor effects by checkpoint-inhibitors in various entities induced by antibiotics known to cause dysbiosis and profound changes in microbiome function. Ethical reasons will understandably impede any randomized clinical trial on the impact of antibiotics on therapeutic endpoints in HCC patients. However, antibiotics have been reported in a recent meta-analysis to associate with worse treatment-related outcomes in cancer patients treated with immune checkpoint inhibitors [559], thus, strongly arguing against their use in this setting.

11. Liver regeneration and tumorigenesis

Feasibility and success of liver resections, mainly performed for oncological reasons, does depend on functional reserve of the remnant liver and its **regenerative capacity**. Fortunately, the liver has an outstanding regenerative capacity for which the gut-liver-axis emerges as key modulator. In experimental models, gut bacterial depletion by non-absorbable antibiotics or colon resection suppress liver regeneration after partial hepatectomy [560,561] which can be normalized by FMT [562]. Gut-derived factors involved in modulating liver regenerative function are bacteria and bacterial products, metabolites and BA/derivatives as well as cytokines.

BA signaling is required for normal liver regeneration with elevated BA levels accelerating regeneration, and decreased levels inhibiting liver growth [563,564]. This corresponds to the clinical observation in patients undergoing major hepatic resections that liver regeneration volumes and rates one week after hemi-hepatectomy are positively associated with serum bile acid levels and those patients with external drainage and thus, lower BA levels regenerate slower [565]. This is in accordance with the early experimental observation that liver regeneration is attenuated in absence of the primary nuclear bile acid receptor FXR [424]. Conventional pan-FxR-knock out mice present with more pronounced suppression of liver regeneration as compared to liver-specific FxR-deletion suggesting that FxR-activation not only within the liver but also in other tissues contributes to liver regeneration [566]. In concordance, the FxR-agonist OCA accelerates liver regeneration after portal-vein-embolization in a rabbit model [567] indicating the potential usefullness of FxR-agonists also in humans. TGR5 is likewise involved in liver regeneration evidenced by reduced liver regeneration in TGR5 knock-out mice after partial hepatectomy [568]. Particularly microbiota-controlled TGR5-activation has been proposed to contribute to liver regeneration [569]. Immunosuppressive effects of secondary BA, derived from 7-alpha-dehydroxylation of gut microbiota, is mediated by TGR5 [570] which inhibits LPS-induced cytokine release and reduces liver injury [571]. Moreover, TGR5 exerts multiple hepatoprotective effects due to its enhancing effect on cholangiocyte-mediated bile secretion and gall-bladder dilatation reducing BA overload in the remnant liver and limiting hepatocyte necrosis [568]. Testing dual FxR/TGR5-activation, by INT-767 would thus appear most reasonable but has not been performed to our knowledge.

As for gut-derived metabolites SCFA and indoles as AhR-ligands have been demonstrated in experimental models to be involved in liver regeneration. Butyrate induces hepatic differentiation of mesenchymal stem cells in 3D collagen scaffolds [572]. AhR knock out mice have reduced liver size with variable degrees of fibrosis [573] but after partial hepatectomy liver regeneration is improved [574]. In terms of bacterial cell wall components and their role for liver regeneration mostly addressed is LPS. Excess LPS can induce various types of liver injury but at lower doses deliver benefits in the process of liver regeneration. As for the latter, mechanisms have been delineated including LPS-TLR4-dependent activation and YAP1 signaling that promotes Sox9 +HNF4α+ hepatocyte- mediated liver regeneration after hepatectomy [575]. Overall impact of LPS on liver regeneration does depend on dose and duration of LPS exposure as well as underlying pathology initiating liver regeneration. The impact of translocating bacteria to the liver on its regenerative capacity has elegantly been shown by Beldi et al. demonstrating that colonization of the murine liver by circulating intestinal microbes, mostly gut-derived, impairs liver regeneration [445]. Regenerative capacity of the liver is dependent on its capability to clear systemic bacteria for which activated hepatic CCR6 + -innate lymphoid cells (ILC-subtyp 3) are key. ILC3 proliferate in response to murine partial hepatectomy and control hepatocyte-derived antimicrobial peptide production. This process is dependent on the presence of microbiota since absent in germ-free mice and is mediated via IL22 produced by ILC3 [445]. IL22 is a critical factor modulating homeostasis in the liver promoting anti-apoptotic, mitogenic and antioxidant molecules in damaged hepatocytes, increasing replication of hepatocytes and contributing to liver regeneration [576]. Another cytokine shown to be pro-regenerative in a non-injurious model of liver resection is IL33, which modulates serotonin release from the gut, namely enterochromaffine cells [102]. Most interestingly exogenous serotonin agonists could normalize liver regeneration in IL33 knock-out mice undergoing partial hepatectomy [102]. Serotonin has been shown before to fundamental for liver regeneration [577] and accredit the fact, that the gut microbiome represents one if not the largest resource of serotonin underlines the basic nature of this liver-gut-axis for liver regeneration.

In cirrhosis liver regeneration is diminished due to multiple reasons [578] including limited hepatocyte self-renewal capacity, reduced availability of growth factors stimulating regeneration [579] but also diminished bacterial clearance function [580]. Therefore, these patients are at increased risks for post-operative failure and infections after liver resection and thus, particularly in need for supportive therapeutic measures. After liver resections, probiotics improve liver regeneration in animal experiments [581] and provide benefits in humans such as improved intestinal barrier markers and reductions in postoperative septicemia [582]. Lactulose, although being a synthetic sugar, exerts multiple probiotic action such as promoting growth of beneficial bacteria and has been shown to accelerate liver regeneration after partial hepatectomy in rats [583].

A symbiotic mixture has shown beneficial effects in a small randomized double-blind-pilot study in patients undergoing right hepatectomy demonstrating increased liver functional capacity in those patients with uncomplicated course [584]. The same authors also could demonstrate that symbiotic (lactic acid bacteria and fibre) reduced bacterial infections rates following liver transplantation in a randomized-double-blind trial [585]. Meta-analysis of available data conclude that perioperative pro-/synbiotics reduce bacterial infections after liver surgery or transplantation [586]. Considering most recent data indicating bacterial infections post-liver surgery being of gut-origin

[445] and capable of impairing liver regeneration [445] thus, makes such symbiotic approaches highly attractive in the setting of liver surgery and transplantation.

Hepatobiliary tumors include cholangiocarcinoma (CCA), hepatocellular carcinoma (HCC) and gallbladder cancer. Among those **HCC** comprises nearly 90% of all primary liver cancer and is the third leading cause of cancer-associated mortality [587]. About 80–90% of HCC do develop in advanced fibrotic or cirrhotic livers and one in three patients with cirrhosis will develop HCC in their lifespan [588]. Thus, cirrhosis per se is the single most important risk factor for HCC and hence, preventing fibrogenesis (see above) is most effective and key for preventing HCC. Gut—derived factors contributing to liver carcinogenesis similarly to fibrogenesis relate to P-I/MAMPs being likewise linked to dysbiosis and leaky-gut with effects being exerted either local or long-distance. In that regard, as stated above healthy lifestyle factors, including mediterreanean diet, low/abstinent alcohol and normal BMI are of fundamental importance for eubiosis and stable intestinal barriers which most likely at least partly are responsible for explaining the marked reduction in risk of HCC (HR 0.13; 95% 0.006–0.30) achieved [589]. Moreover, in an epidemiological study involving more than 125,000 participants [590] increased dietary fibre and whole grains has been linked to lower HCC development with every 100 g/d increase in intake decreasing HCC risk by 8%. Multiple other dietary pre-biotic maneuvers including especially consumption of vegetables [591], rich in inulin, and plant polyphenols (e.g. lignins, flavonoids) [592] have likewise been observed to present strong inverse relationship with liver cancer [591]. In the same line of arguments, physical activity (at least 2 h vigorous activity per week) reduced HCC risk independent from other known risk factors [593] that may even counterbalance moderate regular alcohol consumption [594].

More direct impact of the gut microbiome on liver carcinogenesis has recently been provided. Xenotransplantation of gut microbiota from patients suffering from HCV-related chronic liver disease (CLD) was transferred into a murine NASH-model promoting carcinogenesis [281]. The mechanisms responsible for such impact of microbiota on tumorigenesis have been delineated particularly as for its role for repression of immunosurveillance and modulation of the tumor microenvironment (TIME) [595,596]. Microbes mediate immune escape of HCC through diverse actions including i) microbe-derived metabolites [597,598], ii) intra-tumoral microbes and microbial stimulation of inhibitory checkpoints [596] as well as iii) the LPS-TLR4-axis [599–601].

I) Microbe-derived metabolites include a plethora of agents of whom particularly TMAO, AhR-ligands and BA/derivates have gained much attention. TMAO associates with increased risk for primary liver cancer [597,598]. TMAO has shown to increase proliferation, migration and invasion of murine HCC cell lines at least partly via mTOR signalling [598] providing evidence for its potential direct hepatocellular tumorigenicity. As for microbial tryptophan-derived AhR-ligands suppression of inflammatory T cell infiltration and tumor growth has been demonstrated in murine model pancreatic cancer [602] but data on hepato-carcinogenesis are lacking. Also, BA-/signaling is involved in hepatic carcinogenesis and as stated before is vastly influenced by the microbiome. Secondary BAs increase reactive oxygen and nitrogen species, which can cause DNA damage increasing risk for cancer [603]. DCA as one of the most frequent secondary BA, has been demonstrated to induce hepatic stellate cell senescence provoking secretion of various cytokines that prompt hepato-carcinogenesis in murine tumor models [604,605]. Secondary BA also decrease recruitment of CXCR6 + -NKT-cells favoring immune escape and HCC progression in mice [606]. On the other hand, primary BAs increase accumulation of hepatic CXCR6 + - NKT-cells enhancing tumor inhibition and both effects being regulated by CXCL16 expression of liver sinusoidal endothelial cells [606]. These data indicate an axis of BA-CXCL16-CXCR6 and NKT-cells involved in regulating liver cancer. Novel data by Gou et al. confirm that also in human HCC CXCL16 may trigger hepatic accumulation of NKT cells. Human HCC single-cell RNA-seq-data revealed that NKT-cells in patients with high expression of CXCL16 exhibited higher activation state and produced more INFy [607]. Moreover, simultaneous FxR- and TGR5-activation by OCA and 5β-cholanic acid, respectively, in a orthotopic liver cancer mouse model exerted potent anti-tumor effectivity in conjunction with elevated CXCL16 levels in tumors, serum and livers associating with increased accumulation of intratumoral NKT-cells [607]. This is well in line with early observations that FxR-knock-out mice present with spontaneous HCC-development (Kim et al. Carcinogenesis 2007). In fact, FxR activity has been proposed as major inhibitor of HCC carcinogenesis [608] which in cirrhosis and liver inflammation is suppressed and hence, contributes to bile acid accumulation and carcinogenesis [608,609]. Overall, these results should stimulate clinical trials utilizing FxR-agonists in this setting but so far are lacking. The key mediator for feedback regulation from the ileum to the liver for de novo BA-synthesis, FGF19, also strongly modulates cell proliferation, differentiation and tissue repair [610]. FGF19 signals through FGFR4 and its co-receptor klotho-beta on hepatocytes [611]. Aberrant expression of FGF19/FGFR4 contributes to HCC progression [612] and increases in FGF19 correlates with tumor progression and poorer prognosis of HCC [613,614]. Thus, targeting FGF19 inhibits tumor growth in HCC [615]. A phase-1 trial utilizing Fisogatinib, selective oral FGFR4 inhibitor, has validated aberrant FGF19 signalling as contributing factor in HCC [616] and phase 1b/2 has shown safety and preliminary efficacy data in combination with anti-PD-L1 in advanced HCC presenting with FGF19-overexpression [617].

II) Microbes reside within tumor cells and immune cells suggestive of their role in modulating the TIME [596]. TIME plays an essential role in cancer development, progression and control and is known to be determinate for the efficacy of ICI [618]. This intra-tumoral microbiome is tumor-type-specific [619], and, in HCC, characterized by increased alpha-diversity, and especially increased abundance of *Gammaproteobacteria* (e.g. known to include *Enterobacterales* such as *E. coli*) compared to normal liver [620]. Irrespective of etiology, microbial imprint of HCC has been demonstrated since intestinal *E. coli* overgrowth predicted the presence of HCC with an ROC of 0.74 [621]. Moreover, in cirrhotic livers which present with increased 16 S RNA in patients undergoing liver transplantation oncogenic transcription factors related to cancer development correlate with 16 S rRNA abundance [178]. Finally, immune checkpoint genes and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) show a strong correlation with 16 S rRNA abundance in human cirrhotic livers [178] indicating that bacterial translocation associates with immunosuppression. The gut as major source for those microbes, particularly in case of the liver as target, has been evidence for *E. coli* and its role for occurrence of liver metastasis in colo-rectal cancer (CRC)-patients [622]. *E. coli-17* can disrupt the gut-vascular-barrier enabling its translocation along the gut-liver-axis to the liver where it induces the premetastatic niche in the liver favouring the recruitment of metastatic tumor cells. The mechanism by which *E. coli-17* gains access to the intestinal microcirculation depends on the virulence factor Virf1 and acts via plasmalemma vesicle-1 (PV-1), a blood vessel endothelial-specific protein associated to the diaphragma of the fenestrated endothelium. Most importantly, increased PV-1 detection in colorectal cancer correlates with bacteria translocation and liver metastases [622] rendering PV-1 tumor levels as promising potential prognostic biomarker for those colorectal cancer patients with highest risk for developing liver metastasis. High-PV-1-expression associated with poor prognosis (lower rate of 10 y progression-free survival) but not metastatic regional lymph node status at time of surgery indicating its relevance for haematological blood stream dissemination rather than lymphatic spread of the tumor. Indeed, among lymph node positive as well as negative colorectal cancer patients PV-1-high expression associated with significantly higher risk of malignant relapse rate. Currently, decision for adjuvant chemotherapy in CRC-patients after curative surgery besides other factors is determined mainly according to the presence or absence of lymphovascular invasion/lymph node positivity. Considering the prognostic add-on value of PV-1 expression in

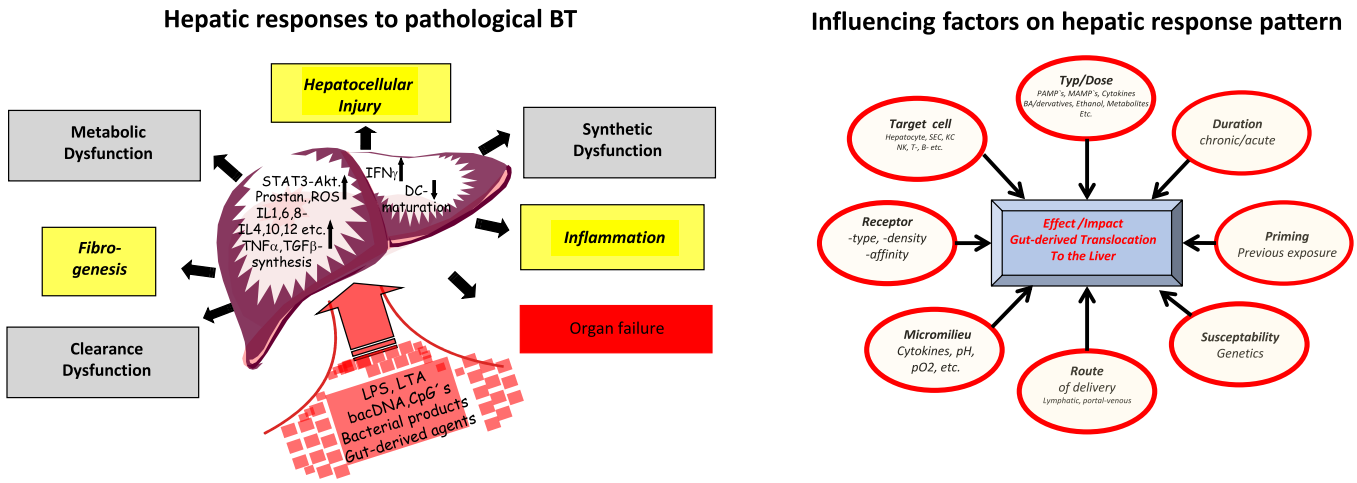

Fig. 2. Factors influencing effect of gut-derived substances on the liver. Various response patterns within the liver can drive hepatcellular injury, inflammation and hence, fibrogenesis stimulated by gut-derived agents. The impact of any agent reaching the liver most likely depends on many different factors modulating typ of effect (signaling pathway and downstream alterations) as well as size and duration of effect.

CRC-patients presented by Rescigno et al. this provides a highly attractive rational for a corresponding randomized-controlled trial. Increased levels of PV-1 have been reported also within the gut of experimental liver cirrhosis [93] as well as a model of increased beta-adrenergic (sympathetic) drive [623]. Thus, it appears tempting to speculate whether the associated opening of the gut-vascular barrier by enabling dissemination of bacteria products also contributes to the pathogenesis of primary liver tumors in such conditions.

III) LPS-TLR4-signalling enhances the invasive ability and epithelial-mesenchymal-transition of HCC cells [600] as well as increases number of cancer stem cells of HCC [601]. In fact, TLR4-inactivated mice or germ-free animals present with reduced volume and number of HCC in animal models [599]. In the same line of evidences, sustained LPS accumulation does represent a pathological mediator of inflammation-associated HCC [624]. Moreover, different potent antibiotic mixtures (achieving gut decontamination and thus, less LPS-availability) reduced liver tumor growth in HCC mouse models [599,604,606]. The role of dysbiotic microbiota, "leaky gut" and TLR4-stimulation for disease progression and tumor development has been elegantly delineated in a mouse model lacking the inflammasome sensor molecule NLRP6 which develops spontaneous steatohepatitis [178]. Dysbiotic microbiota induces a TLR4-dependent expansion of hepatic monocytic myeloid-derived suppressor cells and suppression of T-cell abundance. This phenotype is transmissible via FMT and reversible upon antibiotic treatment. Concomitantly, in mice with hepatocyte-specific deletion of NEMO (regulatory subunit of IKK complex involved in NF-kappaB activation) known to develop spontaneous HCC NLRP6 knock-out augmented liver disease progression and induced a substantial increase in tumor burden [178]. Moreover, under TLR4-/- conditions in those mice liver injury was reduced and tumor burden ameliorated. Human data are scarce but a strong correlation between liver cancer and level of LPS-antibodies in the blood has been observed [625]. Besides LPS, also bacterial DNA and RNA, are present in many human solid tumors [619], but as for HCC, their role has not been addressed so far. Although appearing expedient aiming to lower LPS-delivery to the liver, utilization of antibiotics in humans suffering HCC and treated with sorafenib however, worsened outcome [626]. Reasons for this observation are unclear but rather than targeting patients with established HCC, most attractive and sensible would be its primary prevention hence, translating the experimental evidence of the "leaky" gut and associated LPS-/PBT on hepatic carcinogenesis into clinical preventive measures. This strategy most likely requires long-term or even life-long use that would require upmost safety and compliance for which antibiotics surely do not qualify. Pre- or probiotics however, may well be suitable due to their safety profile and experimental evidence supporting their use [627]. Different probiotic treatments have demonstrated beneficial effects in HCC animal models suppressing carcinogenesis [628,629]. Reported mechanisms mediated by probiotics in these models besides shifts in microbiome composition to beneficial genera such as *Prevotella* [533] include reductions in oxidative stress [629], downregulation of Th17-/IL17-pathway [533], inhibition of angiogenesis [533] as well as PBT of PAMPs (e.g. LPS) and DAMPs (e.g. HMGB1) [628]. In humans, a large retrospective study including 1267 HBV-related cirrhotic patients applying propensity score matching strategies for confounding factors indicates that probiotic consumption is independently protective for HCC development [630]. The adjusted hazard ratio for probiotics suggests a dose-response relation in efficacy reaching up to HR 0.12 (95% CI: 0.03–0.52) and concomitant 3-year HCC-incidence of 3% as compared to 14% in controls [630]. Prebiotics help to maintain microbial stability, mucosal barrier function and decrease pro-inflammatory pathways that can trigger HCC initiation and progression [631] [632]. A study evaluating the relationship between food groups and liver cancer risk reported that specific subgroups of vegetables, rich in inulin and fructo-oligosaccharides had a strong inverse relationship with liver cancer, indicating their protective effects against HCC [591]. Long-term consumption of whole grains has been suggested to reduce the risk of HCC by improving gut integrity and changing microbiota composition [633] Moreover, a meta-analysis of 19 studies involving 1290045 participants (3912 with HCC) showed that every 100 g/d increase in vegetable intake decreases the risk of HCC by 8% [634]. Correspondingly, in accordance with the stated health benefits of anti-inflammatory "Mediterranean" diet, its increased utilization was associated with reduced risk for HCC in a most recent review of 30 observational studies [258].

12. Differences in gut liver axis abnormalities in dependency on etiology and stage of disease

Alcohol is one of the best studied, thus well-defined and characterized trigger disrupting intestinal barriers and hence, increasing gut permeability and activating the gut-liver axis [438]. However, even for alcoholic liver disease susceptibility and hepatic response pattern in terms of timing, course of disease and prognosis are very heterogenous. Most other etiological factors such as insults by "inflammatory" diets impacting on gut barriers are even more heterogenous and complex in terms of effect size, target within the gut and mechanisms involved. Thus, it needs to be emphasized that even beyond these abnormalities in

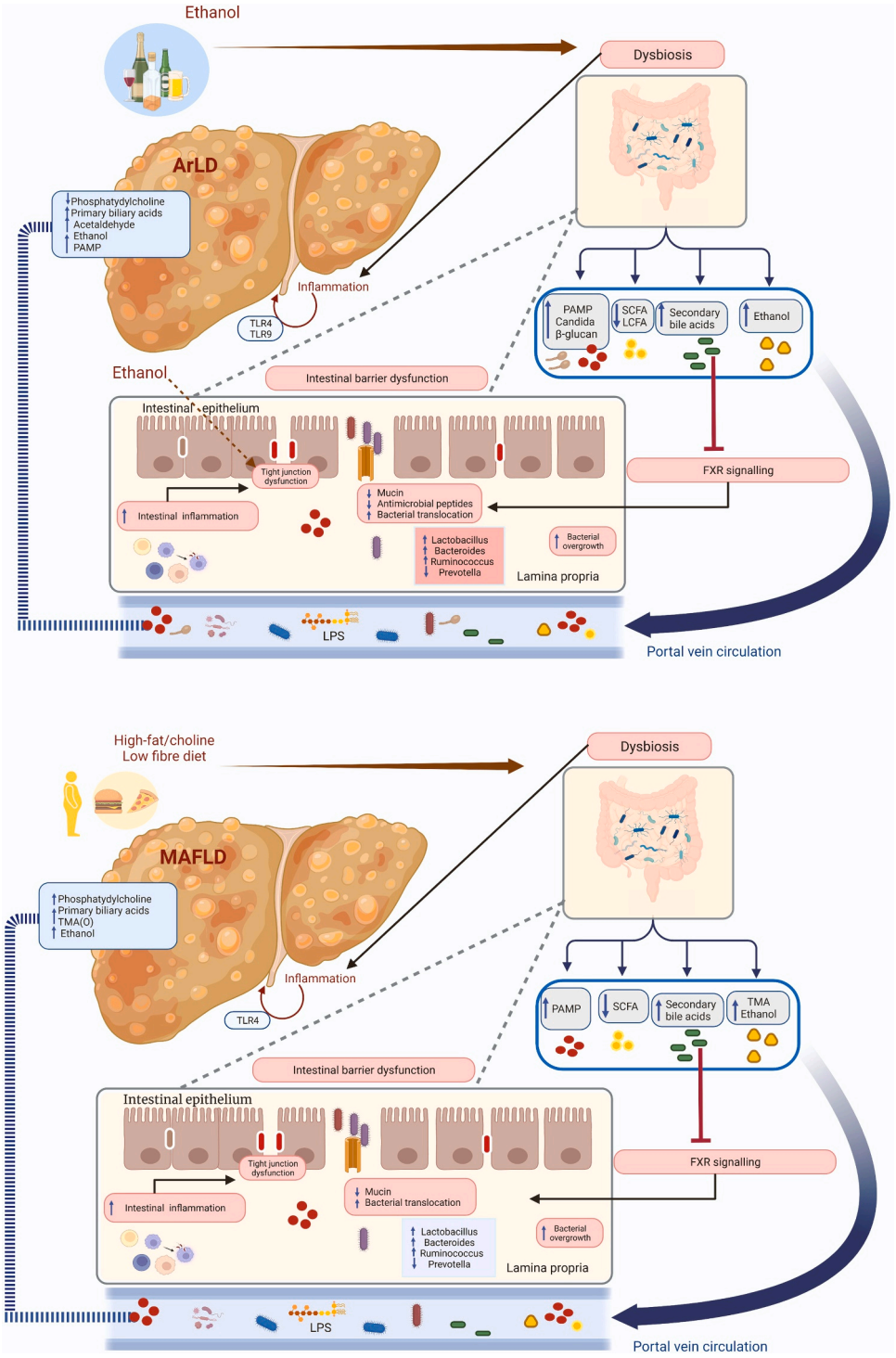

Fig. 3. Pathopyhsiological concept on gut-liver axis: example alcohol-related and metabolic dysfunction-associated-steatotic liver disease (MASLD). Multiple similarities in pathophysiology, microbiome-derived mediators entering the portal venous circulation fueling the "gut-liver-axis" can be appreciated. Dysbiosis being present in both disease states but being caused by different etiolgies (ethanol vs. high-fat/low-fibre diet). Key mediators derived from and/or modulated by the microbiome involved in both scenario include increased levels of secondary BA, PAMPs, TMA and ethanol whereas SCFA are reduced in availability. Net effect on intestinal barriers causes dysfunction via inflammation, alterations in mucus-, AMP-machinery altogether favoring pathological translocation of bacteria/l products, TMAO etc.to the liver. Legend: BA: bile acid; SCFA: short-chain-fatty acid, PAMP: Pathogen-associated molecular pattern; TMA/O: Trimethylamin-N-oxid.

gut barrier function the impact of the same gut-derived stimulus to the liver most likely does vary in dependency on multiple different factors (Fig. 2). Nonetheless, alcoholic and non-alcoholic MASLD share many similiarities in pathophysiological features in terms of alterations within the gut-liver-axis (Fig. 3). Comparative data on differences in gut microbial translocation and/or other abnormalities in gut-liver-axis in different etiologies are scarce and limited [635,636] Conecputally, in experimental models however, translocation of PAMPS (LPS) reaching the peripheral circulation appears to occur in alcoholic as well as non-alcoholic liver disease whereas translocation of living bacteria is restricted to alcoholic etiopathogenesis [637]. Most interestingly, severity of liver injury, inflammation and fibrogenesis was more

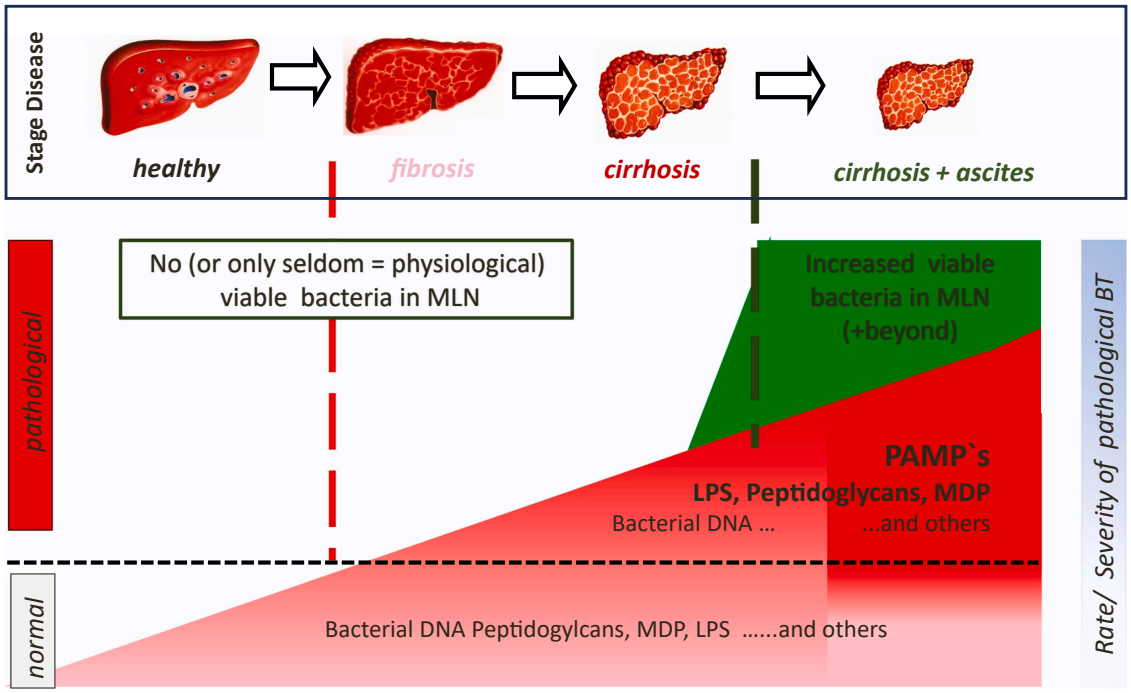

Fig. 4. Stage dependent changes in pathological translocation to the liver. In healthy conditions physiological permeation of gut-derived substances shapes liver immune responses, tolerance and clearence mechanisms (see also introduction "healthy liver stands on healthy gut"). During the course of liver fibrogenesis and cirrhosis rate and severity of PBT increases. Living bacteria reaching the systemic blood stream do occur when advanced cirrhosis with pronounced PBT and deficient hepatic clearance function coexist such as in decompensated cirrhosis with ascites.

pronounced in diet-induced non-alcoholic liver disease models as compared to ethanol-induced liver disease [637]. Thus, more investigations on differences in typ and severity of intestinal hyperpermeability as well as response pattern should be encouraged. In terms of abnormalities along the course of disease it is known for long that ascites formation associates with step-up in PBT [638] being reflected in occurrence of bacteremia [639]. This does reflect translocation of viable bacteria from the gut accessing the blood stream which elsewise is not observed in early compensated stages of liver disease (Fig. 4).

13. Conclusion

Mounting experimental evidence exists delineating specific microbial host interactions and their major pathophysiological role in the gut-liver-axis and multiple in liver diseases. Hence, this represents an outstanding opportunity for clinical scientists to perform translational research. In fact, the microbiome with its myriads of P-/M-/DAMPs along with the gastrointestinal enteroendocrine and lymphatic tissue is of central importance in the causation and progression of chronic liver diseases. The biggest challenge however, will be to translate these outstanding discoveries into humans and assess their clinical relevance. Obstacles are multiple, not limited to, but include the lack of a regulatory road map for microbiome based or -targeted therapies, insufficient global agreements on definitions, standardization on sampling, handling and analysing bacterial consortia, hindering comparison between studies.

Healthy "anti-inflammatory" diet and exercise convincingly are the basis for keeping eubiosis and stable intestinal barriers at work. Pre-and probiotics as well as FMT have demonstrated some efficacy and are mostly well tolerated in clinical trials in liver diseases. However, these therapies are all untargeted and it is becoming clear that individualized precision medicine is what is most needed and most efficient. Individualization of treatment strategies appears most attractive and likely game changing, but does require a better characterization and phenotyping of each patient in terms of microbiome (composition at the strain-level and functionality assessed by metagenomic analysis at best in luminal, mucus and mucosa-compartment), metabolome and particularly host response. Moreover, better diagnostic tools to access the gut-liver-axis at its "heart" namely the portal vein are needed and EUS-based puncture may well proof its value to harvest portal-, hepatic-venous as well as liver biopsies. It is tempting to propose the need for an update of Koch's postulates (define criteria designed to establish a causal relationship between a microbe and a disease) in the area of metagenomic and whole genome shotgun sequencing of microbiota. The latter allows comprehensive sampling of all genes in given samples which together with the establishment of bioinformatic analysis tools can be up-most revealing particularly when being applied to a very well phenotyped patient population. The armamentarium to modulate the microbiome and liver-gut-axis in a very precise targeted manner are becoming available e.g including bio-engineered bacterial strains or bacteriophages modulating specific metabolic pathways as well as BA-modulating modalities (FxR-/TGR-agonists, ASBT-inhibitors etc.). However, anything in clinical practice needs first to be proven safe, secondly easily applicable and thirdly, sufficiently effective on a relevant outcome measure. The hope is that microbial-based therapies will fulfill these criteria and be used in concert with our current standard of care, to improve clinical outcomes in patients with chronic liver diseases.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.smim.2023.101859.

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