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Disruption of the gut-liver axis in the pathogenesis of acute-on-chronic liver failure

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Abstract

Acute-on-chronic liver failure (ACLF) is characterized by organ failure mediated by acute cirrhosis. Recent studies have highlighted the importance of the gut-liver axis and its association with ACLF pathogenesis. In this review, we discuss the mechanisms related to the alteration of the gut-liver axis (GLA) and their involvement in ACLF pathogenesis and suggest some possible therapeutic options that could modulate the GLA dysfunction. This knowledge may provide information useful for the design of therapeutic strategies for gut dysbiosis and its complications in ACLF.

Keywords

The gut-liver axis; acute-on-chronic liver failure

1. Background

Acute-on-chronic liver failure (ACLF) is a condition previously defined as acutely decompensated cirrhosis accompanied by the development of multi-organ failure and has an in-hospital mortality rate of 45–65% [1]. Recent studies have shown that intestinal bacterial translocation (BT), inflammation, and immune disorders play important roles in ACLF pathogenesis [2]. The liver provides immune surveillance against various pathogens, including pathogens from the gut, as well as mucosal immunity and the intestinal

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microbiome affect liver function [3]. A compromised intestinal mucosal barrier and altered bacteria-mediated immune responses promote inflammation in the liver in ACLF [4]. Acute inflammatory storms in the liver caused by BT from the gut, as well as inappropriate responses by the innate immune system, and the subsequent development of intra- and extra-hepatic circulatory dysfunction ultimately lead to multi-organ failure [2].

2. Mechanism underlying gut-liver axis disruption in ACLF

The link between the gut microbiota and host immunity in cirrhosis has been recognized over the last century [5]. The interaction between the gut and the liver is called “gut-liver axis”, Bacteria and bacterial components from the gut microflora affect the liver and are associated with systemic inflammation and severity of liver diseases [4, 6]. Translocated bacteria or their products stimulate and activate the innate immune system and may modify the adaptive immune system, resulting in inflammation, liver cell apoptosis, and progression to liver failure [7]. Recent studies have shown that various immune cells in the intestine and liver are involved in immune responses in ACLF [8, 9]. The liver contains a large number of innate immune cells, such as Kupffer cells (KCs), natural killer (NK) cells, natural killer T (NKT) cells and dendritic cells (DCs), as well as cytotoxic T lymphocytes (CTLs), which can directly induce the death of infected hepatocytes and mediate interferon-γ (IFN-γ) production. These immune cells and their produced cytokines are believed to play pivotal roles in ACLF progression [10].

The mucosal immune system (MIS) comprises the mucosal-associated lymphoid tissue (MALT) and immune cells and is an important part of the immune system [11]. The MALT is stimulated mainly by microbes located in the intestinal mucosa and prevents pathogenic microorganism invasion of the system [12]. The intestinal immune system is closely linked to immune-mediated liver injury through the gut-liver axis [3]. The intestinal mucosa is composed of the epithelium, lamina propria and muscular. The intestinal mucosa functions include innate and adaptive immunity.

2.1 The liver-gut axis related innate immunity

In the intestinal mucosa, phagocytic cells, such as neutrophils, DCs and macrophages, play important roles in innate immunity by non-specifically recognizing and clearing bacteria and bacterial products. The liver is the first extra-intestinal organ encountered by venous blood from the small and large intestines draining from the portal vein. Thus, the liver is susceptible to exposure to bacterial products entering the intestinal lumen through the portal vein. The innate immune system is activated prior to the adaptive immune system and enables the highly specialized adaptive immune system to confer long-term immunological memory [9]. The innate immune system acts as the first-line defense against invading pathogens and other potential threats to the host. Exquisite coordination of multiple innate immune cells is crucial to efficiently destroy and clear invading pathogens and other molecular threat. The occurrence of liver failure results in the destruction of the intestinal immune barrier and enteric dysbiosis, and as a consequence of increased systemic lipopolysaccharide (LPS) and BT. Translocated bacterial products may augment the activation of hepatic immune cells through TLRs, and activate the innate immune system.

LPS and other bacterial components translocated from the gut and TLR recognitions—Under normal circumstances, intestinal mucosal permeability is low. Large molecules and toxins have difficulty passing through the mucosa, which is the first intestinal immune barrier responsible for maintaining gut homeostasis [13]. Bacterial products (e.g., LPS) contain pathogen-associated molecular patterns (PAMPs) that can be recognized by pattern recognition receptors (PRRs) on intestinal epithelial cells [14]. The PRRs include TLRs and NOD-like receptors (NLRs) [15]. Different classes of germ line-encoded PRRs recognize invading pathogens and monitor host cell extracellular and intracellular microbe compartments. PRRs are anchored in innate immune cells as surface or intracellular receptors and have signaling pathways that trigger inflammatory responses and subsequent cellular activation [16]. A multifaceted interplay among different PRRs results in the induction of a complex spectrum of pro- and anti-inflammatory, immunogenic and suppressive responses within the host. Altered PRR expression and functions are well-known features of ACLF [10].

TLRs are a family of PRRs that play critical roles in the activation of the innate immune system by recognizing PAMPs. TLRs identify specific microbial antigens and play key roles in initiating cytokine responses and antigen presentation [17]. In ACLF, local and systemic immune recognition of LPS is mediated through clusters of TLR4 receptor complexes on the surfaces of intestinal epithelial cells and immune cells, predominantly monocytes/macrophages and DCs [18]. LPS recognition results in the subsequent promotion of an intracellular signaling cascade, leading to pro-inflammatory cytokine secretion. Activation of innate immune signaling pathways by TLR4 can induce inflammation, but long-term exposure to LPS can persistently activate the immune system and result in chronic inflammation [19]. Additionally, TLR-associated inflammation may modify epithelial cell survival and homeostasis, epithelial integrity and tight junctions, and mucosal immunity. Long-term bacteria-associated persistent immune activation and inflammation in the MALT may result in liver apoptosis and aggravated liver failure progression.

BT is defined as the migration of bacteria or bacterial products (e.g., LPS, lipoteichoic acid, peptidoglycans, and bacterial DNA) across an anatomically intact intestinal barrier from the intestinal lumen to the mesenteric lymph nodes (MLNs) or extra-intestinal organs and sites [20]. Long-term BT results in persistent inflammation and immune activation, which lead to a microecological imbalance and exacerbate liver disease. Substantial evidence indicates that gut dysbiosis may be responsible for endotoxemia and that translocated LPS or other bacterial products from the gut microflora may induce hepatic microcirculatory disturbances and liver cell death, thereby contributing to ACLF pathogenesis [21]. LPS is one component of the cell wall of gram-negative bacteria, which are enriched in the intestines. Generally, only a small amount of LPS can penetrate the mucosa and enter into portal circulation. LPS induces liver cell apoptosis through CD14, TLR4, NF-κB, and tumor necrosis factor-α (TNF-α) signaling pathways, as well as other signaling pathways [22]. Immune cells expressing CD14 and TLR4 (e.g., macrophages) can recognize and remove LPS and thus play an important role in protection against LPS-mediated damage [23]. Additionally, circulating oxidative stress and protein oxidation lead to human serum albumin (HSA) oxidation, which results in a decreased binding capacity of HSA to LPS and ultimately

reduces the systemic LPS levels [4]. Nonetheless, LPS is cleared mainly in the liver by Kupffer cells [24], thus dysfunction of KCs by liver failure directly may result in uncontrolled plasma LPS. In this review, we focus on LPS, a representative bacterial product, which has been shown to increase in plasma from patients with liver damage [7]. Other bacterial components may also play a role in ACLF disease pathogenesis.

LPS is not a specific protein antigen but can be recognized by the innate immune system through phagocytic cells (neutrophils, monocytes, peripheral macrophages, and KCs). The main cellular components of the innate immune system within the liver are KCs, which represent 80% to 90% of the tissue macrophages within the human body [25]. LPS is the most recognized TLR ligand and activates KCs through the TLR4 signaling pathway [26]. A correlation exists between the functional states of KCs and the extent of liver injury [26].

Translocated LPS induces inflammatory factors, such as TNF-α. When TNF-α levels are low, KCs can clear LPS effectively. However, when the systemic LPS levels are high, KCs cannot remove LPS effectively, which causes more severe disease [27]. Therefore, the deactivation and apoptosis of hepatic macrophages may be a potential link between inflammation and immunoparesis in ALF. A higher incidence of infection, immune perturbations, and monocyte dysfunction are observed in patients with ACLF [28]. The following consequences may be present when liver functions are impaired: 1) persistent immune activation, inflammation and stimulation of reactive oxygen species (ROS) induced by impaired function of KCs and uncontrolled endotoxemia [29][30]. 2) Uncontrolled intestinal bacteria overgrowth due to endotoxemia, immune dysfunction, and TLR-mediated inflammation [31]. 3) An increase in the level of hepatotoxin, a toxic chemical substance that damages the liver, may release to the circulation and result in immune dysfunction [32].

2.2 The gut-liver axis related adaptive immunity

Innate and adaptive immune cells are distributed in the intestinal mucosa and submucosa. The adaptive immune system recognizes and clears specific foreign antigens that are mostly originated from the intestinal flora and other microbe-antigen interactions [33]. Effector immune cells are located primarily in the epithelium and lamina propria, which contain T cells, B cells, DCs, macrophages, eosinophils and mast cells for initiating innate and adaptive immune responses [34]. The MALT, lied in the mucosa and submucosa, is mainly involved in the adaptive immune response. In the liver, ACLF development results in dysfunction of both innate and adaptive immunities [35].

DCs are professional antigen-presenting cells (APCs) that are widely distributed in the liver and intestinal mucosa. The numbers and functions of DCs are closely associated with liver function and the prognosis of liver disease [36]. Significant hepatocyte apoptosis has been observed in ACLF and can mediate DC activation, migration, and accumulation in the liver [37]. DCs play a crucial role in both innate and adaptive immunity against microbial antigens. When LPS or other bacterial products translocate from the gut microflora to the MLNs, intestinal epithelial cells release chemokines that induce the recruitment of DCs to the mucosa. Additionally, activated mature intestinal DCs stimulate naive T cell and B cell differentiation [38], thereby ultimately shaping the adaptive mucosal immune system. Mature T cells and B cells are released into the bloodstream and home back to reside within

the lamina propria due to surface expression of appropriate homing markers. For instance, CD4+ and CD8+ T cells produce cytokines (e.g., IFN-γ) and participate in adaptive mucosal immunity [39]. Microbial antigens are presented to B cells induce a commensal-specific IgA response that aids in the prevention of the straying of commensals beyond the gut mucosa [40].

2.4 Gut microflora-associated inflammatory responses in the liver

Following liver disease progression, increases in intestinal permeability lead to increases in bacteria and bacterial product translocation (e.g., LPS) to the periphery, which may lead to activation, inflammation, and migration of immune cells to the liver [41].

KCs are the first line of defense in the liver and are activated through TLR4, complement receptors (C3R and C5R), and DAMPs [42]. Activated KCs produce a wide variety of inflammatory mediators. The release of massive amounts of local pro-inflammatory cytokines and anti-inflammatory cytokines into the systemic circulation includes, but is not limited to, TNF-α, sTNF-αR1, sTNF-αR2, IL-2R, IL-6, IL-17, CXCL-8, IFN-α, the regulatory cytokines IL-2, IL-4, IL-10, and TGF-β, free oxygen radicals, eicosanoids, and lysosomal and proteolytic enzymes produced at the local site [43]. This first pro-inflammatory response results in immune responses to bacterial products, however, the excessive reaction may contribute to micro-circulatory alterations, tissue edema, and neutrophil recruitment, which finally lead to multiple tissue damages and organ failures in ACLF, as descripted from Gustot's group [44]. This phenomenon leads to quiescent stellate cell activation, differentiation into activated myofibroblasts, and the release of endothelin-1 (ET-1), thromboxane A2, nitric oxide (NO), and prostaglandins. This process causes hepatic microcirculatory dysfunction and high portal pressure [45]. NO release induces the death of hepatocytes via necrosis or apoptosis, which also damages neighboring cells [46]. Plasmacytoid dendritic cells (pDCs) are originated from bone marrow hematopoietic stem cells and resemble plasma cells, whereas myeloid dendritic cells (mDCs) are similar to monocytes or white blood cells. The enrichment of pDCs and neutrophils infiltration in combination with a decrease in mDCs probably occurs through the cytokines IL-8, CXCL1 and IL-1 [47]. This cytokine burst and the release of ROS perpetuate the inflammatory injury and ongoing hepatic apoptosis and necrosis.

Furthermore, T regulatory cells (Tregs) inhibit IFN-γ production, and monocytes assist in the generation of IL-17A-secreting CD4+ T cells through TGF-β and IL-6 secretion [48]. MER receptor tyrosine kinase (MERTK) expression further increases the susceptibility of hepatocytes to infection [49]. This cytokine burst and inflammatory cascade are considered causative events in the development of systematic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS), immunoparalysis, and multiple organ dysfunction (MOD) in ACLF, eventually leading to multiple organ failure, including the liver [50].

2.5 Inflammation in ACLF

Previous studies from Claria's group showed that patients with ACLF had significantly increased levels of IL-6, IL-8, IL-1-beta, the redox state of circulating albumin (a marker of

systemic oxidative stress), renin, and copeptin compared to healthy controls and/or patients without ACLF, and systemic inflammation was tightly associated with the severity, progression, and short-term mortality of ACLF [51, 52].

3. Treatment strategies for gut-liver axis disruption in ACLF

Based on the gut-liver axis theory in ACLF discussed mainly in this review article, we further emphasize on the treatment strategies of gut-liver axis restoration.

3.1 Protection of intestinal mucosal barrier function by intestinal DC activation

Most recent studies regarding this phenomenon have attempted to detect and modify DCs to observe the subsequent changes in their behavior and the effects of these changes on intestinal mucosal immunity. An experimental study that investigated changes in intestinal DC numbers in hepatic failure found that a large number of DCs matured, expressed an activation marker CD86, and activated MHC class II molecular pathways to induce a T cell adaptive immune response [53]. These findings indicate that DCs play an important role in the protection of intestinal mucosal barrier functions. Zhang Y et al found that inhibition of intestinal DC functions impaired intestinal mucosal barrier integrity and that intestinal pathogenic bacteria directly damaged the intestinal epithelium, leading to the translocation of large amounts of intestinal bacteria and the occurrence of severe systemic infections [54]. Another study showed that early infection could drive DC activation through the HSP70/CCR5 pathway and/or the HSP70/TLR4-MyD88-independent pathway to activate Th1 cells, increase IL-12 secretion and bolster immune functions [55]. Other researchers have observed that lactic acid bacteria stimulate DCs to initiate an immune response, reduce systemic levels of LPS and TNF-α, and increase tight junction protein ZO-1 expression in the ileum in mice with ACLF [56]. Taken together, these findings indicate that controlling the function of intestinal DCs can effectively improve intestinal mucosal barrier functions, prevent bacterial translocation and attenuate liver cell damage.

3.2 Reconstruction of the intestinal microecology

Imbalance of the intestinal microbialflora can accelerate ACLF progression via the following mechanisms [57, 58]: 1) enrichment of microbiome in ACLF results in more severe gut permeability and systemic microbial translocation (e.g., LPS), and 2) enrichment of microbiome in ACLF increases pro-inflammatory condition and drives mucosal damage. Y Chen et al [59] demonstrated several progressive changes in the following fecal microbial communities in ACLF: decreased levels of Bacteroidetes, Ruminococcaceae, Porphyromonadaceae and Lachnospiraceae and increased levels of Firmicutes compared to the levels before disease onset. The authors concluded that gut dysbiosis was associated with worse ACLF pathogenesis than its associated pathogenesis in cirrhosis. Additionally, the authors found that the changes in the microbiota composition were correlated with the liver disease severity. For example, levels of Bacteroidetes and Lachnospiraceae were inversely correlated with disease severity, and levels of Proteobacteria, Fusobacterium spp., Enterobacteriaceae, Veillonellaceae and Streptococcaceae were positively correlated with disease severity [59]. Indeed, results obtained using cutting-edge research techniques

indicate that variations in the intestinal bacterial composition can affect liver disease progression [60].

The regulation of the intestinal microecology by microbial ecological agents has been proposed as an emerging therapeutic strategy for ACLF [61]. Microbial ecological agents include at least three classes, probiotics, prebiotics and synbiotics [62]. Probiotics use is giving beneficial bacteria to patients, which have been shown some effects in patients with inflammatory bowel diseases [63]. Prebiotics are defined as non-digestible food ingredients, including oligosaccharides, galacto-oligosaccharides (lactulose), and gluco- and xylo-oligosaccharides [63]. Through selectively stimulating the growth of one or a group of bacteria in the GI tract, prebiotics have been shown to improve mucosal barrier function, stimulate regulatory T cells and reduce pro-inflammatory cytokines [63]. Synbiotics is the combination of prebiotics and probiotics for synergistic effects and are treated and have shown some effects in patients with inflammatory bowel diseases [63]. These agents can increase the normal physiological activity of the intestinal tract, increase the levels of favorable bacterial strains, prevent the growth of pathogens, improve the function of mucosal layer, and preserve intestinal epithelial cells, thereby reducing BT and LPS release [64]. Many experimental observational studies have examined and found that the modification of intestinal flora can improve the survival rate of patients with liver failure [65].

3.3 Inhibition of hepatic inflammatory responses

LPS released from a “leaky” gut can reach the liver via the portal vein and trigger cytokine biosynthesis, thereby promoting inflammatory responses and ultimately resulting in liver dysfunction. Therefore, reducing LPS and inhibiting cytokine biosynthesis to decrease hepatic inflammatory responses and protect against the liver cell apoptosis induced by intestinal bacterial translocation are the focus areas of ACLF treatment strategies.

Inhibition of the biological activity of TLR4—TLR4 is a transmembrane protein that is found mainly in monocytes and macrophages. It plays an important role in recognizing and mediating monocyte and macrophage activation (e.g., KC) and pro-inflammatory cytokine release (e.g., TNF-α) [66]. Increased TLR4 expression has been observed in patients with ACLF [67]. Activated TLR4 initiates pro-inflammatory cascades in which large amounts of cytokines are released to aid in the eradication of bacteria. However, excessive host responses to LPS can lead to SIRS. Significant morbidity associated with ACLF has been found due to SIRS [61]. TLR4 has been shown to play an integral role in the modulation of SIRS [68]; thus, inhibition of the biological activity of TLR4 is a distinct target for preventing ACLF progression.

TLR4 antagonists, such as MD2-I, TAK-242, E5564 and STM28, offer a promising perspective for the reduction of liver injury and neuroinflammation and increased survival in ALF animal models [69]. These antagonists may contribute to the mechanism of treatment of ACLF as follows: 1) reducing TLR4 activity; 2) blocking LPS-induced TNF-α overproduction; and 3) decreasing the SIRS response [70].

MERTK inhibitors—MERTK is expressed in monocytes and macrophages and inhibits innate immune responses. The numbers of monocytes and macrophages that express

MERTK are correlated with the disease severity and inflammatory response [71]. MERTK-expressing monocyte/macrophage populations are a novel finding in the pathogenesis of immune paresis in ACLF [72]. A recent study showed that patients with ACLF had increased numbers of immunoregulatory monocytes and macrophages that expressed MERTK and suppressed the innate immune response to microbes. The numbers of these cells correlated with SIRS components, inflammatory cytokines and subsequent increased infections. MERTK inhibitors restore the production of inflammatory cytokines by immune cells from patients with ACLF and have potential for improvement of innate immune responses in these patients [73].

High-mobility group box 1 (HMGB1)—HMGB1 is a cytokine mediator of inflammation that is secreted by immune cells, such as macrophages and monocytes. High HMGB1 levels have been detected in the sera of patients with acute liver failure [74] and hepatitis B virus-mediated ACLF [75], demonstrating that HMGB1 release is associated with liver cell damage. Moreover, the serum HMGB1 levels were significantly higher in severe hepatitis B and ACLF patients [76]. Animal experiments have confirmed that blockade of HMGB1 can ameliorate ACLF in rats [77]. Blockade of HMGB1 in a rat model mimicking ACLF reduced hepatic apoptosis, hepatic inflammatory responses and SIRS, thereby alleviating liver inflammation and SIRS activation in ACLF patients. Therefore, HMGB1 is a promising therapeutic target for ACLF.

Other options—Other therapeutic options include antibiotics, granulocyte colony stimulating factor (G-CSF), and statin et al. Due to selective bacterial decontamination and increased antibiotic resistance to antibiotics, therapeutic strategies should consider non-antibiotic prevention and treatment [78]. Moreover, G-CSF is the most potent cytokine to mobilize hematopoietic stem cells from the bone marrow, which is used for repopulating hepatocytes and non-parenchymal cells in the liver, as well as immune cells [78]. G-CSF has been shown to prevent infection and sepsis, and increase survival rates in ACLF patients [78]. In addition, statins has anti-inflammation and may have anti-infection effects, which may benefit to patients with ACLF [78].

4. Conclusion

Refining the phenotypic characterization and function of human intestinal monocytes/macrophages and DCs, immune activation, as well as gut barrier disruption would facilitate further investigation of their involvement in ACLF. Further investigation into the direct interactions between gut microbiota, inflammation and multiple organ damage in ACLF may elucidate the interaction of the dynamic alterations of microorganism and disease pathogenesis. In conclusion, an increased understanding on the field of the gut-liver axis disruption may contribute to the understanding of ACLF pathogenesis and will benefit the development of new therapeutic strategies.

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References

1. Laleman W, Verbeke L, Meersseman P, Wauters J, Van Pelt J, Cassiman D, et al. Acute-on-chronic liver failure: current concepts on definition, pathogenesis, clinical manifestations and potential therapeutic interventions. Expert review of gastroenterology & hepatology. 2014; 5(4):523–37.
2. Verbeke L, Nevens F, Laleman W. Bench-to-beside review: acute-on-chronic liver failure-linking the gut, liver and systemic circulation. Critical Care. 2011; 15(5):233. [PubMed: 22104633]
3. Jiang W, Wu N, Wang X, Chi Y, Zhang Y, Qiu X, et al. Dysbiosis gut microbiota associated with inflammation and impaired mucosal immune function in intestine of humans with non-alcoholic fatty liver disease. Scientific reports. 2015; 5:8096. [PubMed: 25644696]
4. Giannelli V, Di Gregorio V, Iebba V, Giusto M, Schippa S, Merli M, et al. Microbiota and the gut-liver axis: bacterial translocation, inflammation and infection in cirrhosis. World journal of gastroenterology. 2014; 20(45):16795–810. [PubMed: 25492994]
5. Phillips GB, Schwartz R, Gabuzda GJ Jr, Davidson CS. The syndrome of impending hepatic coma in patients with cirrhosis of the liver given certain nitrogenous substances. New England Journal of Medicine. 1952; 247(7):239–46. [PubMed: 14947933]
6. Zeuzem S. Gut-liver axis. International journal of colorectal disease. 2000; 15(2):59–82. [PubMed: 10855547]
7. Sandler NG, Koh C, Roque A, Eccleston JL, Siegel RB, Demino M, et al. Host response to translocated microbial products predicts outcomes of patients with HBV or HCV infection. Gastroenterology. 2011; 141(4):1220–30. 30 e1–3. PubMed PMID: 21726511; PubMed Central PMCID: PMCPMC3186837. DOI: 10.1053/j.gastro.2011.06.063 [PubMed: 21726511]
8. Wu Z, Han M, Chen T, Yan W, Ning Q. Acute liver failure: mechanisms of immune - mediated liver injury. Liver International. 2010; 30(6):782–94. [PubMed: 20492514]
9. Wang X, Ning Q. Immune mediated liver failure. EXCLI journal. 2014; 13:1131. [PubMed: 26417328]
10. Moreau, R., editor. Seminars in liver disease. Thieme Medical Publishers; 2016. The Pathogenesis of ACLF: The Inflammatory Response and Immune Function.
11. Sato S, Kiyono H. The mucosal immune system of the respiratory tract. Current Opinion in Virology. 2012; 2(3):225–32. [PubMed: 22542216]
12. Donaldson GP, Lee SM, Mazmanian SK. Gut biogeography of the bacterial microbiota. Nature Reviews Microbiology. 2016; 14(1):20–32. [PubMed: 26499895]
13. Sperandio, B.Fischer, N., Sansonetti, PJ., editors. Seminars in immunology. Elsevier; 2015. Mucosal physical and chemical innate barriers: Lessons from microbial evasion strategies.
14. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. Journal of hepatology. 2015; 63(5):1272–84. [PubMed: 26192220]
15. Fujimoto, Y., Fukase, K. Glycoscience: Biology and Medicine. Springer; 2015. Microbial glycoconjugates recognition with tlrs and nlrs in innate immunity; p. 685-90.
16. Sokol CL, Luster AD. The chemokine system in innate immunity. Cold Spring Harbor perspectives in biology. 2015; 7(5):a016303. [PubMed: 25635046]
17. O'Neill LA, Golenbock D, Bowie AG. The history of Toll-like receptors [mdash] redefining innate immunity. Nature Reviews Immunology. 2013; 13(6):453–60.
18. Clària J, Arroyo V, Moreau R. The Acute-on-Chronic Liver Failure Syndrome, or When the Innate Immune System Goes Astray. Journal of immunology (Baltimore, Md : 1950). 2016; 197(10): 3755–61.
19. Soares JB, Pimentel-Nunes P Jr, R A, Leite-Moreira A. The role of lipopolysaccharide/toll-like receptor 4 signaling in chronic liver diseases. Hepatology International. 2010; 4(4):659–72. [PubMed: 21286336]
20. Garcia-Tsao G, Wiest R. Gut microflora in the pathogenesis of the complications of cirrhosis. Best Practice & Research Clinical Gastroenterology. 2004; 18(2):353–72. [PubMed: 15123075]

21. Alam A, Suen KC, Ma D. Acute-on-chronic liver failure: recent update. The Journal of Biomedical Research. 2017; 31(3):1–18. [PubMed: 28808210]
22. Peng JH, Cui T, Sun ZL, Huang F, Chen L, Xu L, et al. Effects of Puerariae Radix Extract on Endotoxin Receptors and TNF-alpha Expression Induced by Gut-Derived Endotoxin in Chronic Alcoholic Liver Injury. Evid Based Complement Alternat Med. 2012; 2012:234987. PubMed PMID: 23133491; PubMed Central PMCID: PMCPMC3485520. doi: 10.1155/2012/234987 [PubMed: 23133491]
23. Fukui H. Gut-liver axis in liver cirrhosis: How to manage leaky gut and endotoxemia. World journal of hepatology. 2015; 7(3):425–42. [PubMed: 25848468]
24. Bikhazi AB, Jurjus AR, Kamal MT, Al-Housseini AM, Saab RN, Jaroudi WA, et al. Kinetics of lipopolysaccharide clearance by Kupffer and parenchyma cells in perfused rat liver. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology. 2001; 129(4):339–48. [PubMed: 11489431]
25. Kolios G, Valatas V, Kouroumalis E. Role of Kupffer cells in the pathogenesis of liver disease. World journal of gastroenterology. 2006; 12(46):7413. [PubMed: 17167827]
26. Bilzer M, Roggel F, Gerbes AL. Role of Kupffer cells in host defense and liver disease. Liver International. 2006; 26(10):1175–86. [PubMed: 17105582]
27. Chen Y, Yang F, Lu H, Wang B, Chen Y, Lei D, et al. Characterization of fecal microbial communities in patients with liver cirrhosis. Hepatology. 2011; 54(2):562–72. [PubMed: 21574172]
28. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-Chronic Liver Failure Is a Distinct Syndrome That Develops in Patients With Acute Decompensation of Cirrhosis. Gastroenterology. 2013; 144(7):1–9.
29. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010; 140(6):805–20. [PubMed: 20303872]
30. Xu L, Kitade H, Ni Y, Ota T. Roles of Chemokines and Chemokine Receptors in Obesity-Associated Insulin Resistance and Nonalcoholic Fatty Liver Disease. Biomolecules. 2014; 5(3): 1563–79.
31. Wiest R. Bacterial Translocation and Alterations of the Digestive System. Clinical Gastroenterology. 2011:189–218.
32. Arroyo, V., Jalan, R., editors. Seminars in liver disease. Thieme Medical Publishers; 2016. Acute-on-Chronic Liver Failure: Definition, Diagnosis, and Clinical Characteristics.
33. Purchiaroni F, Tortora A, Gabrielli M, Bertucci F, Gigante G, Ianiro G, et al. The role of intestinal microbiota and the immune system. Eur Rev Med Pharmacol Sci. 2013; 17(3):323–33. [PubMed: 23426535]
34. Welty NE, Staley C, Ghilardi N, Sadowsky MJ, Igyártó BZ, Kaplan DH. Intestinal lamina propria dendritic cells maintain T cell homeostasis but do not affect commensalism. Journal of Experimental Medicine. 2013 Jem. 20130728.
35. Sipeki N, Antal-Szalmas P, Lakatos PL, Papp M. Immune dysfunction in cirrhosis. World journal of gastroenterology: WJG. 2014; 20(10):2564–77. [PubMed: 24627592]
36. Tokita D, Sumpter TL, Raimondi G, Zahorchak AF, Wang Z, Nakao A, et al. Poor allostimulatory function of liver plasmacytoid DC is associated with pro-apoptotic activity, dependent on regulatory T cells. Journal of hepatology. 2008; 49(6):1008–18. [PubMed: 18926588]
37. Zhang Z, Zou Z-S, Fu J-L, Cai L, Jin L, Liu Y-J, et al. Severe dendritic cell perturbation is actively involved in the pathogenesis of acute-on-chronic hepatitis B liver failure. Journal of hepatology. 2008; 49(3):396–406. [PubMed: 18644645]
38. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. Journal of Hepatology. 2014; 60(1):197. [PubMed: 23993913]
39. Stefanie H, Sabrina P, Pfeiffer IA, Beatrice ST, Gerold S, Jan D, et al. Concurrent interaction of DCs with CD4+ and CD8+ T cells improves secondary CTL expansion: It takes three to tango. European Journal of Immunology. 2014; 44(12):3543. [PubMed: 25211552]
40. Hapfelmeier S, Lawson MAE, Slack E, Kirundi JK, Stoel M, Heikenwalder M, et al. Reversible Microbial Colonization of Germ-Free Mice Reveals the Dynamics of IgA Immune Responses. Science. 2010; 328(5986):1705–9. [PubMed: 20576892]

41. Szabo G, Petrasek J. Inflammasome activation and function in liver disease. Nature Reviews Gastroenterology & Hepatology. 2015; 12(7):387–400. [PubMed: 26055245]
42. Farrar CA, Kupiec-Weglinski JW, Sacks SH. The innate immune system and transplantation. Cold Spring Harbor perspectives in medicine. 2013; 3(10):a015479. [PubMed: 24086066]
43. Biancofiore G, Bindi L, Miccoli M, Metelli MR, Panicucci E, Baggiani A, et al. Balance of pro- and anti-inflammatory cytokines in cirrhotic patients undergoing liver transplantation. Transplant immunology. 2013; 28(4):193–7. [PubMed: 23597701]
44. Gustot T. Multiple organ failure in sepsis: prognosis and role of systemic inflammatory response. Curr Opin Crit Care. 2011; 17(2):153–9. PubMed PMID: 21346564. DOI: 10.1097/MCC.0b013e328344b446 [PubMed: 21346564]
45. Rockey DC. Stellate Cells and Portal Hypertension. Stellate Cells in Health and Disease. 2015:125.
46. Saracyn M, Brytan M, Zdanowski R, Dyrla P, Patera J. Hepatoprotective effect of nitric oxide in experimental model of acute hepatic failure. World journal of gastroenterology. 2014; 20(46): 17407–15. [PubMed: 25516652]
47. Roh YS, Zhang B, Loomba R, Seki E. TLR2 and TLR9 contribute to alcohol-mediated liver injury through induction of CXCL1 and neutrophil infiltration. Ajp Gastrointestinal & Liver Physiology. 2015; 309(1):G30.
48. Shale M, Schiering C, Powrie F. CD4+ T - cell subsets in intestinal inflammation. Immunological reviews. 2013; 252(1):164–82. [PubMed: 23405904]
49. Mookerjee, RP., editor. Seminars in liver disease. Thieme Medical Publishers; 2016. Prognosis and Biomarkers in Acute-on-Chronic Liver Failure.
50. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. Gut. 2017 gutjnl-2016-312670.
51. Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. Hepatology. 2016; 64(4):1249–64. PubMed PMID: 27483394. DOI: 10.1002/hep.28740 [PubMed: 27483394]
52. Alcaraz-Quiles J, Titos E, Casulleras M, Pavesi M, Lopez-Vicario C, Rius B, et al. Polymorphisms in the IL-1 gene cluster influence systemic inflammation in patients at risk for acute-on-chronic liver failure. Hepatology. 2017; 65(1):202–16. PubMed PMID: 27775822. DOI: 10.1002/hep.28896 [PubMed: 27775822]
53. Cao X, Liu M, Wang P, Liu D-Y. Intestinal dendritic cells change in number in fulminant hepatic failure. World Journal of Gastroenterology: WJG. 2015; 21(16):4883. [PubMed: 25945001]
54. Zhang Y, Zhang J, Xu T, Wu W, Huang F-F, Yu W-q, et al. Allicin ameliorates intraintestinal bacterial translocation after trauma/hemorrhagic shock in rats: The role of mesenteric lymph node dendritic cell. Surgery. 2016
55. Floto RA, Macary PA, Boname JM, Mien TS, Kampmann B, Hair JR, et al. Dendritic cell stimulation by mycobacterial Hsp70 is mediated through CCR5. Science. 2006; 314(5798):454–8. [PubMed: 17053144]
56. Ju, B-l, Li, X., Gui, J-q, Lu, Y. Experimental study about the intestinal barrier dysfunction in the acute liver failure mice. Journal of Tropical Medicine. 2011; 10:009.
57. Yang Y, Jobin C. Microbial imbalance and intestinal pathologies: connections and contributions. Disease Models and Mechanisms. 2014; 7(10):1131–42. [PubMed: 25256712]
58. Ma H-D, Wang Y-H, Chang C, Gershwin ME, Lian Z-X. The intestinal microbiota and microenvironment in liver. Autoimmunity reviews. 2015; 14(3):183–91. [PubMed: 25315744]
59. Chen Y, Guo J, Qian G, Fang D, Shi D, Guo L, et al. Gut dysbiosis in acute - on - chronic liver failure and its predictive value for mortality. Journal of gastroenterology and hepatology. 2015; 30(9):1429–37. [PubMed: 25711972]
60. Goel A, Gupta M, Aggarwal R. Gut microbiota and liver disease. Journal of gastroenterology and hepatology. 2014; 29(6):1139–48. [PubMed: 24547986]
61. Sarin SK, Choudhury A. Acute-on-chronic Liver Failure. Current gastroenterology reports. 2016; 18(12):61. [PubMed: 27747458]
62. Wasilewski A, Zielinska M, Storr M, Fichna J. Beneficial effects of probiotics, prebiotics, synbiotics, and psychobiotics in inflammatory bowel disease. Inflammatory bowel diseases. 2015; 21(7):1674–82. [PubMed: 25822014]

63. Wasilewski A, Zielinska M, Storr M, Fichna J. Beneficial Effects of Probiotics, Prebiotics, Synbiotics, and Psychobiotics in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2015; 21(7): 1674–82. PubMed PMID: 25822014. DOI: 10.1097/MIB.0000000000000364 [PubMed: 25822014]
64. Vieira AT, Teixeira MM, Martins FdS. The role of probiotics and prebiotics in inducing gut immunity. Frontiers in immunology. 2013; 4:445. [PubMed: 24376446]
65. Huang PN, Deng YH. Effects of probiotics on intestinal flora plasma endotoxin and cytokines in patients with chronic liver failure. Chinese Journal of Nosocomiology. 2011; 21(18):3798–800.
66. Carotti S, Guarino M, Vespasiani-Gentilucci U, Morini S. Starring role of toll-like receptor-4 activation in the gut-liver axis. World journal of gastrointestinal pathophysiology. 2015; 6(4):99–109. [PubMed: 26600967]
67. Xing T, Li L, Cao H, Huang J. Altered immune function of monocytes in different stages of patients with acute on chronic liver failure. Clinical & Experimental Immunology. 2007; 147(1): 184–8. [PubMed: 17177978]
68. Roy A, Srivastava M, Saqib U, Liu D, Faisal SM, Sugathan S, et al. Potential therapeutic targets for inflammation in toll-like receptor 4 (TLR4)-mediated signaling pathways. International Immunopharmacology. 2016; 40:79–89. [PubMed: 27584057]
69. Milewski K, Oria M. What we know: the inflammatory basis of hepatic encephalopathy. Metabolic brain disease. 2016; 31(6):1239–47. [PubMed: 26497651]
70. Mencin A, Kluwe J, Schwabe RF. Toll-like receptors as targets in chronic liver diseases. Gut. 2009; 58(5):704–20. [PubMed: 19359436]
71. Guignant C, Venet F, Planel S, Demaret J, Gouel-Chéron A, Nougier C, et al. Increased MerTK expression in circulating innate immune cells of patients with septic shock. Intensive care medicine. 2013; 39(9):1556–64. [PubMed: 23835724]
72. Bernsmeier C, Singanayagam A, Patel VC, Wendon J, Antoniades CG. Immunotherapy in the treatment and prevention of infection in acute-on-chronic liver failure. Immunotherapy. 2015; 7(6): 641–54. [PubMed: 26065379]
73. Bernsmeier C, Pop OT, Singanayagam A, Triantafyllou E, Patel VC, Weston CJ, et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase MERTK. Gastroenterology. 2015; 148(3):603–15. [PubMed: 25479139]
74. Oshima G, Shinoda M, Tanabe M, Ebinuma H, Nishiyama R, Takano K, et al. Increased plasma levels of high mobility group box 1 in patients with acute liver failure. European Surgical Research. 2012; 48(3):154–62. [PubMed: 22585050]
75. Duan X, Hu J, Li C, Liu F, Liu X, Tong J, et al. Relation between serum levels of high mobility group box 1 and hepatitis B virus-related acute-on-chronic liver failure. Zhonghua gan zang bing za zhi= Zhonghua ganzangbing zazhi= Chinese journal of hepatology. 2013; 21(6):434–7. [PubMed: 24034844]
76. Hu Y, Hu D, Fu R. Correlation between High mobility group box-1 protein and chronic hepatitis B infection with severe hepatitis B and acute-on-chronic liver failure: a meta-analysis. Minerva medica. 2016
77. Zhou R-R, Liu H-B, Peng J-P, Huang Y, Li N, Xiao M-F, et al. High mobility group box chromosomal protein 1 in acute-on-chronic liver failure patients and mice with ConA-induced acute liver injury. Experimental and molecular pathology. 2012; 93(2):213–9. [PubMed: 22609241]
78. Yan K, Garcia-Tsao G. Novel prevention strategies for bacterial infections in cirrhosis. Expert Opin Pharmacother. 2016; 17(5):689–701. PubMed PMID: 26799197; PubMed Central PMCID: PMCPMC4988518. DOI: 10.1517/14656566.2016.1145663 [PubMed: 26799197]