Advances in Research on the Relationship Between Veillonella and Liver Diseases Based on the Gut-Liver Axis Theory: A Postprint

Authors: Shi Yufeng, Lu Chenxia, Lü Anqi, Xiaodong Li, Li Xiaodong

Date: 2024-10-17T11:38:55+00:00

Abstract

Veillonella, as an important member of the gut microbiota, has gradually attracted researchers' attention regarding its association with liver diseases. Although existing studies have indicated the potential role of Veillonella in liver diseases, there is currently a lack of effective integration of research findings in this field. This article systematically explores the relationship between Veillonella and liver diseases, including its distribution characteristics in different liver diseases, potential mechanisms affecting liver health, and pathways of action through the gut-liver axis. Through literature review, this article summarizes the enrichment of Veillonella in metabolic-associated fatty liver disease, autoimmune liver diseases, cirrhosis, and primary liver cancer, and explores how it may affect liver health by activating inflammatory responses, influencing intestinal barrier function, and promoting metabolite translocation. Research indicates that the enrichment of Veillonella may be closely related to the pathogenesis and progression of liver diseases, but its specific mechanisms of action still require further investigation. This article provides a theoretical foundation for understanding and utilizing Veillonella in the prevention and treatment of liver diseases, and offers references for future research directions and clinical therapeutic strategies.

Full Text

Research Progress on the Relationship between Veillonella and Liver Diseases Based on the Theory of the Gut-Liver Axis

SHI Yufeng[1], LU Chenxia[2,3,4], LYU Anqi[1], LI Xiaodong[1,2,3,4*]

[1]College of Traditional Chinese Medicine, Hubei University of Chinese Medicine, Wuhan 430065, China

[2]Institute of Liver Diseases, Hubei Key Laboratory of Theoretical and Applied Research of Liver and Kidney in Traditional Chinese Medicine, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan 430061, China
[3]Hubei Shizhen Laboratory, Wuhan 430061, China
[4]Affiliated Hospital of Hubei University of Chinese Medicine, Wuhan 430061, China

Corresponding author: LI Xiaodong, Chief physician/Doctoral supervisor; E-mail: lixiaodong555@126.com

Abstract

As an important member of the intestinal microbial community, Veillonella has gradually attracted researchers' attention regarding its association with liver diseases. Although studies have pointed to potential roles of Veillonella in liver diseases, there remains a lack of effective integration of research findings in this field. This article systematically explores the relationship between Veillonella and liver diseases, including its distribution characteristics across different liver diseases, potential mechanisms affecting liver health, and pathways of action through the gut-liver axis. Through literature review, this paper summarizes the enrichment of Veillonella in metabolic-associated fatty liver disease, autoimmune liver disease, liver cirrhosis, and primary liver cancer, and discusses how it may affect liver health by activating inflammatory responses, influencing intestinal barrier function, and promoting metabolite translocation. Studies have shown that Veillonella enrichment may be closely related to the occurrence and development of liver diseases, though its specific mechanisms of action require further investigation. This article provides a theoretical basis for understanding and utilizing Veillonella in the prevention and treatment of liver diseases, and offers references for future research directions and clinical therapeutic strategies.

Keywords: Liver disease; Veillonella; Gut-liver axis; Intestinal microbiota; Review

---

1. Overview of the Gut-Liver Axis

The gut-liver axis represents the close bidirectional anatomical and functional interaction between the intestine and liver, influenced by diet, genetics, and environmental factors. The portal vein serves as the hub of this interaction, with 75% of venous blood from the small and large intestines entering the liver via the portal vein, delivering nutrients, lipids, microbes, and various metabolites. Meanwhile, the liver secretes bile containing bile acids (BA), cholesterol, phospholipids, and other components into the small intestine, thereby regulating the intestinal microbiota and forming a complete cycle. Bile aids lipid digestion and absorption in the proximal small intestine. In the colon, the gut microbiota converts primary BAs to secondary BAs through dihydroxylation, and

both primary and secondary BAs are reabsorbed into the liver via the portal circulation.

The intestinal barrier is a critical structure for gut-liver interactions, composed of the mucus layer, epithelial cell layer, stromal cells, and intestinal immune system. Under physiological conditions, the intestinal barrier prevents harmful substances such as microbes and toxins from entering the bloodstream while allowing nutrients to reach the liver. Under pathological conditions, impaired intestinal barrier function increases intestinal permeability, causing translocation of metabolites, endotoxins (LPS), and potentially gut microbes to the liver, where they exert direct toxic effects and may induce liver inflammation by binding to specific pathogen recognition receptors, thereby aggravating existing liver diseases and worsening the condition [Figure 1: see original paper].

2. Biological Characteristics and Mechanisms of Veillonella

First isolated in 1898 by French microbiologists Veillon and Zuber, Veillonella is a Gram-negative obligate anaerobic coccus with a diameter of 0.3–0.5 m, appearing Gram-positive initially but turning Gram-negative overnight. It appears as diplococci, sheets, and short chains, without capsule, flagella, or spores. Veillonella species are primarily isolated from the oral cavity and intestines of humans and other warm-blooded vertebrates. Currently, 14 species are known, including *Veillonella parvula*, *Veillonella dispar*, *Veillonella atypica*, *Veillonella rogosae*, *Veillonella denticariosi*, *Veillonella tobetsuensis*, *Veillonella infantium*, *Veillonella criceti*, *Veillonella magna*, *Veillonella caviae*, *Veillonella ratti*, *Veillonella montpellierensis*, *Veillonella seminalis*, and *Veillonella rodentium*.

While Veillonella can be relatively easily identified at the genus level, its lack of discriminative phenotypic characteristics and similar biochemical properties make species-level identification difficult in gut microbiota studies using 16S rRNA gene sequencing. Currently, gene sequences such as *dnaK*, *gltA*, *gyrB*, and *rpoB* are considered more discriminative for accurate species-level identification of Veillonella isolates.

As a member of the gut microbial community, Veillonella may positively influence host health by maintaining microbial community balance and regulating host metabolism and immunity. However, this effect may vary depending on individual differences and environmental conditions, and in some cases, Veillonella overgrowth or specific metabolic activities may be associated with disease development. For instance, *Veillonella parvula* NCTC11810 and its metabolites inhibit proliferation and invasion of oral squamous cell carcinoma (OSCC) cells and promote apoptosis by affecting TROP2-related PI3K/Akt pathway activity, suggesting potential anti-tumor effects. Veillonella is a lactate-utilizing bacterium that converts lactate to short-chain fatty acids (SCFAs) such as acetate and propionate in the gut. Studies have found that Veillonella enriches in the gastrointestinal tract of athletes after exercise, and its SCFA production improves athletic performance.

However, most studies indicate that Veillonella enrichment is associated with disease development. MA et al. found *Veillonella parvula* highly enriched in the oropharynx of COVID-19 patients, correlating with disease severity and systemic inflammatory markers. A retrospective study suggested that preeclampsia is associated with gut dysbiosis, possibly through destruction of the intestinal barrier and translocation of pathogenic bacteria Veillonella and Fusobacterium from the "gut-placenta"axis to the placenta, causing abnormal immune responses. An animal study found that *Veillonella infantium* may translocate metabolites such as lipopolysaccharide and peptidoglycan to the brain via gut-blood, vagus nerve-brain, and gut-blood-brain pathways, causing NF- B-mediated neuroinflammation and cognitive dysfunction.

3.1 Veillonella and Metabolic-Associated Fatty Liver Disease (MAFLD)

MAFLD is a liver disease closely associated with obesity, hypertension, insulin resistance, type 2 diabetes, hyperlipidemia, and metabolic syndrome, with a global prevalence of 25% and a major health burden worldwide. Changes in gut microbiota composition, microbial metabolism, and intestinal barrier function are important factors contributing to MAFLD progression. As a major member of the gut microbiota, Veillonella' s relationship with MAFLD warrants investigation.

Research findings on Veillonella distribution in MAFLD populations remain controversial. MOHAMMADI et al. found that the abundance of Veillonella was significantly higher in the gut of nonalcoholic steatohepatitis (NASH) patients compared to non-alcoholic fatty liver disease (NAFLD) patients. A Mendelian randomization study using inverse variance weighting (IVW) analysis confirmed that increased relative abundance of Veillonella was significantly associated with increased NASH risk. Several other studies reached similar conclusions, showing significantly increased abundance of Veillonellaceae (including Veillonella) in the gut microbiota of NAFLD patients.

Animal experiments demonstrated that high-fat diet (HFD) rats showed significantly increased relative abundance of Veillonella, and compound probiotics improved intestinal barrier function, reduced lipid deposition, and alleviated chronic metabolic inflammation by modulating the gut microbiota and reducing Veillonella abundance. Another animal study found that loquat fruit polyphenol extract (LFP) reduced endotoxin production in high-fructose-fed NAFLD mice by inhibiting Veillonella overgrowth, thereby decreasing inflammation and oxidative stress. LFP protected and repaired the intestinal chemical, physical, and immune barriers through gut microbiota modulation. Additionally, ZHAO et al. found increased Veillonella abundance in the oral microbiota of MAFLD patients, which positively correlated with insulin resistance, suggesting that oral Veillonella may influence disease development through involvement in MAFLD-related glucose metabolism pathways.

However, several studies reached opposite conclusions. One study investigating the interaction between gut microbiome and iron metabolism in NAFLD found that serum ferritin levels positively correlated with hepatic fat accumulation but strongly negatively correlated with Veillonella abundance, suggesting a potential protective role of Veillonella in NAFLD and NASH. LOOMBA et al. conducted a drug trial using Aldafermin, an FGF19 analog that inhibits CYP7A1 to block bile acid synthesis and affects gut microbiota. The study found dose-dependent enrichment of Veillonella in the treatment group, inferred to be associated with reduced toxic bile acids, suggesting that gut microbiota changes (such as Veillonella increase) may influence liver metabolism and reduce inflammatory status through the gut-liver axis.

In summary, current research reveals the multifaceted role of Veillonella in MAFLD development. While most studies support its potential pathogenic role, some suggest protective effects, indicating its role may be more complex than currently understood. Future research should focus on the complex interactions between Veillonella and MAFLD and explore new therapeutic strategies through gut microbiota modulation.

3.2 Veillonella and Autoimmune Liver Disease (AILD)

AILD comprises rare immune-mediated chronic liver diseases characterized by autoimmune attack on liver cells, causing inflammation that can progress to cirrhosis and liver cancer. The main types include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Recent research has focused on microbiota-host interactions, with imbalanced gut microbiota thought to be associated with abnormal immune responses. Metagenomic and metabolomic studies show reduced gut microbial diversity in AILD patients, with enrichment of certain microbes including Veillonella, suggesting that compositional changes may contribute to AILD pathogenesis. Gut microbes regulate host immune responses through SCFA and bile acid metabolites, and dysbiosis may damage intestinal barrier function, allowing bacterial endotoxins to enter systemic circulation and trigger immune responses. Studies confirm that gut microbiota promotes AILD susceptibility, development, and progression through molecular mimicry of self-antigen orthologs, migration of commensal bacteria to the liver, and migration of intestinal immune cells to the liver.

AIH is a chronic inflammatory liver disease mediated by abnormal autoimmune responses, primarily affecting hepatocytes. WEI et al. found reduced alpha diversity in AIH patients' gut microbiota, with *Veillonella dispar* abundance showing the strongest positive correlation with disease severity. Two other studies confirmed significant enrichment of Veillonella in AIH patients' gut microbiota, with positive correlation to liver inflammation markers. Research identified Veillonella, Lachnospiraceae, Bacteroides, Roseburia, and Ruminococcaceae as the optimal microbial markers for distinguishing AIH patients from healthy controls, with an area under the ROC curve (AUC) of 83.25%.

PBC and PSC are chronic cholestatic liver diseases mediated by abnormal autoimmune responses. PBC primarily affects small bile ducts with chronic lymphocytic inflammation and septal bile duct fibrosis, while PSC affects intra- and extra-hepatic large bile ducts with inflammation and fibrosis. A study on BA-microbiota interactions in PBC found abnormal BA metabolism, including reduced conversion of conjugated to unconjugated BAs and primary to secondary BAs, indicating impaired microbial BA metabolism. Secondary BAs such as deoxycholic acid (DCA) and conjugated DCA negatively correlated with enriched Veillonella, suggesting that increased Veillonella affects BA metabolism. TANG et al. found significantly increased Veillonella abundance in PBC patients. Although ursodeoxycholic acid (UDCA) treatment improved gut dysbiosis in PBC patients, Veillonella abundance did not significantly decrease, suggesting its increase relates to PBC pathology rather than just microbial community structural changes. UDCA-poor responders showed higher Veillonella abundance than good responders, indicating association with disease severity or treatment response.

In PSC research, Veillonella was highly enriched in patients' gut microbiota at 4.8 times that of healthy controls and 7.8 times that of ulcerative colitis patients, positively correlating with Mayo risk score (a PSC prognostic indicator). *Veillonella dispar* accounted for approximately 82% and *Veillonella parvula* about 11%. VIEIRA-SILVA et al. found that Veillonella increase positively correlated with intestinal inflammation levels in PSC patients but showed an inverse relationship with proinflammatory *Fusobacterium* abundance, requiring further validation. Several studies consistently found increased Veillonella abundance in PSC patients, independent of concurrent inflammatory bowel disease (IBD), and positively correlated with PSC severity and liver function markers, possibly related to inflammatory and fibrotic processes. Conversely, one study noted that when LC patients were excluded from analysis, the association between PSC and Veillonella became non-significant, suggesting the increase may relate to LC presence rather than PSC itself.

Oral microbiota studies also confirmed significantly increased Veillonella abundance in AIH and PBC patients compared to healthy controls, positively correlating with salivary inflammatory cytokines [interleukin (IL)-1β, IL-8] and immunoglobulin A (IgA) levels. Soluble CD163 (sCD163), an M2 macrophage activation marker involved in autoimmune diseases, was found to positively correlate with Veillonella abundance in PBC patients' oral microbiota and liver function indicators [particularly alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT)]. LAPIDOT et al. also observed *Veillonella parvula* overexpression in PSC patients' oral microbiota. These findings suggest that oral Veillonella dysbiosis may also play an important role in AILD pathogenesis.

In summary, most studies confirm specific alterations in oral and gut microbiota and microbial metabolites in AILD patients, with Veillonella significantly enriched in both compartments. This enrichment may contribute to disease progression, making Veillonella a potential novel microbial biomarker and ther-

apeutic target for AILD diagnosis and treatment. However, no deeper studies have established causal relationships between Veillonella and AILD, necessitating further research into its specific mechanisms and how these findings can be translated into new diagnostic tools and therapeutic strategies.

3.3 Veillonella and Liver Cirrhosis (LC)

LC represents the end-stage pathology of various chronic liver diseases characterized by diffuse fibrosis, pseudolobule formation, intra- and extra-hepatic vascular proliferation, and portosystemic collateral circulation. Chronic liver disease progresses from fibrosis to asymptomatic compensated LC, and finally to decompensated LC with portal hypertension and liver dysfunction. Gut microbiota dysbiosis disrupts intestinal barrier function, increases intestinal permeability and bacterial translocation, leading to systemic inflammation, infection, vasodilation, and contributing to hepatic decompensation and multi-organ failure. Gut microbes and their metabolites may affect neurological function through the gut-liver-brain axis, promoting or triggering hepatic encephalopathy. Current research shows that modulating gut microbiota through fecal microbiota transplantation (FMT) or specific drugs (rifaximin, lactulose, antibiotics) may improve clinical outcomes and prevent decompensation events.

Earlier studies found reduced gut microbial diversity in LC patients, with 75,245 genes showing differential abundance compared to healthy controls, representing 66 clusters of different bacterial species, including enriched Veillonella. A meta-omics study confirmed that opportunistic pathogen Veillonella (including *Veillonella atypica*, *Veillonella dispar*, *Veillonella parvula*, and *Veillonella* sp. ACP1) increased in LC patients' gut microbiota, possibly related to impaired intestinal barrier function and systemic inflammation, with Veillonella abundance continuing to rise during disease progression from compensated to decompensated stages. DENG et al. also found positive correlation between Veillonella abundance and Child-Pugh classification, with levels increasing as liver function deteriorated.

Human leukocyte antigen (HLA) class II genes are major genetic susceptibility factors for PBC. One study found that FHRAC-positive (five-class HLA-DRB1 high-risk allele combination) LC patients showed significantly higher abundance of Veillonella at genus level and *Veillonella atypica* at species level compared to FHRAC-negative and non-LC patients, indicating that Veillonella abundance correlates with HLA class II genetic susceptibility and LC development. An animal study found that splenectomy improved LC in mice by restoring intestinal barrier function and maintaining gut microbiota balance, while *Veillonella parvula* gavage reversed these improvements. In vitro experiments confirmed that *Veillonella parvula* conditioned medium promoted hepatic stellate cell activation and release of IL-6, IL-1β, and TNF-α, induced hepatocyte pyroptosis, and increased ALT and AST release, reflecting LC progression and exacerbated inflammation. Inhibiting the Tlp4/Nlrp3 inflammasome pathway could block *Veillonella parvula*-induced hepatocyte pyroptosis, stellate cell activation, and

LC progression.

SUNG et al. found that Veillonella abundance correlated with LC severity and hepatic encephalopathy episodes, with *Veillonella parvula* enriched 10-fold in the gut of acute overt hepatic encephalopathy (AHE) patients compared to LC patients without AHE. A drug trial showed that rifaximin-α improved clinical outcomes in LC patients by inhibiting Veillonella and other bacteria, reducing hepatic encephalopathy recurrence, improving neurocognitive function and systemic inflammation. Inhibiting these mucin-degrading bacteria promoted beneficial bacteria growth, restored gut microbiota balance, improved intestinal barrier function, reduced permeability, and prevented bacterial and endotoxin translocation. Animal studies yielded similar conclusions: combined rifaximin and lubiprostone treatment modulated gut microbiota in NASH fibrosis rats, reducing Veillonella abundance and sialidase activity, thereby improving intestinal barrier function and exerting positive effects on NASH-related fibrosis. The traditional Chinese medicine formula Danggui Shaoyao San (DSS) effectively treats liver fibrosis by modulating Veillonella and other gut microbes, altering microbiota structure to increase SCFA levels and regulate BA metabolism, thereby alleviating CCl_4-induced hepatic fibrosis and protecting intestinal barrier function. *Veillonella parvula* also correlates with sarcopenia in LC patients, where increased abundance may contribute to reduced muscle mass and function. Although Veillonella abundance is high in LC patients, no significant differences exist between different etiologies (e.g., HBV-related LC and PBC), suggesting the increase relates to LC itself rather than specific causes.

Current evidence indicates that Veillonella closely correlates with LC severity, liver function impairment, and hepatic encephalopathy episodes. Surgical and pharmacological interventions that inhibit Veillonella growth help improve intestinal barrier function, restore gut microbiota balance, and reduce inflammation, exerting positive therapeutic effects. Future research should explore how Veillonella influences intestinal barrier function and systemic inflammation to drive LC progression, reveal its molecular mechanisms, and explore potential of novel drugs or traditional Chinese formulas in modulating Veillonella and improving LC symptoms to develop more effective treatment strategies.

3.4 Veillonella and Primary Liver Cancer (PLC)

PLC is a common malignant tumor in China with high incidence and mortality rates, ranking second among all malignant tumors. The most common types are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). While PLC development is influenced by multiple factors including hepatitis, alcoholic liver disease, MAFLD, AILD, and LC, its exact pathogenesis remains unclear. Recent studies have found close associations between gut microbiota dysbiosis and PLC development. Dysbiosis promotes liver inflammation, fibrosis, hepatocyte proliferation, and activation of anti-apoptotic signals, releases cancer-promoting metabolites (e.g., DCA), increases intestinal permeability, and facilitates translocation of bacteria and their metabolites (endotoxins, β-

glucan, viral/bacterial DNA) to promote PLC development through increased microbial-associated molecular patterns (MAMPs) such as lipopolysaccharide.

As a Gram-negative LPS-producing bacterium, Veillonella can activate TLR4 signaling pathways in various liver cells (including Kupffer cells), leading to increased TNF-β and IL-6 levels and activation of multiple pro-inflammatory and oncogenic pathways. Studies found significantly increased Veillonella abundance in HCC patients' gut microbiota compared to healthy controls, positively correlating with liver function indicators. POMYEN found Veillonella more enriched in iCCA patients' gut than in HCC and healthy controls, with *Veillonella atypica* and *Veillonella parvula* showing the most significant enrichment, enhancing amino acid biosynthesis and glycolysis. In iCCA patients, Veillonella positively correlated with inflammatory markers—neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR)—and negatively correlated with lymphocyte-to-monocyte ratio (LMR). Some studies also found that increased Veillonella abundance significantly correlated with tumor marker alpha-fetoprotein (AFP) and increased mortality risk in Barcelona Clinic Liver Cancer (BCLC) stage B and C patients.

Exploring gut microbiome characteristics for PLC diagnosis revealed its potential as a new non-invasive diagnostic method. TANG et al. identified Veillonella as one of 16 optimal OTU markers for distinguishing HCC from non-HCC in a random forest model. DENG et al. found that a microbiome classification model based on Veillonella and seven other genera showed high accuracy (AUC values of 0.989, 0.967, and 0.920) for distinguishing HCC, iCCA, and healthy individuals, outperforming traditional tumor markers (AFP, CEA, CA-199). ZHENG et al. identified Veillonella as a significantly increased gut microbe in early recurrence (ER) HCC patients and an independent prognostic indicator for predicting ER. Combined detection of Veillonella with Romboutsia and *Veillonella dispar* with Coriobacterium, Atopobium, and Coprococcus were proposed as new HCC diagnostic methods.

In a nivolumab treatment study for HCC, *Veillonella atypica* abundance was identified as a bacterial taxon specific to non-responders, suggesting its presence may correlate with lack of treatment response. However, another study found Veillonella as a dominant bacterium in the gut microbiota of unresectable HCC patients responding to immune checkpoint inhibitor (ICI) therapy, associated with better treatment response and survival outcomes, revealing potential links between gut microbiota and PLC treatment response. Veillonella, as part of the gut microbiota, along with beneficial bacteria like *Akkermansia* and *Bifidobacterium*, showed temporal patterns and causal relationships associated with disease control, suggesting gut microbiota balance may influence ICI therapy responses in PLC patients.

Although findings on intestinal Veillonella vary, all studies emphasize potential links between gut microbiota and PLC patients' responses to ICI therapy. Studies on oral microbiota in liver cancer patients found significantly enriched Veillonella abundance in cholangiocarcinoma patients' oral microbiota compared

to healthy controls, with Veillonella identified as one of the significantly different genera between groups. As part of the oral microbial community, Veillonella abundance changes may reflect oral microbial diversity alterations related to liver cancer development.

In summary, Veillonella is significantly increased in oral and gut microbiota of liver cancer patients, positively correlating with liver function indicators, inflammatory markers, and tumor markers. It also associates with early recurrence, disease progression, and response to ICI therapy, revealing potential links between gut microbiota and liver cancer treatment responses. Further research indicates Veillonella may serve as a new non-invasive diagnostic marker for liver cancer, showing higher diagnostic accuracy than existing tumor markers. Future studies should explore Veillonella' s specific mechanisms in liver cancer, its potential as diagnostic and prognostic markers, and its role in immunotherapy to provide new strategies for early diagnosis, prognosis assessment, and personalized treatment.

3.5 Veillonella and Other Liver-Related Diseases

While most studies have focused on Veillonella's association with MAFLD, AILD, LC, and PLC, its potential role in other liver-related diseases also warrants attention. Studies have found significantly increased Veillonella abundance in the gut microbiota of viral hepatitis patients, positively correlating with hepatitis severity and disease progression. The increase also associated with inflammatory and immune response-related microbial functional changes, such as increased tryptophan metabolism, fatty acid biosynthesis, and LPS biosynthesis. CHEN et al. confirmed reduced gut microbiota diversity in chronic hepatitis B (CHB) patients with significantly increased Veillonella abundance, suggesting microbiota dysbiosis as an important factor in CHB progression to severe liver failure.

Similar conclusions were found in alcoholic hepatitis (AH) and drug-induced liver injury (DILI) patients. AH patients showed Veillonella abundance correlating with disease severity, significantly increased in more severe disease states but reduced after rifaximin treatment, suggesting Veillonella as a potential diagnostic and predictive biomarker for AH. HE et al. identified Veillonella as a DILI-associated gut microbe with significantly increased abundance in DILI patients, suggesting its involvement in DILI pathogenesis.

Although current research on Veillonella in other liver diseases is limited, preliminary findings are consistent with major trends. These studies indicate that Veillonella abundance changes may closely correlate with liver disease severity and progression, warranting further investigation into its potential role and validation of its practical value as a biomarker and therapeutic target.

The gut-liver axis refers to the physiological and pathological pathways connecting the intestine and liver through blood circulation, neural transmission, and immune signals, playing a key role in liver disease development. As a major gut microbiota member, Veillonella plays important roles in various liver

diseases, being commonly enriched in MAFLD, AILD, LC, and PLC patients. This enrichment may relate to its ability to activate inflammatory responses and promote liver injury. Through production of endotoxins and other metabolites, Veillonella may exacerbate liver inflammation and fibrosis, promoting disease progression. Veillonella enrichment may also affect intestinal barrier function, increasing permeability and causing bacterial and metabolite translocation to the liver via the gut-liver axis. However, the specific molecular mechanisms by which Veillonella influences intestinal barrier and gut-liver axis function remain poorly understood. Additionally, Veillonella enrichment in oral microbiota also correlates with liver disease, and although research is limited, evidence suggests the oral-gut-liver axis may also play a key role in liver disease development. Oral Veillonella may affect liver health through blood circulation or direct interaction with gut microbiota. Notably, not all studies show positive correlations between Veillonella and liver disease; some report opposite findings due to differences in sample size, study design, or analytical methods. These inconsistencies suggest complex mechanisms of the gut-liver axis, and that Veillonella-liver disease relationships may be influenced by host genetics, lifestyle, environmental factors, and microbial community interactions.

Despite inconsistent findings, accumulating evidence supports Veillonella' s potential role in liver diseases, particularly in promoting inflammation and liver injury. Future research should explore Veillonella' s specific mechanisms in different liver diseases and evaluate its potential as a biomarker and therapeutic target. Modulating Veillonella levels in the gut and oral cavity may provide new strategies for liver disease prevention and treatment.

References

[1] LIU X, CHEN Y, ZHANG S, et al. Gut microbiota-mediated immunomodulation in tumor[J]. J Exp Clin Cancer Res, 2021, 40(1): 221. DOI: 10.1186/s13046-021-01983-x.

[2] HSU C L, SCHNABL B. The gut-liver axis and gut microbiota in health and liver disease[J]. Nat Rev Microbiol, 2023, 21(11): 719-733. DOI: 10.1038/s41579-023-00904-3.

[3] ROJAS-TAPIAS D F, BROWN E M, TEMPLE E R, et al. Inflammation-associated nitrate facilitates ectopic colonization of oral bacterium Veillonella parvula in the intestine[J]. Nat Microbiol, 2022, 7(10): 1673-1685. DOI: 10.1038/s41564-022-01224-8.

[4] ZHAI Q L, WU H Y, ZHENG S Y, et al. Association between gut microbiota and NAFLD/NASH: a bidirectional two-sample Mendelian randomization study[J]. Front Cell Infect Microbiol, 2023, 13: 1294826. DOI: 10.3389/fcimb.2023.1294826.

[5] MAYNERIS-PERXACHS J, CARDELLINI M, HOYLES L, et al. Iron status influences non-alcoholic fatty liver disease in obesity through the gut micro-

biome[J]. Microbiome, 2021, 9(1): 104. DOI: 10.1186/s40168-021-01052-7.

[6] YAMAMOTO K, HONDA T, INUKAI Y, et al. Identification of the microbiome associated with prognosis in patients with chronic liver disease[J]. Microorganisms, 2024, 12(3): 610. DOI: 10.3390/microorganisms12030610.

[7] TILG H, ADOLPH T E, TRAUNER M. Gut-liver axis: Pathophysiological concepts and clinical implications[J]. Cell Metab, 2022, 34(11): 1700-1718. DOI: 10.1016/j.cmet.2022.09.017.

[8] PABST O, HORNEF M W, SCHAAP F G, et al. Gut–liver axis: barriers and functional circuits[J]. Nat Rev Gastroenterol Hepatol, 2023, 20(7): 447-461. DOI: 10.1038/s41575-023-0011-z.

[9] MASHIMA I, NAKAZAWA F. The interaction between Streptococcus spp. and Veillonella tobetsuensis in the early stages of oral biofilm formation[J]. J Bacteriol, 2015, 197(3): 2104-2111. DOI: 10.1128/JB.02512-14.

[10] MASHIMA I, LIAO Y C, MIYAKAWA H, et al. Veillonella infantium sp. nov., an anaerobic, Gram-stain-negative coccus isolated from tongue biofilm of a Thai child[J]. Int J Syst Evol Microbiol, 2018, 68(4): 1101-1106. DOI: 10.1099/ijsem.0.002632.

[11] DJAIS A A, THEODOREA C F, MASHIMA I, et al. Identification and phylogenetic analysis of oral Veillonella species isolated from the saliva of Japanese children[J]. F1000Research, 2019, 8: 616. DOI: 10.12688/f1000research.18506.5.

[12] KOLENBRANDER P. The genus veillonella[M]//DWORKIN M, FALKOW S, ROSENBERG E, et al. The prokaryotes: a handbook on the biology of bacteria. 3rd ed. New York: Springer, 1992.

[13] CHANG X X, CHEN Y F, CUI D X, et al. Propionate-producing Veillonella parvula regulates the malignant properties of tumor cells of OSCC[J]. Med Oncol, 2023, 40(3): 98. DOI: 10.1007/s12032-023-01962-6.

[14] SCHEIMAN J, LUBER J M, CHAVKIN T A, et al. Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism[J]. Nat Med, 2019, 25(7): 1104-1109. DOI: 10.1038/s41591-019-0485-4.

[15] MA S, ZHANG F, ZHOU F, et al. Metagenomic analysis reveals oropharyngeal microbiota alterations in patients with COVID-19[J]. Signal Transduct Target Ther, 2021 May 13;6(1): 191. DOI: 10.1038/s41392-021-00614-3.

[16] CHEN X, LI P, LIU M, et al. Gut dysbiosis induces the development of pre-eclampsia through bacterial translocation[J]. Gut, 2020, 69(3): 513-522. DOI: 10.1136/gutjnl-2019-319101.

[17] MA X Y, KIM J K, SHIN Y J, et al. Lipopolysaccharide-producing Veillonella infantium and Escherichia fergusonii cause vagus nerve-mediated cognitive impairment in mice[J]. Brain Behav Immun, 2024, 118: 136-148. DOI: 10.1016/j.bbi.2024.02.031.

[18] LANG S, SCHNABL B. Microbiota and fatty liver disease-the known, the unknown, and the future[J]. Cell Host Microbe, 2020, 28(2): 233-244. DOI: 10.1016/j.chom.2020.07.007.

[19] MOHAMMADI Z, POUSTCHI H, HEKMATDOOST A, et al. Gut microbiota profile in patients with nonalcoholic fatty liver disease and presumed nonalcoholic steatohepatitis[J]. J Res Med Sci, 2022, 27: 54. DOI: 10.4103/jrms.jrms_{{{673}}_{{21}}}.

[20] LI F, SUN G, WANG Z K, et al. Characteristics of fecal microbiota in nonalcoholic fatty liver disease patients[J]. Sci China Life Sci, 2018, 61(7): 770-778. DOI: 10.1007/s11427-017-9303-9.

[21] DEMIR M, LANG S, MARTIN A, et al. Phenotyping non-alcoholic fatty liver disease by the gut microbiota: Ready for prime time?[J]. J Gastroenterol Hepatol, 2020, 35(11): 1969-1977. DOI: 10.1111/jgh.15071.

[22] LIANG Y J, LIANG S, ZHANG Y P, et al. Oral administration of compound probiotics ameliorates HFD-induced gut microbe dysbiosis and chronic metabolic inflammation via the G protein-coupled receptor 43 in non-alcoholic fatty liver disease rats[J]. Probiotics Antimicrob Proteins, 2019, 11(1): 175-185. DOI: 10.1007/s12602-017-9378-3.

[23] LI W F, YANG H Y, ZHAO Q, et al. Polyphenol-rich loquat fruit extract prevents fructose-induced nonalcoholic fatty liver disease by modulating glycometabolism, lipometabolism, oxidative stress, inflammation, intestinal barrier, and gut microbiota in mice[J]. J Agric Food Chem, 2019, 67(27): 7726-7737. DOI: 10.1021/acs.jafc.9b02523.

[24] ZHAO F, DONG T, YUAN K Y, et al. Shifts in the bacterial community of supragingival plaque associated with metabolic-associated fatty liver disease[J]. Front Cell Infect Microbiol, 2020, 10: 581888. DOI: 10.3389/fcimb.2020.581888.

[25] LOOMBA R, LING L, DINH D M, et al. The commensal microbe Veillonella as a marker for response to an FGF19 analog in NASH[J]. Hepatology, 2021, 73(1): 126-143. DOI: 10.1002/hep.31523.

[26] ZHENG Y P, RAN Y, ZHANG H X, et al. The microbiome in autoimmune liver diseases: metagenomic and metabolomic changes[J]. Front Physiol, 2021, 12: 715852. DOI: 10.3389/fphys.2021.715852.

[27] WANG R, TANG R Q, LI B, et al. Gut microbiome, liver immunology, and liver diseases[J]. Cell Mol Immunol, 2021, 18(1): 4-17. DOI: 10.1038/s41423-020-00592-6.

[28] WEI Y, LI Y, YAN L, et al. Alterations of gut microbiome in autoimmune hepatitis[J]. Gut, 2020, 69(3): 569-577. DOI: 10.1136/gutjnl-2018-317836.

[29] LIWINSKI T, CASAR C, RUEHLEMANN M C, et al. A disease-specific decline of the relative abundance of Bifidobacterium in patients with autoimmune hepatitis[J]. Aliment Pharmacol Ther, 2020, 51(12): 1417-1428. DOI:

10.1111/apt.15754.

[30] ELSHERBINY N M, RAMMADAN M, HASSAN E A, et al. Autoimmune hepatitis: shifts in gut microbiota and metabolic pathways among Egyptian patients[J]. Microorganisms, 2020, 8(7): 1011. DOI: 10.3390/microorganisms8071011.

[31] LOU J M, JIANG Y, RAO B C, et al. Fecal microbiomes distinguish patients with autoimmune hepatitis from healthy individuals[J]. Front Cell Infect Microbiol, 2020, 10: 342. DOI: 10.3389/fcimb.2020.00342.

[32] CHEN W H, WEI Y R, XIONG A Z, et al. Comprehensive analysis of serum and fecal bile acid profiles and interaction with gut microbiota in primary biliary cholangitis[J]. Clin Rev Allergy Immunol, 2020, 58(1): 25-38. DOI: 10.1007/s12016-019-08771-8.

[33] TANG R, WEI Y, LI Y, et al. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy[J]. Gut, 2018, 67(3): 534-541. DOI: 10.1136/gutjnl-2016-313332.

[34] KUMMEN M, HOLM K, ANMARKRUD J A, et al. The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls[J]. Gut, 2017, 66(4): 611-619. DOI: 10.1136/gutjnl-2015-310500.

[35] VIEIRA-SILVA S, SABINO J, VALLES-COLOMER M, et al. Quantitative microbiome profiling disentangles inflammation- and bile duct obstruction-associated microbiota alterations across PSC/IBD diagnoses[J]. Nat Microbiol, 2019, 4(11): 1826-1831. DOI: 10.1038/s41564-019-0483-9.

[36] BAJER L, KVERKA M, KOSTOVCIK M, et al. Distinct gut microbiota profiles in patients with primary sclerosing cholangitis and ulcerative colitis[J]. World J Gastroenterol, 2017, 23(25): 4548-4558. DOI: 10.3748/wjg.v23.i25.4548.

[37] LAPIDOT Y, AMIR A, BEN-SIMON S, et al. Alterations of the salivary and fecal microbiome in patients with primary sclerosing cholangitis[J]. Hepatol Int, 2021, 15(1): 191-201. DOI: 10.1007/s12072-020-10089-z.

[38] CORTEZ R V, MOREIRA L N, PADILHA M, et al. Gut microbiome of children and adolescents with primary sclerosing cholangitis in association with ulcerative colitis[J]. Front Immunol, 2021, 11: 598152. DOI: 10.3389/fimmu.2020.598152.

[39] SABINO J, VIEIRA-SILVA S, MACHIELS K, et al. Primary sclerosing cholangitis is characterised by intestinal dysbiosis independent from IBD[J]. Gut, 2016, 65(10): 1681-1689. DOI: 10.1136/gutjnl-2015-311004.

[40] ABE K, TAKAHASHI A, FUJITA M, et al. Dysbiosis of oral microbiota and its association with salivary immunological biomarkers in autoimmune liver disease[J]. PLoS One, 2018, 13(7): e0198757. DOI: 10.1371/journal.pone.0198757.

[41] RAO B, LOU J, LU H, et al. Oral Microbiome Characteristics in Patients With Autoimmune Hepatitis[J]. Front Cell Infect Microbiol, 2021, 11: 656674. DOI: 10.3389/fcimb.2021.656674.

[42] LV L X, JIANG H Y, CHEN X X, et al. The salivary microbiota of patients with primary biliary cholangitis is distinctive and pathogenic[J]. Front Immunol, 2021, 12: 713647. DOI: 10.3389/fimmu.2021.713647.

[43] TREBICKA J, MACNAUGHTAN J, SCHNABL B, et al. The microbiota in cirrhosis and its role in hepatic decompensation[J]. J Hepatol, 2021, 75(Suppl 1): S67-81. DOI: 10.1016/j.jhep.2020.11.013.

[44] BAJAJ J S, KHORUTS A. Microbiota changes and intestinal microbiota transplantation in liver diseases and cirrhosis[J]. J Hepatol, 2020, 72(5): 1003-1027. DOI: 10.1016/j.jhep.2020.01.017.

[45] QIN N, YANG F L, LI A, et al. Alterations of the human gut microbiome in liver cirrhosis[J]. Nature, 2014, 513: 59-64. DOI: 10.1038/nature13568.

[46] SHAO L, LING Z, CHEN D, et al. Disorganized Gut Microbiome Contributed to Liver Cirrhosis Progression: A Meta-Omics-Based Study[J]. Front Microbiol, 2018, 9: 3166. DOI: 10.3389/fmicb.2018.03166.

[47] DENG Y D, PENG X B, ZHAO R R, et al. The intestinal microbial community dissimilarity in hepatitis B virus-related liver cirrhosis patients with and without at alcohol consumption[J]. Gut Pathog, 2019, 11: 58. DOI: 10.1186/s13099-019-0337-2.

[48] WU Z, ZHOU H, LIU D, et al. Alterations in the gut microbiota and the efficacy of adjuvant probiotic therapy in liver cirrhosis[J]. Front Cell Infect Microbiol, 2023, 13: 1218552. DOI: 10.3389/fcimb.2023.1218552.

[49] HÖPPNER J, KROHN S, VAN DEN MUNCKHOF E H A, et al. Changes of the bacterial composition in duodenal fluid from patients with liver cirrhosis and molecular bacterascites[J]. Sci Rep, 2023, 13(1): 23001. DOI: 10.1038/s41598-023-49505-3.

[50] HUANG C Y, ZHANG H P, HAN W J, et al. Disease predisposition of human leukocyte antigen class II genes influences the gut microbiota composition in patients with primary biliary cholangitis[J]. Front Immunol, 2022, 13: 984697. DOI: 10.3389/fimmu.2022.984697.

[51] JIN Y, SHI M, FENG J, et al. Splenectomy ameliorates liver cirrhosis by restoring the gut microbiota balance[J]. Cell Mol Life Sci, 2024, 81(1): 32. DOI: 10.1007/s00018-023-05055-5.

[52] SUNG C M, LIN Y F, CHEN K F, et al. Predicting clinical outcomes of cirrhosis patients with hepatic encephalopathy from the fecal microbiome[J]. Cell Mol Gastroenterol Hepatol, 2019, 8(2): 301-318.e2. DOI: 10.1016/j.jcmgh.2019.04.008.

[53] PATEL V C, LEE S, MCPHAIL M J W, et al. Rifaximin-α reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial[J]. J Hepatol, 2022, 76(2): 332-342. DOI: 10.1016/j.jhep.2021.09.010.

[54] ENOMOTO M, KAJI K, NISHIMURA N, et al. Rifaximin and lubiprostone mitigate liver fibrosis development by repairing gut barrier function in diet-induced rat steatohepatitis[J]. Dig Liver Dis, 2022, 54(10): 1392-1402. DOI: 10.1016/j.dld.2022.04.012.

[55] ZHAO Y, ZHAO M, ZHANG Y, et al. Bile acids metabolism involved in the beneficial effects of Danggui Shaoyao San via gut microbiota in the treatment of CCl4 induced hepatic fibrosis[J]. J Ethnopharmacol, 2024, 319(Pt 3): 117383. DOI: 10.1016/j.jep.2023.117383.

[56] ALIWA B, HORVATH A, TRAUB J, et al. Altered gut microbiome, bile acid composition and metabolome in sarcopenia in liver cirrhosis[J]. J Cachexia Sarcopenia Muscle, 2023, 14(6): 2676-2691. DOI: 10.1002/jcsm.13342.

[57] CHEN Y, JI F, GUO J, et al. Dysbiosis of small intestinal microbiota in liver cirrhosis and its association with etiology[J]. Sci Rep, 2016, 6: 34055. DOI: 10.1038/srep34055.

[58] YU L X, SCHWABE R F. The gut microbiome and liver cancer: mechanisms and clinical translation[J]. Nat Rev Gastroenterol Hepatol, 2017, 14(9): 527-541. DOI: 10.1038/nrgastro.2017.72.

[59] TRIPATHI A, DEBELIUS J, BRENNER D A, et al. The gut-liver axis and the intersection with the microbiome[J]. Nat Rev Gastroenterol Hepatol, 2018, 15(7): 397-411. DOI: 10.1038/s41575-018-0011-z.

[60] MAEDA S, KAMATA H, LUO J L, et al. IKKbeta couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis[J]. Cell, 2005, 121(7): 977-990. DOI: 10.1016/j.cell.2005.04.014.

[61] ZHANG W Z, XU X S, CAI L P, et al. Dysbiosis of the gut microbiome in elderly patients with hepatocellular carcinoma[J]. Sci Rep, 2023, 13(1): 7797. DOI: 10.1038/s41598-023-34765-w.

[62] FENG J, WU Y, DAI P, et al. Gut microbial signatures of patients with primary hepatocellular carcinoma and their healthy first-degree relatives[J]. J Appl Microbiol, 2023, 134(10): lxad221. DOI: 10.1093/jambio/lxad221.

[63] POMYEN Y, CHAISAINGMONGKOL J, RABIBHADANA S, et al. Gut dysbiosis in Thai intrahepatic cholangiocarcinoma and hepatocellular carcinoma[J]. Sci Rep, 2023, 13(1): 11406. DOI: 10.1038/s41598-023-38307-2.

[64] DENG T, LI J L, HE B J, et al. Gut microbiome alteration as a diagnostic tool and associated with inflammatory response marker in primary liver cancer[J]. Hepatol Int, 2022, 16(1): 99-111. DOI: 10.1007/s12072-021-10279-3.

[65] ZHANG L, WU Y N, CHEN T, et al. Relationship between intestinal microbial dysbiosis and primary liver cancer[J]. Hepatobiliary Pancreat Dis Int, 2019, 18(2): 149-157. DOI: 10.1016/j.hbpd.2019.01.002.

[66] TANG Y, ZHOU H, XIANG Y, et al. The diagnostic potential of gut microbiome for early hepatitis B virus-related hepatocellular carcinoma[J]. Eur J Gastroenterol Hepatol, 2021, 33(1S Suppl 1): e167-175. DOI: 10.1097/MEG.0000000000001978.

[67] ZHENG C, LU F, CHEN B, et al. Gut microbiome as a biomarker for predicting early recurrence of HBV-related hepatocellular carcinoma[J]. Cancer Sci, 2023, 114(12): 4717-4731. DOI: 10.1111/cas.15983.

[68] XU W, JIANG Y, TAO J, et al. Correlation analysis for alterations of intestinal flora in hepatocellular carcinoma patients: combinatorial detection of Coriobacterium, Atopobium, Coprococcus and Veillonella dispar may be a new method for HCC diagnosis[J]. J Med Microbiol, 2023, 72(6). DOI: 10.1099/jmm.0.001713.

[69] CHUNG M W, KIM M J, WON E J, et al. Gut microbiome composition can predict the response to nivolumab in advanced hepatocellular carcinoma patients[J]. World J Gastroenterol, 2021, 27(42): 7340-7349. DOI: 10.3748/wjg.v27.i42.7340.

[70] LEE P C, WU C J, HUNG Y W, et al. Gut microbiota and metabolites associate with outcomes of immune checkpoint inhibitor-treated unresectable hepatocellular carcinoma[J]. J Immunother Cancer, 2022, 10(6): e004779. DOI: 10.1136/jitc-2022-004779.

[71] PONZIANI F R, DE LUCA A, PICCA A, et al. Gut dysbiosis and fecal calprotectin predict response to immune checkpoint inhibitors in patients with hepatocellular carcinoma[J]. Hepatol Commun, 2022, 6(6): 1492-1501. DOI: 10.1002/hep4.1905.

[72] RAO B C, ZHANG G Z, ZOU Y W, et al. Alterations in the human oral microbiome in cholangiocarcinoma[J]. Mil Med Res, 2022, 9(1): 62. DOI: 10.1186/s40779-022-00423-x.

[73] YANG X, MAI H, ZHOU J, et al. Alterations of the gut microbiota associated with the occurrence and progression of viral hepatitis[J]. Front Cell Infect Microbiol, 2023, 13: 1119875. DOI: 10.3389/fcimb.2023.1119875.

[74] CHEN Z, XIE Y, ZHOU F, et al. Featured gut microbiomes associated with the progression of chronic hepatitis B disease[J]. Front Microbiol, 2020, 11: 383. DOI: 10.3389/fmicb.2020.00383.

[75] LANG S, FAIRFIED B, GAO B, et al. Changes in the fecal bacterial microbiota associated with disease severity in alcoholic hepatitis patients[J]. Gut Microbes, 2020, 12(1): 1785251. DOI: 10.1080/19490976.2020.1785251.

[76] KIM S S, EUN J W, CHO H J, et al. Microbiome as a potential diagnostic

and predictive biomarker in severe alcoholic hepatitis[J]. Aliment Pharmacol Ther, 2021, 53(4): 540-551. DOI: 10.1111/apt.16200.

[77] HE K N, LIU M M, WANG Q, et al. Combined analysis of 16S rDNA sequencing and metabolomics to find biomarkers of drug-induced liver injury[J]. Sci Rep, 2023, 13(1): 15138. DOI: 10.1038/s41598-023-42312-w.

Author Contributions: SHI Yufeng was responsible for conceptualization, literature collection, and manuscript drafting; LU Chenxia contributed to writing guidance and revision; LYU Anqi participated in literature collection and manuscript revision; LI Xiaodong supervised the writing and finalized the manuscript.

Conflict of Interest Statement: The authors declare no conflict of interest.

LI Xiaodong: https://orcid.org/0000-0002-6406-9416

(Received: July 10, 2024; Revised: September 5, 2024)
(Editor: JIA Mengmeng)

Note: Figure translations are in progress. See original paper for figures.