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Gut-liver axis in chronic liver disease: Microbiome disruption and inflammatory pathways.

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Introduction

Chronic liver disease affects millions globally and is driven by diverse etiologies including alcohol, metabolic dysfunction, viral infections, and autoimmune triggers. Recent research emphasizes the central role of the gut-liver axis—an intricate system of communication involving the gut microbiota, intestinal barrier, and hepatic immune response. In a healthy state, this axis maintains tolerance and metabolic balance. However, in chronic liver disease, gut icrobiota dysbiosis, impaired barrier function, and enhanced gut-derived endotoxin exposure amplify hepatic inflammation and fibrogenesis. Understanding these mechanisms is essential for developing novel, microbiome-targeted therapies.[1].

The gut-liver connection is a dynamic, bidirectional relationship where the liver receives approximately 70% of its blood supply from the portal vein, which drains the intestines, pancreas, and spleen. This unique arrangement enables the liver to metabolize dietary and microbial products, filter out pathogens and toxins, and regulate immune responses to gut-derived antigens. In return, the liver influences gut health by secreting bile acids and antimicrobial peptides that help maintain microbiota balance and gut barrier integrity. However, in chronic liver disease (CLD), this balance is disrupted, leading to a shift in the gut microbiota from a healthy, diverse ecosystem to a pro-inflammatory, dysbiotic state. This dysbiosis is characterized by a reduction in beneficial microbes such as Faecalibacterium prausnitzii, an overgrowth of harmful bacteria like Enterococcus and Klebsiella, and increased production of toxic metabolites including ethanol and ammonia .[2].

This microbial imbalance significantly contributes to the progression of chronic liver diseases (CLD) such as NAFLD/NASH, where dysbiosis increases intestinal permeability, allowing lipopolysaccharide (LPS) translocation and activation of TLR4 on Kupffer cells, resulting in hepatic inflammation. In Alcoholic Liver Disease, alcohol disrupts the microbiome and impairs the gut barrier, intensifying endotoxin-mediated liver damage. In cirrhosis, severe dysbiosis, small intestinal bacterial overgrowth (SIBO), and spontaneous bacterial peritonitis (SBP) arise due to immune dysfunction. The intestinal barrier's integrity—dependent on tight junctions, NA to translocate to the liver via the portal vein. These microbial-associated molecular patterns (MAMPs) activate hepatic immune cells, including Kupffer and stellate cells, thereby initiating NF-κB signaling, cytokine release fibrogenesis, and ultimately the progression to cirrhosis. [3].

Inflammatory pathways in the gut-liver axis play a crucial role in the progression of chronic liver diseases (CLD). Toll-like receptors (TLRs), particularly TLR4 and TLR9, expressed on liver cells, detect microbial ligands and initiate pro-inflammatory signaling cascades. The activation of the NLRP3 inflammasome by microbial signals results in the release of IL-1β, leading to hepatocellular injury. Additionally, a cytokine storm involving IL-6, TNF-α, and other cytokines contributes to insulin resistance, steatosis, and fibrosis. The immune crosstalk between gut dendritic cells and T cells significantly influences liver immunity, especially in autoimmune liver diseases. Therapeutic strategies targeting the gut-liver axis, such as the use of probiotics and prebiotics, aim to

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restore microbial diversity and gut barrier function [4].

Rifaximin, a non-absorbable antibiotic, is commonly used in cirrhosis to reduce bacterial overgrowth and ammonia levels, thereby decreasing hospitalizations and improving cognitive symptoms in hepatic encephalopathy. Bile acid modulators such as obeticholic acid, an FXR agonist, help regulate bile acids and reduce inflammation and fibrosis in nonalcoholic steatohepatitis (NASH), while also influencing gut microbiota composition [5].

Conclusion

The gut-liver axis plays a pivotal role in the initiation and progression of chronic liver diseases. Microbiome disruption, increased intestinal permeability, and immune dysregulation create a self-perpetuating cycle of hepatic injury. Targeting this axis through microbiome-centered therapies offers a promising approach to complement conventional liver disease management.

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