Mechanism of Intestinal Flora in Hepatic Fibrosis and Its Therapeutic Progress

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Abstract: Hepatic fibrosis is a common pathological process that progresses to cirrhosis in various chronic liver diseases, and there is a lack of effective treatment at present. In recent years, intensive studies on the intestinal-liver axis theory have shown that intestinal dysbiosis plays a key role in the development of liver fibrosis. This paper systematically reviews the mechanisms of intestinal flora in liver fibrosis, including intestinal barrier dysfunction, translocation of pathogen-related molecular patterns, regulation of flora metabolites, and imbalance of immune-metabolic network. On this basis, therapeutic strategies targeting intestinal flora are summarized, including emerging therapies such as probiotics/synbiotics, fecal flora transplantation, and bile acid modulators. In-depth understanding of the relationship between intestinal flora and liver fibrosis is expected to provide new ideas for the prevention and treatment of liver fibrosis.

***Keywords*:** intestinal flora; liver fibrosis; intestinal-hepatic axis; pyroptosis; Fecal bacteria transplantation

1. Introduction

hepatic fibrosis is the repair response of the liver to various chronic injury factors, characterized by excessive deposition of extracellular matrix, and is a key stage in the progression of chronic hepatitis to cirrhosis and even liver cancer [1]. Liver fibrosis has become a public health problem that seriously threatens human health. It is of great clinical significance to deeply explore the pathogenesis of liver fibrosis and find new therapeutic targets. The theory of intestinal-liver axis suggests that intestinal flora and its metabolites enter the liver through the portal vein and regulate the immune metabolic function of the liver; While the liver affects the stability of intestinal microecology through bile secretion [2]. This disruption of dynamic equilibrium, intestinal dysbiosis, has been shown to be involved in the fibrotic process in a variety of chronic liver diseases. The purpose of this paper is to systematically explain the mechanism of action of intestinal flora in liver fibrosis and summarize the research progress of targeted intestinal flora therapy.

2. Structural characteristics of intestinal flora during hepatic fibrosis

2.1 Changes in flora diversity and composition

Numerous studies have confirmed the presence of significant intestinal dysbiosis in patients with liver fibrosis. Based on 16S rRNA sequencing and metagenomic analysis, the intestinal flora in the process of hepatic fibrosis presented the following characteristics: decreased overall diversity, decreased abundance of beneficial flora (e.g., Bifidobacteria, Faecalobacteria), and increased abundance of conditionally pathogenic bacteria (e.g., Streptococcus, Veloncoccus, Enterobacteriaceae). In liver fibrosis associated with metabolic-related fatty liver disease, bacterial flora such as Enterobacteriaceae can increase disease risk, while ruminococcidae, such as UCG-013, have protective effects [3].

2.2 Flora characteristics of liver fibrosis with different etiologies

Hepatic fibrosis caused by different etiologies is characterized by specific changes in intestinal flora. In cholestatic liver disease, the intestinal flora of the patient is enriched with Streptococcus and Veloncoccus and decreased with Faecalobacter, an alteration that is closely associated with disorders of bile acid metabolism. For MASLD-associated liver fibrosis, studies have shown a positive correlation between dysbiosis and disease severity, with patients with advanced fibrosis exhibiting more significant changes in flora structure.

3. Molecular mechanism of intestinal flora dysbiosis driving liver fibrosis

3.1 Intestinal barrier dysfunction

The intestinal barrier is composed of mucus layer, tight junction between epithelial cells, intestinal vascular barrier and intestinal immune system. It is the first line of defense against the translocation of intestinal flora and its products. In

the process of liver fibrosis, high-fat diet, alcohol, abnormal bile acid metabolism and other factors can lead to impaired intestinal barrier function. Studies showed that the mucus layer was thinned and damaged at the early stage of MASLD, which was related to the decrease of Ctfr gene expression and the hindered mucus synthesis. When the intestinal barrier is impaired, the intestinal flora and its metabolites translocate to the liver through the portal vein, activating the hepatic immune response and promoting fibrosis progression [4].

3.2 LPS/TLR4 signaling pathway and inflammatory response

Under normal circumstances, the intestinal barrier can effectively restrict the entry of LPS into the portal vein. When intestinal permeability increases, LPS translocates to the liver and is recognized by Toll-like receptor 4 (TLR4) on the surface of hepatic stellate cells (HSC), Kupfer cells, etc., initiating a downstream signaling cascade. LPS stimulates TLR4 to activate NF-κ B and MAPK signaling pathways through myeloid differentiation factor (MyD88) -dependent and independent pathways, and promotes the expression of pro-inflammatory cytokines such as TNF-α, IL-1 β, IL-6, and IL-8. On the one hand, these inflammatory factors directly activate HSC, and on the other hand, they amplify the inflammatory response by recruiting immune cells, forming a vicious circle of "inflammation-fibrosis". Clinical studies have shown that serum LPS levels in MASLD patients are significantly higher than those in healthy individuals, and their levels are correlated with the stage of liver fibrosis [5].

3.3 New discoveries of cell pyroptosis pathway

pyroptosis is a form of programmed inflammatory cell death, characterized by cell membrane perforation, release of contents, and strong inflammatory response. Recent studies have revealed the key role of LPS/NLRP3/GSDMD cell pyroptosis pathway in liver fibrosis. Che et al. used a mouse model of liver fibrosis induced by concanavalin A and found that intestinal flora imbalance led to increased LPS translocation, activated NLRP3 inflammasome in the liver, and then cleaved GSDMD protein, causing hepatocyte pyroptosis and collagen deposition. Fecal bacteria transplantation experiments confirmed that the flora of fibrotic mice can aggravate intestinal barrier dysfunction and promote LPS-induced pyroptosis, while antibiotic clearance of the flora can mitigate these effects [6].

3.4 Immune-metabolic network imbalance

The progression of liver fibrosis involves complex immune-metabolic network dysregulation. The "microbial-immune-metabolic" triple network model proposed by Sun et al. systematically expounds this mechanism: intestinal flora dysbiosis affects T cell differentiation, macrophage polarization and inflammasome activation by changing bile acid and SCFAs metabolism; At the same time, metabolic reprogramming (e.g., enhanced aerobic glycolysis, altered lipid and amino acid metabolism) further exacerbates the fibrotic process. The multi-target nature of this network suggests that a single intervention may be difficult to completely reverse fibrosis, and combination therapeutic strategies are worth exploring [7].

4. Anti-hepatic fibrosis therapy targeting intestinal flora

4.1 Probiotics, prebiotics and synbiotics

Probiotics are active microorganisms that can improve the microecological balance of the intestinal tract of the host, mainly including Lactobacillus, Bifidobacterium, etc. Prebiotics are substrates that selectively stimulate the growth of beneficial bacteria (such as fructooligosaccharides and inulin). Synbiotic is a combination preparation of the two, which has a synergistic effect. A number of animal experiments have shown that probiotic/synbiotic intervention can reduce liver fibrosis through a variety of mechanisms: first, regulate the flora structure, increase the abundance of beneficial bacteria such as bifidobacteria, and reduce harmful bacteria such as Allobaculum; The second is to enhance the intestinal barrier function and reduce LPS translocation; The third is to inhibit liver inflammation and cell pyroptosis pathways. Che et al's research showed that synbiotic intervention can significantly inhibit LPS/NLRP3/GSDMD pathway activation, reduce collagen deposition, and improve liver fibrosis. However, clinical research evidence is still relatively limited, and the differences in efficacy of different strains, doses, and courses of treatment need to be standardized and evaluated [8].

4.2 Fecal flora transplantation

Fecal flora transplantation (FMT) is a therapeutic method in which the intestinal flora of a healthy donor is transplanted as a whole into the patient's intestine to achieve flora reconstitution. FMT has achieved remarkable efficacy in recurrent Clostridium difficile infection, and has gradually expanded to the field of liver diseases in recent years.

Animal experiments demonstrated that transplantation of the flora of fibrotic mice to sterile mice induced the hepatic fibrotic phenotype, while transplantation of healthy flora to fibrotic mice had therapeutic effects. In terms of clinical

research, FMT has shown the potential to improve liver function and inflammatory indicators in chronic liver diseases such as MASLD and alcoholic liver disease. However, the standardized protocol, long-term safety and exact efficacy of FMT in liver fibrosis still need to be verified by large-scale clinical studies [9].

4.3 Bile acid signaling pathway modulators

Given the critical role of bile acid-flora interaction in liver fibrosis, drugs targeting bile acid signaling pathways have become a research hotspot. obeticholic acid is an FXR agonist that has been approved by the FDA for the treatment of primary biliary cholangitis. Clinical studies have shown that it can improve liver fibrosis in patients with MASLD. In addition, ursodeoxycholic acid (UDCA), as a commonly used clinical choleretic, can partially reverse flora dysbalance by regulating the flora-bile acid axis. Other bile acid signaling modulators (e.g., TGR5 agonists, FGF19 analogs) are also under development [10].

5. Conclusion and prospect

The role of intestinal flora in liver fibrosis has been widely demonstrated, and the intestinal-liver axis provides a new perspective to understand the pathogenesis of liver fibrosis. Current studies have revealed that dysbiosis drives the process of liver fibrosis through multiple mechanisms such as intestinal barrier destruction, LPS/TLR4 signaling activation, metabolite regulation, and cell pyroptosis induction. On this basis, intervention strategies targeting bacterial flora such as probiotics/synbiotics, FMT and bile acid modulators have shown good application prospects.

However, the field still faces many challenges. Firstly, the etiological heterogeneity of liver fibrosis leads to the difference of flora change spectrum, and it is urgent to establish flora typing standards based on etiology and fibrosis stage. Secondly, most current studies are limited to animal models and cross-sectional observations, and the causal relationship between dysbiosis and fibrosis needs to be further clarified through longitudinal cohort and intervention studies. Third, there are bottlenecks in the clinical translation of flora-targeted therapy, including strain screening, dose optimization, and individualized protocol formulation. Finally, the integrated application of multi-omics technologies (metagenome, metabolome, transcriptome) and the systematic analysis of the "microbial-immune-metabolic" network will provide the basis for precise intervention.

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