Research Progress of Intestinal Microecology in Spontaneous Bacterial Peritonitis in Liver Cirrhosis

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Abstract: Spontaneous bacterial peritonitis (SBP) is a common and serious complication in patients with cirrhosis and ascites. This disease is caused by infection of the abdominal cavity by pathogenic bacteria through the intestinal tract, blood or lymphatic system, and it is one of the important causes of death in patients with end-stage liver disease. The main pathogenesis is bacterial translocation. This article aims to review the research progress of intestinal microecology in the occurrence, progression and treatment of SBP.

***Keywords*:** Intestinal microecology; Liver cirrhosis; Spontaneous bacterial peritonitis.

1. Introduction

Liver cirrhosis is the end-stage of chronic liver disease caused by various causes, and its pathological manifestations are characterized by diffuse fibrosis, pseudolobules and regenerative nodules in liver tissue. Patients in the compensated stage often have no obvious clinical symptoms, while patients in the decompensated stage may have a variety of complications, among which spontaneous bacterial peritonitis (SBP) is a common complication in the decompensated stage of liver cirrhosis. It has the characteristics of insidious onset and high mortality. SBP refers to intra-abdominal infection caused by pathogenic microorganisms invading the abdominal cavity in the absence of any intra-abdominal infection factors (such as intestinal perforation and abscess). The recurrence rate of SBP within 12 months is as high as 40 to 70% in cirrhotic patients with a previous history of SBP[1]. At present, it is believed that the occurrence of SBP is related to increased intestinal mucosal permeability, bacterial translocation and small intestinal bacterial overgrowth. Intestinal microecological disorder plays a crucial role in the occurrence and development of SBP. This article aims to review the research progress of intestinal microecology in the occurrence, development and treatment of SBP.

2. Intestinal microecology

The intestinal microecology is a complex, dynamic, and spatially heterogeneous ecosystem, which is home to countless microorganisms, including bacteria, fungi, archaea, and viruses, which interact and influence each other and with their human hosts[2].

We have known that the human microecosystem includes oral microecosystem, skin microecosystem, urinary microecosystem and gastrointestinal microecosystem, among which the intestinal microecosystem with the largest number of microorganisms occupies the most important position. The most significant feature of the intestinal microecosystem is its strong stability. If the balance is out of balance, a variety of intestinal and external diseases will occur. The core of intestinal microecosystem is gut microbiota.

3. Intestinal microecology and SBP

3.1 Characteristics of gut microbiota in patients with SBP

The main manifestations of SBP are abdominal pain, diarrhea, edema, fever, and continuous increase of ascites, without typical clinical symptoms. For clinicians, early identification and diagnosis of SBP are extremely important, which is conducive to improving the long-term prognosis of patients. In July 2024, Sharma SP et al., in their study, found that fecal samples of patients with cirrhosis complicated with SBP had significantly increased bacteria such as Escherichia coli, Clostridium-multimycobacteria, and Fusobacterium compared with healthy people [3].

3.2 The mechanism of gut microbiota in the pathogenesis of SBP

Alterations in the gut microbiota play an important role, at least in part, in the pathogenesis of several complications caused by end-stage liver disease [4]. Bacterial translocation refers to the migration of intestinal bacteria and their

metabolites across the intestinal mucosal barrier to mesenteric lymph nodes, liver, spleen, kidney and other exenteric tissues. Previous studies have suggested the use of farnesoid X receptor agonists in the treatment of complications associated with cirrhosis[5-8]. Subsequently, Sorribas M et al. proposed that pathological bacterial translocation in liver cirrhosis is a marker of spontaneous bacterial infection in 2019. They found that liver cirrhosis disease itself can promote BT, thereby allowing intestinal bacteria to enter the portal circulation, while FXR can control both vascular endothelial and intestinal epithelial barriers, and FXR agonists can reduce the occurrence of BT [9]. Their experiments were able to demonstrate that FXR can induce the occurrence of SBP, and FXR agonists can also be used for the treatment of SBP.

Then in 2022 Zhou Z et al., in their study, observed the integrity of mucus and epithelial cell junctions (epithelial cadherin and occludin) in colon biopsies from cirrhotic and control patients, and isolated Escherichia coli and Proteus mirabilis that induce SBP from ascites of cirrhotic patients. And cultured with Caco-2 cells to verify the effect of bacteria on cells. Finally, they found a new pathophysiological mechanism of SBP: (1) the decrease of mucus secreted by the colon eventually leads to easier contact between intestinal bacteria and intestinal epithelial cells; (2) Gut bacteria induced the proteasomal degradation of occludin in epithelial cells; (3) mucus-epithelial junction is affected by cleavage of epithelial cadherin by a novel bacterial protease activity [10]. Through the above three mechanisms, intestinal bacteria can more easily reach the intestinal epithelium, destroy the stability of the intestinal barrier, and ultimately promote BT and SBP.

3.3 New diagnostic methods of SBP

With the study of SBP, a new biomarker was found that could be used to diagnose SBP. In a 2020 study in Egypt on cirrhosis due to HCV infection, Keryakos HKH et al. examined serum and ascites IL-17 before and after treatment in 80 patients with HCV-induced cirrhotic ascites but not infected with SBP and 40 patients with HCV-induced cirrhotic ascites with SBP. The results showed that the mean levels of IL-17 in serum and ascites of cirrhotic patients with SBP were significantly higher than those of cirrhotic patients without SBP ($p < 0.001$). In addition, IL-17 levels in serum and ascites decreased significantly after cure of SBP ($p < 0.001$) [11]. They also found that the sensitivity and specificity of serum IL-17 were 100% at a cut-off level of 92 pg/mL. In conclusion, IL-17 can be used as a biomarker for the diagnosis of SBP.

3.4 New treatments for SBP based on gut microbiota

The early treatment of SBP is mainly the timely application of antibiotics, and the American Association for the Study of Liver Diseases 2021 practice guidelines indicate that third-generation cephalosporins are often used in clinical practice and are regarded as first-line antibiotics[12].

The treatment of SBP based on intestinal microecological regulation is an important research direction and adjuvant treatment strategy. The core is to correct the common intestinal flora imbalance in patients with liver cirrhosis, reduce the overgrowth of intestinal bacteria and intestinal barrier dysfunction, so as to reduce the risk of intestinal bacteria translocation to the abdominal cavity and blood, and then prevent and treat SBP. Probiotics are used to supplement beneficial bacteria, competitively inhibit the growth of pathogenic bacteria, enhance the intestinal barrier function, regulate the immune response, and produce antibacterial substances. Long-term use of specific probiotics can reduce the incidence of SBP, improve liver function indexes, and reduce the level of endotoxemia in patients with liver cirrhosis. Prebiotics provide non-digestible food components required for the growth of beneficial bacteria, promote the proliferation of beneficial bacteria, inhibit pathogenic bacteria, produce short-chain fatty acids, nourishing intestinal epithelial cells, enhance barrier function, and regulate immunity. A combination of probiotics and prebiotics designed for synergistic effects. Fecal microbiota transplantation (FMT) involves the infusion of healthy donor feces into the gut of a patient with the goal of reversing dysbiosis by rebalancing the normal gut microbiota. Research is in its early stages in the field of cirrhosis, particularly in preventing SBP or treating recurrent SBP. In addition, non-absorbable antibiotics are also widely used in the treatment of SBP, which are not easily absorbed orally, to selectively remove or inhibit potential gram-negative pathogenic bacteria in the intestine, without significantly affecting anaerobic bacteria, so as to reduce bacterial translocation. Rifaximin is currently the most widely used drug, and as early as 2012 Hanouneh MA et al. found in a retrospective study that the use of rifaximin can be used to prevent SBP[13]. At the same time, several meta-analyses have confirmed the important role of rifaximin in the prevention of SBP[14-17]. Intestinal microecological regulation is an important auxiliary strategy for the prevention and treatment of SBP in liver cirrhosis. Systemic antibiotics are the cornerstone in the treatment of active SBP, and microecological modulation can be used as a subsequent aid to promote recovery and prevent relapse.

4. Deficiencies and Prospects

The existing studies mostly focus on intestinal bacterial communities, and the exploration of fungi, viruses and archaea is insufficient, especially their specific roles in the pathogenesis of SBP have not been fully elucidated. The sample size of

some studies was small, and the patient population was significantly heterogeneous in terms of etiology and disease stage, which may limit the generalization of the research conclusions. Although the association between gut microbiota dysbiosis and SBP has been widely confirmed, the specific molecular mechanisms are still lack of systematic studies.

To promote the clinical application of probiotics, prebiotics, metabiotics and fecal microbiota transplantation, accurately regulate the characteristics of intestinal flora in patients, and explore antibiotic substitution strategies to reduce the risk of drug resistance. Cross cooperation between hepatology, microbiology, immunology and bioinformatics should be strengthened to accelerate the translation of basic research results to clinical practice, such as the development of new drugs or microecological agents targeting the gut-liver axis.

5. Conclusion

In summary, the research on intestinal microecology in SBP is moving from the description of a single flora to the exploration of multi-dimensional mechanisms. In the future, it is necessary to break through the existing limitations through technological innovation and interdisciplinary collaboration, and provide more efficient and personalized solutions for the prevention and treatment of complications of liver cirrhosis.

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