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Research progress on the role of probiotics in acute liver failure

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Acute liver failure (ALF) is a relatively rare disease with a high fatality rate. As early as 1970, ALF was first described as fulminant liver failure, but this term has now been abandoned.[1] ALF is a complex disease involving multiple organ functions. As the course of the disease progresses, cerebral edema, renal failure, respiratory failure, hemodynamic disorders, and coagulation disorders may occur. The main manifestations of ALF are prolongation of prothrombin time/international normalized ratio (PT/INR), decreased mental function, peripheral vasodilatation, systemic inflammatory response syndrome, and eventually multiple organ failure. In different parts of the world, the causes of ALF are different. In developed countries, paracetamol toxicity, ischemia, drug-induced liver injury, hepatitis B virus, and autoimmunity are the five most common causes of ALF. In contrast, viral hepatitis A, B, and E are the main causes of ALF in developing countries. When severe liver dysfunction occurs, in addition to supportive treatment and care for related complications, liver transplantation is still the ultimate treatment for ALF. However, due to the limitations of transplantation conditions, less than 10% of liver transplant patients receive transplantation treatment because of ALF.[2-4]

Therefore, it is imperative to further understand the pathogenesis of ALF and to find a more effective treatment method. Due to the rarity of ALF, there are currently no large-scale randomized trials that have studied it. Although clinical research is lacking, there are an increasing number of studies related to ALF in animal models. The animal model of ALF established by d-galactosamine (d-GalN) combined with low-dose lipopolysaccharide (LPS) has been generally recognized by scholars at home and abroad. This model has high similarity to liver failure caused by viral hepatitis in clinical practice.[5] LPS is a component of the outer cell wall of gram-negative bacteria and is an endotoxin. LPS binds to LPS-binding protein (LBP) and further binds to Toll-like receptor 4 (TLR4) on Kupffer cells of the liver to activate the immune response, thereby producing many inflammatory factors. Among them, tumor necrosis factor-α (TNF-α) secreted in the early stage plays a leading role. It can bind to tumor necrosis factor receptor 1 (TNFR1) on the surface of liver cells to induce cytotoxicity and cause an abnormal increase in liver cell apoptosis by upregulating the expression of apoptosis-related proteins. d-GalN can inhibit the synthesis of biological macromolecules by depleting uridine triphosphate in the liver, causing liver inflammation and liver cell necrosis.

Due to the close physiology and anatomy between the liver and the intestine, changes in liver disease will inevitably cause changes in the intestinal flora. Most liver injuries destroy the intestinal barrier and disrupt the homeostasis of the intestine–liver axis. Destruction of the intestinal barrier will also cause microorganisms and their metabolites to spread throughout the body, enter the hepatic portal vein circulation, aggravate liver damage, and eventually cause endotoxemia and systemic inflammation. As early as 2004, our research team discovered that d-GalN induces intestinal flora imbalance in mice with ALF. The degree

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of intestinal flora imbalance is related to the severity of liver damage. The changes in the intestinal flora may be related to decreased bile secretion and impaired intestinal motility in rats with ALF.[6]

Probiotics are a mixture of living microorganisms and substrates that are selectively used by host microorganisms and are beneficial to the host.[7] Probiotics can inhibit the growth of pathogenic bacteria, reduce bacterial translocation, and increase microbial diversity. They can also improve liver function and improve the immune and metabolic functions of the host. It is worth mentioning that prebiotics are different from probiotics. Prebiotics are nutrients that help probiotics grow and reproduce. Prebiotics cannot directly regulate the intestinal flora. They can be used to promote the growth of probiotics *in vitro* before administering probiotics to contribute indirectly to achieving the treatment goal.

Recently, an increasing number of studies have been conducted on the role of probiotics in ALF. Wang *et al.*[8] found that the probiotic *Lactobacillus casei* Zhang could alleviate the progression of ALF, mainly by decreasing the levels of proinflammatory cytokines and hepatic inflammation. The TLR–MAPK–PPAR-γ signaling pathway was involved in this process. Li *et al.*[9] revealed the potential therapeutic effect of *Bifidobacterium adolescentis* CGMCC 15058 in ALF. They separated CGMCC 15058 from the feces of healthy humans and then gavaged these bacteria into Sprague-Dawley (SD) rats. At the same time, the classic model of ALF caused by d-GalN was used to explore the possible effects of the probiotics. They found that CGMCC 15058 may improve intestinal flora imbalance by reducing cytotoxic factors and inflammatory cytokines to treat ALF. Another study showed that *Lactobacillus helveticus* R0052 plays a protective role in ALF. The researchers collected blood, liver, ileum, feces, and other samples to assess liver damage, liver inflammation, intestinal barrier function, and intestinal metabolism. They found that *L. helveticus* R0052 exhibited anti-inflammatory properties by downregulating the transcription of Toll-like receptors, TNF-α, and NF-κb in liver samples and lowering the plasma concentration of proinflammatory cytokines. *L. helveticus* R0052 can improve intestinal abnormalities by regulating the transcription of the Toll-like receptors, clodin 2, and mucin3 genes in the intestine.[10] In addition, *Lactobacillus reuteri* DSM 17938 and *Bifidobacterium longum* R0175 are both probiotics with anti-liver failure prospects.[11,12] Zhuge *et al.*[13] considered that oral probiotics have certain disadvantages. For example, there is a certain amount of acidic fluid in the gastrointestinal tract, which may modulate the effect of probiotics. Therefore, they tried to improve this situation through closed technology. Specifically, they used microcapsules to encapsulate the probiotics. Microcapsules are composed of polysaccharides, proteins, and fats and can protect probiotics. Finally, their study found that alginic acid–pectin-encapsulated LI01 can improve liver damage and significantly increase the survival rate by reducing inflammation and restoring intestinal barrier function.

Although the overall incidence of ALF is not very high and the mortality rate is declining, the progression of ALF is relatively rapid. Clinically, many patients with ALF experience multiple organ failure in the later stage and the prognosis is very poor. It is of great significance to further study the pathogenesis of ALF and identify potential biomarkers for diagnosis, treatment, and prognosis.[14] Many studies have proven that probiotics can reduce ALF inflammation and improve intestinal flora imbalance, thereby alleviating the progression of ALF. However, there are still several shortcomings and future research needs to further improve on these limitations. First, due to the relatively small number of ALF clinical samples, current research mainly relies on the classic d-GalN/LPS-induced ALF animal model. Although this model can better simulate ALF caused by clinical viral hepatitis, there are still some differences. Second, probiotics come in various forms and have different curative effects, and there are certain obstacles in the selection of patients. The research results have not been well connected with the clinic and applied in the clinic. It is worth mentioning that the future development of science and technology may provide new ideas for the treatment of ALF.

Conflict of Interest

None declared.

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