REVIEW

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The Role of Intestinal Fungi and Its Metabolites in Chronic Liver Diseases

Ningning You[1], Lili Zhuo[1], Jingxin Zhou[1], Yu Song[2], and Junping Shi[1]

[1]Department of Liver Diseases, The Affiliated Hospital of Hangzhou Normal University, and [2]Department of Liver Diseases, Zhejiang Chinese Medical University, Hangzhou, China

Current studies have confirmed that liver diseases are closely related to intestinal microorganisms; however, those studies have mainly concentrated on bacteria. Although the proportion of intestinal microorganisms accounted for by colonizing fungi is very small, these fungi do have a significant effect on the homeostasis of the intestinal microecosystem. In this paper, the characteristics of intestinal fungi in patients with chronic liver diseases such as alcoholic liver disease, nonalcoholic fatty liver disease and cirrhosis are summarized, and the effects of intestinal fungi and their metabolites are analyzed and discussed. It is important to realize that not only bacteria but also intestinal fungi play important roles in liver diseases. **(Gut Liver 2020;14:291-296)**

Key Words: Intestinal fungi; Alcoholic liver disease; Cirrhosis; Non-alcoholic fatty liver disease

INTRODUCTION

The gastrointestinal tracts, as one of the most important and complex micro-ecosystems in human body, harbors large numbers of microorganisms (about 10^{12} to 10^{14}), including bacteria, archaea, virus, and fungi;[1] the enormous quantity and complex structure of intestinal micro-ecology have been a challenge for scientist to have a deep exploration of intestinal microorganism. In recent years, with the advancement of high-throughput sequencing technology, more and more microorganisms have been known and confirmed to be important in maintaining human health, such as immune protection, nutrient absorption, bacterial barrier, anticancer and cancer suppression.[2] However, there are also potentially pathogenic microorganisms containing in the intestinal micro-ecology causing disruption of intestinal homeostasis and alterations in the intestinal microorganisms which contributes to the pathogenesis of many disorders, including liver disease. Many studies over the past couple of decades have documented an important role for intestinal bacteria in liver diseases. Growing evidences indicate that like the bacteria, the intestinal fungi are also closely associated with liver disease.

Intestinal fungi, as an important part of intestinal micro-ecology, though the proportion is very low, its role in human health and disease cannot be ignored. Under physiological conditions, a variety of components on fungal cell wall (including β-glucan, zymosan, mannan, chitosan, DNA, and RNA) can be recognized by host cells to activate innate and acquired immunity. The reaction inhibits the overgrowth of the intestinal fungi or the colonization of exogenous pathogens. When the host immune system is deficient[3] or a large number of antibiotics are used,[4] it will cause changes in the composition of the intestinal microbiota, which will cause a series of liver diseases through the "entero-hepatic axis." In this review, we will combine the current research on intestinal fungus and chronic liver diseases to analyze the relationship between intestinal fungi and alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD) and liver cirrhosis, try to make people realize that not only bacteria but also intestinal fungi play an important role in liver diseases.

THE GUT MYCOBIOME IN HEALTHY COHORT

Fungi are detectable in all sections of the gastrointestinal tract of about 70% of healthy adults, normally at up to 1,000 fungal cells per milliliter or gram of intestinal contents.[5] Culture-independent analyses show that fungi constitute less than 0.1% of the human gut microbiome,[6] while accounting for only 0.03% of the fecal microbiota.[7] Previous traditional culture-dependent techniques can only detect a small number of fungi, with the maturity of high-throughput sequencing technology, it has gradually replaced traditional culture techniques as the best method for studying fungi. Reports using next generation se-

Correspondence to: Junping Shi
Department of Liver Diseases, The Affiliated Hospital of Hangzhou Normal University, 126 Wenzhou Road, Hangzhou 310015, China
Tel: +86-57188358060, Fax: +86-57188021730, E-mail: 13957121199@126.com
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quencing have found diverse fungal communities in all sections of the human gut, consisting mainly of the phyla Ascomycota, Basidiomycota, Zygomycota, and Chytridiomycota.[8-10] The predominant commensal fungal species in the human intestine are *Candida* species, *Saccharomyces cerevisiae*, and *Malassezia* species.[11] The special anatomical and physiological features of the individual compartments of the mouth, stomach and intestine offer disparate ecological niches and they are colonized with site-specific microbe communities. The total number of fungi increases from the ileum to the colon and reaches the highest density in the distal intestine of most monogastric animals.[12]

In 2017, the human microbiome project (HMP) launched the study of the gut mycobiome in human, 317 HMP stool samples were analyzed by sequencing the internal transcribed spacer 2 (ITS2) region as well as the 18S rRNA gene, 701 fungal operational taxonomic units were detected in the sample set, capturing 247 named genera, and the Shannon diversity index varied between 0.004 and 2.94, which was much lower than bacterial communities. The intestinal fungi was dominated by yeast including *Saccharomyces*, *Malassezia*, and *Candida*, and there was the strongest positive correlation between *Sarocladium* and *Fusarium*, while *Candida* and *Saccharomyces* exhibited the strongest negative correlation. Both inter- and intra-volunteer variability in the HMP cohort were high, revealing that unlike bacterial communities, an individual's mycobiome is no more similar to itself over time than to another person's. Besides, this article also indicates that though 18S rRNA gene and whole-genome shotgun metagenomic sequencing aligned with the results of ITS2 sequencing, ITS2 data provided greater resolution of the mycobiome membership, suggesting that ITS2 sequencing is a more accurate and sensitive method for studying the mycobiome in stool samples.[13]

INTESTINAL FUNGI AND ALCOHOLIC LIVER DISEASE

Liver acts as a metabolic site for alcohol, when the body excessively consumes alcohol for a long time and exceeds the metabolic load of the liver, it can cause liver damage through multiple routes, and constantly develop into alcoholic fatty liver, alcoholic hepatitis, alcoholic cirrhosis and even liver cancer.[14] Since 2015, Szabo[15] proposed the role of the enterohepatic axis in ALD, the importance of an imbalanced intestinal flora in the pathogenesis of ALD has gradually been recognized. In ALD, increased ethanol and its metabolite acetaldehyde in the intestinal lumen mediate weakening of intestinal tight junctions. Consequently, increased translocation of microbial-associated molecular patterns and gut metabolites, such as acetaldehyde, acetate, elicits intestinal and hepatic inflammatory responses, leading to progressive liver damage.[16,17]

On the basis of a mature mouse model of ALD, Yang *et al*.[18] performed ITS sequencing on the feces of mice, and found that the richness and diversity of fungi in the intestinal tract of ALD mice are significantly higher than the control group. Compositional changes in the intestinal mycobiome were characterized by significantly increased proportions of *Humicola* species, *Fusarium*, and *Aspergillus*, while proportions of *Candida* species decreased. Besides, it is worth noting that the abundance of albicans *Candida* in ALD group is dramatic overgrowth. The 1,3-β-glucan from fungal cell wall enters the liver by portal vein through the damaged intestinal mucosa, and binds to CLEC7A on the surface of the liver Kupffer cell, then stimulates the Kupffer cell to secrete interleukin-1β (IL-1β), which leads to steatosis and necrosis of hepatocyte. Interestingly, overgrowth of *Candida* was independent of the stage of liver disease, patients with nonprogressive ALD, alcoholic hepatitis, or alcoholic cirrhosis had similar levels of fungal dysbiosis in the intestine. In addition, the study also found that in the ALD patients, the abundance of *Epicoccum*, unclassified fungi, *Galactomyces*, and *Debaryomyces* in the intestinal tract is decreased. *Epicoccum* fungus is known for its potential to produce diverse classes of biologically active secondary metabolites, and has physiological effects such as anti-oxidation, anticancer, and antibacterial,[19,20] but the role in ALD has not been studied.

INTESTINAL FUNGI AND NAFLD

There are few studies on the relationship between intestinal fungi and NAFLD. At present, the most researched is the probiotic *Saccharomyces boulardii*, which has been widely used in clinical practice. It has the function of neutralizing and degrading bacterial toxins, regulating intestinal flora and immune function. In addition, *S. boulardii* is a beneficial aerobic fungal, which can consume oxygen, produce an anaerobic environment conducive to bifidobacteria and lactic acid bacteria, and inhibit the growth of pathogenic microbiome.[21]

Everard *et al*.[22] is the first one who used *S. boulardii* for clinic trial in 2014. After oral administration of *S. boulardii* for 4 weeks, the obese and type 2 diabetic mice has a significant reductions in body weight and fat mass, hepatic steatosis and inflammation are also significantly alleviated. Interestingly, this study found that the effect of *S. boulardii* on host metabolism is related to the local effect of intestinal tract. To a certain extent, it can increase the weight of cecum, and also cause significant changes in the composition of intestinal microorganisms at the level of phylum, family and genus. These changes in intestinal microflora may be related to host metabolic response. Liu *et al*.[23] performed a similar study on NAFLD mice, which not only got the same conclusions that the mice obtained *S. boulardii* showed a significantly amelioration in hepatic steatosis and inflammation, but also found that *S. boulardii* can regulate the ratio of *Escherichia coli*/*Bacteroides* in the intestinal of NAFLD mice, which further illustrates the potential association between gut bacteria and fungi.

In addition, the latest research has also found that metabolic

syndrome, which is closely related to NAFLD, also shows an imbalance in intestinal fungi. There is a study provides evidence that ingestion of a high-fat diet (HFD) is associated with changes to the fungal, though no difference of richness and diversity was existed between the groups, the abundances of the *Alternaria*, *Saccharomyces*, *Septoriella*, and *Tilletiopsis* genera; *S. cerevisiae*; and *Tilletiopsis washingtonensis* were higher in mice fed standard chow.[24] Beside, Mar Rodríguez *et al*.[10] performed ITS analysis on the fecal microbiota of 27 obese patients and 12 healthy controls to analyze the abundance and diversity of intestinal fungal, though there was no evident difference in fungal abundance between the groups, the obese mice has a significantly lower diversity than the control group. And the abundance of the genus *Mucor* and *Penicillium*, which belongs to Zygomycota, was significantly reduced in the nonobese group.

Overall, evidence for a causal role of intestinal fungi in NAFLD in humans is limited because the gold-standard method for assessing and diagnosing NAFLD is still a liver biopsy. Improved noninvasive techniques will help enable well-powered studies to be performed to elucidate the role of the gut mycobiota in NAFLD.

INTESTINAL FUNGI AND END-STAGE LIVER DISEASE

Cirrhosis is a result of advanced liver diseases such as alcoholism, viral hepatitis, and fatty liver disease. It is characterized by replacement of live tissue by fibrosis and regenerative nodules; these changes lead to loss of liver function.[25]

In recent years, more and more studies have found that intestinal fungi have a close correlation with cirrhosis. Patients with cirrhosis are often accompanied by disorders of the intestinal fungi, the main manifestations were the decrease of fungal diversity and species abundance. The abundance of basidiomycetes in the intestinal tract of patients with cirrhosis is significantly reduced, while Ascomycota has an absolute advantage. For Ascomycota, there is a literature report that it is positively correlated with the incidence of end-stage liver disease, and can predict the short-term hospitalization rate of patients with advanced cirrhosis.[26] Most of the patients are hospitalized for infection, such as fungal peritonitis, fungemia, fungal esophagitis, etc., most of the pathogens of these infections are Ascomycetes and have been confirmed as intestinal origin.[11,27,28] This result tells us that liver cirrhosis patients are accompanied by intestinal fungal flora disorder and mucosal permeability destruction at the same time, intestinal fungi can enter the liver or even the whole body through the damaged intestinal mucosa, however, whether the disturbed fungi can in turn aggravate liver damage through the entero-hepatic axis has not been studied.

In another study by Chen *et al*.[29] on the correlation between gastrointestinal fungi and varying degrees of hepatitis B virus (HBV) infection, it is suggested that the hepatitis B cirrhosis and the chronic hepatitis B showed higher fungal diversity than the HBV carriers and the healthy control, and the hepatitis B cirrhosis had the highest diversity and species composition, indicating that the diversity of fungi in the gut is positively correlated with the degree of progression of HBV infection. Besides, the abundance of fungi in hepatitis B cirrhosis was also significantly higher than other groups, this result is consistent with the conclusion that Brown *et al*.[30] and Knoke[31] have confirmed in the preceding years that the increase in the number of fungi was significantly associated with the severity of the disease in HBV-infected patients. The association between chronic hepatitis B cirrhosis and intestinal fungi is related to defects in the host immune response. Mannose-binding protein, a pattern-recognition receptor that binds to mannose on the fungal cell wall and triggers a host immune response, thus playing a key role in combating fungal pathogens. In the course of HBV infection, the lack or dysfunction of mannose-binding proteins may lead to a weakened defense against fungi, leading to increased colonization of these pathogens.

From the above research, we found that liver cirrhosis caused by different etiology showed different changes in the structure and composition of intestinal fungi, which indicates that it is not the state of cirrhosis which causes the changes of intestinal fungi, but the intestinal fungi under the action of different etiology that lead to the occurrence of liver cirrhosis.

FUNGAL METABOLITES ON CHRONIC LIVER DISEASE

Similar to the intestinal fungi, the study on intestinal fungal metabolites are also at a very early stage. We try to elucidate the mechanism of action of these metabolites, combined with the pathogenesis of chronic liver disease, to explore the relationship between them.

1. Penstyrylpyrone

As one of the metabolites of *Penicillium*, penstyrylpyrone can inhibit the activity of protein tyrosine phosphatase 1B (PTP1B), while PTP1B is a major non-transmembrane phosphotyrosine phosphatase, as a negative regulator of the insulin-stimulated signal transduction pathway,[32] is associated with type 2 diabetes and obesity, may also provide a new target for the treatment of NAFLD.

2. *S. boulardii* anti-inflammatory factor

S. boulardii anti-inflammatory factor, a low molecular weight, water soluble factor, play an important role in *S. boulardii* anti-inflammatory properties and assist to modulate a signal transduction pathway including nuclear factor kappa B (NF-κB).[33] While the activation of the NF-κB pathway can stimulate the release of proinflammatory cytokines such as tumor necrosis factor-α, IL-1β, and IL-6, further promotes the generation of reactive oxygen species and exacerbates liver damage both in ALD and NAFLD.[34,35] Besides, *S. boulardii* anti-inflammatory

factor has been suggested to preserve the integrity of tight junctions between enterocytes[36] and has also been found to increase butyrate concentration (probably due to cooperation with bacteria).[37] Moreover, butyrate has been proved to exert protective effects against nonalcoholic steatohepatitis development mainly in alleviation of hepatic injury, fibrosis progression, inflammation, and lipid metabolism and intestinal barrier dysfunction.[38] Above all, *S. boulardii* anti-inflammatory factor may be closely related to chronic liver disease, the direct relationship between them needs to be further studied.

3. Polypeptides and other *S. boulardii*-derived molecules

Polyamines (spermine, spermidine, putrescine), produced by *S. boulardii*, has been found to have a trophic effect on the maturation of enterocytes. Besides, 54-kDa serine protease and 63-kDa phosphatase, produced by *S. boulardii* can directly destroys *Clostridium difficile* toxin A and degrades endotoxin of pathogenic *E. coli* respectively.[39,40] The role of polyamines in chronic liver disease has not been studied.

4. Farnesol

Farnesol is a non-sterol isoprenoid that is produced endogenously through the dephosphorylation of farnesyl pyrophosphate, a key branch-point intermediate of the cholesterol biosynthetic pathway. A lot of research has been done on farnesol, in addition to being functional in stimulating mitochondrial generation of ROS and apoptosis[41-45] as well as decreases intracellular cyclic adenosine monophosphate levels,[46,47] recent study found isoprenoid farnesol can also modulate lipid metabolism and reduces hepatic triglyceride content in steatotic HepaRG cells. This effect involves activation of at least two nuclear receptors, peroxisome proliferator-activated receptor alpha and farnesoid X receptor.[48]

5. Altenusin

Altenusin, a natural nonsteroidal fungal metabolite isolated from the endophytic fungus *Alternaria* sp., as a novel selective agonist of farnesoid X receptor (FXR), protected mice from HFD-induced obesity by reducing the body weight and fat mass. Administration of Altenusin also decreased the level of blood glucose and serum insulin level, even reversed HFD-induced hepatic lipid droplet accumulation and macrovesicular steatosis. Mechanistically, the metabolic benefits of Altenusin might have been accounted for by the increased insulin sensitivity and suppression of genes that are involved in hepatic gluconeogenesis and lipogenesis. In summary, Altenusin can be regarded as a new class of nonsteroidal FXR agonist that shows promise in treating NAFLD and the associated metabolic syndrome.[49]

FUTURE DIRECTION

The role of intestinal microorganisms in the occurrence and development of various diseases has been paid more attention currently, and the relationship between intestinal fungi and bacterial has gradually deepened. In a variety of liver diseases, the intestinal fungi shows a certain structural and compositional changes, which may provide new directions and targets for the treatment of chronic liver disease, such as apply beneficial fungi for the treatment of some disease by means of fecal microbiota transplantation. Furthermore, with the increasing incidence of NAFLD and the risk of NAFLD transitioning to steatohepatitis, cirrhosis and liver cancer, there is no effective drug for the treatment of NAFLD, we need to further explore the characteristics of intestinal fungi in patients with NAFLD, to verify the causal effect between NAFLD and fungal dysbiosis, providing a new direction for the treatment of NAFLD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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ORCID

Ningning You https://orcid.org/0000-0002-1040-4944
Lili Zhuo https://orcid.org/0000-0002-5626-9581
Jingxin Zhou https://orcid.org/0000-0003-3734-9778
Yu Song https://orcid.org/0000-0002-1023-4842
Junping Shi https://orcid.org/0000-0001-9434-897X

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