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Intestinal microbiome and permeability in patients with autoimmune hepatitis

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ABSTRACT

Autoimmune hepatitis (AIH) is a severe inflammatory liver disease. The underlying mechanisms remain unclear, but recent studies provided new perspectives on altered intestinal microbiome and permeability in AIH animal models and patients, highlighting gut-liver crosstalk in the pathogenesis of AIH. Transgenic AIH mice carrying HLA-DR3 showed reduced diversity and total load of gut microbiota. Germ-free mice are resistant to concanavalin A-induced liver injury, whereas enterogenouss antigens induce the activation of natural killer T cells participating in concanavalin A-induced liver injury, supporting the close relationship between microbiota and AIH. Moreover, 'molecular mimicry' provides a plausible interpretation of the immune reactions between microorganic antigens and liver autoantigens, for instance, cytochrome P4502D6, the target of cross-reactivity between virus and self. Nevertheless, direct evidence for the intestinal microbiome and permeability in AIH is still limited. The relationship between AIH susceptibilities and an intestinal microbiome shaped by drugs, diets or genes needs further study.

The gut–liver axis is widely described in numerous diseases, but rarely in autoimmune hepatitis (AIH) [1]. AIH is characterized by liver inflammation and progresses to liver cirrhosis without timely corticosteroid therapy. Blood in the portal vein collecting intestinal antigens returns to the interlobular veins, which are located in the portal area of the liver, indicating that the gut and the liver are correlative in anatomical physiology. Moreover, hepatitis at the portal–parenchymal interface with lymphoplasmocytic infiltrates is typical of AIH [2], which enlightens that the communication of the intestine and the liver may play a pivotal role in AIH pathogenesis.

Intestinal permeability is based on the integrity of intestinal barriers, which are composed of the mechanical, chemical, biological, and immunological barriers. Whichever barrier is ruined, increased permeability of the gut occurs. Intestinal microbiome dysbiosis can be described as altered commensal microbiota and invasion of pathogens. Study of the altered gut microbiome and permeability in AIH will provide new perspectives in elucidating the disease.

1. Intestinal microbiome and permeability in AIH patients or rodent models

Direct evidence of altered gut microbiome in AIH are scanty. Even so, a novel AIH model, based on HLA-DR3^{+} mice immunized with DNA plasmids, which code for human CYP2D6/FTCD fusion protein, showed reduced diversity and total load of gut bacteria [3]. Taxonomic analysis of gut bacteria at the phylum level showed that differences in AIH models, for example, *Bacteroides* and Proteobacteria, strikingly increased [3]. Moreover, intestinal microbiome dysbiosis also occurs in AIH patients. An investigation held in a Chinese group composed of 24 AIH patients and 8 healthy volunteers displayed a reduced number of anaerobes such as *Bifidobacterium* and *Lactobacillus* in the AIH group, whereas the number of aerobes such as *Escherichia coli* and *Enterococcus* remained unchanged [4]. However, those microbiome profiles differ among studies, and the intestinal microbiome data for naïve AIH patients remain absent. Another important observation is from germ free mice, which are resistant to concanavalin A (ConA)-induced liver injury, further indicating the necessity of

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intestinal microbiome in the initiation of immune-mediated inflammation of the liver [5].

To date, study of the intestinal barrier of AIH is still rare. Lin et al. [4] reported that zonula occludens-1 and occludin expression were decreased in the duodenum of AIH patients, implying the impaired integrity of tight junctions in the gut of AIH patients. Taken together, the evidence for intestinal hyperpermeability and dysbiosis in AIH is accumulating. Current data showed significant heterogenicity; thus, it was not possible to distinguish AIH patients from healthy individuals. Further investigations are eagerly awaited.

2. Intestinal microbiome and permeability in other autoimmune disorders

Intestinal microbiome and permeability in autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren syndrome (SS), and diabetes mellitus type 1 (T1DM) have been studied over the years [6,7]. This research may provide useful insights into AIH. It was reported that in the gut of patients with SLE, a decrease in Firmicutes families, with a significantly lower Firmicutes to Bacteroidetes ratio, was detected, which was consistent with another study of an SLE cohort [8,9]. Moreover, the latter study described nine genera of gut microbiota that were SLE-associated, including *Rhodococcus*, *Eggerthella*, *Klebsiella*, with significantly increased quantities, whereas *Dialister* and *Pseudobutyrivibrio* were clearly depleted [9]. Despite the etiological insights, these differences were potential clinical biomarkers for the diagnosis and evaluation of SLE [9].

Sjögren syndrome is one of the most common extrahepatic autoimmune disorders in patients with AIH [10]. It is important to recognize the evidence for microbiome dysbiosis in patients with SS. In patients with SS, increased abundance of pathogenic *Pseudobutyrivibrio*, *Escherichia/Shigella*, *Blautia*, and *Streptococcus* and decreased commensal *Bacteroides*, *Parabacteroides*, *Faecalibacterium*, and *Prevotella* were observed. In particular, the beneficial butyrate producer called *Faecalibacterium prausnitzii* was significantly decreased in the stool samples of SS patients [11]. De Paiva et al. further reported that gut dysbiosis worsened disease in an SS mouse model [11]. Gut microbiota in preclinical T1DM individuals is characterized by Bacteroidetes in the leading position and a lack of butyrate-producing bacteria. The dysbiosis is considered to be involved in autoimmune progression in T1DM [12,13]. These findings provide strong evidence supporting the correlation between gut microbiome and systemic autoimmune disorders. How the immune system of our liver reacts to enriched intestinal antigens carried by the portal vein remains an enigma, especially with respect to the pathogenesis of AIH.

Intestinal permeability in autoimmune diseases varies from trial to trial. In a Cr-51 EDTA permeability test, the authors could not detect the difference in intestinal permeability between SLE and normal individuals [14]. Another study showed that intestinal permeability in patients with Behcet's syndrome was significantly higher [15]. Moreover, increased intestinal permeability precedes and is involved in the onset of T1DM [16–19]. In conclusion, altered intestinal microbiome and permeability are common in autoimmune diseases. However, whether the altered microflora and hyperpermeability in the gut are the causes or the results of autoimmune diseases cannot yet be concluded. Nevertheless, studies in SLE, SS, and T1DM show strong evidences that gut dysbiosis is involved in the onset and progression of these autoimmune diseases, which impels the studies on AIH.

3. Molecular mimicry of microbiome in AIH pathogenesis

Molecular mimicry refers to the cross-reactions between foreign bodies and self, that may be of great significance in the immune cross-talk of the gut and liver. A recent study showed that atypical *p*-ANCAs from patients with AIH or primary sclerosing cholangitis (PSC) were directed against both human beta-tubulin isotype 5 (TBB-5) autoantigen and the bacterial protein FtsZ, suggesting that the molecular mimicry between human autoantigen and intestinal microorganic antigen might play a role in the pathogenesis of AIH or PSC [20,21]. Moreover, antibodies to β-galactosidase of *Lactobacillus delbrueckii* and *Mycoplasma* antigens cross-react with major mitochondrial autoepitopes in patients with primary biliary cholangitis (PBC) [22,23], further supporting the molecular mimicry between autoantigens and the microbiome.

Liver kidney microsomal autoantibody type 1 (LKM1) is a diagnostic antibody of AIH. Cytochrome $P4502D6_{193-212}$ is an epitope for LKM1 in patients with AIH, but the antibody also cross-reacts with hepatitis C virus (HCV) [24]. The molecular mimicry of cytochrome P450 by HCV results in specific autoreactive $CD8^+$ T cells, which are highly related to liver inflammation, suggesting that the molecular mimicry between self and viruses might play an important role in AIH pathogenesis [25]. A case of severe AIH following varicella zoster infection further implies that the virus may cause AIH by molecular mimicry, such as the herpes simplex, Epstein–Barr, measles, and hepatitis viruses [26]. Together, this body of evidence highlights the notion that molecular mimicry between antigens from microorganisms and autoantigens in the host might be parts of the mechanisms of liver inflammation in autoimmune liver disease (AILD) [21].

4. Cross-talk between intestinal microbiome and permeability

The microbiome itself is a part of the intestinal barrier called the biological barrier, which has double-edged effects on intestinal permeability. The intestinal microbiota profile, especially the anaerobic, plays a major role in protecting the intestinal mucosa, in which the intestinal mucosa-associated microflora *Bifidobacterium* and *Lactobacillus* form a defensive bacterial membrane for normal intestinal barrier function [27–29]. Moreover, studies show that probiotics and butyrate can secure or restore intestinal permeability [16,30–33], and oral administration of *Saccharomyces boulardii* ameliorates the intestinal permeability and modulates gut microbial composition [34].

However, pathogenic bacteria or their harmful products transferred from gut to the blood may aggravate the intestinal barrier dysfunction. The *Staphylococcus aureus* alpha toxin in blood may perturb the intestinal epithelial barrier [35]. Enterotoxigenic *Escherichia coli* and *Salmonella enterica* can increase the permeability of the intestine [33,36].

Harmful factors such as endotoxin and alcohol may damage the crosstalk between the intestinal microbiome and permeability, giving us hints about exploring their roles in AIH. Endotoxin, the product of gram-negative bacteria, promotes bacterial translocation from gut to the mesenteric lymph nodes in mice, whereas protein malnutrition cannot promote bacterial translocation even though it does disrupt the indigenous intestinal flora [37]. The study shows that the permeability of the small bowel is increased by alcohol consumption [38]. Furthermore, Engen et al. [39] reveals that alcohol consumption leads to dysbiosis in the gut microbiota of both rodents and humans. Bacterial translocation

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