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Research progress on the effect of intestinal flora changes on liver and kidney function in AIDS patients

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Abstract: *HIV, also known as HIV, infects the body's immune cells, causing immune deficiencies. The intestine is not only the immune organ of the human body, but also includes a large number of intestinal flora, and the intestinal microecology composed of these flora is closely related to immunity. HIV infection itself and its infection caused by intestinal flora imbalance, intestinal mucosal barrier destruction, causing the body's systemic inflammatory cascade reaction, the production of various inflammatory cytokines and metabolites, and eventually cause certain damage to liver and kidney function. This article reviews the mechanism and relationship between the effects of intestinal microbiota changes on liver and kidney function in AIDS patients, and changes the regulation of intestinal microbiota disorders on the microinflammatory state of the body, thereby providing a new entry point for the improvement of liver and kidney function in AIDS patients.*

Keywords: *HIV; Intestinal Flora; Inflammatory Cytokine; Gut-Liver Axis; Gut-Kidney Axis*

AIDS (Acquired Immune Deficiency Syndrome),or Acquired Immune Deficiency Syndrome, is caused by the human immunodeficiency virus (HIV),also known as AIDS virus. By the end of 2020, there will be 37.7 million people living with HIV/AIDS and 1.5 million new HIV infections worldwide.[1] There is no effective cure for AIDS, and patients are currently receiving antiretroviral therapy (ART).

The intestinal tract is the largest immune organ in the body and is inhabited by a significant number and variety of microorganisms that play an important role in the maintenance of host gut function and the participation of intestinal immunity.[2] HIV infection can cause gastrointestinal immune activation and an increase in metabolites, which can further lead to damage of the intestinal immune barrier.Various inflammatory cytokines are released in the intestinal immune activation and affect the hepatic and renal function of the patient either simultaneously or via the intestinal-liver axis[42,43,44] and intestinal-renal axis.[45]

1. Normal intestinal microecology

The gut microbiota (GM) was earlier thought to be about 500-1000 species[3,4] , but recent studies have shown that the human gut microbiota consists of probably more than 35,000 species[3,5].These 35,000 or so species can be divided into five main phyla: Firmicutes and Bacteroidetes account for the major part, about 90%,followed by Actinobacteria,Verrucomicrobia, and Proteobacteria. Proteobacteria)[3,6,7,8].The overall profile volume of the phylum remains stable, and it shows differences in spatial and temporal distribution at the level of the phyla and outside the phylum.For example, the diversity and number of phyla can vary significantly from the distal esophagus to the rectum of a person:the distal esophagus, duodenum and jejunum are dominated by Streptococcus as the dominant genus;Helicobacter pylori is the dominant genus present in the stomach, but also by Prevotella and other dominant genera, and multiple genera together constitute a rich diversity of their microorganisms[3,9,10].The ratio of two phyla, Phyllobacterium and Phyllobacterium, in the large intestine is also associated with disease susceptibility[11].In addition to these two phyla,the human colon contains major pathogenic bacteria,such as Campylobacter jejuni,Salmonella enterica,Vibrio cholerae,Escherichia coli,and Bacteroides fragilis,with low abundance of pathogenic bacteria,accounting for 0.1% or less of the total intestinal microbiota[12,13].The low abundance of metaphyla mostly indicates that the intestinal flora is healthy.In addition to this horizontal

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spatio-temporal distribution variation, there are also axial differences from the intestinal lumen to the intestinal mucosal surface:genera such as Bacillus and Bifidobacterium are the main tubular microbial genera, which can be found in the feces, and genera such as Mucinophilus ackermanni are the main mucosal and mucus-associated genera, which can be found in the mucus layer and epithelial crypt of the small intestine[3,14] .

When the human intestinal flora is in a healthy and stable state, it can live in mutual benefit symbiosis with the host: on the one hand, the intestinal flora can obtain nutrients from the host's diet that it needs for its own reproduction and development; on the other hand, the intestinal flora can also synthesize certain vitamins (B and K) and other nutrients in the host and play an important role in digestive metabolism such as sugar and lipids[3,8,15] . The intestinal flora obtains nutrients from the host's dietary components and shed epithelial cells and is a plastic organ with a wide range of metabolic capabilities and substantial functions[3,16] .

2. Immune activation and altered intestinal flora due to HIV infection

2.1 Immune activation due to HIV infection

After HIV infection, CD4+T cells in the peripheral blood and intestine are greatly reduced while the chronic immune system is activated[17] , infected CD4+T cells synthesize membrane protein antigen glycoprotein 120 (gp120) on the cell membrane and bind to uninfected CD4+T cells to form fusion cells, causing changes in cell membrane permeability and cell lysis and apoptosis[18];in addition, HIV can also infect the cell epidermal membrane protein gp41, which inhibits CD4+T cell mitosis and the proliferative response of immune activated lymphocytes[18,19] .

CD4+T cell subtypes include Th1, Th17, Th2, T follicular helper cells (Tfh) and regulatory T cells (Treg)[20] . After HIV infection, CD4+T cell differentiation produces fewer Th17 cells, a major subset of CD4+T cells, which produce inflammatory cytokines such as IL-17A and IL-22 after immune activation and differentiation[21,22-27].One of the important roles of IL-17A is to regulate the permeability of intestinal epithelial cells and promote epithelial barrier protection[28,29,30];IL-22 and IL-17A acts similarly to IL-17A to induce the production of antimicrobial peptides by epithelial cells and to promote proliferation, survival and tissue repair of epithelial cells in the intestine.[31,32]

2.2 Altered intestinal flora due to HIV infection

It has been found that the number of the Pseudomonas phylum is positively correlated with CD4+T cells[33,34] .HIV infection is associated with a large decrease in CD4+T cells and a consequent decrease in the number of the Pseudomonas phylum and a decrease in short-chain fatty acid (SCFA) producing probiotics; increased abundance of the Aspergillus phylum further induces immune activation and inflammatory responses[35]:increased abundance of several pathogenic bacteria, Pseudomonas spp.[36];Desulfovibrio spp.[37];Campylobacter spp.[38];Escherichia spp.[36] etc.; Immunobacterium spp. can produce lipopolysaccharide (LPS)[38],which is also mostly regarded as a marker of intestinal flora translocation, a component of the cell membrane of Gram-negative bacteria, which enters the circulatory system through the lamina propria of the intestine and activates the release of inflammatory factors such as IL-6, TNF-α, NO, etc. by macrophages in the immune system[8] .

Previous studies have shown that HIV affects the intestinal flora of the population, and that the intestine is an important site of HIV infection, accumulating large amounts of HIV[39].Comparing the composition of the intestinal flora in the HIV-infected and healthy population groups revealed that the index of alpha diversity of the intestinal flora was significantly lower in the HIV-infected group than in the healthy group[40].Clostridium difficile and Shigella coli were specific and highly abundant in the HIV-infected group.[40]

2.3 Intestinal flora translocation

In the early stages of HIV infection, CD4+T cells in the gut-associated lymphoid tissue (GALT) are heavily depleted, leading to damage and dysfunction of the gastrointestinal system,The consequence of deterioration of intestinal homeostasis is chronic immune activation[17].The massive loss of lymphocytes in the intestinal tissues and reduced defense against pathogens leads to impaired tight junctions between the intestinal epithelium and impaired integrity of the intestinal mucosa[8].In addition the altered intestinal flora species due to HIV infection and impaired immunity also cause

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damage to the intestinal mucosal barrier. BPB (butyric acid producing bacteria) have been shown to provide energy to intestinal cells and protect the intestinal barrier. Loss of BPB may lead to loss of intestinal barrier integrity and promotion of inflammation of the intestinal epithelium.All of the above causes underlie the translocation of intestinal flora, causing a long-term chronic inflammatory response in the body's circulation and the production of inflammatory cytokines[32].

3. Altered intestinal flora and hepatic and renal impairment in AIDS patients

3.1. Related Mechanisms

HIV infection and intestinal flora alter the permeability of the intestinal mucosal barrier, and also a large number of flora metabolites enter the circulatory system, inducing a cascade of inflammatory responses in the body through the neuroendocrine, vagal and immune pathways and metabolites, which is sometimes referred to as the "leaky gut syndrome [43]This concept is increasingly recognized as playing a central role in liver and kidney disease, and this overall pathway of inflammation is referred to as the "enterohepatic axis"[42,43,44] and the "entero-renal axis"[45] .

Intestinal mucosal immunity does not cause excessive damage to beneficial bacteria and host tissues[46] . Its central component is the mucosal receptor system, the major classes of which include Toll-like (TLRs, Toll-like receptors) and NOD-like (NLRs, Nod-like receptors) receptors that recognize a variety of bacterial products, including lipopolysaccharide (LPS), flagellin, peptidoglycan, and bacterial DNA. receptor agonism later induces expression of host defense genes by activating some major signaling cascades, such as the NF-κB transcriptional pathway[43].The activation of host defense mechanisms also causes some damage to host tissues. The liver and kidney also express TLR, NLR and NF-κB transcriptional pathways, which play an increasingly important role in liver and kidney diseases. In the presence of bacterial translocation or low concentrations of pathogen-associated molecular patterns (PAMPs)[48] , hepatic TLS/NLR activation increases, resulting in the production of cytokines that lead to liver lesions, fibrosis progression, cirrhosis and hepatocellular carcinoma development[43,47] .

Among these multiple responses, it is worth highlighting the activation of TLR4 by LPS. LPS or endotoxin (a typical PAMP) induces the production of cytokines such as IL-1β and TNF-α in the liver through the activation of NF-κB-dependent responses via MyD88[49] .

In addition to the inflammatory mechanisms of nuclear factor-κB (NF-κB) receptor activation by ex-Toll-like receptors (TLRs) and NOD-like receptors (NLRs), there are also uremic retention molecules (URMs) pathways in the impairment of renal function: alterations in renal function lead to corresponding changes in blood concentrations of many molecules, in particular, substances normally excreted or metabolized by the kidneys accumulate as renal function declines, resulting in resulting in increased blood concentrations[50].These uremic retention molecules (URMs) constitute a long, expanding mass that, once accumulated, can lead to uremic syndrome and further decrease in renal function[50] . URMs are classified according to their origin: endogenous (mammalian metabolism), microbial or exogenous (e.g. dietary). Recently it has also become increasingly recognized that gut microbial metabolism also contributes to the production of numerous URMs[51,52].Compounds produced by gut microbes are usually excreted by the kidneys but can be considered potential URMs[53].The gut microbiota ferments the amino acids tyrosine and tryptophan, producing p-cresol and indole, respectively. After absorption, these compounds are further metabolized in the liver to produce p-cresol sulfate and p-indole sulfate[54] . These toxins are primarily excreted through renal tubular secretion and are therefore considered uremic toxins whose increased levels indicate renal damage[54] . Meijers and colleagues measured p-cresol levels in 499 patients with mild to moderate CKD and found that p-cresol sulfate levels increased with a decrease in estimated glomerular filtration rate (GFR)[55];similarly, elevated p-cresol concentrations were associated with maintenance hemodialysis treatment for end-stage renal disease (ESRD) patients treated with maintenance hemodialysis are associated with an increased risk of death[56] . The role of trimethylamine N-oxide (TMAO), another uremic toxin produced by the gut microbiota, in CKD has also been studied[57] . In a large cohort of CKD patients, Tang and his colleagues found elevated TMAO concentrations in CKD patients. These elevated concentrations were associated with a 70% risk of all-cause mortality, even after adjusting for traditional risk factors and C-reactive protein .[58]

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3.2. Alteration of intestinal flora after liver function injury

Ivana Milosevic et al.[59] found that increased intestinal permeability and bacterial translocation allows microbial metabolites to reach the liver, which impairs bile acid (BA) metabolism and promotes intestinal motility disorders and systemic inflammation[60] . Changes in the composition and structure of the intestinal flora were detected in patients with chronic hepatitis B and cirrhosis: due to low levels of bifidobacteria and lactobacilli and high levels of enterococci and enterobacteria, the ratio of bifidobacteria family/enterobacteriaceae (B/E) was decreased in these patients. In addition, when bacterial translocation and portal endotoxin are present, intestinal permeability is altered, leading to increased hepatic TLS/NLR activation, which results in the production of cytokines that lead to liver lesions, fibrosis progression, cirrhosis and liver cancer development[43,47] . Wei et al. found that the intestinal flora of patients with hepatitis B-associated cirrhosis contained lower levels of B. mimicus (4% vs. 53%) and higher levels of of Aspergillus (43% vs. 4%). The study by Benoit Chassaing et al.[43] also concluded that the intestinal flora had a reduced abundance of Bacillus and increased levels of Enterobacteriaceae and Aspergillus. The results of Xu et al.,however, yielded an increased abundance of Bacillus in the liver fibrosis group, including increased levels of Actinobacter and Spirochetes. It is evident that the results of current studies on changes in intestinal flora in hepatic impairment still vary.

3.3. Changes in intestinal flora after renal impairment

Recent studies have linked gut microbiota dysbiosis to kidney disease, such as changes in gut microbiota complexity and/or structure observed before and after kidney transplantation or kidney stone formation. Li et al.found that the most abundant genus observed in patients with chronic kidney disease (CKD) was Bacillus spp. followed by E. coli/Shigella spp. , Escherichia coli/Vibrio spp., Roseobacter spp. and Clostridium spp. XLVa. This finding contrasts with a previous study by Jiang et al, who found an enrichment of Bacillus spp. in patients with end stage renal disease (ESRD).

Further, a study by Jiang et al.found an enrichment of E. coli spp./Shigella spp. in ESRD patients and a greater abundance of Roseobacter spp. in controls. A study by Nosratola et al. found a significant increase in phragmobacteriaceae, Streptococcaceae, and Enterobacteriaceae in patients with end-stage renal disease (ESRD) compared to healthy subjects. In addition, in a study of animals by Nosratola et al.found significant differences in the abundance of 175 bacterial species between uremic and control animals, most notably a decrease in Lactobacillaceae and Proteaceae. A study by Li et al. also found that the α-diversity, β-diversity of the fecal microbiota was significantly lower in patients with CKD than in healthy controls. feces in the CKD group included Lactobacillus paracasei spp, Lactobacillus spp. and Helicobacter spp. were enriched in the CKD group and were positively correlated with indicators of CKD severity. The relative abundance of warty microorganisms and actinomycetes was lower than that of healthy controls.The results of the above studies on changes in intestinal flora in renal impairment were similarly variable.

4. Relationship between cellular inflammatory factors and hepatic and renal impairment and intestinal flora

4.1. Cellular inflammatory factors and liver function

Xu et al. observed histopathological changes in the intestine and liver of rats with liver fibrosis and found reduced intestinal mucosal occlusion protein expression, increased collagen fibril deposition in liver tissue, increased TLR4, MYD88, NF-κB, TNF-α, IL-1 protein expression, elevated portal LPS levels, and abnormal liver function and coagulation. Wagnerberger S et al. found that intestinal tight junction protein expression that decreased expression of intestinal tight junction proteins correlated with elevated expression of hepatic TLRs, and that elevated expression of hepatic TLRs may promote inflammation when leaky gut microbial products are detected. It has long been suggested that antagonizing TLR4 signaling may be a reasonable means of treating a variety of inflammatory diseases[43] . Antagonizing NLR signaling and or NLR-produced cytokines, particularly IL-1β, has been proposed as a treatment for the metabolic syndrome.

4.2. Cellular inflammatory factors and renal function

Levels of multiple pro- and anti-inflammatory cytokines, including IL-4, IL-6, IL-8, IL-10 and INF-γ have been reported in CKD and are thought to be associated with progression of CKD and

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cardiovascular disease (CVD) complications[57]. IL-10 levels are associated with reduced renal function and risk of cardiovascular events. CKD The levels of pro-inflammatory cytokines IL-4 and IL-6 were significantly higher in the CKD group compared to the HC group. Bifidobacterium and Lactobacillus may exert therapeutic effects by upregulating IL-10 expression in serum.

The mucinophilic Akkermansia was significantly negatively correlated with IL-10 production.Akkermansia has been shown to be important in host physiology and is particularly effective in increasing mucus thickness and intestinal barrier function.IL-10, TGF-β are anti-inflammatory cytokines produced by Treg cells that inhibit the activity of a variety of immune cells and thereby suppressing the immune response .[20]

4.3. Cellular inflammatory factors and intestinal flora

Zhang Mingjun et al.[40] found that Clostridium filiformis spp., Clostridium spp. and γ-Amastigotes spp. were positively correlated with TNF-α, while Agathobacter spp. and Pseudomonas spp. were negatively correlated with TNF-α. Agathobacter was positively correlated with IL-2 and IL-8 levels, and Pseudomonas was negatively correlated with IL-8 levels.

5. Regulation of intestinal flora disorders in AIDS patients to improve liver and kidney impairment

5.1. Use of intestinal microecological agents

Gut microbial agents include probiotics, prebiotics and synbiotics. Symbiosis is a mixture of probiotics and prebiotics[14].The use of microbial agents can improve the dysbiosis of intestinal flora and disruption of the intestinal mucosal barrier. It has been shown that probiotic or synbiotic use in HIV-infected subjects is associated with a decrease in inflammatory markers and a slight significant increase in CD4+T cell counts.There is also some uncertainty in studies as to which probiotic preparations are most beneficial for HIV-1-infected cART receptors, or whether the same probiotic or prebiotic mixture is effective in HIV-1-infected individuals across all demographic characteristics.The two most widely used probiotic formulations, Lactobacillus GG and VSL-3, were significantly effective in SIV-infected Asian macaques receiving cART, reducing fibrosis of gastrointestinal lymphoid follicles and reconstituting intestinal CD4+T cells to near healthy levels.Probiotics can enhance gastrointestinal immunity and thus restore Th17 cells in the mucosa,which also facilitates the maintenance of the intestinal mucosal barrier, thereby reducing translocation of intestinal flora and mitigating long-term chronic inflammation caused by metabolites entering the body circulation.

5.2. Fecal transplantation

Fecal flora transplantation (FMT) is also a means of restoring the ecology of the intestinal flora, mainly by obtaining fecal flora from healthy volunteers and transplanting them into patients in an attempt to re-establish the normal flora microecology of the patients.Some animal studies have shown that FMT altered the composition of the intestinal flora in alcohol-sensitive mice and prevented alcohol-induced liver damage.In a related clinical trial, a pilot study was conducted in eight men with severe alcoholic hepatitis and the results were compared to historical controls, researchers found that one week of FMT was effective and safe in patients with severe alcoholic hepatitis and improved liver disease severity and one year survival.FMT had a better effect on altered intestinal mucosal barrier function compared to probiotics and no serious adverse effects have been reported yet, but FMT should be considered for the risk of pathogenic infection present during transplantation.

6. Summary and Outlook

After HIV infection, the intestinal flora and specific lymphocyte subpopulations in the intestinal tissues react. For the intestinal flora, it is mainly the change of flora species and the increase of flora products, while the lymphocytes in the intestinal tissues are not only directly activated by HIV infection, but also by the effect of the changed intestinal flora species and their products, thus producing the corresponding inflammatory cytokines, which eventually lead to the change of the permeability of the intestinal mucosal barrier, further aggravating the translocation of the intestinal flora, the decrease of probiotic bacteria, and the pathogenic bacteria and their metabolites increase, thus

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causing a long-term state of immune activation in the organism and the continuous production of inflammatory cytokines. In this process, the intestine-hepatic axis, intestine-renal axis and metabolites of the organism are also involved, which to some extent affect the liver and kidney function.

As the mechanism linking intestinal flora alteration and liver and kidney function impairment is emphasized, it is expected to improve the metabolic status through the alteration of intestinal flora disorder status and the corresponding metabolite regulation in AIDS patients, thus providing a new entry point for the treatment of liver and kidney function impairment caused by AIDS.

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