

## Role of gut microbiota on intestinal barrier function in acute pancreatitis

Xue-Yang Li, Cong He, Yin Zhu, Nong-Hua Lu

**ORCID number:** Xue-Yang Li (0000-0001-8161-4781); Cong He (0000-0002-1185-5456); Yin Zhu (0000-0002-4791-6126); Nong-Hua Lu (0000-0003-4373-551X).

**Author contributions:** Li XY and He C conceived and designed the study and wrote the manuscript; Zhu Y and Lu NH made substantial contributions to conception, design and coordination of the study and gave final approval of the version to be published; all authors read and approved the final manuscript.

**Supported by** the National Natural Science Foundation of China, No. 81760120 and No. 81960128; and the Key Program of Science and Technology Department of Jiangxi Province, No. 20171BBG70084 and No. 20192ACBL20037.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

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**Manuscript source:** Invited

**Xue-Yang Li, Cong He, Yin Zhu, Nong-Hua Lu,** Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

**Corresponding author:** Yin Zhu, PhD, Doctor, Professor, Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, 17 Yongwaizheng Street, Donghu District, Nanchang 330006, Jiangxi Province, China. [zhuyin27@sina.com](mailto:zhuyin27@sina.com)

### Abstract

Acute pancreatitis (AP) is a common gastrointestinal disorder. Approximately 15%-20% of patients develop severe AP. Systemic inflammatory response syndrome and multiple organ dysfunction syndrome may be caused by the massive release of inflammatory cytokines in the early stage of severe AP, followed by intestinal dysfunction and pancreatic necrosis in the later stage. A study showed that 59% of AP patients had associated intestinal barrier injury, with increased intestinal mucosal permeability, leading to intestinal bacterial translocation, pancreatic tissue necrosis and infection, and the occurrence of multiple organ dysfunction syndrome. However, the real effect of the gut microbiota and its metabolites on intestinal barrier function in AP remains unclear. This review summarizes the alterations in the intestinal flora and its metabolites during AP development and progression to unveil the mechanism of gut failure in AP.

**Key words:** Acute pancreatitis; Gut microbiota; Short-chain fatty acids; Intestinal barrier

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**Core tip:** Acute pancreatitis (AP) is a common clinical acute abdomen disease, and its incidence is increasing year by year. There are several reviews on the pathophysiology, therapeutic options and clinical trials of AP. However, the real effect of the gut microbiota and its metabolites on intestinal barrier function in AP remains unclear. This review summarizes the alterations in the intestinal flora and its metabolites during AP development and progression to unveil the mechanism of gut failure in AP.

**Citation:** Li XY, He C, Zhu Y, Lu NH. Role of gut microbiota on intestinal barrier function in acute pancreatitis. *World J Gastroenterol* 2020; 26(18): 2187-2193

**URL:** <https://www.wjgnet.com/1007-9327/full/v26/i18/2187.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v26.i18.2187>

## Manuscript

**Received:** January 12, 2020**Peer-review started:** January 12, 2020**First decision:** January 19, 2020**Revised:** March 26, 2020**Accepted:** April 15, 2020**Article in press:** April 15, 2020**Published online:** May 14, 2020**P-Reviewer:** Bramhall SR, Kochhar R, Manenti A**S-Editor:** Wang YQ**L-Editor:** Webster JR**E-Editor:** Zhang YL

## INTRODUCTION

Acute pancreatitis (AP) is a common gastrointestinal disorder. It is a local inflammatory response of the pancreas caused by abnormal activation of pancreatic enzymes by a variety of causes. AP is classified into mild AP (MAP), moderately severe AP (MSAP), and severe AP (SAP) based on the Atlanta Classification of 2012 revision<sup>[1]</sup>. Approximately 15%-20% of patients develop SAP<sup>[2,3]</sup>, and both systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) may be caused by the massive release of inflammatory cytokines in the early stage of SAP, followed by intestinal dysfunction and pancreatic necrosis in the later stage<sup>[4,5]</sup>. Most bacteria causing necrotic infection of pancreatic tissue are from the intestinal flora, such as *Escherichia coli* and *Enterococci*<sup>[6]</sup>. Therefore, the intestinal flora may play an important role in the development of SAP.

The gastrointestinal tract, the largest organ in the human body, provides a broad colonization surface for the flora. It contains 150 times the total number of human genes<sup>[7]</sup>. The human intestinal flora has more than 1500 species and more than 50 phyla, with the largest number of *Firmicutes*, followed by Bacteroidetes, and other common phyla are Proteobacteria, Actinomyces, Actinobacteria, Fusobacteria and Verrucomicrobia<sup>[7]</sup>. In recent years, with the development of metagenomic research, people have become increasingly aware that the intestinal flora plays an important role in human health and diseases, including gastrointestinal diseases, such as inflammatory bowel disease<sup>[8]</sup>, irritable bowel symptoms<sup>[9]</sup>, colon cancer<sup>[10]</sup>, and extragastrointestinal diseases, such as Alzheimer's disease<sup>[11]</sup>, coronary heart disease<sup>[12]</sup>, obesity<sup>[13]</sup>, and diabetes<sup>[14]</sup>. Some studies have found early dysbiosis of the intestinal flora during the occurrence and development of SAP. In addition to intestinal bacteria, their metabolites, such as short-chain fatty acids (SCFAs), also affect the progression of AP.

This review summarizes the alterations in intestinal flora and its metabolites during the development and progression of AP to unveil the mechanism of gut failure in AP and finally provide a potential therapeutic target for AP.

## CHANGES IN THE INTESTINAL FLORA DURING AP

In recent years, an increasing number of studies have found that the intestinal flora changes during the development of AP, which may be related to the severity of the disease. During the AP process, abnormal secretion of trypsin and destruction of pancreatic structure lead to abnormal pancreas secretion, which can cause changes in intestinal homeostasis and the intestinal flora<sup>[15,16]</sup>. Patients with AP had a greater abundance of the phyla Bacteroidetes and Proteobacteria with lower abundance of Firmicutes and Actinobacteria than healthy controls<sup>[17]</sup>. Tan *et al*<sup>[18]</sup> found that the microbial composition shifted significantly between patients with AP and healthy controls (HCs). The abundance of potentially pathogenic bacteria such as *Enterobacteriaceae* and *Enterococcus* was significantly increased, and that of beneficial bacteria such as *Bifidobacterium* was significantly decreased in both the MAP and SAP groups. The abundance of *Enterobacteriaceae* and *Enterococcus* increased by 3.2% and 9.3%, respectively, whereas *Bifidobacterium* abundance decreased by 9.2% in the SAP group compared to that in the MAP group. Our results also showed differences between the AP and HC groups; furthermore, the microbial composition changed further with the worsening of AP, and the abundance of beneficial bacteria such as *Blautia* was decreased in SAP compared with that in MAP and MSAP. It was suggested that the gut microbiota is an important mediator during AP and that its dysbiosis is associated with AP severity<sup>[19]</sup>.

As there were significant changes in the abundance and structure of the intestinal flora in AP patients, researchers continued to study the changes in intestinal flora during AP using animal models. Animal experimental evidence also demonstrated similar intestinal microbiota changes in AP. Chen *et al*<sup>[20]</sup> applied 16S rRNA high-throughput sequencing analysis to study intestinal microbiota changes in rats in a sham-operated group (SO group) and an acute necrotizing pancreatitis (ANP) group. The SO and ANP groups showed structural segregation, and the microbiota diversity of the ANP group significantly decreased. At the phylum level, the abundance of *Saccharibacteria* and *Tenericutes* decreased significantly. At the genus level, the abundance of *Escherichia-Shigella* and *Phascolarctobacterium* increased significantly, while the abundance of *Candidatus\_Saccharimonas*, *Prevotellaceae\_UCG-001*, *Lachnospiraceae\_UCG-001*, *Ruminiclostridium\_5* and *Ruminococcaceae\_UCG-008* decreased significantly. At the same time, the amount of antimicrobial peptides (AMPs) secreted by panspermia cells decreased significantly and was negatively

correlated with the abundance of *Escherichia coli* and *Shigella*. Deficiencies in Paneth cell AMPs were reported to be associated with intestinal barrier failure, leading to bacterial translocation<sup>[21]</sup>. Ye *et al*<sup>[22]</sup> found that obesity could aggravate AP, deteriorate intestinal permeability and aggravate intestinal inflammation. They analysed the faecal microbiota composition and found that obese rats with AP had lower bacterial richness than rats with normal weight. Studies have suggested that faecal bacterial richness is a major marker of gut health<sup>[23,24]</sup>. Our animal research revealed that antibiotic-treated mice and germ-free mice exhibited alleviated pancreatic injury after AP induction and that subsequent faecal microbiota transplantation in turn exacerbated disease. Moreover, our previous results were supported by animal research, which also found that gut microbiota-depleted AP rats displayed less pancreatic injury and lower levels of interleukin (IL)-17A, tumour necrosis factor- $\alpha$  and IL-1beta in the plasma than AP rats with an intact microbiota<sup>[25]</sup>. Many recent studies have shown that this may be related to IgA, a key immune protein that is mainly located in the small intestine and protects the intestinal barrier from pathogenic bacteria. The diversity of bacteria can stimulate the body to produce different IgA and combine with the bacteria<sup>[26]</sup>. Through the combination with bacteria, it can modify the metabolism of bacteria and eliminate the mucosal inflammation response<sup>[27]</sup>, which maintain immune homeostasis. The production of IgA depends on bacterial diversity. Deficiency of IgA in the gut lumen was associated with altered microbiota composition in the small intestine<sup>[28]</sup>, increased susceptibility to induced colitis, and higher bacterial translocation to mesenteric lymph nodes after *Salmonella typhimurium* challenge, which suggested that IgA played a crucial role in the immune regulation between the intestinal flora and the host. Taken together, these studies reveal that the intestinal flora changes during AP and that these changes may be related to the severity of disease.

## GUT MICROBIOTA MAY PROMOTE AP PROGRESSION BY AFFECTING INTESTINAL MUCOSAL BARRIER FUNCTION

Normal gut bacteria play a crucial role in maintaining gut mucosal integrity. However, gut mucosal ischaemia and reperfusion during AP can damage gut barrier integrity and lead to gut bacterial translocation to other locations, causing local and systemic infections<sup>[29,30]</sup>. Studies have revealed that intestinal mucosal barrier injury is one of the major complications of AP. A meta-analysis showed that 59% of AP patients had associated intestinal barrier injury<sup>[31]</sup>, with increased intestinal mucosal permeability, leading to intestinal bacterial translocation, pancreatic tissue necrosis and infection, and the occurrence of MODS. It has been shown that the initial onset of caerulein-driven AP is dependent on the activation of NOD1 in acinar cells by commensal bacteria translocated from the gut, which further induces the expression of inflammatory mediators<sup>[32]</sup>. The intestinal flora can affect intestinal mucosal barrier function in various ways. First, the biological barrier is composed mainly of the normal intestinal flora and can regulate the intestinal microecological balance. In general, the intestinal flora coexists harmoniously with the human body and does not cause intestinal inflammatory reactions. However, when the intestinal flora is out of balance, the intestinal mucosal barrier can be destroyed by affecting intestinal inflammation and the immune response. Tan *et al*<sup>[18]</sup> found that serum IL-6 content was positively correlated with the abundance of *Enterobacteriaceae* and *Enterococcus* and negatively correlated with *Bifidobacterium* abundance, whereas plasma endotoxin content was positively correlated with *Enterococcus* abundance. This finding suggests that the inflammatory response may be related to intestinal flora imbalance. Second, the intestinal flora can also influence the mechanical barrier of the intestinal mucosa. Zhu *et al*<sup>[33]</sup> reported that mice receiving berberine promoted the expression of ZO-1 and Occludin in the intestinal mucosa by increasing the abundance of the beneficial bacteria *Akkermansia* in the intestinal tract, thus thickening the mucous layer of the intestinal mucosa and maintaining the function of the intestinal barrier. Third, *Akkermansia muciniphila* highly produces the pilus-like protein Amuc\_1100, which is involved in host immune homeostasis of the intestinal mucosa and improves intestinal barrier function. In summary, the intestinal flora can affect AP progression by influencing the biological, mechanical and immune barriers of the intestinal mucosa<sup>[34]</sup>.

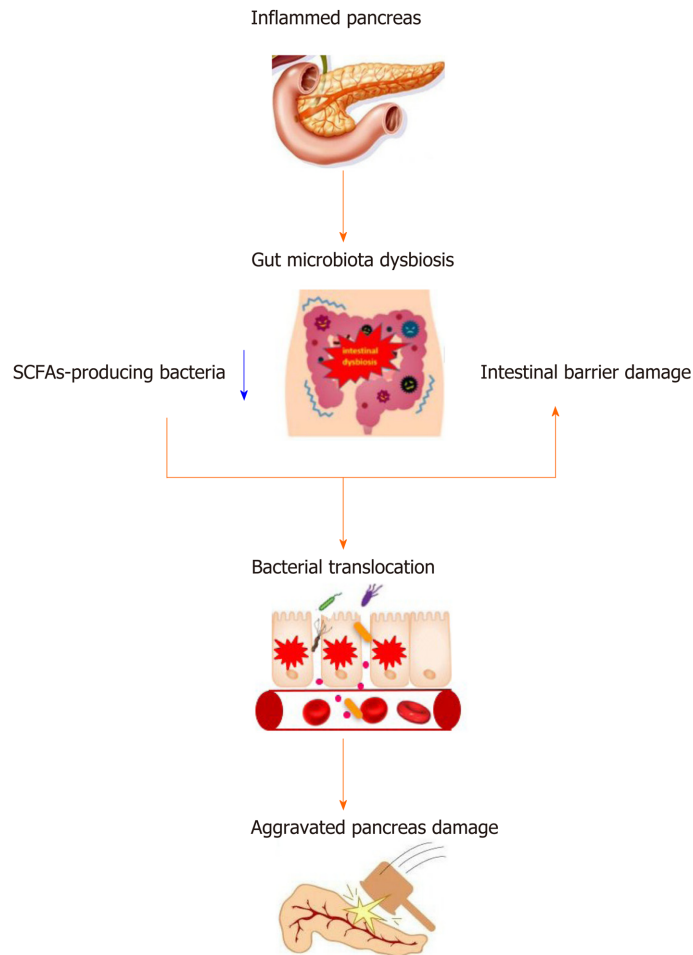
## POSSIBLE MECHANISM BY WHICH THE INTESTINAL FLORA AFFECTS THE INTESTINAL MUCOSAL BARRIER

In recent years, with a better understanding of intestinal microecology, studies have shown that not only the intestinal flora itself but also the metabolites of the intestinal flora participate in the regulation of body activities and metabolism. The metabolites of the intestinal flora consist mainly of SCFAs, indole derivatives, polyamines, organic acids, and vitamins. SCFAs are the most common metabolites of the gut microbiota. They include mainly acetate, propionate and butyrate, while formate, valerate, caproate, *etc.*, are in the minority<sup>[35]</sup>. Acetate and propionate are produced mainly by *Firmicutes* and *Bacteroidetes*, which are the most prevalent bacteria, constituting 80% to 90% of the gut microbiota<sup>[24]</sup>. Acetate and propionate are produced mainly by *Bacteroidetes*, and *Firmicutes* are the primary contributors of butyrate<sup>[36]</sup>. Our previous study results showed that AP patients had intestinal flora imbalance and decreased SCFA content in the early stage of the disease, and the bacteria producing SCFAs and the SCFA contents in SAP patients were significantly reduced compared to those in MAP patients. With an understanding of SCFAs, it has been found that they can maintain intestinal mucosal barrier function.

SCFAs are the main energy source of intestinal epithelial cells (IECs), and SCFAs can promote the proliferation and differentiation of IECs, reduce cell apoptosis, and play an important role in maintaining the mechanical barrier of the intestinal mucosa<sup>[37]</sup>. Studies have also shown that SCFAs can promote intestinal epithelial tight junction protein synthesis, increase the protein expression of Zo-1 and Occludin, inhibit intestinal permeability, and enhance the intestinal mucosa mechanical barrier function<sup>[38]</sup>. Moreover, SCFAs can enhance the intestinal mucosal immune barrier. Antibacterial peptides are small molecular peptides with broad-spectrum antimicrobial activities that are produced by IECs. SCFAs can promote antibacterial peptide production, including lysozyme, defensin and mucin gene expression, and increase the secretion of AMPs to enhance the immunity of the intestinal mucosa<sup>[39]</sup>. In addition, studies have found that supplementing SCFAs can increase intestinal cross-epithelial resistance, reduce intestinal mucosal permeability, and strengthen the function of the intestinal chemical barrier<sup>[40]</sup>. SCFAs can also regulate the intestinal biological barrier. SCFAs can reduce the pH of the intestinal tract, which is conducive to the growth of probiotics, while inhibiting the growth and colonization of pathogenic bacteria, such as *Escherichia coli* and *Shigella*<sup>[41]</sup>. A study revealed that butyrate could ameliorate caerulein-induced AP and intestinal injury<sup>[42]</sup>. Therefore, SCFAs play an important role in the maintenance of intestinal mucosal barrier function. During AP, gut microbiota dysbiosis with the reduction of SCFAs and intestinal barrier damage further aggravates pancreas damage and promotes the progression of AP (Figure 1).

## REGULATION OF THE INTESTINAL FLORA MAY ALLEVIATE DAMAGE TO THE INTESTINAL MUCOSAL BARRIER DURING AP

Changes in the intestinal microbial community lead to alterations of intestinal barrier function, resulting in bacterial overgrowth and impaired immunity<sup>[43]</sup>. In 2002, a randomized double-blind controlled trial studied the efficacy of probiotic lactobacilli in the treatment of AP. The results showed that the incidence of infectious complications, such as infectious pancreatic necrosis and pancreatic abscess, was significantly lower in the probiotic treatment group than in the control group, suggesting that probiotics can improve the prognosis of AP to some extent<sup>[44]</sup>. Probiotics can enhance epithelial barrier function by dampening the proinflammatory cytokine and chemokine response, accelerating reconstitution, and altering commensal microbiota in the absence of a functional mucus barrier. However, a few years later, a study obtained the opposite result<sup>[45]</sup>. Patients who received probiotics had an increased risk of death<sup>[46]</sup>. Therefore, we need to assess the general situation of patients and then provide appropriate treatment. Lutgendorff *et al*<sup>[47]</sup> reported that probiotic pre-treatment beginning five days prior to the induction of AP diminished AP-induced intestinal barrier dysfunction and prevented oxidative stress *via* mechanisms involving mainly mucosal glutathione biosynthesis in rats. Faecal microbiota transplantation (FMT) is a method of reconstructing the normal intestinal flora and an important means of treating various diseases caused by intestinal flora disorders. During treatment, the functional flora from a faecal sample from a healthy donor is transplanted into the intestinal tract of patients, and the intestinal flora with



**Figure 1** The relationship between acute pancreatitis and gut microbiota. SCFAs: Short-chain fatty acids.

normal functions is reconstructed to treat intestinal and extraintestinal diseases. Li *et al*<sup>[48]</sup> used ceftriaxone sodium to alleviate intestinal mucosal barrier injury in mice and found that after FMT treatment, intestinal mucosal injury in mice was effectively alleviated, inflammatory cell infiltration was reduced, and the secretory IgA (SIgA, an important component of the intestinal immune barrier) concentration was increased, suggesting that FMT played a certain role in the treatment of intestinal mucosal barrier injury. Our results showed that in gut microbiota-depleted mice treated with normal mouse faeces, AP induction can further damage the intestinal mucosal barrier compared to that in untreated AP mice. In summary, regulation of the intestinal flora may alleviate damage to the intestinal mucosal barrier during AP.

## CONCLUSION

In summary, damage to the intestinal mucosal barrier can cause intestinal bacteria to migrate to the blood or other tissues and organs to accelerate the progression of and aggravate AP. Changes in the structure and quantity of the intestinal flora during AP are closely related to damage to the intestinal mucosal barrier, and regulating the intestinal flora to improve intestinal mucosal barrier injury may be an effective method for AP treatment. Although FMT has certain therapeutic effects on some intestinal diseases and parenteral diseases related to intestinal flora imbalance, there is a lack of basic research and clinical trials on AP, and its efficacy and safety need to be identified and confirmed to find an effective way to treat injury to the intestinal mucosal barrier during AP.

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