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Review

Alteration of gut microbiota in acute pancreatitis and associated therapeutic strategies

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ABSTRACT

Gut microbiome is considered as a crucial regulator of human health. Alteration of gut microbiome has been reported in acute pancreatitis (AP) and probably contributes to the severity of disease. Explore the precise role of gut microbiome in the pathogenesis of AP could offer new strategies to improve the clinical outcomes of AP. This review summarizes the role of gut microbiome in AP, lists possible mechanisms associated with it and offers an overview of current treatments based on gut microbiome.

1. Introduction

Acute pancreatitis (AP), an inflammatory pancreatic disease, is one of the most common digestive causes of hospital admission worldwide [1]. In recent years, the rate of hospitalization and associated cost of AP have increased in a significant way [2]. Gut homeostasis is disturbed during the pathogenesis of AP, which could lead to intestinal bacterial translocation and secondary infection [3]. Therefore, it is believed that maintaining intestinal homeostasis is essential for the treatment of pancreatitis.

Gut microbiome is an important part of intestinal ecosystem, which can protect the gut barrier and mediate the immune and metabolism of the host [4]. Multiple studies have discovered dysbiosis of intestinal microbiota during AP, which is defined as a reduction in gut microbial diversity with a shift in the balance between commensal and pathogenic microbiota [5]. The alteration of gut microbiota occurs early in AP and perhaps participates in the aggravation of the disease [6]. However, whether gut microbial dysbiosis is one of the causes of infectious complications in AP or merely a consequence of inflammation still needs further study. Gut microbiome is likely to be a potential target for the treatment of AP, as it's affected during the pathogenesis of the disease. Therapies focused on gut microbiome including probiotics, antibiotics and fecal microbiota transplantation have been studied extensively in recent years. In this review, we will describe current findings on the relationship between gut microbial dysbiosis and AP and potential therapeutic strategies based on gut microbiome.

2. Alteration of gut microbiome in AP

Multiple researches have shown that the diversity of gut microbiome and relative abundance of specific bacterial taxa changes during AP. A conspicuous reduction of gut bacterial diversity is observed in patients with severe AP (SAP) comparing with healthy controls [6]. In addition, Huang et al. found lower microbiota diversity in hypertriglyceridemia-related acute necrotic pancreatitis (ANP) rats than that in normal-lipid ANP rats [7]. Meanwhile, during AP, an "AP-associated microbiota" replaces the host-specific microbiota [8]. At phylum level, fecal samples from patients with AP contains more *Proteobacteria* and *Bacteroidetes* and less *Actinobacteria* and *Firmicutes* comparing to healthy controls [9]. At genus level, alteration of gut microbiome characterized by decreased *Bifidobacterium* with increased *Enterobacteriaceae* and *Enterococcus* was detected in patients of AP, but the relative abundance of another important probiotic *Lactobacillus* seemed not affected [6]. Another research conducted by van den Berg et al. [10]

Abbreviations: AMP, antimicrobial peptide; ANP, acute necrotic pancreatitis; AP, acute pancreatitis; BT, bacterial translocation; EN, enteral nutrition; FMT, fecal microbiota transplantation; ICCs, interstitial cells of Cajal; IRI, ischemia-reperfusion injury; LPS, lipopolysaccharide; MAP, mild acute pancreatitis; MLN, mesenteric lymph nodes; MMC, migrating motor complex; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; SCFAs, short chain fatty acids; SIRS, systemic inflammatory response syndrome.

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found that there is an increase of *Escherichia/Shigella* and *Streptococcus* and a decrease of strains that produce butyrate in AP patients. Commensal bacteria such as *Prevotella_9*, *Faecalibacterium*, *Blautia* and *Lachnospiraceae* also reported to be reduced in patients with AP [11]. Experimental AP shows analogous results that at genus level in ANP rats, pathogens such as *Escherichia-Shigella* and *Phascolarctobacterium* increased, while probiotics such as *Candidatus_Saccharimonas*, *Prevotellaceae_UCG-001* and *Lachnospiraceae_UCG-001* decreased [12]. Table 1 summarizes both human and animal studies that explore the alteration of gut microbiome at phylum and genus level with 16S rRNA gene sequencing. To sum up, *Enterococcus*, *Escherichia/Shigella* and some unknown genus at family of *Enterobacteriaceae*, which were considered as pathogenic bacteria, were significantly increased in subjects with AP. Besides, several members in family of *Lachnospiraceae and Ruminococcaceae* were decreased, which were believed to produce SCFAs and have anti-inflammatory property.

In addition, the dominant species of gut microbiome differ in AP with different severity, suggesting the role of specific strains in different stages of AP. The preponderant strains in mild AP (MAP), moderately severe AP (MSAP) and SAP are *Bacteroides*, *Escherichis-Shigella*, and *Enterococcus* respectively [13]. There's no significant difference between the relative abundance of *Escherichis-Shigella* in patients with MAP and that in patients with SAP, but the relative abundance of *Streptococcus* is increased in SAP patients comparing with MAP patients [10]. Zhu et al. also found that *Acinetobacter*, *Stenotrophomonas* and *Geobacillus* increased and *Bacteroides*, *Alloprevotella*, *Blautia* and *Gemella* decreased in a significant way in SAP patients comparing with MAP and MSAP patients [11]. Therefore, detecting gut microbiome of the patients might be able to predict the prognosis of AP. But in consideration of interpersonal variations of gut microbiome, further studies are needed to confirm the effectiveness of this method.

3. Gut microbiota in progression of AP

3.1. Possible mechanisms of gut microbial dysbiosis in AP

Several mechanisms are involved in the gut microbial dysbiosis in AP:

(1) Intestinal dysmotility: Gastrointestinal dysmotility often exists in AP and plays a role in the progression of the disease [14]. Zhou et al. [15] stated that the occurrence of intestinal dysmotility in ANP is related to the dysfunction of interstitial cells of Cajal (ICCs) and myenteric neurons. Increasing duration of migrating motor complex (MMC) might then result in the overgrowth of duodenal Gram-negative and anaerobic microflora [16]. The dysmotility of gut could also lead to the accumulation of detrimental substances and inhibit the growth of probiotics.

(2) Ischemia-reperfusion injury (IRI): In AP, release of proinflammatory cytokines such as TNF-α could lead to IRI of gut mucosa and disturb the intestinal microcirculation [17]. One of the major causes of impaired intestinal microcirculation is the destruction of glycocalyx [18]. In an animal model, alteration of colonic microbiome occurs after intestinal IRI, which is characterized by the overgrowth of *Escherichia coli* and *Prevotella oralis* [19].

(3) Oxidative stress: Severe oxidative stress and activated caspase-3 pathway of intestinal have been found during AP [20]. Oxidative stress not only accelerates the malfunction of gut barrier, but involves in the dysbiosis of gut microbiome as well. An oxidative state might lead to the overgrowth of oxygen-tolerant bacteria of *Proteobacteria* and *Actinobacteria* phyla [21], while reduction of oxidative stress could restore gut microbiome to a normal state and diminish inflammation [22].

Table 1
Comparison of gut microbiome in healthy controls with subjects suffering from AP.

Authors	Reference	Type of sample	Subjects	Phylum[a]	Genus[a]
Tan et al.	[7]	feces	AP patients(n = 76) vs. healthy controls(n = 32)		*Enterobacteriaceae*↑ *Enterococcus* ↑ *Bifidobacterium* ↓
Zhang et al.	[10]	feces	AP patients(n = 45) vs. healthy controls(n = 44)	*Bacteroidetes*↑ *Proteobacteria*↑ *Firmicutes*↓ *Actinobacteria*↓	
van den Berg et al.	[11]	feces	AP patients(n = 35) vs. healthy controls(n = 15)	*Proteobacteria*↑	*Escherichia/Shigella*↑ *Streptococcus*↑ Butyrate producers↓
Zhu et al.	[12]	feces	AP patients(n = 130) vs. healthy controls(n = 35)	*Proteobacteria*↑ *Bacteroidetes* ↓	*Escherichia– Shigella* ↑ *Enterococcus* ↑ An unknown genus in family of *Enterobacteriaceae*↑ *Prevotella_9*↓ *Faecalibacterium*↓ *Blautia*↓ *Lachnospiraceae*↓ *Bifidobacterium*↓
Zhu et al.	[12]	cecum mucosa	AP mice(n = 10) vs. control group(n = 5)		*Escherichia–Shigella* ↑ *Enterococcus*↑ an unclassified member in *Enterococcaceae*↑ *Blautia*↓ members in *Lachnospiraceae and Ruminococcaceae*↓
Chen et al.	[13]	feces	ANP rats(n = 20) vs. sham-operated group(n = 20)	*Saccharibacteria*↓ *Tenericutes* ↓	*Escherichia-Shigella*↑ *Phascolarctobacterium*↑ *Candidatus_Saccharimonas*↓ *Prevotellaceae_UCG-001*↓ *Lachnospiraceae_UCG-001*↓ *Ruminiclostridium_5*↓ *Ruminococcaceae_UCG-008*↓

AP, acute pancreatitis; ANP, acute necrotic pancreatitis.
[a] The arrows indicate the alteration of gut microbiota in AP subjects compared with the healthy controls.

(4) Immune dysfunction: Intestinal immune suppression can be observed in the incipient stage of AP [23], which is related to impaired elimination of proliferative pathogenic bacteria.

3.2. Gut microbial dysbiosis participates in the pathogenesis of AP

Several studies have indicated that dysbiosis of gut microbiome takes part in the development of AP. Gut microbial dysbiosis can be observed at the early stage of AP, which suggests that it might be related to the incidence of secondary infection and organ failure. Tan et al. divided SAP patients into two groups according to their structure of gut microbiome and evaluated the clinical outcomes of these two groups. They found that SAP patients whose gut microbiome were similar to healthy controls exhibited shorter hospital stay and lower rate of infectious complications comparing with those with significantly different gut microbiome from healthy controls [6]. In animal models, comparing to untreated mice, those pretreated with broad-spectrum antibiotics and germ-free mice shows attenuated pancreatic injury after the induction of AP [11]. Van den Berg et al. also discovered that gram-negative gut depletion could decrease the mortality of ANP mice with western-type diet [10]. Therefore, gut microbial dysbiosis is related to the severity of AP and might participate in the pathogenesis of AP.

Damaged gut homeostasis is found in AP, which is characterized by necrosis of gut epithelial cells, thinning of mucus layer, destruction of tight junctions, dysbiosis of gut microbiome and dysfunction of intestinal immune [3,24,25]. With increased gut permeability, intestinal microbiota could pass through the impaired gut barrier defined as bacterial translocation (BT), which would aggravate systemic inflammation and cause secondary infection (Fig. 1). Gut microbial dysbiosis might participate in the disruption of gut homeostasis in AP, but little has been known about its precise role in this process so far. Zhu et al. confirmed that the relative abundance of *Escherichis-Shigella* in gut is positively correlated with the level of pro-inflammatory cytokines in serum such as IL-6 and seems to be associated with the increased gut permeability in AP [11]. Zheng et al. further discovered that commensal *Escherichia coli MG1655* aggravates intestinal epithelial injury through TLR4/MyD88/p38 MAPK signaling [26]. In addition, the alteration of gut microbiome can aggrandize the host's susceptibility to both endogenous and exogenous pathogens in the process of gut-derived infection [27]. Gut microbial dysbiosis also contributes to the recruitment and expansion of intestinal inflammatory cells and accelerate the release of pro-inflammatory cytokines [24]. Li et al. found that gut microbiota could influence the severity of AP by interacting with inflammasome NLRP3 in a mice model [28]. Further researched are needed to define the exact relationship between gut microbial dysbiosis and AP, which might provide new therapeutic strategies to improve the clinical outcomes of AP.

Bacterial translocation from gut is considered to be one of the major causes of pancreatic infection and subsequently sepsis in SAP [29]. By bacterial culture method, gut-origin microflora can not only be detected in peripheral blood, but mesenteric lymph nodes (MLN) and distal organs such as liver, spleen and lung as well [30]. In recent years, BT in AP patients have been detected by 16 s rDNA sequencing. Comparing with healthy controls, the blood samples of SAP patients contain more *Bacteroidetes* and *Firmicutes* and less *Actinobacteria* [31]. In addition, Li et al. found that opportunistic pathogens originated from gut are the main composition of translocated bacteria, which is consisted of *Escherichia coli*, *Shigella flexneri*, *Enterobacteriaceae bacterium*, *Acinetobacter lwoffii*, *Bacillus coagulans*, and *Enterococcus faecium* [32]. These results are consistent with the alteration of gut microbiome in AP mentioned above. The possible routes of BT in AP might be hematogenous dissemination, transperitoneal spread, ascites, transmural translocation and reflux into the pancreatic duct [33].

3.3. Alteration of gut bacterial metabolites during AP

Change of the gut microbial composition leads to metabolite alterations that might also have a crucial role in the pathogenesis of AP. For the last few years, the most widely studied metabolite involved in AP is short chain fatty acids (SCFAs), production of probiotics through fermenting dietary fiber. Among SCFAs, acetic, propionic and butyric acids are most abundant. SCFAs are important mediators in maintaining the intestinal homeostasis, including gut barrier protection, intestinal immune regulation and gut microbial modulation [34].

In AP, the major alteration of microbiota at phylum level is increasing *Proteobacteria* with decreasing SCFAs-producing strains [10], thus intestinal SCFAs are significantly reduced, resulting in the interruption of gut homeostasis. Yu et al. also discovered that *Eubacterium hallii*, one of the major butyrate-producing bacteria, was the most decreased strain in both MASP and SAP patients [13]. The inhibition towards the growth of bacteria that produce butyrate might be resulted from increased oxidative stress in AP, since the main butyrate-producing bacteria are anaerobic. Decreased butyrate in the intestine could further lead to reduced intracellular butyrate/PPARγ signaling and *Enterobacteriaceae* overgrowth [35]. Supplement of SCFAs has been confirmed effective in attenuating AP. Pan et al. found that the pancreatic injury was relieved by butyrate, which is related to the elimination of pro-inflammatory factors and the inhibition of NLRP3 inflammasome [36]. In addition, butyrate can ameliorate pancreatitis through suppressing NF-κB activation and HMGB1 expression [37]. Thus, SCFAs supplement might be a potential therapy to improve gut homeostasis and decrease the incidence of infectious complications in AP.

4. Microbiota-based treatment of AP

Several methods have been adopted to modulate gut microbiota for

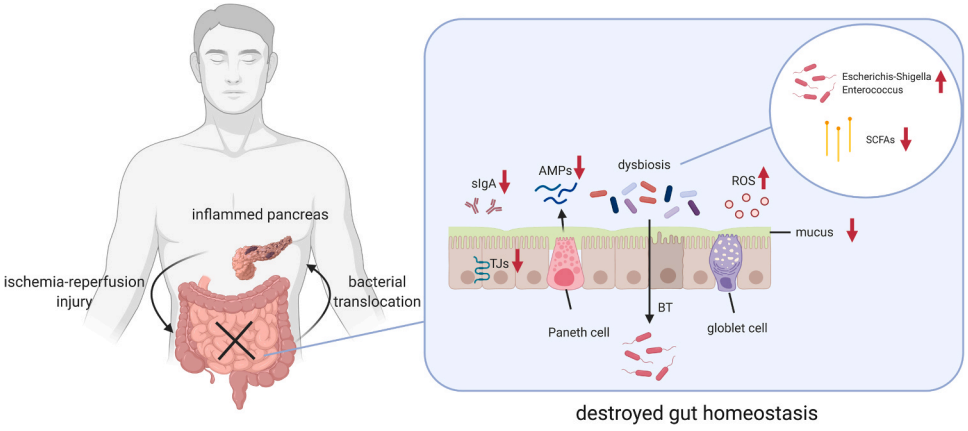

Fig. 1. Gut microbial dysbiosis during the development of AP. Dysbiosis of gut microbiota during AP destroys gut homeostasis and further worsens the disease. Gut microbial dysbiosis and the reduction of SCFAs are associated with damaged intestinal epithelium, increased gut permeability and the imbalance of intestinal immune system. They're also responsible for the expansion of inflammatory cells and aggravating bacterial translocation in AP. AP acute pancreatitis, BT bacterial translocation, ROS reactive oxygen species, SCFAs short chain fatty acids, sIgA secretory immunoglobulin A.

therapeutic benefit in AP. Microbiota-based treatment mainly focus on replenishing anti-inflammatory bacteria and their metabolites, removing pathogenic bacteria or resetting the entire microbiome (Fig. 2). Besides, several strategies could protect the gut barrier and indirectly modulate gut microbiota or its metabolites, which are also potential therapies for alleviating bacterial translocation and inflammation during AP.

4.1. Probiotics

Probiotics is defined as "live microorganisms that confer a health benefit when consumed in adequate amounts", suggested by the Food and Agriculture Organization/World Health Organization in 2002 [38]. Probiotics are considered to contribute to human health in following four patterns: (1) Specific strains such as *Lactobacilli* and *Bifidobacterial* function as microbial barrier that directly exclude or inhibit pathogens [39]. (2) Probiotics can enhance the gut barrier via multiple pathways which involve in inducing the production of mucus [40] and AMP [41], enhancing the tight junctions [42] and attenuating apoptosis of epithelial cells [43]. (3) Probiotics can modulate the immune system both locally and systemically [44]. (4) Probiotics are able to affect gut motility probably through increasing production of SCFAs and interacting with enteric nervous system [45].

Although probiotics have various benefits mentioned above, results to date have still been controversial in patients with AP. A number of researches have indicated positive effect of probiotics on AP. The earlier studies usually used a mixture of 6 probiotics, including *Lactobacillus acidophilus* (W70), *Lactobacillus casei* (W56), *Lactobacillus salivarius* (W24), *Lactococcus lactis* (W58), *Bifidobacterium bifidum* (W23) and *Bifidobacterium lactis* (W52), with a dose of 5.0×10^9 CFU per day. Lutgendorff et al. found that probiotics can increase the biosynthesis of glutathione and reduce oxidative stress both in pancreas [46] and ileum [47] in experimental AP. In addition, there is evidence showing that probiotics are effective in modulating gut microbiome, preserving intestinal epithelial barrier and cutting down the rate of bacterial translocation [48], which contribute to a reduction in the incidence of infectious complications in AP rats. Rychter et al. [49] found that prophylactic treatment with multispecies probiotics for 2 days rather than treatment after the induction of AP abolished intestinal barrier dysfunction in the late period of AP. Moreover, after pretreating AP rats with this mixture of probiotics, Gerritsen et al. [8] found increased relative abundance of a novel strain mostly correlated with *Clostridium lituseburense*, the relative abundance of which is positively related to declined overgrowth of gut bacteria. Hooijmans et al. [50] conducted a meta-analysis in 2012, analyzing 13 studies with various types and doses of probiotics, timing of probiotic supplementation and duration of intervention and illustrating that probiotic supplementation attenuated the pancreatic injury and bacterial translocation in preclinical animal studies of AP. Another meta-analysis conducted in 2018 also demonstrated a significant decline in the duration of hospital stay after treatment with probiotics in Chinese patients with SAP [51]. However, some researches exhibit opposite results. The PROPATRIA (Probiotics in Pancreatitis Trial) study conducted by Besselink et al. showed that after treating AP patients with the mixture of 6 probiotics mentioned above plus cornstarch and maltodextrins for 28 days with a total daily dose of 10^{10} bacteria, the incidence of infective complications didn't reduce and that the risk of mortality increased unexpectedly [52]. They also found that probiotics treatment within the first possible onset of AP seems to increase the rate of bacterial translocation in AP patients with organ failure [53]. Besides, Sharma et al. stated that no significant effect of probiotics on gut permeability and endotoxemia was found after 7 days of probiotic mixture intervention in patients with AP [54]. Several factors should be taken into account to explain opposite therapeutic effects of probiotics on AP, including timing to start the treatment, course of the therapy, species and dose of probiotics and individual differences. Hence whether applying probiotics as a routine therapy in AP still need further investigation.

4.2. Antibiotics

Pathogenic microbiome from the gut plays a central role in driving local and systemic inflammation during AP. However, most studies don't support prophylactic application of antibiotics in patients with SAP so far. The meta-analysis carried out by Wittau et al. [55] suggested that antibiotics prophylaxis was not related to a significant reduction in mortality, the rate of infectious complications and surgical interventions. Soares et al. found that the translocation of multidrug-resistant (MDR) strains caused by the abuse of broad-spectrum antibiotics increased the fatality rate of mice with AP [56]. Therefore, American Gastroenterological Association (AGA) suggested against the use of prophylactic antibiotics in patients with SAP and ANP [57]. However, it's worth noting that according to Jia et al. [58], the combination usage of vancomycin, neomycin and polymyxin b could attenuate the severity of experimental AP, suggesting that certain antibiotics might still be an effective therapy for AP. Besides, selective decontamination of digestive tract (SDD) can decrease the incidence of infectious complications and mortality rate in both animal models and patients with SAP [10,59].

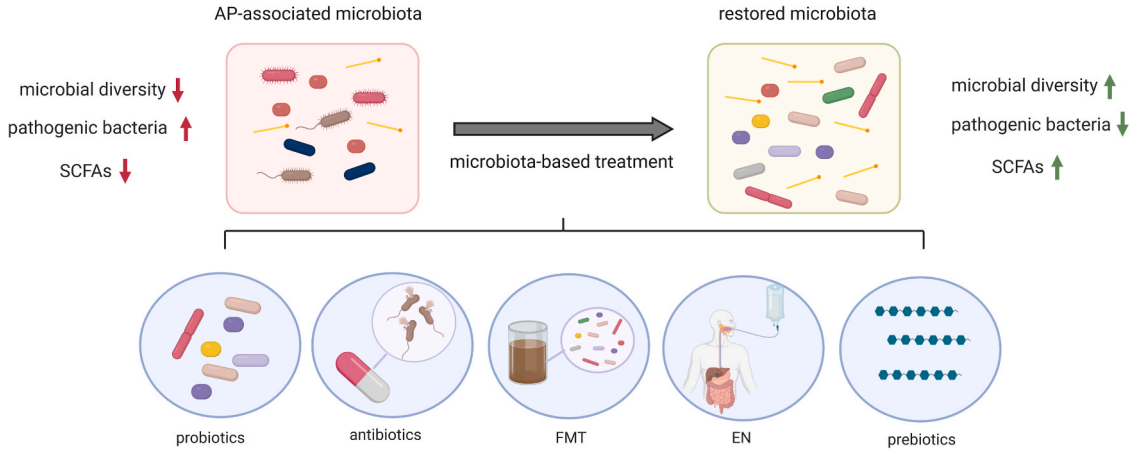

Fig. 2. Microbiome-based treatments for AP. Restoring the balance of intestinal microbiome could reduce gut inflammation and preserve the gut barrier. Current therapies based on gut microbiome is aimed at replenishing anti-inflammatory bacteria (probiotics, FMT), eliminating pathogenic bacteria (antibiotics) or indirectly modulating gut microbiota and its metabolites (EN, prebiotics). AP acute pancreatitis, SCFAs short chain fatty acids, FMT fecal microbiota transplantation, EN enteral nutrition.

4.3. Fecal microbiota transplantation (FMT)

FMT is a procedure when feces of healthy donors is implanted into patients' intestine [60]. FMT is aimed at restoring the disturbed microbiota and curing the disorders [61]. It has already been recommended as a treatment for recurrent *Clostridium difficile* infection [62]. Besides, some clinical trials have shown FMT to be effective in other conditions correlated with gut microbial dysbiosis, such as ulcerative colitis [63], irritable bowel syndrome [64] and hepatic encephalopathy [65]. However, current studies of experimental AP didn't show positive effect of FMT. Zhu et al. [11] found that FMT led to more significant pancreatic damage and aggravated AP. Van den Berg et al. [10] also discovered increasing mortality and bacterial translocation rate after treated with FMT in mice with AP. Therefore, the exact role of FMT in AP still need further research.

4.4. Therapies altering gut microbiome indirectly

Enteral nutrition (EN) is recommended to adopted in patients with AP. Early application of EN has a positive effect on preventing gut barrier damage and reduce the rate of bacterial translocation [66], which contributes to a decreased rate of infectious complications and shortens the duration of hospital stay [67]. Zou et al. [30] observed that enteral immunonutrition (EN combined with glutamine, arginine, and probiotics) is more effective on maintaining gut barrier in pigs with SAP. Besides, Jin et al. [68] found that early EN supplemented with *Bifidobacterium* can decrease bacterial translocation and relieve inflammation, therefore reducing the recovery time of patients with AP.

Prebiotics are undigestible ingredients that stimulate the proliferation of probiotics and promote health of the hosts. Prebiotics are effective management for patients with AP that are able to preserve gut barrier, modulate gut microbiome and alleviate bacterial translocation. For instance, inulin is capable of modulating gut immune and maintaining gut barrier integrity in experimental AP [69]. Hydroxyethyl starch can relieve microcirculation disturbance in SAP, thus improving gut barrier function and lowering the rate of infection [70]. Chitosan oligosaccharides could attenuate AP partly through modulating gut microbial community and restoring gut homeostasis in a mice model [71]. EN combined with prebiotic fibers can improve the outcomes for AP patients compared with routine EN [72]. In addition, compared with prebiotics alone, synbiotics (combination of probiotics and prebiotics) show reducing incidence of organ failure in SAP [73].

Strategies involving in specific signaling pathways have also been taken into account to improve gut microbiome and reduce BT during AP. Infliximab, an anti-TNF-α monoclonal antibody exhibits positive effects on bacterial translocation in experimental necrotizing pancreatitis [74]. Poly (ADP-ribose) polymerase inhibition by hyperbaric oxygen (HBO) and 3-aminobenzamide (3-AB) cotreatment is also capable of attenuating BT and inflammation in experimental SAP [75]. Inhibition of P38 mitogen-activated protein kinase (MAPK) signaling pathway is able to significantly increase the richness and diversity of gut microbiome in rats with SAP [76]. Production of specific probiotics might also be a considerable way to treat AP. Pretreatment of bacillopeptidase CFR5 from Bacillus subtilis CFR5 can relieve inflammation of the intestine during cerulein-induced pancreatitis [77].

In conclusion, treatments mentioned above are capable of preserving gut barrier and modulating gut microbiota in an indirect way, ultimately resulting in a decline in BT during AP. The precise effect of these therapies on gut microbiota can be further studied to better guide the treatment.

4.5. Potential treatments

Several novel approaches to modulate human commensal microbiota have been studied in recent years. For example, Nurminen et al. [78] found an increased α-diversity of fecal microbiota in study subjects after two-week exposure to nature-derived microbiota, which could be further developed for testing their efficacy in the treatment and prevention of immune-mediated diseases. Roslund et al. [79] discovered that intervention of environmental biodiversity could modify the gut microbial community, suggesting that biodiversity intervention may be a promising approach to reduce the risk of immune-mediated diseases in urban societies. Although these strategies have not been studied in the context of AP yet, they could be considered as potential treatments for AP patients to reshape gut microbial community.

5. Conclusions

Gut microbiome plays an important part in AP. Declined diversity of gut microbiome has been reported and is related to the progress of AP. Gut microbial dysbiosis might not be the initial cause of AP, but develop as the disease progresses and contribute to the deterioration of AP. Imbalance of intestinal flora is responsible for further destruction of gut homeostasis and aggravates inflammatory response during AP. Another factor participating in AP is the change of SCFAs produced by gut microbiota. However, the link between AP and gut microbial dysbiosis is not fully understood and need further elucidation. In order to better comprehend the relationship between gut microbiome and AP and its mechanism, additional information is needed from future studies. Future researches might focus on seeking specific strains crucial to AP or other metabolites involved in AP.

As a participant in the pathogenesis of AP, gut microbiome is a potential target for treatment. According to studies to date, the therapeutic effect of treatment based on gut microbiome has not been clear yet. Therefore, large-scale and multiple-center trials are required to further explore the best therapeutic plan of probiotics, prebiotics or FMT for AP.

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CRediT authorship contribution statement

Ying Zhu: Writing - original draft. **Qixiang Mei**: Writing - review & editing. **Yang Fu**: Data curation **Yue Zeng**: Writing - review & editing, Conceptualization, Funding acquisition.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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