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The role of gut microbiota in acute pancreatitis: new perspectives in pathogenesis and therapeutic approaches

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Abstract

Acute pancreatitis (AP) is one of the most common acute abdomen diseases with increasing incidence and substantial healthcare burden. Gut microbiota disturbance, mucosal barrier failure, and bacterial translocation are identified as the dominant cause of infected pancreatic necrosis and high mortality. With the advance of high-throughput sequencing, imbalance between beneficial and facultative pathogenic microorganisms with their metabolic activities in the development of AP has been increasingly recognized, whereas it remains unclear whether dysbacteriosis is the dominant cause of aggravating AP, or merely reflecting different epidemiological or environmental factors at the individual level. This review discussed the alterations of the gut microbiota and their metabolites during AP with detailed molecular mechanisms. Importantly, it highlights microbiome-based medical therapies which influence gut barrier function and immune homeostasis to mitigate inflammatory responses in AP. Our review will provide a novel roadmap of gastrointestinal microecology in AP progression, and contribute to the future development of microbiome-based diagnostic and therapeutic strategies in clinical practice.

Keywords: Acute pancreatitis, Immunity, Metabolites, Microbiome-based therapeutics, Microbiota

Introduction

Acute pancreatitis (AP) is a prevalent acute abdominal disease with fluctuating courses that are difficult to predict in its initial development, and about 20% to 30% of patients will progress to moderate or severe acute necrotizing pancreatitis (ANP) with considerable morbidity,[1] which is mostly attributed to systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) in the early stages and infectious complications in particular infected pancreatic necrosis (IPN) in the later stage. Emerging evidence indicated that infectious complications in AP patients involve a series of events starting with the disturbances of gut microbiota, immune homeostasis disorder, mucosal barrier failure, and pro-inflammatory responses resulting in the translocation of intestinal bacteria, such as *Escherichia coli* and *Enterococcus faecalis*.[2] Therefore, restoring the balance of gut microbiota may represent a potentially effective therapeutic strategy for the treatment of AP.

In recent years, human microbiota as the second genome has emerged as an important frontier in understanding pancreatic diseases.[3] The largest microbial community is found in the human gastrointestinal tract, which is inhabited by over 100 trillion (10^{14}) microorganisms.[4] The intimate interaction of intestinal microbiota with pancreas adds the complexity and diversity of the mechanisms involved in the inflammatory reaction of AP. On the one hand, the pancreas affects the composition of the gut microbiome through both its exocrine function via pancreatic duct[5] and endocrine cells, such as antimicrobial peptides secreted by β-cells.[6] On the other hand, gut flora and their metabolites could migrate into the pancreas and influence the inflammatory microenvironment of AP.[7] Recent studies have demonstrated the shift in the proportion of commensal and pathogenic microbiota during pancreatitis,[8] however, it is still uncertain whether the change of gut microbiota is a driving force in AP, or merely a collateral response to inflammatory states. Meanwhile, intestinal microbiota-associated metabolites such as short chain fatty acids (SCFAs)[9] and nicotinamide mononucleotide (NMN)[10] present the promising avenue for drug or dietary intervention tactics in AP treatment.[11] In this review, we will provide an overview of recent progress in comprehending the correlation between gut microbiota and the pathogenesis of AP, and speculate potential therapeutic strategies (Fig. 1). Our review indicates that while the prospects of this field are promising, it is still in the early stages of investigation.

Database search strategy

We conducted a systematic literature search through the PubMed, EMBASE and Google Scholar for English articles, China national knowledge infrastructure and Wanfang database

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Zu-Chao Du and Guan-Qun Li contributed equally to the writing of the manuscript.

Xue-Wei Bai and Bei Sun jointly supervised and mentored this work.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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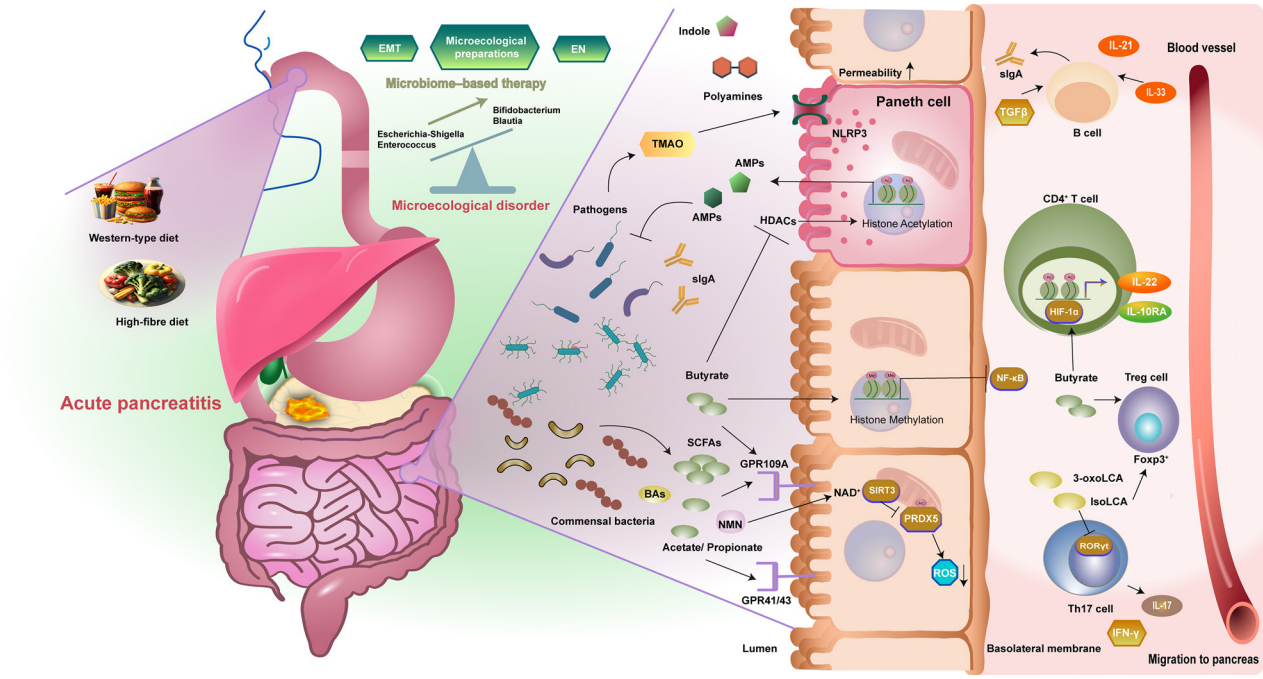

Figure 1. Interactions between microecological disorders and the development of acute pancreatitis. Multiple studies have implicated microbiota-derived metabolites modulate intestinal immune homeostasis and barrier function. This figure presents the key metabolic product in acute pancreatitis and microbiome-based treatments for restoring intestinal microecological balance. AMPs = antimicrobial peptides, BAs = bile acids, EN = enteral nutrition, FMT = fecal microbiota transplant, NMN = nicotinamide mononucleotide, ROS = reactive oxygen species, SCFAs = short chain fatty acids, TMAO = trimethylamine *N*-oxide.

for Chinese articles. The database search of papers published in English and Chinese between January 1990 and March 2023 was performed by selecting following key words: gut microbiota, acute pancreatitis, microbial dysbiosis, metabolites, microbiome-based therapy. All relevant guidelines, original articles, reviews, and meta-analysis were included.

Microbial dysbiosis in the pathogenesis of AP

The altered structure of microbial community during AP

Multiple studies have demonstrated changes in the abundance and diversity of gut microbiota during different stages of AP. Patients with early AP frequently exhibit intestinal flora disorders, which might exacerbate the impairment of the intestinal barrier typically occurring within 1 to 2 weeks of AP onset, allowing the translocation of intestinal flora and endotoxins into the blood. This, in turn, could lead to gut-derived infections and enhanced systemic inflammatory responses.[12] A prospective controlled study showed that circulating bacterial DNA representative of intestinal flora was detected in the peripheral blood from 68.8% of AP patients, and more than half of the patients encountered polymicrobial flora.[13]

Recent advances in high-throughput sequencing have facilitated whole genome sequencing available as a routine tool for the investigation of cross talk and bidirectional modulation between gut microbiota and pancreas during the progression of AP in unprecedented detail, as presented in Table 1. Tan et al[14] found reduced diversity of fecal microbiota in AP patients using polymerase chain reaction-denaturing gradient gel electrophoresis (PCR-DGGE) technique, indicating that dysbiosis of gut flora with increased potential pathogenic bacteria (eg, Enterobacteriaceae and *Enterococcus*) and reduced beneficial bacteria (eg, *Bifidobacterium*) might occur before SIRS, which was positively correlated with serum pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α.[14] Zhu et al identified the disordered gut microbiota in AP patients including the elevated levels of *Escherichia–Shigella* and the decrease in *Blautia* through 16S rRNA gene sequencing, reflecting the depletion of SCFA-producing bacteria.[12] Another research using shotgun metagenomic sequencing found the increased taxa of *Streptococcus*, *Escherichia coli*, and *Enterococcus* may play important roles in the inflammatory process of AP.[20]

During AP, the replacement of host-specific microbiota by opportunistic pathogens was found to correlate with the disease severity. Yu et al[19] found that *Bacteroides*, *Escherichia-Shigella*, and *Enterococcus* were the dominant microbial species in rectal swab samples of patients with mild AP, moderately severe AP, and severe AP, respectively, suggesting the potential role of disturbed microbiota in the progression of AP. In an animal experiment, Liu et al compared the compositional and functional changes of gut microbiota during different stages of AP, which revealed that Firmicutes/Bacteroidetes (F/B) ratios were significantly higher in severe AP group while lower in the mild AP group compared with control group at 72 hours after AP induction.[22] Zhu et al demonstrated that compared to mild and moderately severe AP, some specific microbiota of severe AP including *Acinetobacter, Geobacillus*, and *Stenotrophomonas* exhibited positive correlation with inflammatory cytokines (eg, TNF-α and IL-1β) as well as gut barrier injury indexes (eg, D-lactate and diamine oxidase).[12] Chen et al examined the classification of microbial community in ANP rat model and found the relative higher abundance of *Escherichia–Shigella* and *Phascolarctobacterium* in fecal samples from ANP group compared with the control group, and reductions in Paneth cell-derived antimicrobial peptides due to intestinal flora disorder may contribute to the development of intestinal barrier dysfunction in ANP.[15] Moreover, another study showed *Enterococcus faecium* and *Finegoldia magna* could be considered as potential biomarkers for predicting IPN on admission.[26]

The most common causes of AP include gallstones, alcohol abuse, and hypertriglyceridemia, among which hypertriglyceridemia-associated acute pancreatitis (HTGP) was often accompanied with the malfunction of Paneth cells and dysbiosis of intestinal microbiota structure in rat models.[24] Hu et al demonstrated that HTGP was associated with a higher abundance of

Table 1

Summary of major microbiota alteration involving the process of acute pancreatitis

Authors (year)	Study population	Specimen	Subjects	Microbial evaluation	Microbiota at phylum level	Genus or species level	Ref.
Li et al (2013)	Human	Peripheral blood	MAP vs SAP	PCR-DGGE	NA	↑ *Escherichia coli* ↑ *Enterococcus faecium* ↑ *Bacillus coagulans*	[13]
Tan et al (2015)	Human	Feces	AP vs HC	PCR-DGGE	NA	↑ *Enterobacteriaceae* ↑ *Enterococcus* ↓ *Bifidobacterium*	[14]
Chen et al (2017)	Rat	Feces	ANP vs Sham	16s rRNA gene amplicon sequencing	↓ *Saccharibacteria* ↓ *Tenericutes*	↑ *Escherichia–Shigella* ↑ *Phascolarctobacterium* ↓ *Candidatus_ Saccharimonas* ↓ *Lachnospiraceae* ↓ *Ruminiclostridium* ↓ *Prevotellaceae*	[15]
Zhang et al (2018)	Human	Feces	AP vs HC	16s rRNA gene amplicon sequencing	↑ *Bacteroidetes* ↑ *Proteobacteria* ↓ *Firmicutes* ↓ *Actinobacteria*	NA	[16]
Li et al (2018)	Human	Peripheral blood	SAP vs HC	16s rRNA gene amplicon sequencing	↑ *Bacteroidetes* ↑ *Firmicutes* ↓ *Actinobacteria*	↑ *Bacteroides* ↑ *Stenotrophomonas* ↑ *Serratia* ↑ *Rhizobium* ↑ *Prevotella* ↑ *Paracoccus* ↑ *Prevotellaceae* ↓ *Acinetobacter* ↓ *Lactococcus* ↓ *Dietzia,* ↓ *Flavobacterium* ↓ *Pseudomonas* ↓ *Corynebacterium* ↓ *Sphingobium* ↓ *Brevundimonas*	[17]
Zhu et al (2019)	Human	Feces	AP vs HC	16s rRNA gene amplicon sequencing	↑ *Proteobacteria* ↓ *Bacteroidetes*	↑ *Escherichia–Shigella* ↑ *Enterococcus* ↑ *Enterobacteriaceae* ↓ *Prevotella_9* ↓ *Faecalibacterium* ↓ *Blautia* ↓ *Lachnospiraceae* ↓ *Bifidobacterium*	[12]
Tao et al (2019)	Rat	Feces and gut tissue	AP vs Sham	16s rRNA gene amplicon sequencing	↑ *Fusobacteria* ↑ *Proteobacteria* ↓ *Tenericutes* ↓ *Bacteroidetes*	↑ *Lactobacillus* ↑ *Gemella* ↑ *Bacteroides*	[18]
Yu et al (2020)	Human	Rectal swab	MAP vs MSAP vs SAP vs HC	16s rRNA gene amplicon sequencing	NA	MAP: ↑ *Bacteroides* ↑ *Finegoldia* ↓ *Eubacterium hallii* ↓ *Blautia* MSAP: ↑ *Escherichia-Shigella* ↑ *Anaerococcus* ↑ *Finegoldia* ↓ *Eubacterium hallii* SAP: ↑ *Enterococcus* ↑ *Escherichia-Shigella* ↓ *Eubacterium hallii*	[19]
Yu et al (2021)	Human	Feces	MAP vs MSAP vs SAP vs HC	Shotgun metagenomic sequencing	↑ *Crenarchaeota* (Thermoprotei class)	MAP: ↑ *Streptococcus* ↓ *Anaerostipes* MSAP: ↑ *Sulfolobus* ↑ *Escherichia* ↓ *Anaerostipes hadrus* SAP: ↑ *Enterococcus* ↓ *Blautia*	[20]

(Continued)

Table 1

(Continued)

Authors (year)	Study population	Specimen	Subjects	Microbial evaluation	Microbiota at phylum level	Genus or species level	Ref.
Van den Berg et al (2021)	Humans	Feces	AP vs HC	16s rRNA gene amplicon sequencing	↑ *Proteobacteria*	↑ *Escherichia–Shigella* ↓ Streptococcus	[9]
Van den Berg et al (2021)	Mice	Pancreas and intestinal tissue	ANP vs Sham	16s rRNA gene amplicon sequencing	↑ *Verrucomicrobia* ↑ *Firmicutes*	↑ *Akkermansia muciniphila* ↑ *Escherichia–Shigella* ↑ Erysipelotrichaeceae ↓ Lachnospiraceae ↓ Rumminococcaceae	[2]
Jin et al (2022)	Mice	Feces	SAP vs Sham	16s rRNA gene amplicon sequencing	↑ *Proteobacteria* ↓ *Firmicutes*	↑ *Prevotellaceae* ↑ *Epsilonproteobacteria* ↓ *Clostrdium*	[21]
Liu et al (2022)	Rat	Feces	MAP vs SAP vs Sham	16s rRNA gene amplicon sequencing	MAP: ↑ *Bacteroidetes* ↓ F/B ratio SAP: ↓ *Bacteroidetes* ↑ F/B ratio	↑ *Romboutsia* ↑ Allobaculum ↑*Clostridium_sensu_ stricto 1* ↓ *Lactobacillus* ↓ *Bifidobacterium*	[22]
Glaubitz et al (2023)	Mice	Duodenal aspirates and feces	AP vs Sham	16s rRNA gene amplicon sequencing	NA	↑ *Escherichia–Shigella* ↑ *Enterobacteriaceae diversa* ↑ *Enterococcus* ↑ *Staphylococcus*	[23]
Huang et al (2017)	Rat	Feces	HTG-Related ANP vs Sham	16s rRNA gene amplicon sequencing	↑ *Actinobacteria* ↓ *Tenericutes* ↓ *Candidatus_ Saccaribacteria*	↑ *Allobaculum* ↑ *Parasutterella* ↓ *Anaerotruncus* ↓ *Alloprevotella* ↓ *Ruminiclostridium_5*	[24]
Hu et al (2021)	Human	Feces	HTG-Related AP vs AP with non-HTG etiology	16s rRNA gene amplicon sequencing	↑ *Firmicutes* ↓ *Lachnospiraceae* ↓ *Bacteroidaceae*	↑ *Finegoldia* ↑ *Enterococcus* ↑ *Escherichia-Shigella* ↓ *Bacteroides ovatus* ↓ *Blautia wexlerae* ↓ *Dorea longicatena*	[25]

↑ = increased levels, ↓ = reduced levels, ANP = acute necrotic pancreatitis, AP = acute pancreatitis, F/B = Firmicutes/Bacteroidetes ratio, HC = healthy controls, HTG = hypertriglyceridemia, MAP = mild acute pancreatitis, MSAP = moderately severe acute pancreatitis, NA = not available, PCR-DGGE = polymerase chain reaction-denaturing gradient gel electrophoresis, SAP = severe acute pancreatitis.

Finegoldia, *Enterococcus*, *Peptoniphilus*, and *Anaerococcus*, and lower abundance of *Akkermansia* and *Lachnospiraceae* as compared to the non-HTGP group.[25] Considering the underlying effect of hyperglycemia on the balance of intestinal flora, modifying blood lipid level might contribute to restoring the secretory function of Paneth cells and alleviate microbiota disorders in HTGP patients.[24] Recent studies have also revealed the complex interaction between alcohol and intestinal microbiota in AP patients. Gut bacteria metabolize ethanol to acetaldehyde, which may disrupt epithelial junctions and increase intestinal permeability, to promote the translocation of pathogens and endotoxins into the bloodstream.[27] Vonlaufen et al reported that endotoxin-induced activation of TLR4 plays a primary role in the pancreatic injury of alcohol-fed rat models,[28] indicating modulation of the intestinal microbiota and endotoxin levels as potential targets for alcoholic pancreatitis. Thus, understanding the causal mechanism of microbial disturbance in AP will pave the way towards the improvement of therapeutics.

Mechanisms of gut microbiota dysbiosis in AP progression

Increasing evidence indicated that healthy gut microbial ecosystem plays an important protective role in preventing exogenous pathogen infections, maintaining mucosal barrier and immune homeostasis, while intestinal microecological disorder might promote the progression of AP through multiple mechanisms.[9] Research by Li et al demonstrated the depletion of gut microbiota in germ-free or antibiotic-treated mice could mitigate pancreatic injury and suppress the systemic inflammatory response, and fecal microbiota transplantation (FMT) has been shown to reverse this process.[29] These results support the hypothesis that "gut-pancreas" axis determines the onset and progression of AP.

The potential mechanisms underlying microbial disturbance in AP include reduced zymogen secretion, mitochondrial dysfunction, increased oxidative stress, imbalance of immunological homeostasis,[14] intestinal microcirculation and barrier disturbance.[21] During AP, reduced zymogen secretion may induce imbalances in gut microbiota, and excessive production of reactive oxygen species (ROS) by disrupted acinar cells and infiltrating immune cells could exacerbate the impairment of intestinal barrier and microbial dysbiosis, such as overgrowth of *Proteobacteria* and *Actinobacteria* phyla, through TLR4/NF-κB signaling pathways.[30] In turn, several gut bacterial metabolites including hydrogen sulfide, indole-3-acetic acid, and lipopolysaccharides may contribute to mitochondrial dysfunction and ROS production, whereas beneficial microbiota-derived NMN could reduce mitochondrial oxidative injury via promoting the activation of mitochondrial deacetylase SIRT3.[10] Therefore, regulating microbial metabolites may represent a promising strategy to protect AP-mediated oxidative damage.

In the early stage of AP, hypovolemia and subsequent massive fluid resuscitation may cause intestinal ischemia-reperfusion (I/R) injury, leading to intestinal barrier impairment and increased gut permeability.[31] Paneth cells located at bottom of

the crypts of Lieberkühn within small intestine and play a pivotal role in maintaining mucosal barrier and immune homeostasis through secreting a variety of antimicrobial peptides,[32] such as lysozyme, α-defensins, and Reg3r.[15] Previous studies have showed that Paneth cells dysfunction induced by high-fat diet or long-term fasting might result in increased intestinal permeability and bacterial translocation, which can aggravate AP development.[33] Moreover, *Lactobacillus* may activate Paneth cells and protect mice from AP-associated intestinal impairment in a NOD2-dependent manner. Therefore, antimicrobial peptides supplementation partially restoring the function of Paneth cells may represent a promising therapeutic modality to alleviate intestinal dysfunction and gut microbiota dysbiosis in AP.

The intestinal mucosa immunity is vital for the interactions between gut microbiota and host immune system. During AP, intestinal immune dysregulation may contribute to increased gut permeability and overgrowth of facultative pathogens, such as *Escherichia–Shigella* and *Enterococcus*.[14,34] Evidence has emerged that Treg/Th17 ratio is crucial for stabilizing gut immune homeostasis in preclinical AP models.[35] A recent study by Glaubitz et al indicated that $CD25^+/FOXP3^+$ Treg could attenuate antimicrobial barrier through preventing the activation of the lamina propria $ROR\gamma t^+$ Th17 and $CD8\alpha^+/\gamma\delta TCR^+$ intraepithelial lymphocytes in the duodenum, while depleting Tregs by diphtheria toxin mitigated microbial dysbiosis in AP and prevented facultative pathogens from duodenum translocating into the area of pancreatic necrosis through enhancing sIgA secretion and intestinal barrier function.[23]

As the AP progresses, local immune dysregulation and inflammatory responses may spill into systemic circulation. Sendler et al have elucidated NLRP3 inflammasome play an essential role in balancing pro- and anti-inflammation via modulating the differentiation of pancreatic infiltrating pro-inflammatory immune cells (eg, T_H1) and anti-inflammatory immune cells (eg, T_H2/Treg).[36] Evidence indicated NLRP3 inflammasome activated not only in pancreas but in gut and spleen of AP mice. Li et al reported the cross talk between NLRP3 inflammasome and gut flora determined the severity of inflammation in AP.[29] Specifically, NLRP3 knockout could promote the restoration of gut microbial ecology, including the increased abundance in *Lactobacillus* and *Roseburia*, and decreased abundance in *Escherichia–Shigella*, which compensate for the intestinal mucosal barrier damage by increasing the expression of claudin-1 and occludin during AP recovery. The activation of IL-1β mediated by NLRP3 could promote the secretion of another pro-inflammatory factor IL-17, which is also closely related to the microbial dysbiosis through immune-mediated intestinal microcirculation and mucosal barrier disruptions.[37] Furthermore, IL-17 involved in recruitment of neutrophils to the damaged region of pancreas in a PADI4-dependent manner, and amplify the inflammatory cascade during AP through enhancing ROS concentrations and neutrophil extracellular traps formation.[38] Future studies are warranted to evaluate the gut microbiome as a whole bidirectionally interacting with the immune system, which may provide novel therapeutic targets to counterbalance the inflammatory responses.[34]

Gut-lung axis in the pathogenesis of AP-associated lung injury

Acute lung injury (ALI) are most frequent and potentially fatal extra-pancreatic complications in AP. Current research on the gut-lung axis has indicated the bidirectional interactions between intestinal microflora and AP-associated ALI.[39] Considered from the embryological perspective, the gut and lung were both differentiated from the endoderm and have similar mechanisms in mucosal immunity, where symbiotic microorganisms and epithelial barrier synergistically maintain the balance of immunity homeostasis to reduce the inflammatory responses.[40] Deitch presented the gut-lymph hypothesis that illustrated lung was the first organ exposed to gut-derived bacteria or endotoxin carried in mesenteric lymph, occurring early in the course of AP-associated ALI before portal circulation spread.[41] Besides facultative pathogens, recent findings suggest bioactive microbial metabolites also participate in the pathological process of AP-associated ALI, such as SCFAs, free fatty acids (FFA), trimethylamine N-oxide (TMAO), and tryptophan.[42,43] For example, SCFAs were reported to relieve the severity of ALI via protecting pulmonary microvascular endothelial cells, modulating the hyperactivation of neutrophil extracellular traps, and maintaining the immune homeostasis, the specific molecular mechanisms of which would be discussed in the next section. Considering the interplay between microbial gut-lung translocation and host immune responses, it may be feasible to develop novel therapeutic strategies by regulating of the gut-lung axis to attenuate AP-associated ALI.

Effects of microbial metabolites on clinical course of AP

Alterations in the composition of the gut microbiota could contribute to the modification of host metabolic activities, which might involve in the pathogenesis of AP. Gut microorganisms could produce different bioactive metabolites from dietary components, exerting beneficial or harmful effects on host, including SCFAs, lactic acid, bile acids (BAs), indole compounds, biogenic amines and nicotinamide adenine dinucleotide (NAD^+)-associated metabolites. The summary of main microbial metabolites is presented in Table 2.

The anti-inflammatory role of SCFAs in AP

SCFAs are saturated fatty acids with 6 or fewer carbon atoms in length, comprised mainly of acetate, propionate, and butyrate.[59] Among them, butyrate serves as the essential energy source for colonocytes to maintain the gut barrier function and inhibit the activation of pro-inflammatory factors, mediated by activating G-protein–coupled receptors (GPRs) and inhibiting histone deacetylase (HDAC). In addition, acetate and propionate are primarily taken up by hepatocytes or adipocytes, respectively, consumed as the substrate for lipogenesis or gluconeogenesis.[60] Research suggested the relative abundance of butyrate-producing bacteria including *Alloprevotella*, *Bacteroides*, and *Blautia* was significantly reduced in the fecal samples of SAP patients compared with MAP, indicating SCFAs as the potential mediators in alleviating pancreatic injury.[12] Pan et al reported that butyrate could attenuate the caerulein-induced AP though acting as the HDAC1 inhibitor and GPR109A agonist in the gut to inhibit the activation of STAT1/AP1-NLRP3 inflammasome pathway.[44] Recent studies have demonstrated the possible mechanisms of butyrate as anti-inflammatory modulators in both innate and adaptive immunity. For example, gut microbiota-derived butyrate could promote IL-22 production by innate lymphoid cells and $CD4^+$T cells to maintain intestinal immunity homeostasis.[45] Van et al revealed oral and intraperitoneal butyrate reduced the development of taurocholate-induced ANP via driving macrophage towards the antimicrobial phenotype and restoring intestinal barrier function.[9,44] At present, there were only few studies investigating the role of acetate and propionate in AP. Maslowski et al reported acetate decreased the surface expression of neutrophil C5aR and CXCR2 presumably through binding to GPR43 to down-regulate inflammatory responses.[47] Experimental studies by Tian et al demonstrated elevated propionate could attenuate AP-associated ALI via modulating TLR4 receptor.[49] The efficacy of prophylactic SCFAs administration in clinical patients with AP remains to be further validated.[61]

Bile acids metabolism in AP

The gut microorganisms modulate BAs synthesis and metabolism through interaction with farnesoid-X-receptor and G-protein–coupled membrane receptor 5 to perform anti-inflammatory

Table 2

Summary of the possible mechanisms of major microbial metabolites in the pathogenesis of acute pancreatitis

Metabolites	Source genus	Source species	Receptors and downstream effectors	Metabolic effects	Ref.
SCFAs					
Butyrate	*Anaerostipes, Alloprevotella, Clostridium, Faecalibacterium, Gemella, Holdemanella, Ruminococcus*	*Anaerostipes caccae, Clostridium butyricum, Clostridium leptum, Eubacterium hallii, Eubacterirum rectale, Faecalibacterium prausnitzii, Roseburia inulinivorans*	GPR41, GPR43, GPR109A, HDACs, AHR	Suppress the activation of pro-inflammatory factors; Promote the expression of claudin-1 and ZO-1 to restore gut barrier function; Drive macrophage toward an antimicrobial phenotype	[9,12,44–46]
Acetate	*Blautia, Bacteroide, Clostridium, Prevotella, Ruminococcus, Streptococcus*	*Blautia hydrogenotrophica, Bacteroides vulgatus, Bacteroides thetaiotaomicron, Prevotella corporis, Eubacterium hallii*	GPR41, GPR43, HDACs, C5aR, CXCR2	Ameliorate the inflammatory responses in the gut and lung; Suppress the activation of pro-inflammatory factors, such as IL-17A, IL-6, and IL-1β	[47,48]
Propionate	*Akkermansia, Bacteroides, Coprococcus, Dialister, Megasphaera, Parabacteroides*	*Akkermansia muciniphila, Coprococcus catus, Coprococcus comes, Dialister hominis, Megasphaera elsdenii*	GPR41, GPR43, HDACs, TLR4, PPARγ	Reduce neutrophil infiltration; Impair T_H2 cell differentiation; Alleviate ischemia-reperfusion lung injury	[49]
Bile acids	*Actinobacteria, Bacteroides, Bifidobacterium, Clostridium, Eubacterium, Lactobacilli,*	*Clostridium perfringens, Eubacterium lentum, Lactobacillus plantarum, Ruminococcus gnavus, Mediterraneibacter faecis*	FXR, TGR5, PXR, RORγt	Inhibit NF-κB and other inflammatory pathways; Maintain metabolic and immune homeostasis; Inhibiting acinar cells apoptosis	[48,50–52]
Indole compounds	*Allobaculum, Lactobacillus*	*Faecalibacterium prausnitzii, Lactobacillus rhamnosus*	AHR, Estrogen receptors, 5-HT receptors	Enhance intestinal barrier function; Modify the host immune response	[53,54]
Polyamines	*Bacteroides, Bifidobacterium, Fusobacterium, Lactobacillus, Shigella*	*Bifidobacterium animalis, Enterococcus faecalis, Streptococcus pneumoniae, Saccharomyces boulardii, Shigella flexneri*	AHR, CaSR	Decrease serum inflammatory factors such as TNF-α and IL-6; Reduce ROS production and mitochondrial damage	[55]
TMAO	*Anaerococcus, Bacteroides, Clostridium, Escherichia, Prevotella*	*Anaerococcus hydrogenalis, Clostridium asparagiforme, Clostridium hathewayi, Escherichia coli, Escherichia fergusonii, Providencia rettgeri*	SR-A1, CD36, TLR4, GC5A	Activate inflammatory cytokines, such as TNF-α and IL-1β; Trigger NLRP3 activation and ROS production	[56,57]
NMN	*Anaerovibrio, Coriobacterium, Prevotella, Paraprevotella, Mucispirillum*	*Anaerovibrio lipolyticus, Candidatus stoquefichus, Prevotellaceae_UCG-001, Prevotellaceae NK3B31, Mucispirillum schaedleri*	SIRTs, TLR4	Modulate macrophage polarization; Inhibit oxidative stress injury; Maintain intestinal homeostasis	[10,58]

AHR = aryl hydrocarbon receptor, CaSR = extracellular calcium-sensing receptor, FXR = farnesoid-X-receptor, GPR = G-protein–coupled receptors, HDACs = histone deacetylases, NLRP3 = NOD-like receptor pyrin domain containing 3, NMN = nicotinamide mononucleotide, PPARγ = peroxisome proliferatoractivated receptors γ, PXR = pregnane-X-receptor, RORγt = retinoic acid receptor-related orphan nuclear receptor γt, ROS = reactive oxygen species, SIRTs = sirtuins, SR-A1 = scavenger receptor A1, TGR5 = G-protein–coupled membrane receptor 5, ZO-1 = Zonula Occludens-1.

functions by inhibiting the NF-κB pathway.[50] Emerging evidence indicates the biphasic effects of systemic BAs on modulating the severity of AP. Tran et al elucidated BAs could exacerbate L-arginine or pancreatic duct ligation induced AP, while protect against caerulein or biliopancreatic duct ligation induced pancreatic injury.[48] Recent studies showed gut flora and their enzymes could convert lithocholic acid into 3-oxolithocholic acid and isolithocholic acid, which block Th17 cell differentiation via inhibiting RORγt.[51] The role of liver-BAs-microbiota axis in improving insulin sensitivity and immunological balance during AP requires further exploration.[52]

Microbial-derived amino acid metabolites during AP

Disturbance of microbial community and amino acid homeostasis exert negative impacts on the progression of AP. Aromatic amino acids could be fermented into indole compounds by multi-species microorganisms, such as *Bifidobacterium*, *Lactobacilli*, and *Peptostreptococcus*. Recent studies indicated indole and its derivatives generated by the catabolism of tryptophan may enhance the barrier function of intestinal epithelial cells through upregulating the expression of tight and adherence junctions associated molecules.[53] Additionally, indole derivatives were recently identified as the ligands of aryl hydrocarbon receptor to maintain intestinal immune homeostasis via regulating local IL-22 production.[54] The catabolism of gut microorganisms is considered the major source of colonic polyamines, mainly including spermidine, putrescine, and spermine, which enter the circulation through the intestinal mucosa to maintain membrane stability and improve mitochondrial function.[62] Polyamine depletion through spermidine/spermine N1-acetyltransferase increased trypsin activation and acinar cell necrosis, while supplementation with exogenous

polyamine analog could mitigate pancreatic injury.[55] Another microbiome-derived metabolite, TMAO, is the amine oxidation product transformed from trimethylamine,[56] which contributes to the development of AP through promoting the activation of NLRP3, NF-κB and other pro-inflammatory cytokines.[63] Yang and Zhang demonstrated that TMAO aggravated pancreatic injury in the mice model of HTGP via TLR/p65 pathway.[56] Additionally, TMAO could induce endoplasmic reticulum stress in HTGP via activating IRE1α/XBP-1 pathway.[57] The potential of TMAO as the therapeutic target and biomarker for AP has to be further validated in clinical settings.

Nicotinamide adenine dinucleotide–associated metabolites

NAD^+ and reduced equivalents NADH are essential redox factors in hundreds of redox reactions, participating in multiple cellular processes, such as genome stability, energy metabolism, and inflammatory reaction.[64] Recent studies revealed the host-microbe metabolic crosstalk could promote NAD biosynthesis, which exerted anti-inflammatory effects through the activation of sirtuins (SIRTs) in cerulein-induced AP model.[65] NMN and nicotinamide riboside are key intermediates of NAD^+ biosynthesis. Evidence suggested that NMN supplementation could boost cellular NAD concentrations with lower adverse effects and toxicity, which alleviate oxidative stress, insulin resistance, and ischemic-reperfusion injury[66] by activating SIRT protein family. Huang et al demonstrated exogenous NMN supplementation improved intestinal barrier function via increasing the relative abundance of beneficial microorganisms and reducing opportunistic pathogens.[58] Our team recently reported that gut microbiota-derived NMN could attenuate oxidative damage and inflammatory response in AP though converting to NAD^+ and activating the SIRT3-PRDX5 pathway.[10] Mechanistically, our study illustrated normobiotic FMT increased NMN levels in AP models, thereby alleviating AP-mediated mitochondrial ROS production and oxidative stress injury via SIRT3-PRDX5 axis. Another research by He et al conversely showed that nicotinamide phosphoribosyltransferase (NAMPT), as the rate-limiting enzyme of NAD^+ salvage pathway, could induce pancreatitis-associated M1 macrophage polarization, while NAMPT inhibitor (FK866) reversed metabolic remodeling and pro-inflammatory polarization of macrophage in alcoholic and biliary AP.[67]

Other metabolites in the pathogenesis of AP

Metabolites from probiotic strains *Bifidobacterium*, *Lactobacillus*, and *Lactococcus* are important for regulating immune homeostasis. Recent study showed lactate derived from commensal *Bifidobacterium* ameliorated pancreatic local and systemic inflammation by suppressing the activation of TLR4-MYD88-NF-κB pathway.[68] Reduced glutathione, as the potent intracellular antioxidant, could defend against excess ROS and oxidative stress injury. Lutgendorff et al confirmed probiotic pre-treatment, including mainly *Lactobacillus* and *Bifidobacterium* could alleviate experimental AP-induced intestinal barrier dysfunction and acinar cell injury via inducing reduced glutathione biosynthesis.[69] Urolithin A and its derivatives are mainly produced from the ellagic acid of gut flora, and studies suggested they could inhibit endoplasmic reticulum stress and the activation of TXNIP-NLRP3-IL-1β signaling in AP model.[70]

Therapeutic strategies targeting gut microbiota dysbiosis in AP

Several microbiome-based therapies have been developed to modulate host-microbial homeostasis. Microbiome-based therapies mainly focus on modulating the gut microbial community structure and controlling the abundance of their metabolites, such as FMT, probiotics, prebiotics, synbiotics, and recently postbiotics. Our review extends the understanding of gut microbes and host immunity in the pathogenesis of pancreatic injury and provide profound evidence of utilizing microecological agents to alleviate AP (Fig. 2).

Effects of probiotic, prebiotic, symbiotic, and postbiotic treatments on AP

The ISAPP scientific consensus defined probiotics, prebiotics, and synbiotics as "live microorganisms with host health benefits," "substrates selectively utilized by host microbes to confer health benefits" and "combinations of probiotics and substrates selectively utilized by host microorganisms to confer health benefits" respectively.[71] Mechanisms of microecological preparations contributing to human health include: (1) functioning as microbial barrier directly inhibiting the growth and spread of pathogens; (2) boosting gut barrier and enhancing the tight junctions; (3) repressing the apoptosis of intestinal epithelial cells; (4) modulating the immune system; (5) affecting gut motility via metabolites and interacting with the enteric nervous system.[72] Despite the various theoretical benefits, the efficacy of probiotic preparations still remains debated. The role of probiotics in AP was firstly explored by Olah et al in a single-center randomized controlled trial (RCT), which enrolled 45 non-biliary AP patients randomized to treatment group (receiving live *Lactobacillus plantarum* with the oat fiber substrate) and control group (receiving heat-killed *Lactobacillus plantarum*).[73] The occurrence rate of IPN was significantly lower in the probiotic treatment group than that of the control group (4.5% vs 30.4%), and supplementing with probiotics was confirmed to be effective in reducing surgical interventions in AP patients. Although the results are encouraging, small sample size and statistical power limit the generalizability of these findings. Hence, the Dutch Acute Pancreatitis Study Group designed a nationwide PROPATRIA trial to assess the safety and efficacy of probiotic prophylaxis in reducing the complications of SAP patients.[74] The final results of PROPATRIA suggested probiotic therapy with Ecologic 641 in a daily dose of 10^{10} microorganisms was associated with the higher risk of bowel ischemia and increased mortality, with no significant difference in infectious complications.[75] The reassessment of PROPATRIA trial suggested starting probiotic treatment too late (more than 72 hours after the onset of symptoms) and preparations with insufficient amounts of beneficial bacteria and excessive polysaccharides that promote the production of lactic acid, might contribute to the increased risk of bowel ischemia and mortality.[76] The meta-analysis conducted by Tian et al concluded that probiotic supplementation reduced the hospital length of stay in SAP cohorts, indicating probiotic treatment remains promising in specific populations.[77]

The supplement of prebiotics and synbiotics might also bring potentially positive effects on anti-inflammatory effects. The sample size RCT conducted by Karakan et al suggested prebiotic fiber supplementation could improve hospital length of stay and acute phase of inflammatory response.[78] Another study reported that early nasojejunal feeding of symbiotics within 24 hours of admission might prevent organ dysfunctions in SAP compared to patients received only prebiotics.[79] Despite the promising results, a recent updated meta-analysis revealed neither beneficial nor harmful effects of prebiotics and synbiotics on the clinical outcome of SAP patients.[80] The discrepant results of RCT trials might attribute to the initial treatment time of therapy, composition of microecological preparations and individual heterogeneity, and future clinical studies could be undertaken across diverse populations.

Postbiotics, referring to inanimate microorganisms and their metabolic byproducts with host health benefits, have been considered as the next horizon in microbiome-based therapy.[81]

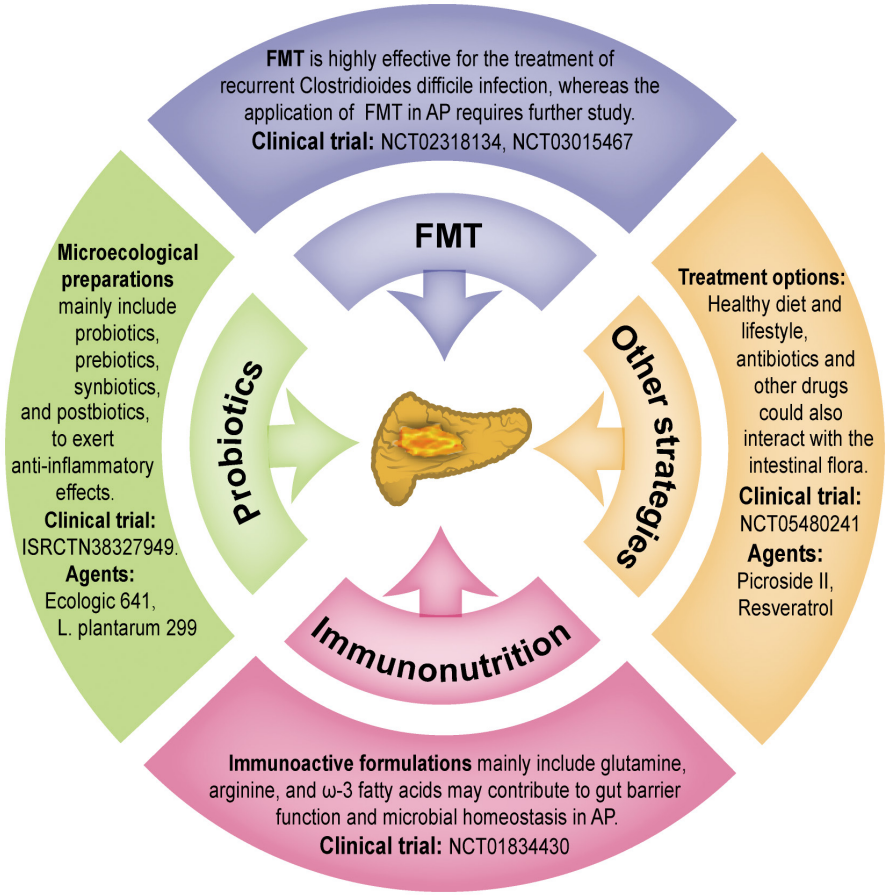

Figure 2. Microbiome-based therapeutic strategies to modulate host-microbial homeostasis in AP. AP = acute pancreatitis, FMT = fecal microbiota transplant.

Currently, the widely studied postbiotics include SCFAs, extracellular polysaccharides, bacterial lysate, and membrane vesicles.[82] Takauji et al demonstrated *Lactobacillus brevis*–derived polyphosphate could reshape the gut microbiome and protect the intestinal barrier integrity by upregulating the expression of ZO-1 and occluding of epithelial cells.[83] In cerulein-induced AP model, orally administered polyphosphate for 7 or 24 days before the induction of AP was associated with the increased abundance of *Candidatus_Saccharimonas*, and decreased abundance of *Desulfovibrio spp.*, contributing to mitigating the severity of experimental AP.[83] In preclinical studies, short-term NMN supplementation may also ameliorate various inflammatory and ischemic diseases by activating SIRTs and NAD salvage pathways, expected to benefit the clinical treatment of AP.[10]

Therapeutic effect of FMT

FMT, also known as fecal bacteriotherapy, is a promising treatment strategy for intestinal flora disturbance related diseases, in which fecal microbiota are transferred from the healthy screened donor into the gastrointestinal tract of patients. FMT has emerged as the effective therapy for refractory *Clostridioides difficile* infections, and currently explored as the potential ecological treatment for other gastrointestinal disorders.[84] Compared to other sources of microbiota, FMT derived from healthy donors is more compatible with the pattern of human intestinal microecology, and may change the disturbed microbial composition more robustly.[72] However, a recent RCT by Ding et al found no effect of FMT on intra-abdominal hypertension and infectious complications of AP patients.[85] Van den Berg et al suggested that FMT increased the mortality of western diet feeding ANP mice and promote the dissemination of pathogenic bacteria in both necrotic tissue and peripheral blood.[9] Liu et al found normobiotic FMT feces from healthy controls may ameliorate the severity of AP through inducing the production of NAD^+ associated metabolites.[10] At present, research on the application of FMT in non-necrotizing AP is rather limited, which requires further exploration.

Impact of antibiotics on gut microbiota composition in AP

Although pathogenic microorganisms play an important role in local and systemic inflammation during AP, prophylactic antibiotics in the early phases of disease remain controversial. In ANP model, Fritz et al revealed prophylactic antibiotic treatment with meropenem within 24 hours of AP induction was superior to on-demand antimicrobial treatment.[86] Conversely, Soares et al revealed pre-treatment of meropenem may induce the dissemination of multidrug-resistant bacteria into peripheral blood and aggregate the severity of obstructive AP.[87] Recent PROCAP trial suggested procalcitonin-guided antibiotic treatment could significantly reduce the overuse of antibiotics without increasing the risk of infectious complications.[88] In clinical settings, the novel biomarkers to guide the precise application of antibiotics provide a promising way to prevent pancreatic superinfection and emergence of multidrug-resistant bacteria.

Early enteral nutrition

Accumulating evidence has indicated the positive effect of enteral nutrition (EN) on maintaining the gut microbial balance, intestinal barrier function, and preventing bacterial translocation.

The multicenter PYTHON trial suggested as compared with on-demand oral diet at 72 hours, there is no advantage of early nasoenteric tube feeding within 24 hours in reducing the rate of infectious complications and mortality.[89] Given this, on-demand oral diet should be initiated once patients can tolerate enteral feeding within 72 hours, with tube feeding only if patients with oral feeding intolerance and insufficient caloric intake, to prevent gut dysfunction.[90] Recently, immunoactive enteral formulations, such as glutamine, arginine, short peptide, and ω-3 fatty acids have been applied in nutritional management of AP patients. Experimental study suggested immunonutrition contribute to gut barrier function and immune homeostasis in taurocholate-induced AP model.[91] However, the meta-analysis by Petrov et al indicated immunonutrition has no additional beneficial effects on infectious complications, length of hospital stay or mortality compared with standard EN.[92] Research on early EN supplemented with probiotic preparations remains in the relatively preliminary stage. Jin et al reported early EN combined probiotic preparations contained mainly *Bifidobacterium spp*. could improve the immunoinflammatory response and shorten the recovery time of SAP patients.[93] A single-center RCT study suggested early nasojejunal EN supplemented with prebiotic multifibers for SAP may improve hospital stay and duration of nutrition therapy.[78] Further long-term follow-up studies with larger sample sizes are needed to confirm precise effects of early EN in combination with microecological preparations on the recovery of AP patients.

Other therapies modifying gut microbiota

Traditional Chinese medicine, including herbal medicine and acupuncture, could also modulate the composition and metabolism of gut microbiota, and microbiota may transform herbal medicines into bioactive compounds in vivo.[94] Zhang et al reported the resveratrol pre-treatment alleviated oxidative stress-induced pancreatic injury through inhibiting NF-κB signaling and improving intestinal flora disturbance in HTGP model.[95] Another study suggested Picroside II may contribute to the restoration of intestinal barrier function and gut microecological homeostasis in taurocholate-induced SAP.[96] Therefore, natural compounds derived from herbal medicine may serve as the potential therapies to correct intestinal microflora disturbance in AP.

Conclusions and perspectives

Currently, the new front in the research on gut microbiota-pancreas axis has opened with accumulated evidence for the role of microbial dysbiosis in AP development. However, most of the host-microbiota studies were limited by the cross-sectional and associative design, thereby not enough to make causal inference. Further investigation is required for more detailed knowledge of whether the altered microorganisms are the cause or result of AP process, or merely epidemiological differences. The additional challenge in microbiological research is clarifying specific sources for metabolites relevant to AP at the species or strain level. Drawing causal connections between the gut microbiome, metabolites and their impacts on AP is critical for the development of microbiota-based treatments.

To address these problems, many recent studies have begun to utilize germ-free animals, culturomics and immunoglobulin sequencing. Germ-free models could rule out interference from the host indigenous microbial community and have emerged as the gold standard for causality research when colonized with the specific microbe or microbial community.[97] Culturomics are based on diversification of culture conditions and the application of 16S rRNA gene amplicon sequencing and matrix-assisted laser desorption ionization-time of flight mass spectrometry to identify the vast majority of microbial species,[98] and culturable microbes could be transplanted into germ-free animal models to assess the effects of specific groups of microorganisms on host. Additionally, replacement of loss microbial taxa in AP mouse models to reverse the dysbiosis of microbial community is an ideal tool to verify the function of beneficial species. Given the limitations of single-omics analysis, future research could integrate multi-omics data in multiple and complementary modalities, including metagenomics, metabolomics, metatranscriptomics, metaproteomics, and culturomics, etc. The application of complementary technologies will expand our understanding of the disturbance in microbial niches and community functions during AP.

Modulation of the gut microecology represents a novel and promising strategy for individualized prevention, diagnosis, and treatment of AP patients. However, the current animal and clinical research data remains equivocal, making it challenging to draw consistent conclusions. Future study design should consider minimizing disparities in baseline microbial composition of patients, dosage regimens, and administration frequency of microecological agents to establish robust insights into microbiota-based therapeutics. Integration of experimental approaches and computational models will inform the design of microbial preventive and therapeutic strategies to match the genetic, microbial, and metabolic profiles of AP patients with different etiologies. With advances in microbial genetic engineering technology, it is feasible to design synthetically engineered microbiomes with specific metabolic and immunomodulatory activities,[99] which may pave the way for individualized diagnosis and management of AP patients, and ultimately improve patient-centered outcomes.

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Author contributions

BS: conception and design. ZCD, GQL, YL: collected data and wrote the manuscript. ZCD, GQL: graphics drawing. BS, XWB: revision of the manuscript. All authors approved the final version of manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

Our review did not involve any clinical or animal experiments and was analyzed only using published open-source studies, therefore did not involve the approval of the Institutional Review Board.

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