



REVIEW ARTICLE

Gut microbiota in pancreatic diseases: possible new therapeutic strategies

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Pancreatic diseases such as pancreatitis, type 1 diabetes and pancreatic cancer impose substantial health-care costs and contribute to marked morbidity and mortality. Recent studies have suggested a link between gut microbiota dysbiosis and pancreatic diseases; however, the potential roles and mechanisms of action of gut microbiota in pancreatic diseases remain to be fully elucidated. In this review, we summarize the evidence that supports relationship between alterations of gut microbiota and development of pancreatic diseases, and discuss the potential molecular mechanisms of gut microbiota dysbiosis in the pathogenesis of pancreatic diseases. We also propose current strategies toward gut microbiota to advance a developing research field that has clinical potential to reduce the cost of pancreatic diseases.

Keywords: gut microbiota; pancreatic diseases; type 1 diabetes; acute pancreatitis; chronic pancreatitis; pancreatic cancer

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INTRODUCTION

The gut microbiota has recently emerged as an essential mediator of human health, acting by interfering with host functions, including metabolism, digestion, and gut mucosal immune responses and integrity. The interplay among the gut microbiota, intestinal barrier and immune system maintains gut homeostasis and protects the host from pathogenic flora [1], and disruption of this homeostasis leads to an imbalance of the gut microbiota called “dysbiosis” [2]. To date, gut dysbiosis has been reported to participate in the pathogenesis of several gastrointestinal diseases, including inflammatory bowel disease [3], irritable bowel syndrome [3], and other diseases, such as obesity [4], metabolic syndrome [5, 6], Parkinson’s disease [7], and pancreatic diseases [8].

The human pancreas is crucial for maintenance of metabolism and health due to its endocrine (the vital metabolic hormone insulin) and exocrine (digestive enzymes) functions [9]. Recent studies support the existence of interactions between the gut microbiota and pancreas. On the one hand, the pancreas is connected to the gastrointestinal tract via the pancreatic duct, exocrine pancreatic function is an important host factor affecting the composition and diversity of gut microbiota [10], and pancreas-derived antimicrobial peptides can influence the gastrointestinal microbiota [11]. On the other hand, gut microbes and their derivatives can migrate into the pancreas to influence the pancreatic microenvironment. Alterations in the gut microbiota are associated with several pancreatic diseases, such as type 1 diabetes (T1D), acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic cancer (PC) [8, 12–15]. However, no direct causal relationship has been established between gut dysbiosis and pancreatic diseases. Thus, here, we view relevant animal and human studies to explore the crosstalk between the gut

microbiota and pancreas and discuss the roles and potential mechanisms of dysbiosis in the pathogenesis of pancreatic diseases.

ROLE OF THE MICROBIOTA IN THE DEVELOPMENT OF TYPE 1 DIABETES

T1D is an autoimmune disorder characterized by T-cell-mediated destruction of insulin-producing β -cells in pancreatic islets [16]. Genetic predisposition (low-risk human leukocyte antigen, balance of protective and susceptibility alleles for T1D) and environmental factors (antibiotics, hygiene, diet, and seasonality) are important elements in the development of T1D [17]. Environmental factors related to T1D development, such as diet, antibiotics and pH of drinking water, also have an impact on the gut microbiota. Changes in the gut microbiota and its metabolites (such as short-chain fatty acids (SCFAs)) may subsequently increase intestinal permeability, instigate abnormal immune cell functioning, and promote the development of proinflammatory niches, thus stimulating β -cell autoimmunity and T1D development [18–20]. Here, we summarize the current knowledge about the relationship between the microbiota and T1D and explore possible mechanisms of gut dysbiosis in T1D development based on both animal and human studies.

Animal studies

Evidence supporting the role of the gut microbiota in T1D development is largely derived from two rodent models of autoimmune diabetes, including nonobese diabetic (NOD) mice and Bio-Breeding diabetes-prone (BB-DP) rats. Both NOD mice and BB-DP rats carry the risk genes of T1D and develop spontaneous

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T1D, similar to humans. In both models, gut microbes are necessary for host health, and perturbations to the normal composition of commensal communities disrupt homeostasis and increase susceptibility to T1D [21, 22]. Specifically, Roesch et al. found that the abundances of bacteria of the genera *Bacteroides*, *Eubacterium*, and *Ruminococcus* increased, whereas those of *Lactobacillus*, *Bryantella*, *Bifidobacterium*, and *Turicibacter* decreased, in BB-DP rats compared with Bio-Breeding diabetes-resistant rats [23] (Table 1). Similarly, different microbiota compositions were also found between NOD and nonobese diabetes-resistant (NOR) mice, and NOD mice had a lower *Firmicutes/Bacteroidetes* ratio as well as a lower abundance of *Prevotella* than the NOR mice [24]. Meanwhile, a reduced abundance of SCFA-producing bacteria was found in individuals diagnosed with T1D, indicating that certain commensal bacterial populations and their metabolites contribute to protection against T1D [25–27].

Indeed, interventions such as antibiotic treatment, probiotic supplementation, dietary supplementation, or FMT to perturb the gut microbiota composition were proven to delay or accelerate T1D progression [28–33]. It was reported that alterations in the gut bacterial profile caused by vancomycin markedly increased the incidence of T1D [28, 29]. Dietary factors such as gluten and fiber may change the incidence of T1D by altering the composition of the gut microbiota, and low-ester pectin, a novel dietary fiber, could decrease the diabetes incidence in NOD mice by selectively enriching specific microbial species that produce SCFAs [30]. In addition, early oral administration of the probiotic *Clostridium butyricum* (CB0313.1) in NOD mice induced the onset of diabetes by selectively modulating the structure of the intestinal microbiota, including increasing the *Firmicutes/Bacteroidetes* ratio and changing the abundances of *Clostridium* and butyrate-producing bacteria [31]. Transfer of *Akkermansia muciniphila* was also effective in delaying the onset of diabetes in NOD mice, which is mediated by increased expression of the antimicrobial peptide Reg3 γ , lowered serum endotoxin levels, reduced islet toll-like receptor (TLR) expression, increased forkhead box P3 positive (Foxp3⁺) regulatory T-cell (Treg) abundance in islets, and increased interleukin-10 and transforming growth factor beta expression in pancreatic lymph nodes [32]. Similarly, a protective role against T1D was found for *segmented filamentous bacteria* in NOD mice [33], and *segmented filamentous bacteria*-positive females could more strongly induce a robust T-helper cell type 17 (Th17) population in the small-intestinal lamina propria than males. Therefore, it is clear that the gut microbiota and its metabolites exert profound effects on T1D development and can be used as biomarkers for T1D prediction, and therapeutic strategies targeting the gut microbiota might be effective in controlling diabetes [34, 35].

Human studies

The role of the intestinal microbiota as an important regulator of autoimmune diabetes in animal models is well established, and consistent alterations in the gut microbiota have also been observed in humans with T1D [36, 37] (Table 1). A study by Giongo et al. analyzed bacteria in fecal samples of infants and young children and discovered that children who developed T1D had lower proportions of bacteria from the *Firmicutes* phylum and higher proportions of bacteria from the *Bacteroidetes* phylum than age-matched healthy controls at 4–8 months of age [38]. De Goffau et al. compared the intestinal microbiota composition between children with at least two diabetes-associated autoantibodies and autoantibody-negative children matched for age, sex, and early feeding history. They found that a decreased abundance of *Bifidobacterium* and an increased abundance of the *Bacteroides* genus in children with β -cell autoimmunity and a low abundance of lactate-producing and butyrate-producing species were associated with β -cell autoimmunity [39]. In another study,

De Goffau et al. analyzed the gut microbiota of children aged 1–5 years with new-onset T1D vs age-matched healthy controls and demonstrated that the healthy children had a more balanced microbiota than the diabetic children and that butyrate-producing species appear to hold a pivotal position in T1D prevention [25]. Consistent with this, a case-control study by Murri et al. also demonstrated that gut microbiota dysbiosis was a stimulant of T1D, and the *Firmicutes/Bacteroidetes* ratio was negatively correlated with the plasma glucose level, while the quantity of *Clostridium* was positively correlated with the plasma glucose level. In addition, diabetic children had decreased abundances of *Bifidobacterium*, *Lactobacillus*, the *Blautia coccooides/Eubacterium rectale* group and *Prevotella* compared with healthy children, and the quantity of bacteria that was essential for maintenance of gut integrity was significantly lower in children with diabetes than in healthy children [36]. Moreover, Mejía-León et al. compared the structure of the fecal microbiota in mestizo children with T1D at onset, T1D after 2 years of treatment, and healthy controls [40]. They found that the newly diagnosed T1D cases had high levels of the genus *Bacteroides*, whereas the gut microbiota in healthy controls was dominated by *Prevotella*, and children with T1D treated for ≥ 2 years had similar levels of *Bacteroides* and *Prevotella* compared to those in the control group [40]. Based on the above findings from human studies, we can conclude that gut microbiota dysbiosis is strongly associated with β cell autoimmunity or T1D development; however, whether microbial alteration is involved in disease causation or is a consequence of selection by the host remains unclear.

To reveal the causal relationship, several cohort studies have been conducted and identified that changes in gut microbiota composition occurred before T1D development [37, 38]. For instance, Endesfelder et al. investigated the fecal microbiomes of 22 children who developed anti-islet cell autoantibodies and 22 matched control children who remained islet autoantibody negative from ages 3 to 36 months. During the first year of life, the microbiome changed markedly and was affected by breastfeeding, food introduction, and birth delivery mode, and there were no differences between anti-islet cell autoantibody positive and negative children in terms of bacterial diversity, microbial composition, or single-genus abundances. However, at ages 0.5 and 2 years in the children who developed anti-islet cell autoantibodies, substantial alterations in microbial interaction networks were observed [41]. Similarly, Huang et al. investigated relationships between the composition of the gut microbiome and T1D progression in Han Chinese subjects between the ages of 12 and 33, and they observed that Han Chinese T1D patients had an increased *Bacteroidetes/Firmicutes* ratio and a positive correlation of *Bacteroides* abundance with the presence of anti-islet cell autoantibodies compared to healthy subjects [42]. In addition to cohort studies, intervention studies have also been performed to certify a causal contribution of the microbiota to the T1D pathology. Recently, a single-center, randomized, double-blind, placebo-controlled pilot study conducted in children with T1D for at least 1 year showed that consumption of prebiotics could alter the gut microbiota composition and decrease intestinal permeability, leading to improved beta cell function [43]. In addition, Uusitalo et al. reported that early supplementation with probiotics during the first 4 post natal weeks reduced the risk of beta cell autoimmunity in infants genetically susceptible to T1D compared to those with no supplementation [44]. Nevertheless, such randomized controlled clinical trials are still rare, and individual bacterial species that are associated with T1D have not been identified. Overall, these findings in human studies have strongly demonstrated that the gut microbiota plays a pivotal role in the pathogenesis of anti-islet cell autoimmunity and T1D development. Altered microbial interactions in early life result in aberrant microbial development in later life and thus influence T1D development [13, 45].

Table 1. Summaries of major gut microbiota involved in pancreatic diseases.

Reference	Sample number	Species	Sample	Disease states vs control	Bacterial population evaluation	Increased bacterial population	Decreased bacterial population
Roesch et al. [23]	10/10	Rats	Feces	T1D vs normal	16S rRNA sequencing	<i>Bacteroides</i> , <i>Eubacterium</i> , <i>Ruminococcus</i>	<i>Lactobacillus</i> , <i>Bryantella</i> , <i>Bifidobacterium</i> , <i>Turicibacter</i>
Hu et al. [134]	39T1D/24 normal	Mouse	Feces	Pre-T1D vs normal		Gram-negative, Gram-positive	<i>Bacteroidetes</i> <i>Erysipelotrichaceae</i>
Leiva-Gea et al. [37]	15T1D/13 normal	Human	Feces	T1D vs normal	16S rRNA sequencing	<i>Bacteroides</i> , <i>Ruminococcus</i> , <i>Veillonella</i> , <i>Blautia</i> , <i>Streptococcus</i>	<i>Bifidobacterium</i> , <i>Roseburia</i> , <i>Faecalibacterium</i> , <i>Lachnospira</i>
Murri et al. [36]	16T1D/16 normal	Human	Feces	T1D vs normal	PCR-DGGE and RT-qPCR	<i>Clostridium</i> , <i>Bacteroides</i> , <i>Veillonella</i>	<i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Blautia</i> <i>coccoides</i> / <i>Eubacterium rectale</i> , <i>Prevotella pseudocatenulatum</i>
de Goffau et al. [39]	18T1D/18 normal	Human	Feces	T1D vs normal	16S rRNA sequencing	<i>Bacteroides</i>	<i>Bifidobacterium adolescentis</i> , <i>Bifidobacterium pseudocatenulatum</i>
Giongo et al. [38]	4T1D/4 normal	Human	Feces	T1D vs normal	16S rRNA sequencing	<i>Bacteroides ovatus</i>	<i>Firmicutes</i>
Davis-Richardson et al. [135]	29T1D/47 normal	Human	Feces	T1D vs normal	16S rRNA sequencing	<i>Bacteroides dorei</i> , <i>Bacteroides vulgatus</i>	NA
Huang et al. [42]	12T1D/10 normal	Human	Feces	T1D vs normal	16S rRNA sequencing	<i>Bacteroidetes</i>	<i>Firmicutes</i>
Zhu et al. [14]	41MAP/59MSAP/30SAP/35 normal	Human	Feces	SAP vs MAP and MSAP	16S rRNA sequencing	<i>Escherichia-Shigella</i>	<i>Blautia</i>
Zhang et al. [136]	45AP/44 normal	Human	Feces	AP vs normal	16S rRNA sequencing	<i>Bacteroidetes</i> , <i>Proteobacteria</i>	<i>Firmicutes</i> , <i>Actinobacteria</i>
Tan et al. [78]	32MAP//44SAP/32 normal	Human	Feces	AP vs normal	PCR-DGGE and RT-qPCR	<i>Enterobacteriaceae</i> , <i>Enterococcus</i>	<i>Bifidobacterium</i>
Chen et al. [65]	20 AP/20 normal	Rats	Feces	AP vs normal	16S rRNA sequencing	<i>Escherichia-Shigella</i> , <i>Phascolarctobacterium</i>	<i>Saccharibacteria</i> , <i>Tenericutes</i>
Han et al. [92]	8CP/8 normal	Mouse	Colon feces	CP vs normal	16S rRNA sequencing	<i>Bacteroides</i> , <i>Alloprevotella</i>	<i>Lachnospiraceae</i> <i>Mk4A136</i> , <i>Ruminiclostridium</i> , <i>Roseburia</i>
Zhou et al. [100]	71CP/69 normal	Human	Feces	CP vs normal	16S rRNA sequencing	<i>Proteobacteria</i>	<i>Firmicutes</i> , <i>Actinobacteria</i>
Jandhyala et al. [104]	30CP/10 normal	Human	Feces	CP vs normal	16S rRNA sequencing	<i>Firmicutes</i> / <i>Bacteroidetes</i>	<i>Faecalibacterium prausnitzii</i> , <i>Ruminococcus bromii</i>
Gorovits et al. [137]	96 CP	Human	Feces	CP vs normal	gas-liquid chromatography analysis	<i>Enterobacter</i> , <i>Proteus</i> , <i>Klebsiella</i> , <i>Morganella</i>	<i>Bifidobacterium</i> , <i>Lactobacillus</i>
Farrell et al. [115]	27CP/28 normal	Human	Oral	CP vs normal	qPCR	<i>Streptococcus mitis</i>	<i>Granulicatella adiacens</i>
Michaud et al. [138]	405PC/416 normal	Human	Plasma	PC vs normal	Antibiotics to oral bacteria	<i>Porphyromonas gingivalis</i>	<i>Streptococcus mitis</i>
Fan et al. [139]	361/371 normal	Human	Oral	PC vs normal	16S rRNA sequencing	<i>Porphyromonas gingivalis</i> , <i>Aggregatibacter actinomycetemcomitans</i>	<i>Fusobacteria</i> , <i>Leptotrichia</i>
Torres et al. [140]	8PC/22 normal	Human	Oral	PC vs normal	16S rRNA sequencing	<i>Leptotrichia</i> , <i>Bacteroides</i> ,	<i>Porphyromonas gingivalis</i> , <i>Neisseria elongate</i> , <i>Aggregatibacter actinomycetemcomitans</i>
Half et al. [141]	15PC/15 normal	Human	Feces	PC vs normal	16S rRNA sequencing	<i>Bacteroides Verrucomicrobia</i> , <i>Sutterella</i> , <i>Veillonella</i> , <i>Bacteroides</i> , <i>Odoribacter</i> and <i>Akkermansia</i>	<i>Firmicutes</i> , <i>Actinobacteria</i>
Lin et al. [142]	13PC/12 normal	Human	Oral	PC vs normal	16S rRNA sequencing	<i>Bacteroides</i>	<i>Corynebacterium</i>
Farrell et al. [115]	38PC /38 normal	Human	Oral	PC vs normal	16S microarray	<i>Granulicatella adiacens</i>	<i>Neisseria elongate</i> , <i>Streptococcus mitis</i>
Ren et al. [129]	85PC/57 normal	Human	Feces	PC vs normal	16S rRNA sequencing	<i>Bacteroidetes</i>	<i>Firmicutes</i> , <i>Proteobacteria</i>

T1D type 1 diabetes, AP acute pancreatitis, MAP mild acute pancreatitis, MSAP moderately severe AP, SAP severe acute pancreatitis, CP chronic pancreatitis, PC pancreatic cancer, qPCR real-time quantitative PCR, SAP severe acute pancreatitis.

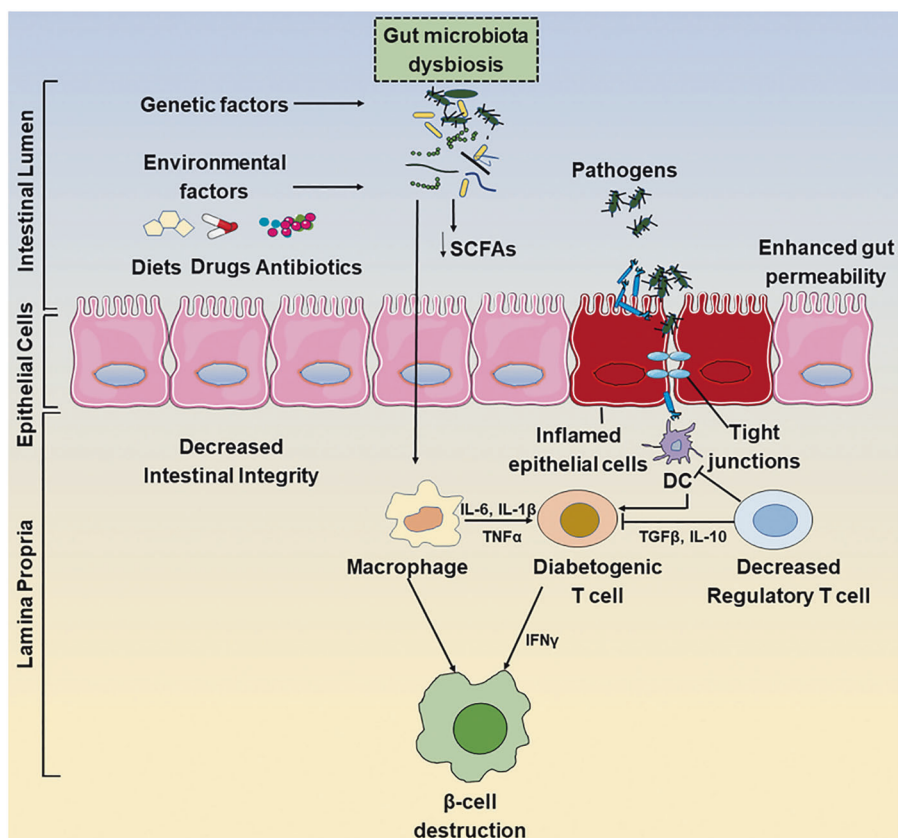


Fig. 1 Interactions between gut microbiota dysbiosis and the development of type 1 diabetes. Gut microbiota dysbiosis causes the disassembly of tight junctions, thereby disrupting the integrity of the intestinal barrier and allowing unregulated passage of environmental pathogens such as microbes and their products. The translocated pathogens could be taken up by antigen-presenting cells, including macrophages and dendritic cells, which can process and present antigens to autoreactive T cells and subsequently promote the destruction of pancreatic beta cells in genetically predisposed individuals. DC dendritic cells, SCFAs short-chain fatty acids.

Mechanisms by which the gut microbiota affects T1D development. The above animal and human studies suggested that compositional changes in the gut microbiota are involved in the pathophysiology of T1D, and gut dysbiosis-mediated immunological deregulation and gut leakage are possible pathogenic mechanisms (Fig. 1). The gut microbiota is considered the largest organ of the immune system owing to its ability to constantly interact with immunological cells [46]. On the one hand, gut dysbiosis causes the disassembly of tight junctions, thereby disrupting the integrity of the intestinal barrier and allowing unregulated passage of environmental antigens such as the microbiota and their products [47]. The translocated microbial antigens could be taken up by antigen-presenting cells, including macrophages and dendritic cells (DCs), and then processed and presented to autoreactive T cells, resulting in the conversion of Th0 to Th1 and Th17 cells and in the destruction of islet beta cells [20]. In addition, the maturation of the Tregs expressing the transcription factor Foxp3 is crucial for immune homeostasis, and the reduced frequency or function of Foxp3⁺ Tregs in NOD mice stimulates the onset of T1D [41, 48]. Moreover, several studies have pointed out that not only the gut microbiota but also its metabolites, especially SCFAs play pivotal roles in promoting mucosal immune homeostasis and host health via their direct immune-modulatory effects on immune cells. Among metabolites, butyrate provides energy for colonic epithelial cells and enhances the abundance and function of splenic and colonic Foxp3⁺ Tregs via histone modification [49]. More interestingly, we previously showed that gut microbiota-derived SCFAs could promote cathelicidin-related antimicrobial peptide expression in pancreatic cells, which protects against autoimmune diabetes in NOD mice

[11]. Similarly, Miani et al. demonstrated that gut microbiota-derived molecules, namely, aryl hydrocarbon receptor ligands and butyrate, promote interleukin-22 secretion by pancreatic innate lymphoid cells, which induce the expression of mouse β -defensin 14 in endocrine cells and subsequently prevent autoimmune diabetes in NOD mice [50].

On the other hand, gut microbe-derived pathogen-associated molecular patterns can be recognized by pathogen recognition receptors such as TLRs and subsequently initiate the innate immune response to address T1D. The first attempt to investigate the innate immune pathway associated with microbial exposure in T1D was conducted in myeloid differentiation primary response protein (MyD88)-deficient NOD mice. MyD88 is an adaptor protein of multiple TLR family receptors that can recognize microbial stimuli and contribute to downstream signaling pathways of TLRs [51]. SPF NOD mice lacking MyD88 were completely protected from T1D, and the protective effect was derived from the beneficial microbial composition [52]. Conversely, MyD88-deficient mice had an increased risk of developing T1D under germ-free conditions, while the incidence of diabetes was attenuated in these mice under exposure to a defined microbial mixture, which further supports the notion that the microbial community interacts closely with the host innate immune system [52]. In addition, Peng et al. found that the transfer of the gut microbiota from MyD88-deficient NOD mice to wild-type NOD mice delayed the onset of diabetes, while the destruction of the gut microbiota by broad-spectrum antibiotics increased the incidence of T1D [53]. Moreover, TLR2 and TLR4 are used to modulate T1D development through the “balanced signal” hypothesis, in which microbes provide prediabetic or tolerizing

signaling to promote or inhibit autoimmune T1D through TLR2 and TLR4, respectively [54, 55]. Collectively, the above findings indicate that the commensal microbiota is important for the prevention of T1D, and the different compositions of the intestinal microbiota could affect the mucosal innate immune system and modify the T1D pathology.

ROLE OF THE MICROBIOTA IN THE DEVELOPMENT OF ACUTE PANCREATITIS

In addition to T1D, AP is another common pancreatic disease and is caused by premature intra-acinar activation of trypsinogen and other proteolytic enzymes, resulting in pancreatic acinar injury and an inflammatory response. AP is characterized by the following two criteria: acute abdominal pain and increased circulation of pancreatic enzymes (amylase, lipase) due to pancreatic acinar cell death [56]. The common causes of AP are biliary obstruction by gallstones (40%), alcohol misuse (30%), and hypertriglyceridemia (2%–5%) [57]. Systemic injury manifested in the form of organ failure is the result of severe AP, and severe AP has high morbidity and mortality in up to 20% of cases, which contributes to substantial hospitalization and health-care costs for many people worldwide [58–61]. Disruptions of the epithelial barrier and increased gut permeability have been frequently observed in AP pathology, including alterations in tight junction proteins [62, 63]. For instance, Sonika et al. reported reduced expression of claudin-4 in duodenal biopsies of AP patients [63]. The gut microbiota and antimicrobial peptides have also been recognized as key components of the intestinal barrier, and they interact with each other to maintain gut homeostasis and barrier function [64–67]. Once the enteric microenvironment is altered, some intestinal bacteria (*Staphylococcus*, *Enterococcus*, *Escherichia coli* and *Klebsiella*) migrate into the pancreas and worsen the local inflammatory condition, resulting in bacterial translocation and overgrowth and mucosal immune dysfunction [68–70]. Identification of the underlying role of the altered gut microbiota in AP could lead to novel therapeutic strategies that would improve the clinical outcome. Therefore, several animal and human studies have been used to interpret the correlation between the gut microbiota and AP development.

Animal studies

Bacterial infections, especially those caused by pathogenic bacteria, are commonly associated with AP. However, whether intestinal microbiota dysbiosis is involved in the progression of AP remains largely unknown. To reveal the role of the gut microbiota in AP, Zhu et al. compared the microbial structure between AP mice and healthy controls. AP mice had a higher level of *Escherichia-Shigella*, *Enterococcus* and an unclassified member of *Enterococcaceae* and a lower level of *Blautia* than healthy mice. In addition, pancreatic injury was alleviated in antibiotic-treated mice and germ-free mice after AP induction. While fecal microbiota transplantation (FMT) into gut microbiota-depleted mice could exacerbate the disease, these mice exhibit more serious morphological damage, such as necrosis, inflammatory infiltrate and pancreatic edema, compared to mice without FMT. Thus, it was concluded that gut dysbiosis could worsen the severity of AP in mouse models [14]. In addition, Chen et al. found increased numbers of *Escherichia-Shigella* and *Phascolarctobacterium* and decreased numbers of *Candidatus_Saccharimonas*, *Prevotellaceae_UCG-001*, *Lachnospiraceae_UCG-001*, *Ruminiclostridium_5*, and *Ruminococcaceae_UCG-008* in AP rats. Simultaneously, they found that lysozyme and α -defensin5 mRNA expression levels (Paneth cell antimicrobial peptide) decreased significantly in the AP group, and the abundance of *Escherichia-Shigella* was correlated inversely with the decrease in lysozyme levels [65]. Concomitant with gut dysbiosis, gut barrier dysfunction occurred, as indicated by higher plasma diamine oxidase and D-

lactate levels in AP mice [65]. Based on the fact that the intestinal microbiota and antimicrobial peptides participate in the protection of the intestinal barrier, it was concluded that gut dysbiosis and decreased antimicrobial peptide levels destroyed the intestinal barrier during acute necrotizing pancreatitis [65]. In another study, Zheng et al. investigated the effect of another *Escherichia* commensal strain, *E. coli* MG1655, on AP in a rat model, and *E. coli* MG1655-monocolonized rats presented more severe injury in the pancreas and intestinal barrier dysfunction than gut microbiota-depleted rats [71]. The above two studies indicated that nonpathogenic commensals could also exhibit adverse effects in the context of AP. More interestingly, enteric viruses, as a part of the gut microbiota, also play a crucial role in experimental AP. We previously showed that the depletion of enteric viruses by an oral antiviral cocktail (AVC) could alleviate experimental AP. Meanwhile, AVC treatment suppressed innate immune cell infiltration and TLR9 expression and signaling and modulated inflammatory responses, thereby protecting mice from experimental AP by inhibiting TLR9 signaling [72]. From the above findings, altered gut microbiota composition is closely associated with AP development, and gut dysbiosis and subsequently impaired antimicrobial peptide production in Paneth cells worsen AP.

To date, the exact predominant bacteria in AP pathogenesis unknown, but previous studies (listed in Table 1) have suggested that animals with AP have greater abundances of the phyla *Proteobacteria* and *Bacteroidetes* and lower abundances of the phylum *Firmicutes* than healthy controls. Considering the role of gut dysbiosis in AP development, some potential therapeutic strategies (such as enteral nutrition, probiotics, and symbiotics) targeting the gut microbiota have emerged for the treatment of AP in animals. In the study of van Minnen et al., multispecies probiotics (*Lactobacillus acidophilus* W70, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, and *Lactococcus lactis* W58, *Bifidobacterium bifidum* W23 and *Bifidobacterium infantis* W52; each probiotic at 5×10^9 CFU/mL) were used to explore whether the modulation of the intestinal flora could reduce bacterial translocation or improve outcome in a rat model of AP. The results showed that modification of the gut microbiota with multispecies probiotics contributed to reduced bacterial translocation and mortality in the course of AP [73]. The beneficial effects of probiotics on AP can be attributed to their capability to enhance pancreatic glutathione biosynthesis and reduce oxidative stress [74]. In addition, Akyol et al. evaluated the effects of probiotics alone (*Saccharomyces boulardii*, 25 mg/d) or combined with two antibiotics (ciprofloxacin and meropenem) on experimental AP, and they found that probiotic treatment alone could reduce bacterial translocation, and probiotic-antibiotic combination therapy was shown to improve histopathologic scores and oxidative parameters in experimental AP [75]. Interestingly, a study found that pretreatment but not treatment with multispecies probiotics alleviated intestinal barrier dysfunction in a murine model of AP [76]. Furthermore, enteral nutrition was proven to be an effective way to attenuate AP, and the protection is attributed to specific immunomodulatory nutrients, such as glutamine, arginine, and n-3 fatty acids, which help to maintain mucosal health and gut function as well as stabilize the gut microbiota [77].

Human studies

Based on animal studies of AP, a large number of clinical studies have been used to explore the relationship between gut dysbiosis and AP development in humans. Zhu et al. collected fecal samples from 165 adult participants, including 41 with mild AP, 59 with moderately severe AP, 30 with severe AP, and 35 healthy controls. They found that the composition of the gut microbiota between AP patients and healthy subjects was significantly different, and gut dysbiosis was closely correlated with systematic inflammation

and gut barrier dysfunction. In addition, the microbial composition changed further with the worsening of AP. In severe AP cases, the abundances of beneficial bacteria such as *Blautia* decreased compared with those in other groups. It was also observed that bacterial invasion of epithelial cells in AP is highly correlated with the abundances of *Escherichia-Shigella* and *Enterococcus*, potential pathogenic bacteria that are enriched in AP. This study indicated that some members of the gut microbiota could form niche-specific relationships and that gut microbiota dysbiosis is associated with gut barrier impairment and subsequent AP severity, suggesting its role as a potential therapeutic target [14]. Similarly, Tan et al. conducted a clinical study of 108 participants, including 44 with severe AP, 32 with mild AP, and 32 healthy volunteers, with ages ranging between 25 and 65 years. Fecal sample sequencing suggested that *Enterobacteriaceae* and *Enterococcus* populations were more abundant in all patients with AP than in healthy subjects, while the abundance of the beneficial bacterium *Bifidobacterium* was lower in all AP patients than in healthy participants, which further indicates that gut dysbiosis worsens the severity of AP in humans [78].

Recently, modulation of the gut microbiota was considered as a potential therapeutic approach for AP control. In a study by Roberts et al., early enteral nutrition was beneficial in severe AP patients, and its use was linked to improved glycemic control, reduced infectious complications, and reduced multiorgan failure and mortality [79]. These results can be attributed to the role of nutrient levels in the maintenance of the gut flora. In addition, a few studies have examined probiotic prophylaxis in patients with AP, and conflicting results have been observed. Oláh et al. first conducted a human study of probiotics (*Lactobacillus plantarum* 299) for the treatment of pancreatitis, and they found that *L. plantarum* 299 had no adverse effects and was effective in reducing pancreatic sepsis and the number of surgical interventions [80]. In a subsequent study by Oláh et al., four species of lactic acid bacteria (LAB)—*Lactobacillus paracasei* subsp. *paracasei* 19, *L. plantarum* 2362, *Pediococcus pentosaceus* 5–33:3, and *Leuconostoc mesenteroides* 32–77:1—together with four prebiotic fibers were administered to 31 severe AP patients, and the above symbiotic therapy significantly decreased the cumulative incidence of systemic inflammatory response and multiorgan failure and increased the recovery rate of patients [81]. However, in a study by Besselink et al., the “Probiotics in Pancreatitis Trial” indicated that a multispecies probiotic mixture (*L. acidophilus*, *L. casei*, *L. salivarius*, *L. lactis*, *B. bifidum*, and *Bifidobacterium lactis*) did not reduce the risk of infectious complications and was associated with an increased risk of mortality [82], which prevented many researchers from further exploring the therapeutic use of probiotics in patients with pancreatitis. In another retrospective study, no positive or negative impact of probiotic treatment was demonstrated in patients with predicted severe AP without initial organ failure [83]. This controversial effect of probiotics on clinical AP across studies is mainly attributed to the different compositions, dosages, and treatments of probiotic therapy, since only a few of the thousands of bacteria that have been investigated as potential probiotics have probiotic and anti-inflammatory properties. Therefore, new specific probiotics or new cocktails of probiotics are needed, and extensive preclinical studies are essential for application in clinical practice.

Mechanisms by which the gut microbiota affects AP development. The development of animal model studies and human studies helps provide a full understanding of the immune mechanisms by which the gut microbiota affects AP development. As shown in Fig. 2, gut dysbiosis and the resultant suppression of antimicrobial peptide production lead to gut barrier impairment and pathogenic microbiota translocation through the intestinal epithelium. Subsequently, microbial components such as lipopolysaccharide can activate the host innate immune system via pattern

recognition receptors such as TLRs. Some studies reported that the lack of TLR4 could ameliorate the severity of AP in mice and protect against damage, while TLR2 does not participate in the pathogenesis of AP in mice [84, 85]. In addition, we previously suggested that the depletion of enteral viruses could modulate experimental AP by suppressing TLR9 signaling. It was observed that AP mice treated with a TLR9 agonist had aggravated AP-related symptoms and decreased chemokine production. Conversely, TLR9 antagonists exert protective effects against AP [72]. Furthermore, damage-associated molecular pattern molecules (DAMPs) released from injured tissue can serve as TLR ligands and are important mediators of the pathogenesis of AP. Extracellular high mobility group box 1 (HMGB1), a kind of DAMP molecule, can activate TLR9 and help immune activation and sensing of necrotic cells [86, 87], and increased HMGB1 production is positively associated with severe AP [88, 89].

According to Watanabe et al., the activation of innate immune responses by translocated commensal organisms is necessary to trigger inflammation during AP, and the activation of nucleotide-binding oligomerization domain 1 in acinar cells is an essential component of the innate immune response, resulting in the activation/production of nuclear factor- κ B (NF- κ B) and type I interferon [90]. Following gut dysbiosis-mediated activation of innate immune signaling pathways and associated tissue injury, neutrophil infiltration and macrophage recruitment into the pancreas accelerate the progression of AP. In addition, a member of the IL-1 superfamily of cytokines, IL-33, released during cell injury, was shown to be protective against AP by well-defined wound healing and reparative roles of activated macrophages. However, there is limited evidence supporting the role of the gut microbiota in modulating these immune cells and cytokines. Therefore, exploring the role of the gut microbiota in the innate immune system and adaptive immune system will help us to better understand the potential effects of the gut microbiota in AP pathology.

ROLE OF THE MICROBIOTA IN THE DEVELOPMENT OF CHRONIC PANCREATITIS

Long-term and recurrent AP could progress to CP. CP is characterized by a long-term or recurrent process of inflammation with concurrent sequelae of an acute episode, which is often accompanied by pancreatic exocrine insufficiency, eventually affecting the gut microenvironment and microbiota [91]. Recent evidence indicates that the intestinal microbiota impacts the course of CP, and these findings deserve further exploration in humans.

Animal studies

The microbial influence on CP is being increasingly recognized, supported by emerging evidence in experimental models. The study by Han et al. demonstrated that there were significant alterations in the gut microbiota in CP mice compared to control groups, as revealed by decreased abundances of *Lachnospiraceae_NK4A136*, *Ruminiclostridium*, and *Roseburia* and increased abundances of *Bacteroides* and *Alloprevotella*, indicating that gut dysbiosis is closely associated with CP development [92]. Likewise, Leppkes et al. found that when specific pathogen-free (SPF) mice were pretreated with the feces of CP mice by oral gavage before IL-17A expression was induced, they developed severe CP, whereas untreated SPF mice did not. It has been demonstrated that the gut microbiota is a necessary factor in IL-17A-induced CP [93]. In addition, CP could affect the exocrine function of the pancreas, and pancreatic exocrine insufficiency was proven to be the most important host factor involved in shaping the human intestinal microbiome. For example, Nishiyama et al. found that supplementation with pancreatic digestive enzymes induced the colonization of beneficial bacteria, including *A. muciniphila* and

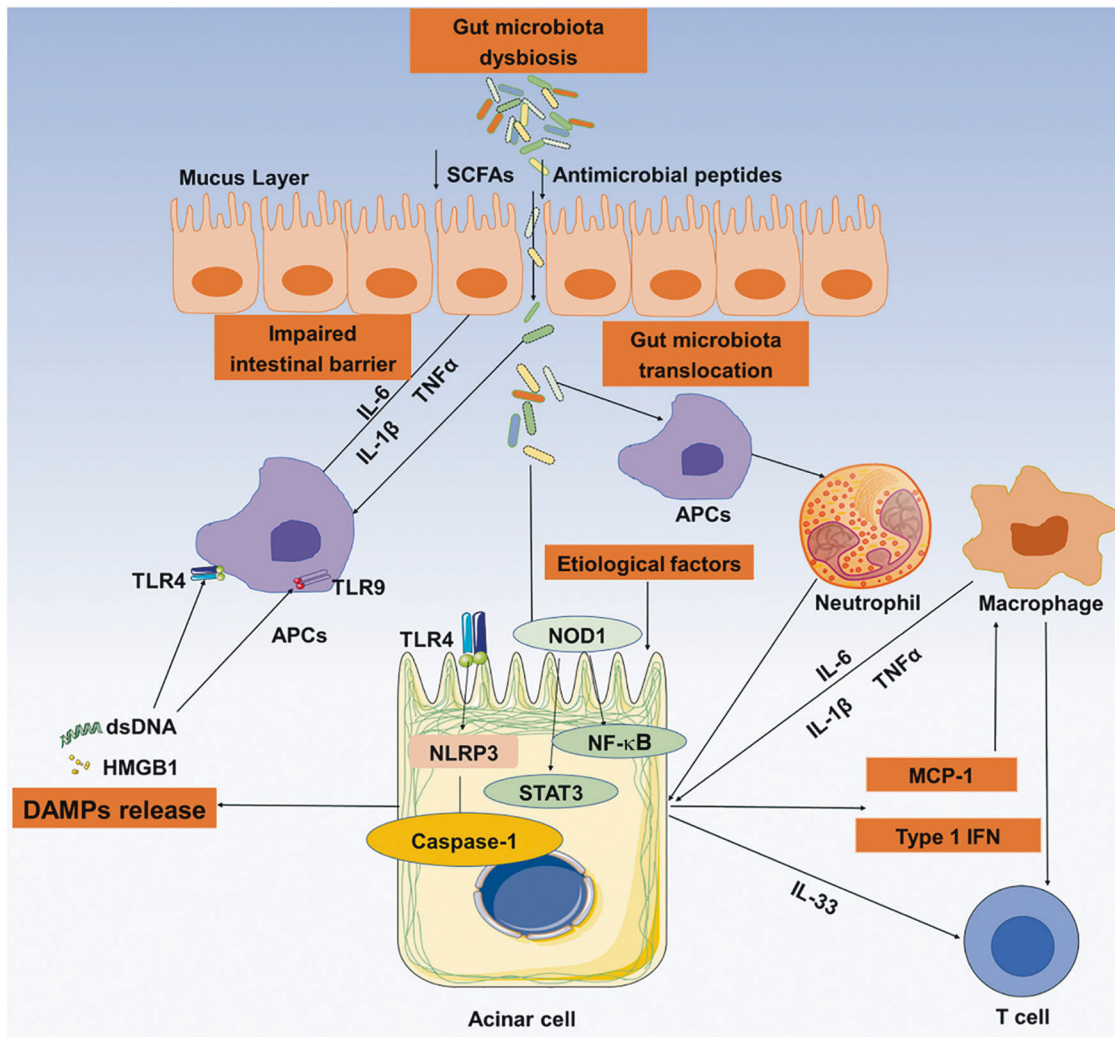


Fig. 2 Interactions between intestinal microbiota dysbiosis and the development of acute pancreatitis. Gut microbiota dysbiosis and the resultant suppressed antimicrobial peptide production lead to gut barrier impairment and pathogenic microbiota translocation through the intestinal epithelium. The translocated gut microbiota can activate the host innate immune system via TLR-mediated signaling. Following gut dysbiosis, neutrophil infiltration, and macrophages are recruited into the pancreas to promote the progression of acute pancreatitis (AP). Furthermore, damage-associated molecular pattern molecules (DAMPs) released from damaged acinar cells can serve as TLR ligands and are important mediators of the pathogenesis of AP. AP acute pancreatitis, APCs antigen-presenting cells, DC dendritic cells, DAMPs damage-associated molecular pattern molecules, SCFAs short-chain fatty acids, TLRs Toll-like receptors.

Lactobacillus reuteri and inhibited proinflammatory bacteria, thereby contributing to gut barrier enhancement and attenuation of CP [94]. These findings suggest the potential of FMT and probiotics to treat CP.

Similar to AP, enteral nutrition via a jejunal tube is replacing parenteral nutrition but requires repeated trials [79, 95]. Moreover, antibiotic use in CP mice is also under debate [96, 97]. However, prebiotics such as natural polysaccharides are efficient in the attenuation of CP symptoms and modulation of the gut microbiota. For instance, Hu et al. observed that *Inonotus obliquus* polysaccharide could regulate gut microbiota composition and diversity in mice with CP. The microbial diversity of *I. obliquus* polysaccharide-treated groups was lower than that of the controls. In addition, *I. obliquus* polysaccharide treatment increased the proportion of *Bacteroidetes* and decreased that of *Firmicutes* [98]. Similarly, *Ganoderma lucidum* polysaccharide treatment could also alter the composition and diversity of the intestinal microbiota by decreasing the relative abundance of *Bacteroidetes* and increasing that of *Firmicutes* at the phylum level. In addition, supplementation with *G. lucidum* polysaccharides increased the relative

abundances of beneficial bacteria such as *Lactobacillus*, *Roseburia* and *Lachnospiraceae* at the genus level [99]. These results revealed that the potential mechanism of action of prebiotics on CP might be intestinal microbiota dependent. However, whether probiotics are capable of decreasing the risk of CP in mice has not been thoroughly studied.

Human studies

Given that gut dysbiosis is closely associated with CP, the investigation of potential microbes involved in CP has proven to be beneficial for the identification of high-risk patients. A study conducted by Zhou et al. showed that the composition and diversity of the gut microbiota were changed in the CP group compared to the healthy group, and the CP group showed higher *Proteobacteria* abundances and lower *Firmicutes* and *Actinobacteria* abundances than the healthy group (Table 1). This alteration was closely associated with fecal elastase 1 activity, an index of pancreatic exocrine insufficiency [100]. In addition, exocrine pancreatic function is the most important host factor involved in shaping the human intestinal microbiome, as suggested by Frost

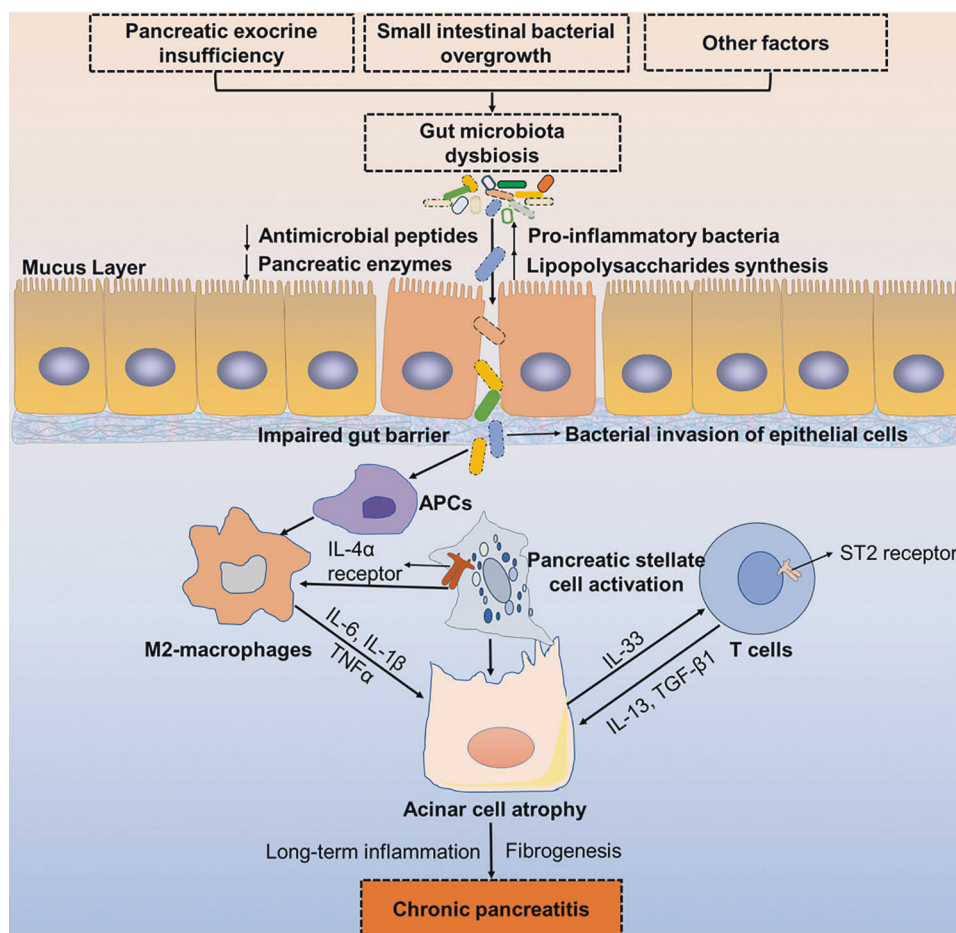


Fig. 3 Proposed relationship between gut microbiota dysbiosis and the development of chronic pancreatitis. In the context of CP, pancreatic exocrine insufficiency, gut bacterial overgrowth, and other environmental factors account for gut dysbiosis and suppressed antimicrobial peptide production, resulting in an impaired gut barrier and leaky gut. Thereafter, proinflammatory bacteria and toxins translocate through the leaky gut to the pancreas and recognize antigen-presenting cells (APCs) to activate M2 macrophages. Acinar cells are injured or apoptotic due to the release of $\text{TNF}\alpha$, IL-6, and IL-1 β in macrophages, resulting in IL-33 production. The proinflammatory cytokine IL-33 acts on T cells via the ST2 receptor to induce fibrogenic mediators such as IL-13 and TGF- β 1, which further aggravates acinar cell atrophy and pancreatic inflammation, resulting in chronic pancreatitis. APCs antigen-presenting cells, CP chronic pancreatitis, $\text{TNF}\alpha$ tumor necrosis factor α , TGF- β 1 transforming growth factor- β 1, ST2 suppression of tumorigenicity 2.

et al. They found a significant correlation between pancreatic elastase levels and changes in microbial diversity. Meanwhile, an increase in *Prevotella* and a decrease in *Bacteroides* were found in CP patients in a population-based study [10]. In addition, small-intestinal bacterial overgrowth in patients with CP is supportive evidence for the involvement of gut microbial dysbiosis in CP, which often causes chronic intestinal symptoms, including abdominal pain, bloating, and malabsorption [101, 102]. In turn, gut dysbiosis leads to reduced pancreatic synthesis of antimicrobial peptides, exacerbating small-intestinal bacterial overgrowth and pancreatic exocrine insufficiency, thus playing a critical role in the CP pathology. In a meta-analysis conducted by Capurso et al., the combined prevalence of bacterial overgrowth in patients with CP was 36%, accounting for one-third of CP patients [101]. The above findings were also proven by Kurdi et al. [102]. In a subsequent study, the proportions of *Bacteroides*, *Streptococcus*, and *Clostridium* species were higher in patients with CP. The authors speculated that gut dysbiosis may further reflect malabsorption and/or decreased levels of pancreatic enzymes, thus affecting CP development [103]. Jandhayala et al. examined the taxonomic and functional alterations in the intestinal microbiota in 16 patients with CP, 14 patients with CP combined with diabetes and 10 healthy controls. They observed an increase in the *Firmicutes/Bacteroidetes* ratio in all CP patients and a

reduction in the abundances of *Faecalibacterium prausnitzii* and *Ruminococcus bromii* in patients with CP with and without diabetes compared to the controls. The abundance of *F. prausnitzii* was negatively correlated with the plasma endotoxin level and glycemic status, and plasma endotoxin levels were positively correlated with blood glucose levels and negatively correlated with plasma insulin levels, indicating that gut microbial dysbiosis was associated with the metabolic alterations of CP [104]. These data indicate that particular changes in intestinal flora composition are associated with CP, gut dysbiosis may act as a diagnostic biomarker for CP, and future approaches involving therapeutic modulation of the intestinal microflora may be effective for CP treatment. However, the literature related to probiotic application in CP patients is still limited, and this aspect needs to be further explored.

Mechanisms by which the gut microbiota affects CP development. As illustrated in Fig. 3, long-term inflammation, acinar cell atrophy, and invariable pancreatic stellate cell activation associated with pancreatic fibrosis are notable features in the pathological process of CP [105, 106]. In CP development, T cells and macrophages are the two predominant types of immune cells [107, 108]. Acinar cells are injured or apoptotic in chronic inflammation due to the release of $\text{TNF}\alpha$ in macrophages, resulting in IL-33 production,

which could act via the suppression of the tumorigenicity 2 (ST2) receptor on T cells to induce fibrogenic mediators such as IL-13, the profibrogenic mediator acting on M2 macrophages to induce the production of TGF- β 1 [90]. Furthermore, gut dysbiosis also affects mucosal immune cell phenotypes, but the molecular mechanisms underlying the microbiota-immune interactions in the pathogenesis of CP are still unclear [109]. Therefore, elucidation of the crosstalk between the gut microbiota and mucosal immune system will provide us with a mechanistic understanding of CP development. With a deeper understanding of their interaction, precise manipulations of the intestinal flora may be possible and will lead to innovative new approaches for CP treatment.

GUT MICROBIOTA AND PANCREATIC CANCER DEVELOPMENT

CP is a high-risk factor for PC development, and PC is a highly lethal disease, leading to the death of 93% of patients within 5 years of diagnosis [110]. Genetic factors, pancreatitis, smoking, and excess body weight are risk factors for PC [111–114]. In addition, *H. pylori* infection is another considerable risk factor for PC. Fungi and the oral microbiota may also play a role in pancreatic carcinogenesis [115–117]. Early detection of PC would provide the optimal opportunity to improve the survival rate of patients, but to date, there are no well-recognized screening tools or biomarkers for PC at the population level. Recently, an increasing number of studies have demonstrated that the gut microbiota might influence PC susceptibility and tumor progression and can eventually influence therapeutic efficacy by promoting inflammation, activating the immune response, and perpetuating cancer-associated inflammation [116, 118–120]. Therefore, we discuss the role of the gut microbiota in PC in studies conducted in animals and humans in the following section, hoping to reveal microbiota-targeted interventions with therapeutic potential for PC.

Animal studies

The gut microbiota might play an important role in PC development. A study conducted by Pushalkar et al. suggested that ablation of the microbiome with antibiotics protected against PC, whereas transfer of the fecal samples from PC-bearing hosts to wild-type mice reversed the tumor protection [121]. *Bifidobacterium pseudolongum* (*B. pseudolongum*) occupies a large portion of the gut and tumor and finally accelerates oncogenesis in a TLR-dependent manner, and cell-free extracts from *B. pseudolongum* can upregulate tolerogenic cytokines such as IL-10 [121]. Moreover, antibiotic treatment in *Kras*^{G12D/+}/*PTEN*^{lox/+}/*Pdx1-Cre* mice (a genetically engineered mouse model of pancreatic adenocarcinoma) showed a decreased proportion of poorly differentiated tumors compared with nontreated mice, as reported by Thomas et al. [122]. A study conducted by Sethi et al. showed that gut microbiota depletion significantly reduced tumor burden in models of PC, colon cancer and melanoma, and the protective effects of the gut microbiota on PC were related to a significant increase in interferon gamma-producing T cells and decrease in IL-17A and IL-10-producing T cells [120]. Collectively, these data strongly suggest that gut dysbiosis promotes pancreatic oncogenesis in mouse models, and certain commensal microbes may play a protective role in the tumor microenvironment by modulating immune systems. Furthermore, gut dysbiosis has been proven to be correlated with inflammation, which could further aggravate gut dysbiosis and increase the vulnerability to pathogens [123]. Many studies have demonstrated that the gut microbiota and its metabolic components lead to the susceptibility of PC via multiple pathways. Mendez et al. tested the role of the gut microbiome and its metabolites in the early detection of PC. Their results showed that *Proteobacteria* and *Firmicutes* were dominant in the early stages of PC development, and microbial metabolites such as

polyamine were significantly elevated in the serum of KPC mice (a genetically engineered PC murine model). Moreover, there was a strong correlation between microbial alterations and the release of metabolites. Therefore, they concluded that microbial dysbiosis and polyamine metabolism could be predictive markers for the early detection of PC [124]. Thus, combining metabolites and microbiome analyses could help to elucidate interactions between the gut microbiota, metabolism, and the host, and clarifying how gut dysbiosis impacts host response and inflammation will be critical to obtaining an accurate picture of the role of the microbiome in PC development.

Human studies

Accumulating evidence from animal models shows that certain microbes and gut dysbiosis can potentiate PC tumor development by releasing tumor-related metabolites and activating immune responses. Thus, the gut microbiota may also participate in the pathogenesis of PC patients (see Table 1) [115, 125]. Riquelme et al. analyzed the tumor microbiome composition in PC patients with short-term survival and long-term survival. They found that the higher tumor microbial diversity in patients exhibiting long-term survival and an intra-tumoral microbiome signature (*Pseudoxanthomonas-Streptomyces-Saccharopolyspora-Bacillus clausii*) can be used to predict long-term survival in patients with PC [126]. Meanwhile, the authors found that the tumor microbiome can be modulated and tumor growth as well as tumor immune infiltration can be affected by humans-to-mice FMT experiments [126]. In addition, an altered oral microbiota has also been reported in relation to PC (Table 1). In study by Farrell et al., the oral microbial compositions of 28 patients with PC and 28 healthy controls were investigated, and they found that the taxa *Firmicutes*, *Proteobacteria*, *Actinobacteria*, *Cytophaga*, *Fusobacterium*, and *Bacteroides* were the predominant microbes in PC patients, and *Neisseria elongata* and *Streptococcus mitis*, as valid biomarkers for managing PC progression, were significantly decreased in PC patients compared with healthy controls [115]. Similarly, *Pseudomonas aeruginosa*, a unique ligand for taste receptor 2 member 38 (T2R38, expressed in both oral cells and PC cells), has been proven to be involved in cancer invasion and metastasis [127]. In addition, *Fusobacterium* species are regarded as independent negative prognostic biomarkers of PC due to their low abundance in PC tissues [128]. Furthermore, another study showed that PC patients had decreased gut microbial diversity compared with healthy controls, characterized by an increase in certain pathogens and LPS-producing bacteria and a decrease in probiotics and SCFA-producing bacteria, indicating that the unique gut microbial profile can be regarded as a biomarker for PC diagnosis [129]. These data provide evidence for the potential role of the gut microbiota and its metabolites in influencing PC susceptibility, while the related mechanisms of gut dysbiosis in the carcinogenesis of PC have still not been deciphered and require more attention.

Mechanisms by which the gut microbiota affects pancreatic cancer development. During PC, the composition of the gut microbiota changes, and the gut barrier is impaired. As a result, certain gut microbes could translocate to the pancreas and colonize the pancreas to induce a suppressive microenvironment that facilitates PC progression (Fig. 4). Specifically, microbiome ablation improves tumor immune surveillance and responses to programmed cell death protein 1 blockade, which contributes to a reduction in myeloid-derived suppressor cells (MDSCs), induces macrophage polarization to M2-like tumor-associated macrophages, and increases CD4⁺ T-helper 1 cell and CD8⁺ T-cell activation [55, 121, 130]. Gut microbes interact with the innate immune system via pattern recognition receptors in PC, since TLR-deficient mice (including TLR4, TLR7, TLR9) exhibit slower progression of PC [131–133], and then activate pro-

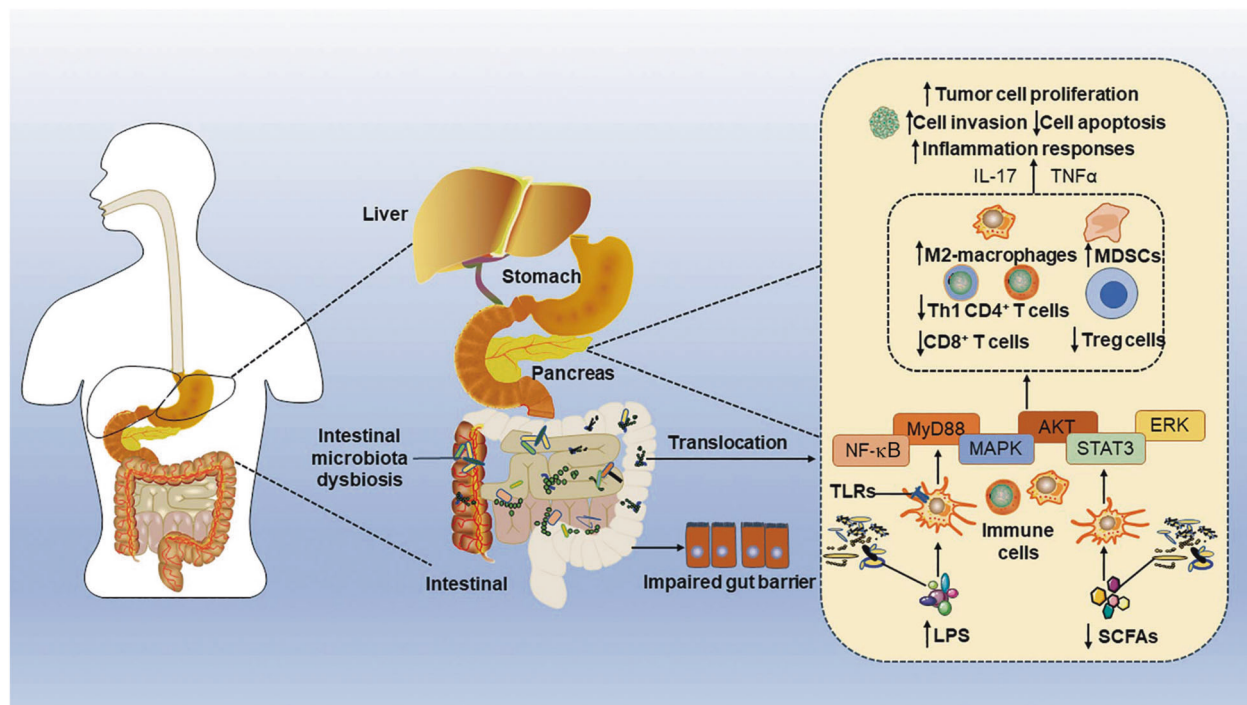


Fig. 4 Proposed relationship between gut microbiota dysbiosis and pancreatic cancer development. Gut dysbiosis during pancreatic cancer (PC) is responsible for impairment of the gut barrier and translocation of the microbiota and microorganism-associated molecular patterns, such as lipopolysaccharide (LPS), to the pancreas. The leakage of LPS, which activates Toll-like receptors (TLRs) that are expressed on various immune cells, activates the myeloid differentiation primary response protein (MyD88), nuclear factor- κ B (NF- κ B), mitogen-activated protein kinase (MAPK), and signal transducer and activator of transcription 3 (STAT3) signaling pathways, ultimately inhibiting Treg polarization of the T cell response and decreasing Th1 CD4⁺ T cell and CD8⁺ T cell recruitment, and supporting M2 macrophage polarization and myeloid-derived suppressor cell (MDSC) production. Consequently, these processes initiate the inflammatory response and tumor cell invasion and proliferation, and finally promote the progression of pancreatic cancer. LPS lipopolysaccharide, MAPK mitogen-activated protein kinase, MDSCs myeloid-derived suppressor cells, MyD88 myeloid differentiation primary response protein, NF- κ B nuclear factor- κ B, PC pancreatic cancer, SCFAs short-chain fatty acids, STAT3 signal transducer and activator of transcription 3, TLRs Toll-like receptors.

tumorigenic signaling pathways such as NF- κ B, signal transducer and activator of transcription 3 (STAT3) and mitogen-activated protein kinase (MAPK) signaling pathways, finally promoting the progression of PC [131, 132]. In addition, Sethi et al. found that depletion of the gut microbiota by oral antibiotics significantly reduced tumor burden in wild-type C57BL/6J mice but did not reduce tumor growth in Rag1 knockout mice (lacking mature T and B lymphocytes), suggesting that the regulatory effect of the gut microbiota on PC requires active participation of adaptive immunity [120]. Meanwhile, gut microbiome depletion by oral antibiotics significantly increased the numbers of Th1 (IFN γ ⁺CD4⁺CD3⁺), Tc1 (IFN γ ⁺CD8⁺CD3⁺), and IFN γ -secreting T cells (IFN γ ⁺CD3⁺) and decreased the numbers of protumor IL-17a (IL17a⁺CD3⁺) and IL-10 (IL10⁺CD4⁺CD3⁺) secreting T cells [120]. Moreover, the bitter receptor T2R38 can be activated by N-acetyl-dodecanoyl homoserine, a quorum sensing molecule of *P. aeruginosa*, and then increase the expression of multidrug resistance protein 1, thus linking the gut microbiota and PC [127]. Above all, the gut microbiota plays a pivotal role in PC pathogenesis by modulating innate and adaptive immune systems. With a better understanding of the role of the gut microbiota in PC progression, manipulation of the gut bacteria could emerge as a novel immunotherapeutic strategy.

CONCLUSIONS

In conclusion, the crosstalk between the gut microbiota and host response indicates the role of bacteria in pancreatic diseases. Although the mechanistic understanding of this relationship is still limited, it is clear that this field of research is moving forward and

that novel therapeutic interventions based on bacteria-related functions could be generated in the near future.

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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