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The Gut Microbiome in Pancreatic Disease

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Abstract

The gut microbiome is increasingly recognized for its role in human health and disease. Initial evidence indicates that gut microbial dysbiosis is associated with several pancreatic diseases. Although it is not known if these associations are causative, gut dysbiosis is hypothesized to mediate chronic pro-inflammatory changes in the pancreas. Further mechanistic and epidemiological studies of the microbiome are needed. Ultimately, targeted modulation of the microbiota could have therapeutic value.

Introduction:

The human gastrointestinal tract has a rich microbial community consisting of more than 10^{14} microorganisms and over 5,000,000 genes.[1, 2] *Firmicutes* and *Bacteroidetes* are the most prevalent bacteria constituting 80–90% of the gut microbiota[3]. Gut microbiota play a major role in human physiology through effects on metabolism, modulation of the mucosal immune system, vitamin production, facilitation of digestion and modulation of intestinal architecture. The gut microbiome influences the immune system through its effect on systemic metabolism effects as well as its antigenic effects. Normal gut bacteria play a crucial role in maintaining gut mucosal integrity. The interplay between the gut microbiota, immune system and intestinal barrier limits the growth of pathogenic flora[4] and disruption

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of this homeostasis leads to microbial imbalance known as 'dysbiosis'.[5] The gut microbiome is known to have major effects on systemic metabolism[6,7] but there are thousands of metabolites in the plasma and in the gut, many of which remain uncharacterized.[7] A large portion of the variance in fecal metabolites can be explained by the composition of the fecal microbiome.[7,8] Dysbiosis is associated with the pathogenesis of several gastrointestinal diseases (inflammatory bowel disease, irritable bowel syndrome)[9], as well as other diseases such as obesity, the metabolic syndrome, diabetes[10–12] and pancreatic diseases including pancreatic cancer.[13,14]

The normal pancreas is not in direct contact with the gut microbiota and was previously not considered to have a microbiome of its own. However, gut flora can migrate into the pancreas and may influence the pancreatic microenvironment even in subjects with an otherwise normal pancreas.[15] Gut microbiota alterations are found in pancreatic disease and may play a role in the pathogenesis of several pancreatic diseases including acute pancreatitis, chronic pancreatitis and pancreatic cancer.[14] However, there is still only limited evidence supporting a causal relationship between gut dysbiosis and pancreatic diseases. Many common factors influence the composition of the human microbiome including diet[16,17], commonly used medications (e.g. proton pump inhibitors[18], metformin[19]), and genetics[20–22] necessitating carefully controlled studies to evaluate relationships between the microbiome and disease. For this reason, many of the insights to date have come from animal models. In this review, we will discuss relevant human and animal studies that have provided insights into the role of the gut microbiome in the pathogenesis of pancreatic diseases.

Acute pancreatitis

Acute pancreatitis is among the most common gastrointestinal disorders requiring hospitalization with an annual incidence of 13–45 cases per 100,000 persons in United States.[23,24] Regardless of the etiology, acute pancreatitis is the result of premature intra-acinar activation of trypsinogen and other proteolytic enzymes resulting in pancreatic acinar injury, upregulation of pro-inflammatory mediators, release of cytokines, systemic inflammatory response and microcirculatory injury.[25] In the setting of acute pancreatitis, microcirculatory injury and hypovolemia can lead to can lead to gut mucosal ischemia and reperfusion injury resulting in loss of gut barrier integrity and translocation of gut flora causing local and systemic infections.[26] In a meta-analysis of 18 studies, Wu et al. found that 59% of patients with acute pancreatitis have gut barrier dysfunction.[27] In one study, circulating bacterial DNA representative of gut microbiota was found in 68.8% patients with acute pancreatitis.[28] Circulating bacteria likely contribute to the mortality from acute pancreatitis by causing infection within necrotic areas of the pancreas. Mortality in patients with infected pancreatic necrosis and organ failure is approximately double that found in patients with sterile pancreatic necrosis and organ failure.[29] The microbial composition of infected pancreatic necrosis was previously dominated by gram-negative flora of GI origin, such as *Enterobacteriaceae*. However, in the recent years, the widespread use of prophylactic antibiotics have shifted the dominant flora to Staphylococcus, *Enterococcus* and *Candida*.[30] Patients at higher risk of infected pancreatic necrosis are those who have been previously treated with antibiotics. While patients with infected pancreatic necrosis have higher

mortality, the microbial spectrum of infected necrosis does not appear to influence mortality.[31]

Necrotizing pancreatitis is known to impair gastrointestinal motility and in animal models results in small intestinal bacterial overgrowth (SIBO). In these models, duodenal bacterial overgrowth is associated with bacterial translocation and pancreatic infection.[32] In a rat model of necrotizing pancreatitis, bacterial translocation and subsequent infected pancreatic necrosis was found to be more frequent from the small bowel than the colon.[33]

Experimental necrotizing pancreatitis induces pro-inflammatory cytokines and reduces antimicrobial peptide expression (alpha-defensins and lysozyme) in the distal ileum.[34] These antimicrobial peptides help maintain gut microbiota homeostasis and barrier function.[35] Antimicrobial peptides are also secreted by pancreatic acinar cells. Knockout of the Ca^{2+} channel Orai1 in pancreatic acinar cells ($Orai1^{-/-}$) in mice reduced secretion of cathelicidin-related peptide (CRAMP), the major antimicrobial secreted by the pancreas, and resulted in increased small bowel and colonic bacterial colonization, increased intestinal permeability and bacterial translocation with resultant systemic infection and mortality. Mortality was reduced with antibiotics, short chain free fatty acids, and synthetic CRAMP.[36]

Interestingly, in pancreatic acinar cells, sensing of bacterial antigens by pathogen recognition receptors such as Toll like receptors (TLR), and the nucleotide binding oligomerization domain (NOD)-like receptors (NLRs) are thought to contribute to the pathogenesis of pancreatitis. Pancreatitis in mice can develop by chronic low-dose cerulein stimulation with NOD1 agonist stimulation, effects that are prevented in NOD1 knockout mice.[37] NOD1 can bind to peptidoglycan peptides in pancreatic acinar cells.[38]

Patients with acute pancreatitis are more likely than healthy volunteers to have gut dysbiosis (higher *Enterobacteriaceae* and *Enterococcus* populations, lower *Bifidobacteria)*.[39] These pre-clinical and human studies that implicate a role for intestinal dysbiosis in the pathogenesis and severity of acute pancreatitis raise the question of whether modulating the gut microbiome might be beneficial. Altering the ‘acute pancreatitis-associated microbiota’ with ‘physiological gut microbiota’ using broad-spectrum antibiotics and antimicrobial peptides might be expected to improve outcome. Benign physiological gut microbiota such as *Lactobacillus* alone and *Bifidobacterium* are thought to help maintain gut barrier function and limit the growth of pathogenic flora. The potential value of using probiotics for patients with severe acute pancreatitis has been evaluated in randomized controlled trials and summarized in a Cochrane review and a meta-analysis.[40, 41] Overall, probiotics have been shown to have no significant beneficial nor adverse effects in patients with severe acute pancreatitis. One caveat is that these trials had significant heterogeneity with respect to patient characteristics and probiotic regimens. One of these trials, conducted in the Netherlands, the ‘Probiotics in Pancreatitis Trial’ (PROPATRIA),[42] randomized 296 patients with predicted severe acute pancreatitis to a multispecies probiotic mixture containing two different *Bifidobacterium* species, three different *Lactobacillus* species and one *Lactococcus* species versus placebo. The infectious complications were similar among the two groups, but the probiotic group had higher mortality (16% vs 6%) and incidence of bowel ischemia (6% vs 0%) compared to the placebo group. The high load of probiotic mixture used in this

study was suspected to be a cause of the increased mortality in the treated group.[43] These studies highlight the challenges of trying to beneficially manipulate the gut microbiome in the setting of acute pancreatitis.

Chronic pancreatitis

Several studies have evaluated the gut microbiome in patients with chronic pancreatitis.[44] Evidence for gut microbial dysbiosis is suggested by the frequent observation of small intestinal bacterial overgrowth (SIBO) in patients with chronic pancreatitis. SIBO is thought to be more likely to arise in patients with chronic pancreatitis as a result of reduced pancreatic synthesis of anti-microbial peptides, impaired motility, abnormal chyme formation in the small intestinal lumen and from reduced alkalization due to reduced bicarbonate rich pancreatic secretory capacity.[45, 46] SIBO can exacerbate pancreatic exocrine insufficiency (PEI) suggesting that treatment of SIBO would help patients with PEI.[47] In a meta-analyses by Capurso et al., the mean prevalence of SIBO in patients with chronic pancreatitis was reported to be 36% (95%CI 17–60%),[48] although significant heterogeneity between studies was noted. In a subsequent study, Jandhayala et al. examined 16 patients with chronic pancreatitis, 14 with chronic pancreatitis with diabetes and 10 healthy controls.[49] Phyla abundances were different in the three patient groups, with reductions in the abundance of *Bacteroidetes* and increases in the ratio of *Firmicutes* to *Bacteroidetes* ratio among patients with chronic pancreatitis. There was a significant reduction in *Faecalibacterium prausnitzii* and *Ruminococcus bromii* between the control, chronic pancreatitis without diabetes and chronic pancreatitis with diabetes groups. *Faecalibacterium prausnitzii* is known to contribute to intestinal barrier homeostasis and integrity.[50, 51] Plasma endotoxin was detected in many of these patients and correlated negatively with glycemic status indicating that gut microbial dysbiosis was associated with the metabolic alterations of chronic pancreatitis.[49] Additional studies are needed to evaluate the role of gut dysbiosis in the setting of chronic pancreatitis.

Pancreatic cancer

The incidence of pancreatic cancer has been rising and is expected to be the second leading cause of death in United States by 2030.[52] The reasons for this increase in incidence are not fully understood but could in part be related to an increased incidence of known risk factors for pancreatic cancer including obesity, diabetes and the metabolic syndrome. Obesity and diabetes are known to be associated with changes in the gut microbiome,[10–12] and some of their metabolic consequences could be mediated in part through effects on the gut microbiome. Chronic pancreatitis is also a risk factor for developing pancreatic cancer, with the risk increasing with the duration of disease.[53–55] Since gut dysbiosis has been postulated to contribute to chronic pancreatic inflammation, it may also contribute to the pathogenesis of pancreatic cancer in the setting of chronic pancreatitis.

Gut dysbiosis has been hypothesized to promote the development of many types of cancer through systemic mechanisms, particularly metabolic changes that can influence precancerous cells and immune cells.[56] For example, short chain fatty acids produced in the gut with the help of the gut microbiome have metabolic effects on immune cells.[57] In the colon, adherent bacteria such as *Bacteroides fragilis* are thought to promote adenomas and

cancers as they produce enterotoxins that have tumorigenic effects including effects on signaling, cell adhesion molecules and cytokine alterations.[58, 59] Consistent with their role in modulating the immune response, gut bacterial profiles are recognized as influencing the immune response directed towards tumors.[15, 60] Several studies have shown that gut microbiome profiles influence the immune therapy response to checkpoint inhibitor therapy.[61–63]

Several studies have evaluated the influence of the microbiome on the pathogenesis of pancreatic cancer (summarized in Table 1). For example, several studies have found differences in the oral microbial flora between patients with pancreatic cancer compared to controls. Fan et al.[64] and Michaud et al.[65] found higher levels of *Porphyromonas gingivalis* in patients with pancreatic cancer than controls; the highest concentration of *Porphyromonas gingivalis* was associated with a twofold increase in pancreatic cancer risk, although a smaller study did not find this association.[66] *Porphyromonas gingivalis* is an important contributor to periodontal disease and has been postulated to cause systemic inflammation.[67] Other oral microbial differences found between patient groups with pancreatic cancer, chronic pancreatitis and healthy controls were described by Farrell et al.[68] Since these were case/control studies, it is not yet clear if these microbial changes contribute to disease pathogenesis or are merely a consequence of the disease. Recent studies have also identified bacteria within the tumor microenvironment of human pancreatic cancers [15] and within other tumors.[69] The bacteria identified in human pancreatic cancers are representative of the major genus of gut bacteria such as *Proteobacteria*.[6915] Recent studies in genetically engineered mouse models of pancreatic neoplasia have shed additional light on the role of gut bacteria in pancreatic tumorigenesis. Using the $Ptf1a^{Cre}$; $LSL\text{-}Kras^{G12D}$ (KC) and $Ptf1a^{Cre}$, $LSL\text{-}Kras^{G12D}$, $Trp53^{R172H}$ (KPC) mouse models of pancreatic neoplasia, *Pushalkar* et al. found oral antibiotics protected against neoplastic progression. They also found repopulating germ free KC mice with feces from pancreatic cancer bearing KPC mice or with *Bifidobacterium pseudolongum* accelerated disease progression. *B. pseudolongum* could also be detected within the pancreata of treated mice. Changes in the gut microbiome resulted in changes in immune cells within the tumor microenvironment. Microbial ablation led to a reduction in immunosuppressive $CD206^+$ M2-like tumor-associated macrophages (TAMs) with a concomitant increase in tumor-protective M1-like TAMs, and an increase in the CD8/CD4 ratio within the tumor microenvironment, changes that reversed with repopulation of the microbiome. Similarly, another recent study using wild type C57BL/6J, Rag1 knock-out (lacks mature T and B cells), KPC and $Pten^{fl/fl}$ mice demonstrated that gut microbial depletion with antibiotics resulted in an increase in Th1 ($IFN\gamma^+CD4^+CD3^+$) and Tc1($IFN\gamma^+CD8^+CD3^+$) cells in the tumor microenvironment and a reduction in pancreatic tumor burden.[70]

Experimental models have also found that intratumoral bacteria alter the metabolism of nucleoside chemotherapeutics such as gemcitabine.[6971] Bacteria are also detected in pancreatic cyst fluids including cysts associated with IPMN as well as non-neoplastic cysts, but the significance of these bacteria is not clear.[72] Despite these intriguing studies, the evidence that bacteria within the pancreas contributes to human pancreatic cancer pathogenesis is still limited.

Conclusions:

Gut microbial dysbiosis is thought to contribute to the pathogenesis of pancreatic diseases (Figure 1). Much of the evidence for this comes from animal models and these models will continue to be valuable for testing hypotheses. There is still much to understand about the causes and consequences of gut microbial dysbiosis as well as the contributions played by alterations in the abundance of different species. There are many large-scale efforts underway to characterize the human microbiome, the dietary, genetic, pathologic and pharmacological variables that influence it and its metabolic effects. Unraveling these associations is a necessary step towards better understanding the role of the microbiome in human pancreatic disease. Evaluating the gut microbiome of patients at risk of pancreatic disease in prospective studies is necessary to better understand the role of gut dysbiosis in human pancreatic disease pathogenesis.

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Abbreviations:

SIBO	Small intestinal bacterial overgrowth
DNA	Deoxyribonucleic acid
CRAMP	Cathelicidin-related anti-microbial peptide
TLR	Toll like receptors
NLR	Nucleotide binding oligomerization domain (NOD)-like receptors
PEI	Pancreatic exocrine insufficiency
LPS	Lipopolysaccharide
IFN γ	Interferon gamma
TAM	Tumor-associated macrophages

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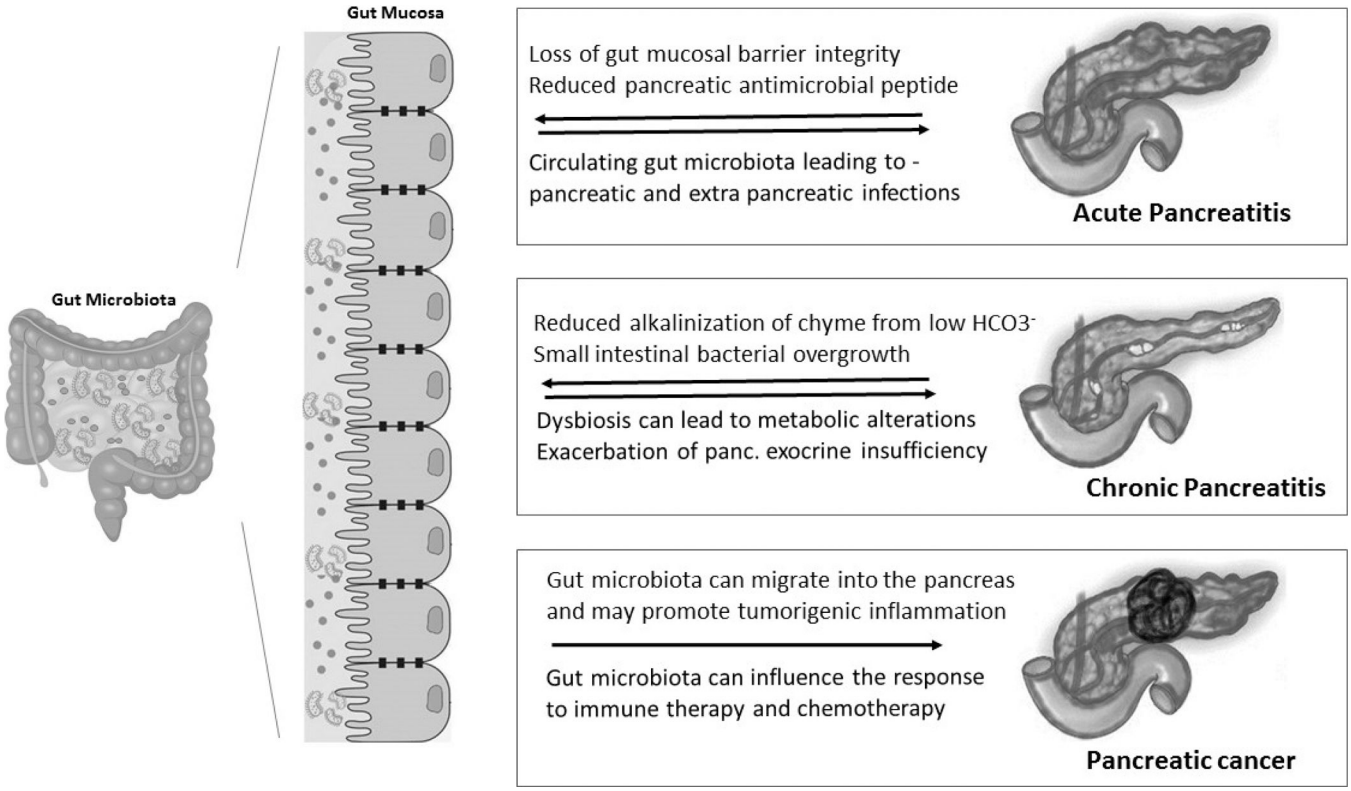

Figure 1:
Overview of interactions between gut microbiota and pancreatic disease

Table 1:

Studies examining microbiota alterations in patients with pancreatic cancer

Study author, year of publication	Number of cases with pancreatic cancer, number of controls	Sample type and microbial characterization	Microbial alterations (increases)	Microbial alterations (decreases)	Limitations
Pushalkar et al, 2018[15]	32, 31	Fecal, 16S rRNA gene sequencing	*Proteobacteria, Actinobacteria, Fusobacteria, Verrucomicrobia*		*sample size*
Pushalkar, 2018[15]	12, not reported	pancreatic cancer, 16S rRNAgene sequencing	*Proteobacteria, Sphingobacteria*		*sample size*
Fan et al, 2018[64]	361, 371	Salivary, 16S rRNA gene sequencing	*Porphyromonas Aggregatibacter*	*Leptotrichia, Fusobacteria*	
Geller et al, 2017[69]	113, 20	Pancreatic tumors, 16S rRNAgene sequencing	*Proteobacteria*		
Torres et al, 2015[66]	8, 22	Salivary, 16S rRNA gene sequencing	*Leptotrichia Bacteroides*	*Porphyromonas*	*sample size*
Michaud et al, 2013[65]	405, 410	Plasma antibody levels to oral bacteria	*Porphyromonas gingivalis*	*Streptococcus mitis*	
Farrell et al, 2012[68]	38, 38	Salivary, 16S rRNA gene sequencing		*Neisseria elongate, Streptococcus mitis*	*sample size*