



The association between exocrine pancreatic insufficiency and changes in gut microbiota: a narrative review

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Abstract

Due to their physical proximity, the healthy pancreas and the gut microbiome are known to interact in a variety of ways. The gut microbiota has been recognized as a potential factor in the development and progression of exocrine pancreatic insufficiency through several mechanisms. Pancreatic diseases like chronic and acute pancreatitis or pancreatic cancer are frequently accompanied by pancreatic exocrine insufficiency which affects the gut microbiota. Firstly, the gut microbes are controlled by antimicrobial pancreatic secretions, while themselves induce the secretion of substances by the pancreas through metabolite production, such as short-chain fatty acids. Secondly, dysbiosis, the alteration in the abundance and diversity of different species, has been observed in patients with pancreatic diseases. Dysbiosis influences carcinogenesis in pancreatic cancer in ways that are either procarcinogenic or anticarcinogenic and finding these connections will have clinical implications. Identifying microbial biomarkers allow for an earlier diagnosis, improved therapy and prognosis in pancreatic cancer. The gut microbiome has a role in the pathogenesis of pancreatitis by either a bacterial translocation or a host immune response mechanism. The disruption of the normal gut barrier is believed to be the primary source of bacteria in acute pancreatitis which leads to infected pancreatic necrosis.

In this paper, we review the current data about the association between pancreatic diseases linked to exocrine insufficiency and gut microbiota.

Keywords: gut microbiota, dysbiosis, pancreas, exocrine pancreatic insufficiency, chronic pancreatitis, acute pancreatitis, pancreatic cancer, pancreatic ductal adenocarcinoma

Introduction

The pancreas is anatomically connected to the gastrointestinal tract via the pancreatic ducts and communicates with the liver via the common bile duct. This close connection raises the question of whether the intestinal microbiota or an intrinsic pancreatic microbiota gives homeostatic benefits for the pancreas [1]. The gut microbiota has an impact on the physiological functions of the healthy pancreas. Bacterial metabolites, such as short-chain fatty acids, or the regulation of immune responses may contribute to the beneficial effect on the pancreas. On the other hand, the composition

and functional characteristics of the gut microbiota may be significantly influenced by pancreatic factors, such as the pancreatic excretion of antimicrobials [2].

The relationship between gut microbiota and exocrine pancreatic insufficiency has become a subject of interest. Impairment of the exocrine pancreatic function has significant consequences on the gut microbiota, as it serves as one of the most important mechanism for nutrition and food digestion. In several studies, the modulation of gut microbiota has been observed to influence the exocrine pancreatic function, establishing a

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bidirectional relationship between the two [3]. Although chronic pancreatitis is the most common cause of exocrine pancreatic insufficiency, other conditions, such as pancreatic cancer, cystic fibrosis or pancreatic resection cause exocrine pancreatic insufficiency. In 2019 the global incidence rate of acute pancreatitis (AP) was 34 cases per 100,000 population, 10 cases per 100,000 population for chronic pancreatitis (CP), and 8 per 100,000 person-years for pancreatic cancer (PC) [4]. Numerous potential options for new therapeutic targets exist in the microbiome. Targeted microbiome modification via probiotic, prebiotic, symbiotic, postbiotics and fecal microbiota transplantation is studied in order to ameliorate dysbiosis and metabolic pathways associated with exocrine pancreatic function, but further interventional trials are needed [3,5].

While several previous reviews have been published on the relationship between gut microbiota and pancreatic diseases, they primarily focused on investigating the differences in microbial composition. However, there is a growing tendency in research, involving both murine models and human subjects, which recognizes the significance of exocrine pancreatic function as a pivotal factor in microbiome studies.

In this review, we will explore the current data regarding the association of several pancreatic diseases that result in exocrine pancreatic insufficiency (pancreatitis and pancreatic cancer) with the gut microbiome. We will also discuss the role of dysbiosis and its microbial metabolites in pancreatic diseases. By understanding the intricate relationship between gut microbiome and pancreatic diseases, we aim to take a significant step forward in developing novel diagnostic tools and therapeutic interventions in exocrine pancreatic insufficiency.

Gut microbiota

The human gastrointestinal microbiota consists of more than 10^{13} - 10^{14} microorganisms, similar to the number of human cells, and includes at least 1000 distinct species, including bacteria, viruses, yeasts and archaea. In contrast, the term “microbiome” defines the complete genome sequence of gut microbiota which consists of more than 5 million genes [6,7]. The study of genetic material discovered in an environmental sample is known as metagenomics. All bacterial genomes contain the specific 16S rRNA gene and, as a result, the gut microbiota is extensively studied in many disorders using 16S rRNA gene sequencing [8]. Our understanding of the microbiome and its interactions is increasing rapidly since research into this subject has exponentially appeared. The gut microbiome plays a crucial role in gut innate immunity, such as immune development, immune responses and metabolism, and protection against infections. Furthermore, the microbiota has the ability to increase energy and nutrient extraction from food, to

synthesize amino acids, vitamins, as well as antimicrobial peptides and substances [7].

In healthy individuals, the microbiota is characterized by a wealth of microorganisms and a high species diversity, predominantly bacteria. *Firmicutes* (gram-positive bacteria) and *Bacteroidetes* (gram-negative bacteria) account for up to 85-90% of all bacteria, while *Actinobacteria*, *Proteobacteria*, *Fusobacteria* and *Cyanobacteria* are less abundant, accounting for up to 10% of microorganisms. This condition is called “eubiosis”. Human fecal metagenomes from four different countries were sequenced, and three separate enterotypes were proposed: *Bacteroides* species are present in enterotype 1, while numerous *Prevotella* and *Firmicutes* species are present in enterotypes 2 and 3, respectively [9].

Alterations in bacterial compositions, also known as “dysbiosis”, appear when there is a health condition, such as use of medications (antibiotics, proton pump inhibitors), diet modifications, host genetic features and motility disorders. Gut microbial dysbiosis was found to be a contributing factor to gastrointestinal diseases, such as inflammatory bowel diseases, irritable bowel syndrome, celiac disease, colorectal and stomach cancer, acute and chronic pancreatitis, pancreatic cancer, as well as rheumatologic disorders, Alzheimer’s disease, multiple sclerosis [10].

Exocrine pancreatic insufficiency

The human pancreas secretes 1-1.5 liters of juice every day into the duodenum that contains digestive enzymes and antimicrobial substances. The acinar cells synthesize most of the digestive enzymes, whereas its ductal cells secrete large volumes of water and bicarbonate. In order to avoid cell damage, some of the enzymes are synthesized and stored as inactive precursor forms before entering the duodenum. However, the pancreas contains many essential digestive enzymes in their active forms, including amylase and lipase [11]. These enzymes are shown in table I. Antibacterial peptides are secreted by intestinal cells, but other organs, including the pancreas, also secrete antibacterial matter into the intestine. Antimicrobial pancreatic secretion plays a significant role in gut innate immunity [12].

Table I. Proenzymes and enzymes in the pancreas [11].

| PROENZYMES (inactive) | ENZYMES (active) |
|-------------------------|------------------|
| Trypsinogen | Amylase |
| Chymotrypsinogen | Lipase |
| Procarboxypeptidase A,B | DNase |
| Prophospholipase (I,II) | RNase |
| Proelastase | |
| Mysotrypsin | |

Table II. Causes of exocrine pancreatic insufficiency [14].

| Loss of pancreatic parenchyma | Suppression of pancreatic secretion | Pancreatic asynchrony |
|------------------------------------|-------------------------------------|-----------------------|
| Chronic pancreatitis (most common) | Ampullary cancer | Short bowel syndrome |
| Pancreatic cancer | Pancreatic head adenocarcinoma | Gastric resections |
| Cystic fibrosis | Zollinger-Ellison syndrome | Crohn's disease |
| Pancreatic resections | Diabetes mellitus | Diabetes mellitus |
| | Crohn's disease | |

Exocrine pancreatic insufficiency (EPI) is caused by the loss of exocrine acinar cell functions, which results in maldigestion, malabsorption of micronutrients and macronutrients and malnutrition. There is carbohydrate, protein and fat malabsorption, with the latter being the most obvious clinical manifestation. Symptoms of EPI include abdominal pain, bloating, excessive flatulence, steatorrhea, diarrhea and weight loss [13]. The administration of prebiotics, probiotics or synbiotics, and fecal microbiota transplantation are used in order to manipulate the microbiota for patients with exocrine pancreatic insufficiency who do not respond to standard treatments. There are several conditions that are associated with EPI as shown in table II [14,15].

Microbiota-pancreas axis

Research studies have shown that the pancreas, once believed to be sterile, contains a microbiome in normal and disease states. The mechanisms by which bacteria can reach the pancreas are debated, however literature supports a number of ways, such as oral route, translocation from the lower gastrointestinal tract through the portal circulation or mesenteric lymph nodes and directly via the pancreatic duct [1]. Islands of bacterial

adhesion were found in almost 70% of the pancreatic duct biopsies acquired during endoscopic retrograde cholangiopancreatography from individuals with benign or malignant obstruction of the pancreatic duct [6].

According to studies, the pancreas secretes antimicrobials to control the intestinal microbiota. Pancreatic B-cells of adult mice produce the cathelicidin-related antimicrobial peptide (CRAMP) under the control of gut microbiota via short chain-fatty acids (SCFAs) (Figure 1). The antibacterial action results from the permeabilization of bacterial membranes. Studies suggest that the development of autoimmune diabetes was also attributed to improper production of SCFAs, which resulted in low amounts of CRAMP. This research raises the possibility that dietary changes might have a direct influence on the synthesis of antimicrobial peptides via SCFAs, preserving pancreas immunological homeostasis [12].

Another study that analyzed microbial and metabolomics data from separate population-based cohorts, consisting of 2226 volunteers, suggests that pancreatic function is linked to changes in plasma metabolite composition through the modulation of microbiota, which, in turn, may affect exocrine pancreatic function [3].

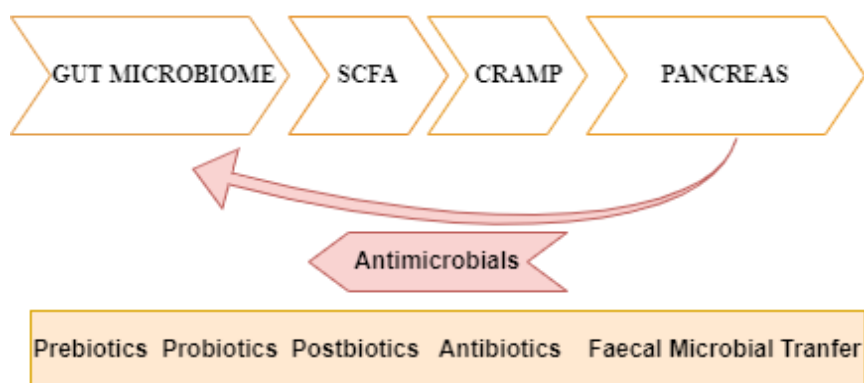


Figure 1. Two-way communication between gut microbiome and pancreas. SCFA, short-chain fatty acids; CRAMP, cathelicidin-related antimicrobial peptide; ORAI calcium release activated calcium modulator [12].

The findings of a study involving murine models and human clinical trials show the relevance of gut microbiota in exocrine pancreatic function and its role in obesity and metabolic conditions. In this study, the mice were fed either a chow diet or a high-fat diet, with subsequent manipulation of the gut microbiome using oral vancomycin or metronidazole. The results revealed that alterations in the gut microbiome induced by a high-fat diet led to increased pancreatic growth and a reduction in pancreatic enzymes, which were effectively reversed by antibiotic treatment. To further validate these findings, the study conducted a transfer of gut microbiota from donor mice to germ-free mice, which reproduced the observed changes. Notably, the clinical relevance of the study was demonstrated by significant increase in amylase and elastase levels in obese man with prediabetes following vancomycin administration [16].

Ahuja et al. showed that gut innate immunity is regulated by the release of antimicrobial proteins by pancreatic acinar cells with the help of calcium selective ion channel Orail. They observed that the intestinal microbiota of Orail-deficient mice had bacterial overgrowth, in particular *Proteobacteria*, with increase in *Succinivibrionaceae*, *Enterobacteriaceae*, and *Prevotella* spp. Hence, inhibiting acinar cell exocytosis of these proteins in mice resulted in gut dysbiosis, inflammation, systemic bacterial translocation, and eventually death [17]. Several studies have shown that gut dysbiosis can influence the production and secretion of pancreatic enzymes. In a population-based study, the analysis of pancreatic elastase levels and quantitative imaging of secretin-stimulated pancreatic fluid secretion from 1795 volunteers with no history of pancreatic disease was performed. When compared to participants' age, body mass index, sex, smoking, alcohol use, or dietary variables, differences in pancreatic elastase levels were considerably more correlated with changes in microbiota diversity. Even though the correlation was weaker, variations in microbial diversity were also correlated with variations in pancreatic fluid secretion. The 16S ribosomal RNA gene sequencing analysis of stool samples showed an increase in *Prevotella* and a decrease of *Bacteroides*, which revealed a change in enterotype from type-1 to type-2 [18].

Dysbiosis can cause altered immune responses, including low-grade inflammation, which leads to the development of EPI. Although the abundance of *Prevotella* colonization and its low pathogenicity, chronic inflammation was linked to some strains of *Prevotella* strains [19]. Moreover, some species have the ability to produce hydrogen sulfate, a substance that has been shown to cause pancreatic injury by inducing apoptosis. As a result, the exocrine pancreatic function progressively deteriorate [20].

Gut microbiota and pancreatitis

Acute pancreatitis (AP) is an inflammatory disease of the pancreas characterized by abdominal pain and elevated levels of pancreatic enzymes. The majority of cases are caused by chronic alcohol consumption and gallstone migration. The Atlanta Classification divides the severity of AP into three categories: mild, moderately severe and severe pancreatitis which includes pancreatic and peripancreatic necrosis and hemorrhage.

Prematurely activated pancreatic enzymes inside the pancreas result in autodigestion of the gland and local inflammation. Further, these enzymes can enter the bloodstream, producing inflammatory cytokines, which leads to the systemic inflammatory response syndrome (SIRS) [21]. As a consequence, a rapid decline in arterial blood pressure is typically accompanied with multi-organ failure and inflammation of many organs, as well as leading to a disturbed integrity of the gut barrier and translocation of intestinal bacteria [22]. Dysbiosis contributes to further pancreatic injury and inflammation during acute pancreatitis.

In 1996, C.D. Johnson et al. initially showed the efficacy of early antibiotic prophylaxis in preventing systemic gastrointestinal bacterial shifts in acute pancreatitis. Since it was recognized that the microbiota has a beneficial role in inflammatory and chronic illnesses, and that dysbiosis plays a major role in the development of severe forms of AP, antibiotics are recommended only in the presence of infection, such as cholangitis and infected pancreatic necrosis [10]. According to Fritz and colleague's study, bacteria translocate to necrotic collections from the small intestine rather than the colon [23].

Only 20% of patients with acute pancreatitis develop pancreatic necrosis, and only 6% of these patients have subsequent infection. Mortality is mostly determined by infected pancreatic necrosis which may be 32%-50%. *Enterococcus faecalis* and *faecium*, and *Escherichia coli*, were shown to occur most commonly in a study of 40 patients undergoing minimal access retroperitoneal pancreatic necrosectomy [24]. In a different study of patients who had both percutaneous and endoscopic drainage, gastrointestinal flora was also observed in infected pancreatic necrosis. There was a change from gram-negative bacteria to gram-positive bacteria, including *Enterococcus* spp., *coagulase-negative Staphylococcus* and *Candida* spp [25].

Zhu and colleagues performed 16S marker gene sequencing of stool samples and showed noticeably differences in the gut microbiota's structure between acute pancreatitis patients and healthy controls. This was strongly associated with impaired gut barrier function and systemic inflammation. In addition, the microbial composition changed with the course of the disease and a decrease of beneficial bacteria, such as *Blautia*, with

different severity of pancreatitis was shown. Compared to healthy controls, acute pancreatitis patients had a lower concentration of commensal species, such as *Prevotella*, *Faecalibacterium* and *Bifidobacterium* [26]. According to a number of studies, severe AP is linked to increased levels of *Bacteroides*, *Enterococcus*, *Escherichia* and *Shigella* [8].

Chronic pancreatitis (CP) is an inflammatory disorder of the pancreas characterized by irreversible morphological alterations due to repeated acute attacks, which results in exocrine dysfunction (pancreatic exocrine insufficiency) and/or endocrine dysfunction (diabetes mellitus).

Dysbiosis of gut microbiota can exacerbate inflammation in chronic pancreatitis and promote pancreatic damage by causing both local and systemic inflammation, with an overgrowth of bacteria in the small intestine (SIBO) potentially playing a role along with a decrease in beneficial gut bacteria [27].

SIBO, a condition that describes the microbial dysbiosis in the small bowel, can cause multiple gastrointestinal symptoms such as abdominal distension, bloating and flatulence [28]. Although the pathogenesis of SIBO is incompletely understood, it develops after anatomical and mucosal alterations, and stagnation [13]. There are several predisposing factors that contribute to SIBO, such as fat malabsorption, impaired bowel mobility in diabetic neuropathy and surgical procedures, as well as use of proton pump inhibitors, non-steroidal analgesic use and alcohol intake. A meta-analysis by Capurso et al. with 336 patients revealed that one-third of patients with CP have SIBO [27]. The interaction between SIBO and EPI is complex, as both have an impact on one another. On one hand, the lack of digestive enzymes in EPI results in malabsorption of nutrients and causes an environment that promotes bacterial overgrowth in the small intestine. On the other hand, SIBO can mimic and exacerbate EPI symptoms by interfering with nutrients digestion and absorption. The treatment of pancreatic exocrine insufficiency symptoms includes pancreatic enzyme replacement therapy (PERT). Therefore, when PERT fails to relieve these symptoms, it has been proposed that other reasons, such as SIBO, to be considered [27].

The analysis of gut microbiota in patients with type 1 autoimmune pancreatitis and chronic pancreatitis revealed distinct levels of bacterial species, notably higher proportions of *Bacteroides*, *Streptococcus*, and *Clostridium* species in CP patients. Increased bacterial species may be due to decreased pancreatic enzymes and malabsorption, common in CP [29].

Another study investigated the gut microbiota changes in patients with or without EPI. In chronic pancreatitis patients with EPI, the dominant genera was *Eubacterium rectale* group, *Coprococcus*, *Sutterella*

and *Eubacterium ruminantium* group. Fecal elastase 1 positively correlates with *Bifidobacterium* and *Lachnoclostridium* [30].

Faecalibacterium prausnitzii is a butyrate-producing commensal microorganism found in the human microbiota that serves as energy source for colonic epithelial cells, supporting their proliferation and growth. Along with its anti-inflammatory properties, it enhances the intestinal barrier function by producing tight junction proteins and mucus [31]. In one study, there was a decrease in the abundance of *Faecalibacterium prausnitzii* from healthy controls to non-diabetic CP patients to diabetic CP patients. This was likely to have compromised the intestinal mucosal barrier integrity. Furthermore, they also found a decrease in the abundance of *Ruminococcus bromii* in non-diabetic and diabetic CP patients, which was likely to have contributed to the breakdown of the gut mucosal barrier and changed bacterial metabolism within the intestinal microbiota [32].

Gut microbiota and pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive and lethal cancer with an overall 5-year survival rate between 2% and 5% for the past decades. By 2030, it is anticipated to be the second most common cause of cancer-related death [7].

About 10-20% of human malignancies are thought to be caused by microbes [33]. The poor outcome of pancreatic cancer is attributed to the lack of biomarkers that identify this cancer at an early stage, as well as to locally advanced and metastatic disease at presentation, early recurrence and resistance to therapies. Research into the microbiota of pancreatic adenocarcinoma has revealed that it may contribute to early diagnosis, therapy and prognosis [7].

Studies have linked oral dysbiosis to pancreatic carcinogenesis. Changes in the oral microbiome that accompany periodontal disease, including gingivitis and periodontitis, and tooth loss are an independent risk factor for developing PDAC and they might be used as predictive biomarkers of PDAC, especially as saliva sample is non-invasive and simple [7,34].

According to Farrell et al., *Neisseria elongate* and *Streptococcus mitis* were found in salivary microbiota from pancreatic cancer patients when compared with healthy controls. This two bacterial biomarkers were able to identify cases of PDAC from controls with 96.4% sensitivity and 82.1% specificity [35]. Moreover, numerous research studied the relationship between oral infections with *Porphyromonas gingivalis*, *Fusobacterium*, *Neisseria elongata*, and *Streptococcus mitis*, *P. gingivalis* and PDAC carcinogenesis, with the latter demonstrating a strong association with PDAC [7].

The findings of many studies on PDAC and

gut microbiome are partially comparable, but also contradictory, suggesting that larger studies are required [34]. Ren et al. discovered that patients with PDAC have a lower gut microbiota diversity with an increase in potential pathogens (e.g., *Enterobacteriaceae*, *Veillonellaceae*, and *Streptococcaceae*) as well as lipopolysaccharide-producing bacteria (e.g., *Prevotella*, *Hallella*, and *Enterobacter*), and a decrease in some probiotics (e.g., *Bifidobacterium*) and butyrate-producing bacteria (e.g., *Coprococcus*, *Clostridium IV*, *Blautia*, *Flavonifractor* and *Anaerostipes*) [36].

The inflammation of the pancreas caused by microbes is a crucial factor in the development and progression of pancreatic cancer, *H. pylori* was the first pathogen found in pancreatic tumor tissue and linked

to 75% pancreatic cancer patients and 60% of chronic pancreatitis patients. None of the healthy controls had infection with *H. pylori*. Moreover, the quantities of *Fusobacterium spp*, Firmicutes, Proteobacteria and the fungal *Malassezia spp* were shown to be considerably higher in PDAC tissue compared to controls [34].

Mei et al. demonstrated that inflammatory factors, such as CRP and IL-6, were significantly higher in pancreatic head cancer patients, as was the incidence of *H.pylori* infections and an increase in abundance of *Acinetobacter*, *Aquabacterium*, *Oceanobacillus*, *Rahnella*, *Massilia*, *Delftia*, *Deinococcus*, and *Sphingobium*. On the other hand, *Porphyromonas*, *Paenibacillus*, *Enhydrobacter*, *Escherichia*, *Shigella*, and *Pseudomonas* were found in the duodenal microbiotas of healthy controls [37].

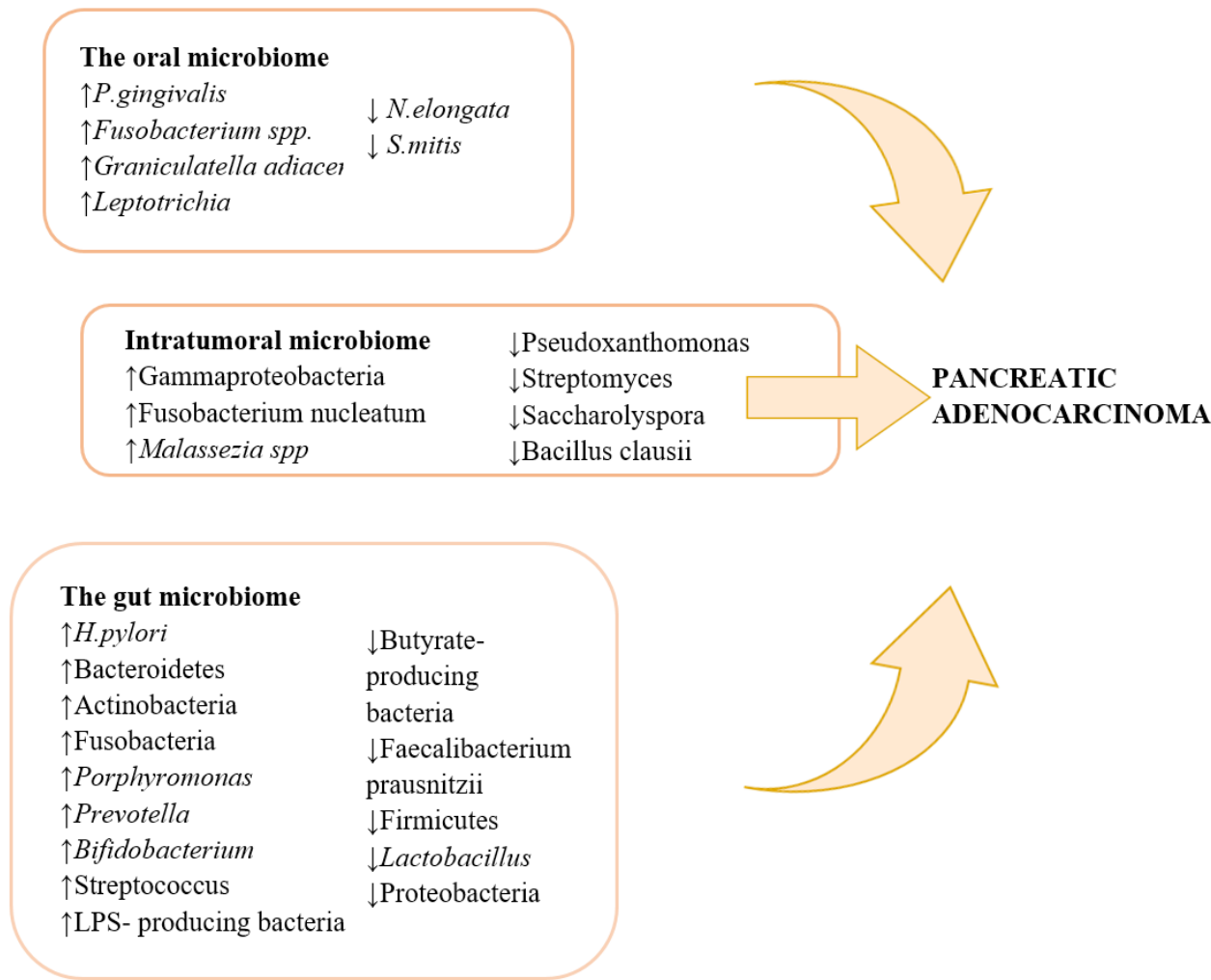


Figure 2. Some of the reported alterations of oral, intestinal and pancreatic microbiota features in pancreatic cancer [4,16,34], ↑, higher abundance in pancreatic cancer; ↓, lower levels; LPS, lipopolysaccharides.

Conclusions

There is evidence from several studies indicating the existence of the microbiota - pancreas axis and that one affects the other.

Exocrine pancreatic insufficiency is an important cause of malabsorption, maldigestion and malnutrition, which result from pancreatic diseases, such as chronic and acute pancreatitis, pancreatic neoplasms, pancreatic resection, cystic fibrosis and other conditions.

According to different studies, the gut microbiota has a role in the development and progression of exocrine pancreatic insufficiency through several mechanisms, such as metabolite production, immune modulation and inflammation, impaired intestinal barrier function. Innovative diagnostic biomarkers and therapeutic targets are essential for a better management of EPI associated with pancreatic diseases, optimizing patient outcomes and improving the quality of life.

There are intriguing connections between gut microbiome patterns and exocrine pancreatic insufficiency, but further research is required to determine if the microbiome causes, attenuates or co-evolves with exocrine pancreatic insufficiency. Additionally, future research should focus on individual variations of gut microbiota in order to make personalized approaches.

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