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PANCREAS AND MICROBIOME

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Abstract – *Via* the secretion of proteases, peptides and bicarbonate, the pancreas strongly impacts the microbiota environment in the small bowel. Inflammatory and malignant pancreatic diseases are associated with distinct changes in gut microbiota composition, mostly analyzed from fecal contents. Between April 2022 and March 2023 several papers have been published, adding to the body of knowledge on these changes, most of them observational studies on rather small groups of patients. However, significant differences in microbiota structure between patients with mild and severe courses of acute pancreatitis were observed, pointing even to a predictive role of microbiota composition at the admission of patients with acute pancreatitis during the course of the disease. During the development of chronic pancreatitis, significant alterations in gut microbiota composition in humans and in a mouse model were evident in published data. Furthermore, samples from pancreatic cancer tissue from long-term surviving patients harbor distinct microbiota compared to those surviving short-term. However, data derived from large and prospectively analyses of patients with pancreatic disease opening the window for gut microbiota directed therapies to influence the course of inflammatory or malignant pancreatic disease is still lacking.

Keywords: Pancreatitis, Microbiome, Microbiota, Gut microbiota, Review.

INTRODUCTION

As an endocrine gland, the pancreas is one of the central organs of the digestive tract and is in intense interaction with the intestinal microbiota. By secretion of bicarbonate, proteases and peptides, the pancreas strongly modulates the environment in the small bowel. Distinct changes in gut microbiota composition have been characterized in association with acute and chronic pancreatitis as well as with pancreatic cancer.

Microbiota and Acute Pancreatitis

The course of acute pancreatitis is classified as either mild, moderate or severe, with a mortality of up to 50% in patients with a severe course of disease. While in the early phase mortality is driven by systemic inflammatory response syndrome (SIRS) with the potential of organ dysfunction, infection of pancreatic necrosis is the main cause of mortality in the late phase[1]. Several factors potentially impact on the course of disease in both, early and late phase, including gut microbiota composition, intestinal barrier function and mucosal immune dysfunction and

are influenced by impaired exocrine pancreatic function[2]. Pathogen-associated molecular patterns (PAMPs) from translocated bacteria binding to host pattern recognition receptors such as Toll-like-Receptors (TLRs) and nucleotide oligomerization and binding domain (NOD)-like receptors play a role in sustaining pancreatic inflammation once pancreatic injury is initiated by activating a cascade of inflammatory signalling[3]. By this, intestinal microbiota plays a crucial role in the course of acute pancreatitis.

A search in PubMed for papers on acute pancreatitis and microbiota or microbiome published between April 2022 and March 2023 revealed 35 papers, with 11 of those being reviews focusing on the role of intestinal microbiota in the pathophysiology of acute pancreatitis and its complications.

Acute respiratory distress syndrome (ARDS) is the most common cause of organ failure in acute pancreatitis. Within a prospective observational cohort study from Bejiing including 26 patients with acute pancreatitis and ARDS, 39 patients with acute pancreatitis without ARDS and 20 healthy controls, rectal swabs were collected within 24 hours of onset of acute pancreatitis and analyzed by 16S rRNA sequencing[4]. PCoA for the beta diversity results clearly distinguished the three groups with overlap between the acute pancreatitis groups indicating a difference in the microbiota structure between healthy controls and patients with acute pancreatitis and similarities between patients with acute pancreatitis with and without ARDS. The composition of the gut microbiota was significantly different among the three groups. In patients who developed ARDS in acute pancreatitis, higher abundances of Proteobacteria phylum, *Enterobacteriaceae* family, *Escherichia-Shigella* genus, and *Klebsiella pneumoniae*, but lower abundances of *Bifidobacterium* genus in comparison to patients with acute pancreatitis without ARDS were depicted. As these changes were already obvious on admission, the authors conclude a potential prognostic role of gut microbiota composition for the development of ARDS in acute pancreatitis.

In a rat model, the intestinal bacterial community structure and function was changed during the initial 72h in AP, and Firmicutes/Bacteriodetes ratio and the relative abundance of *Lactobacillus* have been suggested as potential markers to distinguish between mild and severe acute pancreatitis in this study[5].

Zou et al[6] analyzed the potential predictive role of gut microbiota profiles for the development of necrotizing complications of acute pancreatitis. They compared gut microbiota composition analyzed from rectal swabs on admission by 16S rRNA gene sequencing of 58 patients with acute pancreatitis of whom 19 developed necrotizing AP and used 20 healthy individuals as a control. As a result, significant differences were obvious between the groups. Patients with necrotizing pancreatitis had reduced microbial diversity, higher abundance of *Enterobacteriales*, but lower abundance of *Clostridiales* and *Bacteroidales* compared with patients without pancreatic necroses. On species level, the abundance of *Enterococcus faecium* discriminated best between patients with and without necrosis, and *Finegoldia magna* had comparable accuracy with the Balthazar CT score to detect patients with infected necrosis[6].

Bearing in mind the negative results in terms of mortality of the PROPATRIA study that evaluated the effect of treatment with probiotics on the course of predicted severe acute pancreatitis, research on the therapeutic effect of gut microbiota alterations has returned to the experimental stage[7]. So far, it is not comprehensively understood how intestinal microbiota composition is linked to the course of acute pancreatitis. Gut microbiota-derived metabolites including short-chained fatty acids (SCFA) and nicotinamide adenine dinucleotide (NAD+)-associated metabolites ameliorate oxidative stress and immune inflammation and are hypothesized to impact on the course of acute pancreatitis. To examine whether fecal microbiome transplantation results in higher concentrations of nicotinamide mononucleotide (NMN; the NAD^+ precursor) in the pancreas and ameliorates the course of disease, sodium taurocholate (TLCS)-AP was induced in male Wistar rats that were further treated with antibiotics or FMT and compared to controls or rats with acute pancreatitis without specific treatment. In this model, FMT attenuated acute pancreatitis (AP) damage and ameliorated gut microbiota dysbiosis. In this model, normobiotic FMT induced higher levels of NAD^+. In a further analysis in mice with Caerulein (CRE)-AP treated with NMN, this resulted in alleviation of AP, and the effect is hypothesized to be caused by an activation of the SIRT3–PRDX5 pathway[8]. However, earlier studies in a mouse model revealed a negative impact of FMT on the course of AP[9].

A further study in germ-free and oral antibiotic-treated mice with AP revealed a positive impact of colonization with *Bifidobacterium* spp., particularly *B. animalis*, on pancreatic tissue damage in caerulein-induced AP[10].

Toll-like receptors (TLR) are key activating receptors of innate immune response, and their role in acute pancreatitis has moved into the focus of research. During acute pancreatitis, TLR4 is highly expressed in the intestine. To explore the relationship between intestinal TLR4 and gut microbiota during AP, acute pancreatitis was induced in wild-type and TLR4-knock-out-mice and fecal microbiota analyzed by 16S rRNA sequencing. In TLR4-knock-out mice, acute pancreatitis was more pronounced than in controls in a microbiota-dependent manner with decreased relative abundance of *Lactobacillus* and number of Paneth cells. Treatment with *L. reuteri* ameliorated the consequences of AP in the TLR4 knock-out mice[11].

Paneth cells are secretory cells in the intestinal epithelium and are an important component of the intestinal barrier, secreting antimicrobial peptides. It has been shown previously that a transient ablation of Paneth cells aggravates intestinal and pancreatic injury in a rat model of acute pancreatitis[12]. In a small study in patients with acute pancreatitis, it was now shown that in the early phase of acute pancreatitis, Paneth cell counts in the duodenum are significantly decreased in comparison to healthy controls. In a mouse model of acute pancreatitis, the number of Paneth cells was decreased by the intraperitoneal treatment with dithizone leading to aggravation of acute pancreatitis, higher intestinal permeability and bacterial translocation, which was accompanied by shifts in gut microbiota composition analyzed from cecal contents[13].

Diaminopimelic acid (DAP), a component of bacterial cell walls, is a specific ligand of NOD1 that regulates the NOD1/RIP2/NF-kB signaling pathway and shows increased concentrations in a rat model of severe acute pancreatitis [3]. In this experimental study, the administration of the traditional Chinese medicine Qingyi Keli (QYKL) led to a reduction of DAP containing bacteria and reduced the severity of AP. A similar traditional medicine was studied in a further experimental study focusing on its effects on lung injury in acute pancreatitis. In rats with severe acute pancreatitis, the administration of Qingyi decoction ameliorated AP-associated lung damage, potentially via the inhibition of ferroptosis[14].

In summary, there is growing evidence that the triangle of gut microbiota, intestinal barrier and mucosal immune function plays an important role in the pathophysiology of acute pancreatitis. However, at this point, there is no evidence proven intervention targeting gut microbiota composition to ameliorate the course of disease.

Microbiota and its Role in Chronic Pancreatitis

In chronic pancreatitis, progressive fibrosis, as a consequence of chronic inflammation, frequently leads to exocrine pancreatic insufficiency. The exocrine pancreas is one of the most important host factors regulating gut microbiota composition in healthy individuals, and in patients with chronic pancreatitis a significant gut microbiota dysbiosis with significantly reduced diversity and increased abundance of opportunistic pathogens has been evidenced[15].

In a prospective observational study fecal microbiota composition of 20 patients with severe chronic pancreatitis being evaluated for pancreatectomy with islet autotransplantatioin (TPIAT) was analyzed and compared to 14 healthy stool donors. A significantly lower alpha diversity than in healthy controls was observed in patients with chronic pancreatitis, with a significantly decreased mean relative abundance of Faecalibacterium compared to healthy controls. Among participants with CP, those with lower alpha diversity reported worse functional abdominal symptoms[16].

A further study not only evaluated differences between 40 patients with chronic pancreatitis and 38 healthy family members with respect to fecal microbiota composition but also analysed changes in the metabolome. Amongst other taxonomic differences, the abundance of *Bifidobacterium* was lower in the CP group at genus level. Using GC-TOFMS, 115 fecal metabolites were recognized and quantified, and significantly different abundances of 18 metabolites were depicted. 13 metabolites significantly differed in terms of concentration. There was a negative

correlation between the abundance of 3-methylindole and the abundance of *Bifidobacterium*, while the abundance of oxoadipic acid, citric acid, l-tyrosine and d-2-hydroxyglutaric acid was positively correlated. The authors conclude that the microbial-host cometabolism might play a role in CP pathogenesis[17].

In a mouse model of cerulein-induced chronic pancreatitis fecal microbiota composition was analysed at two different time points and revealed pronounced alterations in microbiome composition, diversity, and function during the development CP. At 10 weeks, bacteria from genera *Bifidobacterium, Akkermansia*, and *Desulfovibrio* were enriched, while at 16 weeks bacteria from genera *Allobaculum, Prevotella,* and *Bacteroides* were more abundant pointing at a dynamic progress of changes[18].

Microbiota and Pancreatitic Cancer

The role of microbial composition and its role in diagnosis, treatment and its predictive value for therapy response in patients with pancreatic ductal adenocarcinoma (PDAC)n is an emerging area.

During the last decade, several studies examined the association of distinct oral bacteria with the risk to develop pancreatic cancer[19-21]. Some studies reported an association between *Porphyromonas gingivalis* and *Fusobacterium nucleatum* with pancreatic cancer, where mainly *F.nucleatum* in pancreatic cancer tissue is associated with poor prognosis[22]. In a recent preliminary study, an enrichment of oral bacteria in the gut microbial community of PDAC patients compared to healthy controls was evident. In addition, distinct changes of bacterial metabolites were detected in the feces of PDAC patients, with a decrease in intestinal propionic acid and deoxycholic acid[23].

It was shown, that samples from pancreatic cancer tissue from long-term surviving patients harbors distinct microbiota compared to those surviving short-term. Long-term surviving patients presented a higher alpha-diversity with a specific intra-tumoral microbiome signature, including *Pseudoxanthomonas, Streptomyces, Saccharopolyspora and Bacillus clausii.* Following these findings, fecal microbiota transfer from both long- term and short-term survivors into mice enabled the modulation of tumor microbiome as well as tumor immune infiltration and tumor growth[24]. Differences in microbial profiles were not only detected in tumor samples but also in feces and duodenal aspirates[25,26].

Furthermore, in 2022 a Chinese group analyzed the gut microbiome and fecal metabolome of resectable and unresectable PDAC. Comparing these different groups for clinical management *Alistipes, Anaerostipes, Faecalibacterium* and *Parvimonas* were shown to be reduced in feces of unresectable PDAC patients, whereas *Pseudonocardia, Cloacibacterium, Mucispirillum* and *Anaerotruncus* were increased in this group. In addition, distinct metabolic markers correlated with survival time of patients. More detailed stage dependend analyses are needed to test the potential of these markers to distinguish between resectable and unresectable PDAC[27].

The usability of microbial signatures as a diagnostic biomarker was studied by a Spanish-German group studying microbial signatures of saliva and feces from 212 subjects. Fecal analysis performed better than saliva to discriminate PDAC patients from healthy subjects or chronic pancreatitis patients (AUROC 0.84). Combining the bacterial-based signatures with serum levels of Ca19-9, the AUROC improved to 0.94[28].

Microbiota and Therapy Response in PDAC Patients

Cachexia is a frequent complication of PDAC, leading to intolerance of tumor-directed therapy and premature death. Interventional studies aiming at the stabilization of body weight detected distinct changes of gut microbiota with a significantly increased abundance of *Veillonella* in effectively supported PDAC patients over time. These observations might generate interventional concepts to modulate gastrointestinal microbiota in PDAC patients[29].

In a mouse model, it was shown that Type I collagen (Col1) heterotrimer (α1/α2/α1) produced by fibroblasts which is correlated with overall survival and immune cell infiltration could

be deleted by increased microaerophilic Campylobacterales. An antibiotic intervention might have the potential to improve survival and immune cell infiltration to enable the effects of PD-1- immunotherapy[30].

CONCLUSIONS

Via the exocrine system, the pancreas is one of the modulators of the intestinal microbial community. Both inflammatory and malignant diseases of the pancreas have been linked with changes in intestinal microbiota structure and function and alterations of the intestinal barrier and intestinal immune system. Whether microbiota-targeted interventions have the potential to ameliorate the course of pancreatic diseases still needs to be elucidated.

Conflict of Interest

Both authors declare no conflicts of interest.

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Informed Consent

Not applicable.

Authors' Contribution

CS drafted and wrote the article, revised it critically for important intellectual content and has given final approval of the version; KS drafted and wrote the article, revised it critically for important intellectual content and has given final approval of the version.

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