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GUT MICROBIOTA AND PANCREATIC DISEASES

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Abstract. This review presents scientific data on the features and mechanisms of the formation of gut microbiota in various pancreatic diseases, as well as factors affecting chronic inflammatory processes.

Key words: *gut microbiota; pancreatic diseases; pancreatitis; diabetes mellitus; metabolic syndrome*

КИШЕЧНАЯ МИКРОБИОТА И ЗАБОЛЕВАНИЯ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

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Резюме. В обзоре представлены научные данные об особенностях и механизмах формирования кишечной микробиоты при различных заболеваниях поджелудочной железы, а также факторах, влияющих на хронический воспалительный процесс.

Ключевые слова: *кишечная микробиота; заболевания поджелудочной железы; панкреатит; сахарный диабет; метаболический синдром*

The state of the intestinal microbiota significantly affects the onset and development of pancreatic diseases. Studies conducted in experimental conditions and clinical observation confirm the correlation between the gut microbiome and chronic pancreatic inflammation. In addition, the mechanism of chronic inflammation associated with dysbiosis may have a complex effect in causing such conditions as pancreatitis, metabolic syndrome, type 2 diabetes mellitus, and pancreatic tumors. Changes in gut microbiocenosis can be both primary and secondary, they also may affect an organ that does not have its own microbiota.

CHANGES IN THE MICROBIOTA IN ACUTE, CHRONIC AND AUTOIMMUNE PANCREATITIS

Changes in the intestinal microbiome are possible in acute and chronic pancreatitis [109, 123] and may even represent a complete diagnostic tool [8].

The occurrence of **acute pancreatitis** is associated with an imbalance between pro- and anti-inflammatory cytokines [77, 123]. Experimental models revealed hypersecretion of pro-inflammatory TNF-α, IL-1β, IL-6, IL-17A, CXCL1 and IL-18 with a concomitant decrease in Paneth cell-associated antibacterial peptides such as alpha-defensins and lysozyme [42, 44, 111].

Antimicrobial peptides produced by acinar cells and Paneth cells are necessary for intestinal homeostasis, maintenance of intestinal immunity, and control under microbiome composition [128, 131]. Using a mouse model, Ahuja et al. showed that deletion of the Orai1 Ca^{2+} channel in pancreatic acinar cells (Orai1$^{-/-}$ mice) induces several signs of intestinal inflammation and bacterial overgrowth, leading to bacterial translocation, systemic infection and death [72]. Experimental evidence supports the importance of pancreatic antimicrobial secretion in modulating intestinal/pancreatic homeostasis and the integrity of the intestinal immune system.

As inflammation provokes the damage of tissue, pancreatic acinar cells produce several molecules that may have the function of damage-associated molecular patterns (DAMPs) [39], such as high mobility group protein 1 (HMGB1), heat shock protein 70 (Hsp70), cytosolic protease — caspase 1, nucleotide binding domain (NLRP3), adenosine triphosphate (ATP) and DNA [10, 23, 93]. DAMPs contribute to the activation of Toll-like receptors (TLRs) which cover epithelial cells, immune cells, macrophages and other cells that have recognition function (PRRs) and can identify pathogen-associated molecular patterns (PAMPs) [16]. At least 10 different TLRs have been recognized [1] in humans, as well as polymorphisms in TLR3 and TLR6 genes and the extent of expression of long non-coding RNA. They are associated with the severity of pancreatitis [14, 78] and lead to the activation of specific intracellular signaling pathways as well as produce inflammatory cytokines and chemokines [60], which simultaneously protect the host by promoting regeneration of damaged tissue and mucosal immune response [10].

Pancreatitis can be considered as a unique form of immune-mediated inflammation [122], where damaged acinar cells begin to produce the pro-inflammatory cytokine IL-33, which determines the activation of T-cell subpopulations involved in pancreatic inflammation [58].

In acute pancreatitis, inflammation causes intestinal damage by several concomitant pathogenic mechanisms such as alterations in microcirculation, visceral vasoconstriction, and ischemia [12, 71], which increases intestinal permeability and facilitates the translocation of bacteria and toxins to the pancreas and may lead to fibrosis or necrosis [68]. Bacterial translocation may also be responsible for secondary infections associated with a high risk of death [67, 80].

In addition, acute pancreatitis development is associated with an increase in the number of pathogenic bacteria from the families Enterobacteriaceae and Firmicutes and a decrease in the number of beneficial *Bacteroidetes* and *Lactobacillales* [123]. Serum IL-6 levels directly correlated with the number of Enterobacteriaceae and Enterococci and inversely with the number of Bifidobacterium clusters and Clostridium cluster XI. Furthermore, the degree of changes in the gut microbiota determined the severity of disease progression and the likelihood of systemic complications [99].

Acute pancreatitis is also associated with some populations of commensal bacteria. Their occurrence is related to decreased levels of inflammatory cytokines such as IL-1-beta, TNF-alpha, CXCL1 and IL-18, and inversely correlates with the severity of pancreatitis and systemic infectious complications. From a clinical perspective, restoring the physiologic composition of the gut microbiota may be a useful strategy for the treatment of acute pancreatitis [48, 69, 73, 139]. Qin et al. demonstrated that restoring the physiologic ratio of commensals/pathogens in 76 patients with acute pancreatitis resulted in limiting systemic infectious complications [64]. In a number of other studies, oral administration of probiotics showed no significant effect on the outcome of the disease or prevention of complications [62, 73, 75].

Chronic pancreatitis is the outcome of long-term inflammation leading to chronic damage and dysfunction of the gland [5, 13].

In 30% of patients, chronic pancreatitis is accompanied by a syndrome of bacterial overgrowth, but specific changes in the composition of the microbiota are not fully understood [51–81]. Some authors have observed an increase in *Firmicutes* and a relative decrease in *Bacteroidetes* [109]. Patients with pancreatitis are also affected by progressive and duration-dependent decrease in the commensal bacteria *Faecalibacterium prausnitzii* [28, 109], which promote mucin production and tight junction protein synthesis [65], induce the anti-inflammatory cytokine IL-10 [89], and regulate intestinal T-cell responses indicating a prolonged impairment of mucosal integrity [109]. The level of *Faecalibacterium prausnitzii* was negatively correlated with the level of endotoxins in plasma, its elevation is associated with disorders of carbohydrate metabolism. In addition, patients with chronic pancreatitis have reduced levels of *Ruminococcus bromii* [109], which play an important physiologic role in starch degradation in the colon [133]. Its decrease is associated with disruption of the intestinal mucosal barrier as well as altering glucose metabolism.

Several studies indicate a decrease in *Bacteroidetes* gram-negative bacteria, which are a source of lipopolysaccharides. In fact, lipopolysaccharides may activate the production of pro-inflammatory cytokines associated with NF-κB by binding TLR4 [54]. Patients with chronic pancreatitis have higher levels of lipopolysaccharides and endotoxin which correlate with disease duration and may cause pancreatic beta-cell dysfunction, exacerbating impaired glucose metabolism [2] and involving pancreatic islet cells in the inflammatory process. Chronic pancreatitis results in an increase in both Th1 and Th17 cells [96] which are associated with proinflammatory cytokines such as IFN-γ in pancreatic islets [104].

Autoimmune pancreatitis accounts for approximately 5% of all cases of pancreatitis and is often associated with other autoimmune diseases [55, 110]. One of the diagnostic criteria is elevated serum IgG4 levels [33, 38]. A genetic predisposition to autoimmune pancreatitis has been found [30], but the pathogenesis of the disease remains incompletely understood [121].

Helicobacter pylori is associated with autoimmune pancreatitis [61, 79]. The bacterium triggers immune responses against host tissues because of its molecular similarity [57]. Guarneri et al. reported homology between human carboanhydrase II (CA-II) and *Helicobacter pylori* alpha-carboanhydrase (HpCA). CA-II is a pancreatic epithelial enzyme. Its specific serum antibodies characterize AIP. At the same time, the bacterial homolog segments contain a high-risk HLA-DR allele binding motif. Thus, *Helicobacter pylori* may cause disease in genetically predisposed individuals [36].

Other studies demonstrate the relationship of bacterial infection with the development of autoimmune pancreatitis. In particular, *Escherichia coli* provokes severe pancreatic inflammation with subsequent fibrosis in the mouse model which is similar to the human morphological picture [87]. A number of specific microbial antigens can induce the development of pancreatitis by activating immune responses. Gram-negative bacteria associated with LPS are able to activate the immune response through TLRs [1]. Several TLRs (TLR2, TLR3, TLR4, TLR5 and TLR7) have been affiliated with the development of AIP [10, 119, 120]. Among them, TLR3 usually recognizes microbial ds-RNA that activates FAS/FasL-mediated cytotoxicity that is responsible for chronic inflammation [136]. Finally, TLR7 is capable of recognizing viral ssRNA, thereby activating proinflammatory signaling cascades [91].

MICROBIOTA CHANGES IN TYPE 1 DIABETES MELLITUS

Type 1 diabetes mellitus (type 1 DM) is characterized by loss of insulin secretion due to damage of pancreatic beta cells caused by an autoimmune process against a background of bacterial infection [107].

Several changes in the composition of the intestinal microbiota have been linked to the development of type 1 DM. In a recent study of 76 children at high genetic risk, it was demonstrated that early changes in the composition of the intestinal microbiome predict the onset of type 1 DM [21, 29]. Specifically, *Bacteroidesdorei* and *Bacteroidesvulgatus* are elevated in the microbiome of the type 1 DM predisposed children. In contrast, individuals with late-onset type 1 DM show both similar increase in Bacteroides species and decrease in *Clostridium leptum* [10, 82].

A number of bacterial or viral antigens (Coxsackie A and B viruses, Echo, enterovirus, and others) have been associated with the development of type 1 DM in children and adolescents [27, 115].

Type 1 D is accompanied by profound changes in the composition of the gut microbiota and associated metabolites [25, 100]. Significantly, changes occur in the ratio of butyrate-producing *Bacteroidetes* and *Firmicutes bacteria* [32–66]. The number of butyrate-producing and mucin-degrading bacteria (*Prevotella* and *Akkermansia muciniphila*) decreases [117], while there is an overgrowth of *Klebsiella* bacteria producing short-chain fatty acids (SCFAs).

F. Semenkovich et al. demonstrated bidirectional links between changes in gut microbiota and inflammation associated with type 1 DM. The gut microbiota in the NOD mouse model was able to drive hormonal changes in the testosterone axis (in males) that led to susceptibility to type 1 DM. In turn, hormonal levels were able to alter the microbial landscape in the gut. This phenomenon may be a possible explanation for the different susceptibility between the sexes [25, 31].

There was detected decreased levels of *Lactobacillus* and *Bifidobacterium species*, lymphopenia [108] and upregulation of Th17 cells [52] in a mouse model with type 1 DM [26]. These data support the hypothesis that changes in the composition of the gut microbiota are associated with mucosal immune system abnormalities and that both mechanisms are involved in the pathogenesis of type 1 DM [125]. Increased gut permeability provokes the course of type 1 DM either through beta-cell injury or through bacterial translocation

and associated antigen presentation [94], or directly through beta-cell dysfunction mediated by microbial toxins such as streptozotocin [125].

The effects of diet and drugs have been studied in a similar manner. A study in non-obese diabetic mice showed that exposure to acidified water was able to increase the presence of mucosal and spleen T-regulatory cells (Tregs) and decrease the number of Th17 cells, thereby reducing the likelihood of developing type 1 DM [50]. Modeling in mice has demonstrated that insulin treatment can positively influence the restoration of a healthy gut microbiocenosis [105]. At the same time, oral administration of vancomycin during the newborn period in diabetic mice without obesity reduced the presence of several major genera of Gram-positive and Gram-negative bacteria and resulted in the formation of a single dominant species, *Akkermansia muciniphila* [37].

In addition, innate and acquired mucosal immunity plays a special role in the pathogenesis of type 1 DM. Nucleotide-binding protein 2 containing oligomerization domain (Nod2) has been identified as a susceptibility factor for type 1 DM [137]. Nod2, mainly expressed by neutrophils and monocytes/macrophages, recognizes bacterial molecules that possess the muramyl dipeptide (MDP) fragment and stimulates the immune response by inducing $CD4^+$ Th1 and $CD4^+$ Th17 cells in pancreatic tissue, promoting autoantibody production and tissue damage [102, 130].

Li et al. bred Nod2–/– non-obese diabetic (NOD) mice with a different composition of gut microbiota compared to Nod2+/+NOD mice. The Nod2–/–NOD animal line appears to be more protected against diabetes and shows a significant decrease in pro-inflammatory cytokines coding immune cells and an increase in Tregs [137]. When mice of the Nod2–/–NOD line were co-housed with mice of the Nod2+/+NOD line, Nod2–/–NOD mice lost their protection against the development of type 1 diabetes. This suggests that the susceptibility of Nod2–/–NOD mice to type 1 DM depends on changes in the gut microbiota as it influences beta cells that produce immunoglobulin A (IgA), as well as the level of interleukin-10 (IL-10), which stimulates the activity of T-regulatory cells.

Several studies have investigated the role of adaptive immune cells in the pathogenesis of type 1 DM. There is evidence that beta cell damage occurs via $CD8^+$ cytotoxic T cells. Their abnormal activation is a consequence of molecular similarity and bacterial infections triggering the immune response. The possible role of TLRs is also discussed. pancreatic beta cells express TLR4, which make them sensitive to lipopolysaccharides (LPS), stimulating and activating the transcription of NF-κB-related pro-inflammatory genes that provoke an immune response against microbial invasion. Thus, the increased level of TLR4 is another mechanism for understanding the pathogenesis of type 1 DM [61].

MICROBIOTA CHANGES IN METABOLIC SYNDROME, TYPE 2 DIABETES MELLITUS

Metabolic syndrome is a symptom complex including visceral obesity, impaired glucose metabolism, dyslipidemia and arterial hypertension. Metabolic syndrome is associated with an increased risk of developing type 2 diabetes mellitus (type 2 DM) and cardiovascular pathology [49]. The disease is characterized by increased production of cytokines (mainly TNF-α and IL-1β) [118], and persistent inflammation [70].

The correlation between the gut microbiota, the pathogenesis of metabolic syndrome and type 2 DM was demonstrated by Guo et al. A line of obese mice demonstrated that diet can alter the gut microbial landscape as well as the production of antibacterial peptides associated with Paneth cells and even increase circulating pro-inflammatory cytokines such as TNF-alpha, IL-6 and IL-1beta [132]. Thus, it is diet-related gut dysbiosis, rather than adipose tissue itself, that plays a key role in the development of chronic intestinal inflammation [92].

Affecting energy production and storage, the gut microbiota can influence body weight and obesity, tissue pro-inflammatory activity, peripheral insulin resistance, pancreatic intestinal hormone production, and bile acid metabolism [63, 101]. Consequently, an increase in the Firmicutes/Bacteroidetes ratio corresponds to body weight and promotes hydrolysis of non-digestible polysaccharides in the intestine, which in turn contributes to an increase in calories extracted from food in metabolic syndrome [47, 88]. Several studies examining fecal samples from metabolic sydrome patients with type 2 DM have reported there is an increase in *Lactobacillales* with a decrease in *Roseburiaintestinalis*, *Faecalibacterium prausnitzii, Bacteroides*, *Prevotella genera*, *Bifidobacterium animalis* and *Methanobrevibacter smithii* compared to healthy subjects. Increased levels of Staphylococcus aureus, *Escherichia coli* and *Lactobacillus reuteri* may be associated with the development of obesity [84].

Tannerella spp. bacteria associated with oral infections and periodontal diseases provoke an increase in several pro-inflammatory cytokines

such as TNF-alpha, IL-1beta and IL-6 [116]. Lipopolysaccharide induced by Gram-negative bacteria is able to evoke an immune response through lipopolysaccharide-binding protein (LBP), which in turn binds the macrophage receptor CD14. The complex formed by lipopolysaccharide-lipoprotein-binding protein and CD14 can activate the pro-inflammatory genes NF-kB and AP-1 via TLR4 [74], and the absence of TLR4 protects against insulin resistance [114].

Gut dysbiosis can also mediate changes in the balance of Th17/Tregs cells. Thus, disruption of the physiologic balance between pro- and anti-inflammatory T cell subpopulations may be responsible for the development and progression of a number of inflammatory diseases, both gastrointestinal and systemic, including obesity-related metabolic syndrome and type 2 DM [70]. Thus, gut dysbiosis is closely associated with significant changes in the Th17/Tregs balance contributing to obesity, metabolic syndrome, and type 2 DM, allowing for new strategies for the treatment of the aforementioned diseases.

CHANGES IN THE MICROBIOTA IN PANCREATIC TUMORS

Pancreatic cancer is an aggressive disease with an uncertain prognosis. By the time of the diagnosis, only 25% of pancreatic cancer cases are amenable to radical surgical treatment. About 95% of cases are adenocarcinomas derived from glandular, ductal or acinar cells of the exocrine pancreas [6].

An association between dysbacteriosis, chronic inflammation and pancreatic cancer has been established [17–24], but dysbacteriosis does not have direct effects that disrupt cell cycle control, activate oncogenic signaling pathways and produce tumor metabolites [41–85]. However, gut dysbiosis can activate the immune system through several pathways that include tumor-infiltrating lymphocytes (TILs) and their associated cytokines, innate immune cells, TLRs, and others. Thus, TILs produce pro-inflammatory mediators that induce STAT3 and NF-κB pathways, which act as oncogenic factors by enhancing cell proliferation and inhibiting apoptosis [15–98].

Several microbe-free mouse lines have made it possible to understand the significant role of the gut microbiome which influence carcinogenesis. The probability of cancer development is significantly reduced, possibly due to the absence of gut dysbiosis and associated chronic inflammation [135]. A similar effect was found in mice after antibiotic treatment, which may indicate a reduced influence of pathogens in the intestinal mucosa [24]. Other experimental evidence suggests a close association between diet, xenobiotics, gut microbiota and cancer [20]. One study found an increased risk of tumor development in mice that were genetically predisposed to colorectal cancer and had a certain composition of gut microflora. This tumor predisposing phenotype could be transferred to healthy mice after microbiota transplantation using fecal samples. Interestingly, antibiotics were able to limit tumor development, likely by blocking the intestinal gut microbiota in the mice. Boursi et al. performed a large population-based study showing that repeated exposure to antibiotics, particularly penicillin, may contribute to the development of esophageal, gastric, pancreatic, and rectal cancers, probably due to changes in the microbiota [4].

In chronic pancreatitis, people with KRAS mutation have an increased risk of pancreatic cancer [9, 95, 131, 132], and gut dysbiosis can accelerate pancreatic carcinogenesis through mutated KRAS hyperstimulation [40, 43]. Gram-negative LPS-TLR4 was linked in inducing chronic inflammation and cancer as well [56]. Ochi et al. experimentally discovered the influence of lipopolysaccharides in the pathogenesis of pancreatic cancer [56]. LPS administration in mice was able to significantly accelerate carcinogenesis, while TLR4 inhibition limited cancer progression.

Bacterial pathogens are capable of acting as carcinogenic factors. Among them, *Helicobacter pylori* plays a special role [79], which can promote gastric, liver and pancreatic cancer by inducing activation of nuclear factor NF-κB and its pro-inflammatory cytokines such as IL-1β [53]. Some Fusobacterium species have also been associated with the development of pancreatic cancer, and they are associated with worse prognosis [138].

Ren et al. found decreased microbiota diversity in 85 pancreatic cancer patients compared to 57 healthy individuals [22]. Patients with pancreatic tumor have a specific microbial profile characterized by an increased presence of some pathogens such as *Veillonella*, *Klebsiella* and *Selenomonas*, as well as bacteria capable of producing lipopolysaccharides (LPS) including *Prevotella, Hallella* and *Enterobacter*. Related to this, there was a decrease in some commensal microorganisms, such as *Bifidobacterium*, and a decrease in bacteria that produce butyrate, such as *Coprococcus, Clostridium IV, Blautia, Flavonifractor* and *Anaerostipes*. Evidence of an increase in LPS-producing bacteria supports the role of dysbiosis in mediating chronic inflammation and oxidative

damage, activating the NF-κB pathway and associated production of pro-inflammatory cytokines. Thus, prolonged chronic inflammation and oxidative damage provoke carcinogenesis.

In addition, pancreatic cancer correlated with a change in the physiological composition of the oral microbiota towards predominance of microbial associations associated with periodontal diseases [45]. Farrell et al. performed a study analyzing the salivary microbiota of several patients with pancreatic cancer and chronic pancreatitis compared to healthy controls. The researchers found specific changes in the composition of the salivary microbiota (decrease in *Neisseria elongata, Corynebacterium* spp. and *Streptococcus mitis* and increase in *Granulicatella adiacens* and *Porphyromonas gingivalis*) [45, 46]. Torres et al. conducted a cross-sectional study showing an increase in *Leptotrichia* spp. and a decrease in *Porphyromonas* spp. in the saliva of a pancreatic cancer patient; thus, a higher *Leptotrichia / Porphyromonas (L/P)* ratio may be an important biomarker for the diagnosis of pancreatic cancer [19]. Michaud et al. found that the highest concentration of serum antibodies to *Porphyromonas gingivalis* bacteria (associated with periodontal disease) was associated with a twofold increased risk of pancreatic cancer [35], which can be used as a tool to detect early pancreatic cancer using blood, saliva and fecal samples. However, further studies on the relationship of gut microbial changes in the mechanism of pancreatic cancer are required.

In conclusion, pancreatic cancer is considered an insidious and aggressive disease characterized by late diagnosis and lack of effective screening methods. The use of gut microbiome modulation for therapeutic purposes is unlikely in general clinical practice; however, the determination of the gut microbiocenosis pattern may become a diagnostic tool in predicting the development of pancreatic cancer, thereby improving survival rates.

CONCLUSIONS

The gut microbiota plays a central role in the development and modulation of gut homeostasis and mucosal immune system integrity. It plays an important role in protection against pathogenic microbes by maintaining gut integrity and regulating the permeability of the intestinal barrier.

The pancreas does not possess its own microflora, and evidence suggests that alteration of the gut microbiota, which determines dysbiosis and bacterial translocation, correlates with the duration and prognosis of several pancreatic diseases, including pancreatitis, diabetes, and cancer. However, it remains unclear whether gut dysbiosis is a cause or a consequence of such pathologic conditions.

ADDITIONAL INFORMATION

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