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Review Article

The Role of Gut Microbiota and Genetic Susceptibility in the Pathogenesis of Pancreatitis

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Pancreatitis is one of the most common inflammatory diseases of the pancreas caused by autodigestion induced by excessive premature protease activation. However, recognition of novel pathophysiological mechanisms remains a still challenge. Both genetic and environmental factors contribute to the pathogenesis of pancreatitis, and the gut microbiota is a potential source of an environmental effect. In recent years, several new frontiers in gut microbiota and genetic risk assessment research have emerged and improved the understanding of the disease. These investigations showed that the disease progression of pancreatitis could be regulated by the gut microbiome, either through a translocation influence or in a host immune response manner. Meanwhile, the onset of the disease is also associated with the heritage of a pathogenic mutation, and the disease progression could be modified by genetic risk factors. In this review, we focused on the recent advances in the role of gut microbiota in the pathogenesis of pancreatitis, and the genetic susceptibility in pancreatitis. **(Gut Liver 2022;16:686-696)**

Key Words: Pancreatitis; Gut microbiota; Genetic susceptibility; Pathogenesis

INTRODUCTION

Pancreatitis, one of the most common gastrointestinal diseases, is the main cause for hospital admission, and the incidence of pancreatitis is increasing worldwide, which is associated with the elevated socioeconomic burden.[1] The annual incidence of acute pancreatitis (AP) is approximately 34 per 100,000 in developed countries and it keeps a continuous growth worldwide.[2] AP is usually caused by structural obstruction of the biliary tract, alcohol consumption, endoscopic retrograde cholangiopancreatography and drugs, which ultimately lead to acinar cell death, inducing local and systemic inflammation.[3-5] Chronic pancreatitis (CP) often occurs in patients with recurrent pancreatic injury or prolonged AP. Despite many advances have been made in respects of the pathophysiology of pancreatitis, there are still no medication available to treat or prevent AP at present.[6] Additionally, in many cases, individuals who even have attacks of alcoholism and gallstones do not suffer from AP.[7,8] This inclined us to further explore the underlying mechanism of pancreatitis.

The pathogenesis of disease is generally related with genetic and environmental factors, while human gut microbiome is recognized as a potential source of environmental effect on illness.[9] Recent studies regarding the role of gut microbiome in the pathophysiology of the pancreas are increasing, during which immune regulation and interplay between host microbiomes and the pancreas attract much attention.[10-14] These studies have initiated new insight into pancreatic diseases from the perspective of the gastrointestinal microbiota. On the other hand, it has long been suspected that genetic susceptibility factors conduce to the pathogenesis of the disease, since only a small proportion of alcoholics finally develop CP.[15] Various groups of genetic mutations, such as the serine peptidase inhibitor Kazal type 1 (SPINK1), anionic trypsinogen serine protease 2 (PRSS2), cationic trypsinogen serine protease 1 (PRSS1), cystic fibrosis transmembrane conductance regulator

(CFTR) genes and so on, were observed in various types of pancreatitis.[16,17] These specific genetic mutations instruct us to uncover the underlying mechanism of pancreatitis on a genetic and cellular level.

In this review, we summarize recent advances in research of gut microbiota and genetics related to pancreatitis, and analyze the role of the gut microbiota and genetic susceptibility in the pathogenesis of pancreatitis. Additionally, we discuss the relationship between gut microbiota and genetic susceptibility in patients with pancreatitis and are attempting to speculate the pathogenesis of pancreatitis from a novel perspective.

THE ROLE OF GUT MICROBIOTA IN PANCREATITIS

1. Acute pancreatitis

During the course of AP, microcirculatory injury and hypovolemia would emerge,[18] which could cause intestinal mucosal ischemia and subsequent reperfusion injury, leading to dysfunction of intestinal barrier and gut microbiota translocation. Current investigations have shown heterogeneity in intestinal microbial composition between pancreatitis patients and healthy controls. Zhang *et al.*[19] made use of high-throughput 16S rRNA gene amplicon sequencing to detect the gut microbiome of 45 AP patients and 44 healthy individuals, and analyzed the differences between the two groups. The results showed that the composition of intestinal flora in AP patients was remarkably changed, and the diversity of their phyla was significantly reduced. Moreover, samples from AP patients had a higher abundance of Proteobacteria and Bacteroidetes, while the abundance of Firmicutes and Actinobacteria was relatively lower when compared with those from healthy individuals (Table 1). Although the imbalance of gut microbiota of AP patients is causative or reactive is still unclear, it is speculated that this may be the inevitable process of the onset and development of AP. Li *et al.*[20] detected DNA of *Escherichia coli*, Shigella and other bacteria in the blood of AP patients, further confirming that intestinal opportunistic bacteria can enter the blood circulation of AP patients through the damaged intestinal barrier, thus aggravating the progression of the disease and the occurrence of infectious complications (Table 1).

When it comes to the evaluation of severity and prognosis of AP, the imbalance of bacterial composition and altered gut microbiota diversity are two overlooked factors and have been gradually emphasized by researchers in recent years. Yu *et al.*[21] found that *Bacteroides*, *Escherichia* and *Shigella*, and *Enterococcus* were dominant intestinal bacterial community in mild, moderately severe, and severe AP, respectively. Moreover, they investigated the relationship between the alterations of gut microbiota and prognosis in hypertriglyceridemia-associated acute pancreatitis (HTGAP) patients in follow-up studies, which showed that HTGAP group had worse prognosis (higher proportion of organ failure and longer hospital stay) and poorer microbial diversity when compared to AP patients with other etiologies (Table 1).[22] Similarly, Zhu *et al.*[23] also reported that the severity of AP is associated with gut microbiota dysbiosis in both human and animal models. These studies suggest the role of gut microbiota might play in evaluating patients and as potential target for treatment.

Though the efficacy of probiotics, such as *Bifidobacterium* and *Lactobacillus*, in treatment of severe acute pancreatitis (SAP) is controversial according to earlier clinical trials,[24-27] updated studies hold optimistic view in application of probiotics in therapy with SAP. One recent meta-analysis concluded that probiotics have beneficial effects on decreasing duration of hospital stay and reducing risk of organ failure in patients with SAP.[28] In animal models, Lei *et al.*[29] found that *Parabacteroides* could alleviate AP in heparanase-transgenic mice by reducing neutrophil infiltration. Their mechanism research indicated that acetate derived from this gut microbiota genera reduced neutrophils in blood and resulted in less neutrophil infiltration in the pancreas, and thereby enhancing the host defense against pancreatic inflammation. These studies enriched our knowledge of AP and laid the foundation for future translation work.

2. Chronic pancreatitis

CP with its damaged pancreatic acinar cells, can result in pancreatic exocrine insufficiency and small intestinal bacteria overgrowth. Small intestinal bacteria overgrowth appears to be more likely to occur in CP patients, due to intestinal dysmotility and reduced alkalization of intestinal fluid, as well as reduced pancreas-derived antimicrobial peptide.[30] In a meta-analysis performed by Memba *et al.*,[31] three of 10 studies that met the inclusion criteria have assessed the gut flora in patients with CP.[32-34] They manifested that the abundance of Bifidobacterium or Lactobacillus were lower, while the abundance of Enterobacteriaceae was higher in CP patients (Table 1). Although data are still limited, lower levels of Bifidobacterium are observed both in AP and CP. Moreover, Bifidobacterium probably has beneficial role in other diseases like obesity, cystic fibrosis, inflammatory bowel disease, and irritable bowel syndrome.[35] Clinically, this effect might be transformed into a potential therapeutic intervention to pancreatitis.

Autoimmune pancreatitis (AIP), a unique form of CP,

Table 1. Studies about Alterations in Microbiome Composition Involving Pancreatitis Patients

Disease	Author (year)	Study type	Disease states vs control	Sample type	Microbial evaluation	Microbial alterations
AP	Zhang *et al.* (2018)[19]	Controlled	AP vs healthy participants	Fecal	16S rRNA gene sequencing	AP: ↑Bacteroidetes and Proteobacteria ↓Firmicutes and Actinobacteria
	Li *et al.* (2013)[20]	Controlled	MAP vs SAP	Blood	16S rDNA gene sequencing	SAP: ↑*Escherichia coli*, *Shigella flexneri*, *Enterobacteriaceae* bacterium, *Acinetobacter lwoffii*, *Bacillus coagulans*, and *Enterococcus faecium*
	Yu *et al.* (2020)[21]	Controlled	MAP vs MSAP vs SAP	Fecal	16S rRNA gene sequencing	MAP: ↑Finegoldia ↓Blautia MSAP: ↑Anaerococcus ↓*Eubacterium hallii* SAP: ↑Enterococcus ↓*Eubacterium hallii*
	Hu *et al.* (2021)[22]	Controlled	HTGAP vs AP by other causes	Fecal	16S rRNA gene sequencing	HTGAP: ↑Escherichia/Shigella and Enterococcus ↓*Dorea longicatena*, *Blautia wexlerae*, and *Bacteroides ovatus*
CP	Jandhyala *et al.* (2017)[32]	Controlled	CP vs healthy participants	Fecal	16S rRNA gene sequencing	CP: ↑ Firmicutes ↓ Bacteroidetes
	Gorovits *et al.* (2013)[33]	Observational	CP vs healthy people from literature reference ranges	Fecal	Bacteriological and gas-liquid chromatography analysis	CP: ↑Bifidobacterium and Lactobacillus ↓Enterobacter, Proteus, Kleibsella, and Morganella
	Savitskaia *et al.* (2002)[34]	Observational	CP vs healthy people from literature reference ranges	Fecal	Bacteriological analysis	CP: ↑*Escherichia coli*, *Enterococcus faecalis*, and *Enterococcus faecium* ↓Lactobacillus
	Hamada *et al.* (2018)[36]	Controlled	CP vs AIP	Fecal	16S rRNA gene sequencing	CP: ↑Bacteroides, Streptococcus, and Clostridium

AP, acute pancreatitis; CP, chronic pancreatitis; MAP, moderate acute pancreatitis; SAP, severe acute pancreatitis; MSAP, moderate severe acute pancreatitis; HTGAP, hypertriglyceridemia-associated acute pancreatitis; AIP, autoimmune pancreatitis; 16S rRNA, 16S ribosomal ribonucleic acid.

characterizes by storiform fibrosis and periductal lymphoplasmacytic infiltrate with or without granulocyte epithelial lesions, and depending on which to be divided into two types.[37] The most important feature of AIP (solely for type 1) is the elevation of serum immunoglobulin G4. One study found that *E. coli* could generate AIP-like pathophysiological changes in the pancreas of control mice.[38] Besides, this research also indicated that the antibody titers against *E. coli* in AIP patients were significantly higher than the titers of healthy controls.[38] This may be another evidence that antigens of the intestinal microbiota could influence disease progression of pancreatic disorders. On the other hand, autoimmune response in AIP and malnutrition in CP could result in dysregulation of intestinal microbiota and influence gut microenvironment. Hamada *et al.*[36] analyzed the fecal samples of eight CP patients and 12 AIP patients before steroids therapy. They found that no significant alterations were observed in gut microbiota between CP and AIP patients at the phylum level.[36] However, Streptococcus, Bacteroides, and Clostridium were more abundant in the fecal samples of patients with CP compared with patients with AIP (Table 1). The reason for the elevated abundance of these bacterial species is still not very clear, but it may reflect a decrease in trypsin or malabsorption associated with CP.

3. Pathogenesis hypothesis

It is well-known that gut microbiota takes part in human physiological activities via influences on regulation of the mucosal immune system and intestinal architecture, involvement of digestion and metabolism.[39] It is still controversial whether microorganisms inhabit normal pancreas.[10,11] But it is a great chance that translocation of intestinal flora would occur, since the pancreas is linked to the gastrointestinal tract anatomically via the pancreatic duct and the route of mesenteric venous and lymphatic drainage (Fig. 1). Gut microbiota is confined to gastrointestinal tract in physiological conditions due to gastrointestinal mucosal barriers, including mechanical barrier, immune barrier, and biological barrier, which can effectively prevent the intestinal pathogenic bacteria and toxins to reach outside the gut. Once this homeostasis is disrupted, intestinal opportunistic pathogens can enter the blood circulation of AP patients through the damaged intestinal barrier, thus aggravating the progression of disease and the occurrence of infectious complications. In a meta-analysis of 18 studies, approximately 59% of patients with pancreatitis had intestinal barrier imbalance.[40] Inflammation is the main pathophysiological response in pancreatitis, which is driven by either an infectious or a sterile event. Though bacteria are not the

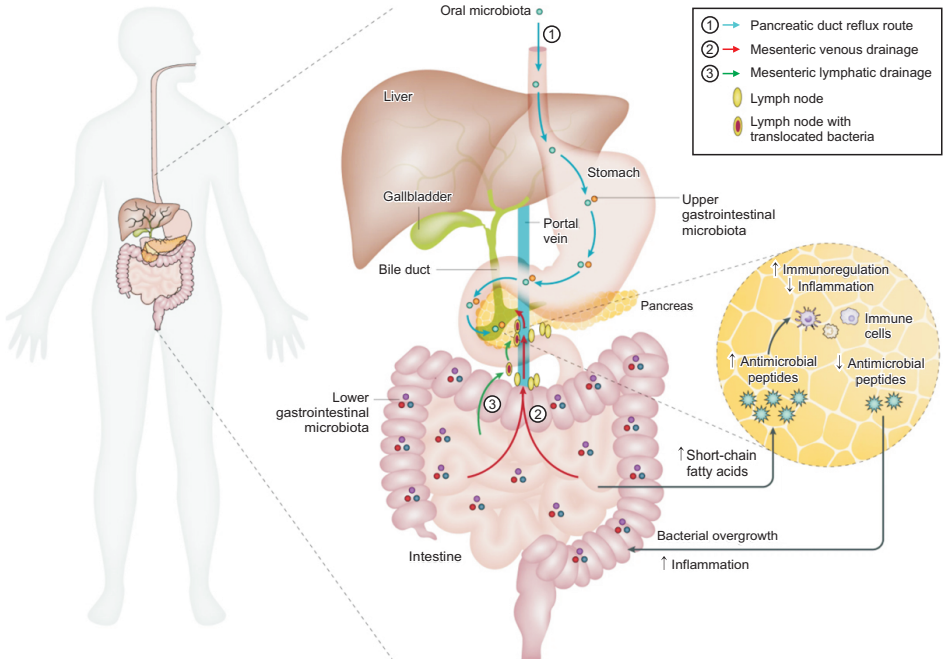

Fig. 1. Proposed routes of bacterial translocation to the pancreas and host response. The controversial routes whereby bacteria access the pancreas: however several mechanisms, such as the oral route (1), translocation from the lower gastrointestinal tract through the portal circulation (2), or mesenteric lymph nodes (3) are supported by the literature and are illustrated. Additionally, pancreatic antimicrobial peptides can have homeostatic bidirectional communication with the gastrointestinal tract, whereby the lower gastrointestinal microbiota influences pancreatic antimicrobial peptide production through short- chain fatty acid metabolites to induce an immunoregulatory pancreatic environment with decreased pro- inflammatory immune cells. Conversely, decreased antimicrobial peptide production by the pancreas enables gastrointestinal microbiota overgrowth and the development of a pro-inflammatory phenotype. Adapted from Thomas RM, *et al.* Nat Rev Gastroenterol Hepatol 2020;17:53-64, with permission from Springer Nature.[41]

directly cause of pancreatitis, the microorganisms can enter the pancreas in the inflammatory environment and aggravate the local and systemic inflammation. This is consistent with theories that the gut is the origin of clinical sepsis.[42,43]

In recent years, the role of immune cells in the pathogenesis of pancreatitis has been paid much attention, and further understanding of immune signaling pathway have been utilized to identify new therapeutic targets that may alter disease progression.[44,45] The relationship between gut microbiota and host immune system is intimate and complex. Host-microbiota communication is mainly based on one group of host receptors, the pattern recognition receptors (PRRs) of the innate immune system, such as Toll-like receptors, C-type lectin receptors, and nucleotide-binding oligomerization domain (NOD)-like receptors.[46-48] In pancreatic acinar cells, inflammation and immune response can be triggered by sensing of microorganism antigens by PRRs, which is involved in the pathogenesis of pancreatitis.[39] In animal models, pancreatitis in mice model could be induced by chronic low-dose cerulein (cholecystokinin receptor agonist) stimulation collaborating with NOD1 agonist stimulation, while this effect is prevented in NOD1 knockout mice.[49] One study indicated that gut microbiota could trigger non-infectious pancreatic inflammation through NOD1 signaling pathway in pancreatic acinar cells by binding to a peptide derived from peptidoglycan.[50]

Antimicrobial peptides (AMPs) are secretory components in the gastrointestinal tract. Though most proteins in pancreatic juice are contributed by digestive enzymes, the AMPs secreted by pancreatic acinar cells are also very important component of pancreatic juice.[51,52] Pancreatic AMPs have a prominent role in regulating the gut microbiota that is essential for gut innate immunity. There is an intimate bidirectional communication between pancreatic AMPs and gut microbiota. On one hand, the lower gut flora could influence the production of pancreatic AMP to produce an immunoregulatory pancreatic environment by decreasing pro-inflammatory immune cells through short-chain fatty acids which are anti-inflammatory metabolites produced by intestinal microbiome, also facilitate integrity of intestinal epithelium.[12] On the other hand, lack of AMP by the pancreas disrupts the gut microbiome homeostasis and leads to intestinal bacteria overgrowth and development of a pro-inflammatory status (Fig. 1). Additionally, the secretion of cathelicidin-related antimicrobial peptide (CRAMP) decreases when the Ca^{2+} channel Orai1 is knocked out in pancreatic acinar cells (Orai1$^{-/-}$) of adult mice, and resulted in systemic infection and high mortality rate due to intestinal bacterial overgrowth, elevated intestinal permeability and bacterial translocation.[13]

THE ROLE OF GENETIC SUSCEPTIBILITY OF PANCREATITIS

1. Hereditary/familial pancreatitis

Hereditary pancreatitis (HP) is defined as the condition in a family with two or more members suffered from recurrent acute pancreatitis (RAP) or CP in two or more generations, or perhaps pancreatitis which is associated with the pathogenic mutation of the cationic trypsinogen PRSS1 gene.[53] This gain-of-function mutation of the cationic trypsinogen gene was first discovered by Whitcomb *et al.* in 1996,[54] which brought new insights into pathogenesis of pancreatic disorders from the perspective of genetics. Most HP cases are inherited in autosomal dominant, whereas familial pancreatitis is used to describe recessive or complex phenotypes by clinical investigators or geneticists.[55] HP usually manifests as AP presented in childhood and subsequently resulting in the morphologic changes of CP with more frequent attack. As time going on, a variety of complications followed by CP, including pancreatic fibrosis, pancreatic exocrine insufficiency, pancreatic ductal adenocarcinoma and so on, might emerge.[56,57]

Recent HP-related investigations have shown the mechanism and process of a primary susceptibility factor, such as PRSS1 R122H, turn into risk factors for AP and CP via RAP.[58-60] These findings confirmed the trypsin dependent theory in which gain-of-function mutations brought about trypsinogen or trypsin to be resistant to degradation. Besides, the activation of premature trypsin might take an alternate path resulting in RAP, thereafter part of the patients subsequently develop to CP. There are some known genetic contributors to familial pancreatitis including loss-of-function mutations of genes which encode the SPINK1, CFTR and variants in other genes.[61-65] Whitcomb *et al.*[66] have shown that the gene-environment interactions regarding HP are very complex by using a genome-wide association study analysis performed by next-generation sequencing.

2. Genetic risk factors in pancreatitis

The well-known mechanism of pancreatitis is trypsin premature activation, causing extensive zymogen activation, followed by pancreatic self-digestion, excessive immune response, and subsequent effects.[67] Making use of candidate gene approaches, alterations in several distinct genes are associated with the regulation of trypsin in the pancreas, which is correlated with the pathogenesis of pancreatitis. To better understand the role of genetics in pancreatitis, we should firstly focus on the normal pancreas exocrine function, activity and regulation of trypsinogen, a zymogen precursor to trypsin. Trypsin is a protease produced and secreted by pancreatic acinar cells and upstream

duct cells and activates other zymogens in the duodenum under a physiological state. Premature activation of trypsin could trigger an excessive, uncontrolled inflammatory response in pancreas, as seen in AP.[68] The two most common forms in pancreatic trypsinogen are the cationic (PRSS1) and anionic (PRSS2) forms. In the physiologic condition, autolysis could prevent from premature or excessive trypsin activation in pancreatic acinar and ductal cells. However pathogenic PRSS1 mutations can induce trypsin prematurely activated or degradation-resistant and meanwhile upgrades the level of autoactivation of mutant trypsinogens and trypsin activity within pancreas.[8,63,69] As for PRSS2, pathogenic PRSS2 variants were not identified in HP or sporadic CP, whereas a variant in the noncoding region of the *PRSS1-PRSS2* locus leads to a remarkably decrease in PRSS1 expression, mitigating the risk of pancreatitis.[66,70] These mutations underline the importance of trypsinogen in the pathogenesis of pancreatitis.

During the inflammatory response of the pancreas, SPINK1 is significantly elevated to prevent excessive activation of trypsinogen and pancreatic damage through feedback inhibition of trypsin. This is the first line of defense against premature activation of intracellular trypsin. The most common p.N34S SPINK1 mutation was first mentioned to be correlated with CP in 2000.[71] Although the underlying mechanism of CP remains mystery, a meta-analysis has discovered that the SPINK1 N34S variant could increase the risk of alcoholic, idiopathic, and tropical CP.[72] Moreover, it seems to be essential for patients with heterozygous SPINK1 mutations to be linked to RAP or CP in collaborate with additional contributing factors related to recurrent activation of trypsin (like PRSS1 or CFTR).[73-75] This suggests that heterozygous SPINK1 mutations could not increase susceptibility of pancreatitis directly, but aggravate recurrent pancreatic injury correlated to the activation of trypsin and promote the progression of CP.

CFTR, an AMP-regulated anion channel located in epithelial cell membranes, mediates the secretion of bicarbonate-rich juice which is vital for secreting pancreatic zymogens. The dysfunction of the *CFTR* gene can make the acinar cells fail to alkalinize, resulting in zymogens remaining in the ducts, where they could become active and start to digest peripancreatic tissue, thus contributing to pancreatitis. *CFTR* mutations can affect the channel activity or membrane protein levels, and ultimately determine whether individuals would develop cystic fibrosis diseases and to what extent. While not only *CFTR* mutations causing cystic fibrosis are risk factors for pancreatitis, but those less penetrant CFTR alleles namely non-cystic fibrosis-causing variants, may also augment the risk of pancreatitis. Previous researches in different countries have indicated that individuals with idiopathic CP had higher rate of a *CFTR* mutation than the control group.[76-78]

Although the pathogenic role of PRSS1, SPINK1, and CFTR variants in pancreatitis is more widely known, a few uncommon genes also contribute to this process. These genes include calcium-sensing receptor (CASR), chymotrypsin C (CTRC), carboxypeptidase A1 (CPA1), and claudin-2 (CLDN2) gene, which are considered disease modifiers rather than disease initiators (Table 2, Fig. 2).[79]

3. Genetic predisposition to alcoholic/HTG pancreatitis

Although genetic etiology accounts for around 25% of all cases of CP, it should be highlighted that about 40% of cases are thought to be idiopathic.[80] The most common etiology of pancreatitis is still biliary disease, hypertriglyceridemia (HTG) and alcoholism.[81] There have not been observed that genetic factors are involved in bile duct obstruction, pancreatic divisum, or the dysfunction of Oddi sphincter. The emergence of alcohol-related CP is often clustered in families, and this would further indicate a genetic predisposition.[82] Epidemiological studies have unexpectedly found that only a small ratio of heavy drinkers (less than 3%) would develop CP, but the risk of alcoholic pancreatitis is low when smoking is adjusted in regression analysis.[7,83] Moreover, a threshold of more than five drinks a day (1 drink=4 g of alcohol) or 35 drinks a week must be achieved before the risk of pancreatitis significantly increase.[84] These observations suggest that alcohol consumption is stronger modifier factor than a susceptibility factor, especially with smoking[83] and CLDN risk variants.[66] The CLDN2 gene, encoding claudin-2, is expressed at low levels in pancreatic ducts as a tight junction protein. This high-risk gene variant triggers alcohol-related CP in men whose probability are greater compared with women with a high-risk locus near CLDN2 on the X chromosome correlated to pancreatitis.[66,85,86] Further mechanisms of action of this risk locus need to be clarified.

Like alcohol-induced CP, only a small ratio of patients with HTG develop pancreatitis, which has inclined us to investigate genetic susceptibility factors.[87] HTG-induced pancreatitis attacks typically from one or more secondary causes, such as medications, diabetes, alcoholism, pregnancy, in patients with potentially common genetic abnormalities of lipoprotein metabolism. Common variants in genes such as APOA5 (encoding apo A5), GCKR (encoding glucokinase regulatory protein), LPL (encoding lipoprotein lipase) and APOB (encoding apo B), associated with lipoprotein metabolism, can lead to a rise in serum triglyceridemia to the extent of incurring pancreatitis.[88] A detailed process of triglyceridemia metabolism can refer

Table 2. Genetic Susceptibility Factors in Pancreatitis

Genetic risk factors in pancreatitis	First discovered concerned with pancreatitis	Most common pathogenic variant	Mechanism of action	Role in the disease	Phenotype in pancreatitis
PRSS1	Whitcomb *et al.* (1996)[54]	PRSS1 (R122H, N29I, A16V)	Prematurely activated or degradation-resistant Trypsin in acinar cells	Disease initiator	Hereditary pancreatitis
SPINK1	Witt *et al.* (2000)[71]	SPINK1 (N34S)	Decrease levels of trypsin inhibitor in acinar cells	Disease modifier	Familial pancreatitis
CFTR	Kerem *et al.* (1989)[92]	CFTR (F508del)	Fail to alkalinize acinar cells, result in retention of zymogens in the duct, and cause ductal obstruction and epithelial damage	-	Hereditary pancreatitis Idiopathic pancreatitis Recurrent acute pancreatitis
CTRC	Rosendahl *et al.* (2008)[93]	CTRC (G60G)	Disrupt trypsin inactivation and protective function of CTRC-mediated trypsinogen degradation	Disease modifier	Recurrent acute pancreatitis Chronic pancreatitis
CASR	Felderbauer *et al.* (2003)[94]	CASR (R990G)	Lost control of pancreatic juice calcium concentration and increases risk of trypsinogen activation and stabilization of trypsin	Disease modifier	Chronic pancreatitis
Multigenic variants: CFTR/SPINK1; CTRC/SPINK1; CASR/SPINK1	-	-	-	-	Recurrent acute pancreatitis Chronic pancreatitis

PRSS1, serine protease 1; SPINK1, serine peptidase inhibitor Kazal type 1; CFTR, cystic fibrosis transmembrane conductance regulator; CTRC, chymotrypsin C; CASR, calcium-sensing receptor.

Fig. 2. Genetic susceptibility factors related to the trypsin pathways to pancreatitis. A summary of genetic factors that contribute to the pathogenesis of pancreatitis.
AP, acute pancreatitis; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; PRSS1, serine protease 1; PRSS2, serine protease 2; SPINK1, serine peptidase inhibitor Kazal type 1; CFTR, cystic fibrosis transmembrane conductance regulator; CTRC, chymotrypsin C; CASR, calcium-sensing receptor.

to elsewhere (see review).[89] Focused on genetic factors to HTG pancreatitis, Chang *et al.*[90] assessed the frequency of mutations in PRSS1, SPINK1, CFTR, and tumor necrosis factor superfamily member 2 (TNF2) genes in 126 HTG patients including 46 patients with hyperlipidemic pancreatitis (HLP) and 80 patients without HLP. The frequency of CFTR (M470V) and TNF (863A) mutations in HLP patients was significantly higher than patients with HTG alone, which showed that *CFTR* mutation and *TNF* promoter polymorphism probably involved in the development of HLP in HTG patients. In another study, a cohort of patients with severe, intractable HTG (triglyceride level above 2,000 mg/dL) with and without AP, AP group were significantly younger with higher fasting glucose and lower high-density lipoprotein cholesterol, indicating a stronger genetic background for HTG in this group.[91] More researches are necessary to investigate the role of genetic factors in increasing the risk of pancreatitis in patients suffered from severe/critically severe HTG.

ASSOCIATION BETWEEN GUT MICROBIOTA AND GENETIC VARIATIONS IN THE PATHOGENESIS OF PANCREATITIS

The causation between microbiota and host genetics remains to be elucidated, since our knowledge of the host side is limited and recognition of which bacterial genes are

implementing the crosstalk with the host is poorer.[95] What we have already known is that the gut microbiota diversity, structure, and composition are associated with host genetic variations.[96,97] These associations are specifically motivated by host genetic variation in immunity-related pathways.[98] Meanwhile, one report demonstrates that genetic risk for developing type 1 diabetes autoimmunity is linked with significant changes in the gut microbiota,[99] which is a manifestation of interaction between gut microbiota and host genetic factors in pancreas disorders. As for pancreatitis, another study reported that children with CP who carry different genetic variations concerned with abnormal activation of trypsinogen and secretions in the pancreatic duct present different abundances of gut microbiota genera.[100] Their findings support that disordered gut microbiota may affect host gene expression and then disturbing normal physiology function and contributing to the development of disease. On basis of above evidence, we can raise the hypothesis that the pathogenesis of pancreatitis might be influenced by the interactions of both genetic and microbial factors. However, the in-depth mechanism needs to be further investigated.

CONCLUSIONS

Growing evidence regarding the role of gut microbiota and genetic variations in pathophysiologic mechanism of pancreatitis has provided us with new insights into AP and CP. We now know that pancreatitis is not only a dysfunction of acinar cells, but a multi-factorial complicated pancreatic disorder involving gut microbiota, host immune system, environmental factors, and genetic causes. Although mechanistic understanding of these two rare factors is limited, it is clear that continued advances in bacteria-related function and genomic technologies would act as novel therapeutic interventions for pancreatitis in the near future.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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