Review Article

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Immunological Responses Involved In Promoting Acute and Chronic Pancreatitis

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ABSTRACT

Pancreatitis is the inflammatory disease of pancreas induced by unusual food habit, alcohol abuse, and genetic defect in cationic trypsinogen gene. Initial occurrences are termed as acute pancreatitis and if proper consideration is not provided then leads to the chronic pancreatitis followed by fibrosis. During the complex process of pancreatitis several pro-inflammatory cells, cytokines and chemokines play very critical role in initiation and progression of the disease. The etiology of the eosinophilic pancreatitis (EP) is poorly understood and role of inflammatory cytokines, immune cells and its mediators are not well explored. The factors involved in promoting chronic pancreatitis from acute pancreatitis are completely unidentified that progresses into the pancreatic fibrosis and further leads to the pancreatic malignancy. Therefore, an urgent need to understand the immune mechanism involved in promoting pancreatitis. The current review provides a comprehensive understanding and crucial role of complex interwoven network of various immune related cell types such as neutrophils, eosinophils, mast cells, T cells, dendritic cells, pro-inflammatory cytokines (TNF α, IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-13, IL-18, IL-33) and chemokines (MCP-1, MIF, CXCL-8, CXCL-1, Eotaxin-1, Eotaxin-2) in the development of pathogenesis of acute and chronic pancreatitis; that might be useful for scientists and physician to focus on the role of particular cell types and their associated mediators in pancreatitis pathogenesis. We hope that better understanding on the mechanism of the development of pancreatitis will help to design specific therapy to treat pancreatitis. Therefore, attention should be given to identify the focused immune mechanism that promotes pancreatitis in human.

Keywords
Pancreatitis, Interleukins, Chemokines, Immune Cells.

Introduction

Pancreatitis is the inflammation of the parenchyma of pancreas and it arises due to several reasons such as alcohol abuse, mutation in trypsinogen gene, initial onset of pancreatitis is termed as acute pancreatitis and its repeated episodes leads chronic pancreatitis and pancreatic fibrosis [1,2]. History of pancreatitis is very interesting and it was found that an early account of acute pancreatitis might have been provided by the death of most influenced Greek Ruler "Alexander the Great" [Alexander III of Macedon (20/21 July 356–10/11 June 323 BCE)]. Sbarounis 1997, proposed that "Alexander the Great" died of acute pancreatitis due to heavy alcohol consumption and a very rich meal preceded the onset of disease and were probably the main contributing factors; the course of the disease was typical of acute pancreatitis in its onset, severity and irreversibility; fever and the further systemic effects lead towards acute necrotizing pancreatitis with multiple-organ failure [3,4].

However, the current available data indicates, 13 to 45/ 100,000 people in United States are having acute pancreatitis (AP) annually [5], whereas chronic pancreatitis (CP) varies from 4.4 to 11.9/100,000 [6-9]. Several clinical reports indicate that men are more likely suffered from chronic pancreatitis as compared to

women [1,9]. Pancreatic pathogenesis involves variety of immune cells and inflammatory cellular infiltrates [10,11] that promotes cell injury as well initiate tissue repair by activating several molecular pathways [1,12]. The main key player in the pancreatitis is the acinar cells that following the injury and inflammation lead activation of pancreatic stellate cells (PSCs) and promotes fibrosis and malignancy. During the complex process of pancreatitis, several pro-inflammatory cells are involved like neutrophils, eosinophils, mast cells, dendritic cells, monocytes, macrophages, T cells subsets, cytokines and chemokines [1,2,13]. Current review provides the detailed understanding of variety of immune effector cells in the development of pancreatitis pathogenesis and will help to understand the underlying molecular mechanism of initiation and progression of acute- to chronic-pancreatitis and fibrosis including malignancy. Notably, pancreatic fibrosis is the major concern for the failed therapies in chronic pancreatitis and pancreatic malignancy.

Inflammatory cells, cytokines and chemokines in acute and chronic pancreatitis

Several immune related cells types such as neutrophils, eosinophils, mast cells, T cells, dendritic cells, pro-inflammatory cytokines (TNF α, IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-13, IL-18, IL-33) and chemokines (MCP-1, MIF, CXCL-8, CXCL-1, Eotaxin-1, Eotaxin-2) play a major role in the development of pathogenesis of acute and chronic pancreatitis. The details of each cell types, cytokines, chemokines and their role involved in the pathogenesis of pancreatitis have been summarized.

Neutrophils

Neutrophils play very important role to defend against variety of infectious diseases and are key regulators of the immune response. Neutrophils serve as early modulators of inflammation and very quickly recruited at sites of acute inflammation by the help of several chemokines such as CXCL8 (IL-8) in human as well as CXCL1 (cytokine-induced neutrophil chemoattractant-1; CINC-1) in rodent [14,15]. Recently, it has been shown that CXCL4 (platelet factor 4) is one of the most abundant chemokine in platelets, and found to be involved in platelet-dependent accumulation of neutrophils via generation of CXCL2 in AP [16]. In normal conditions, these neutrophils reside in the blood circulation with a very short life time of only 6–8 h [17]. However, during inflammatory conditions these resting neutrophils get activated, and their lifespan increases and regulate the inflammatory response mediated various pro-inflammatory mediators [1,2]. Neutrophils play a significant role in the development of local, as well as, systemic complications of severe acute pancreatitis (SAP). Neutrophils have been proposed to have important role in the early phage of AP development, and mediate intra-pancreatic trypsin activation in murine experimental acute pancreatitis [18]. Trypsin is synthesized in its precursor zymogen form termed as trypsinogen and its activation is the key step for the progression of pancreatitis [19].

Neutrophil Extracellular Traps

Neutrophils form neutrophil extracellular traps (NETs) of decondensed DNA and histones that trap and immobilize particulate matter and microbial pathogens like bacteria and orchestrate initiation and resolution of inflammation [20]. NETs are formed in the pancreas of mice during AP and cause induction of trypsin and promote pancreatitis pathogenesis. The level of NET was found increased in the plasma of AP patients [21]. NETs form a barrier between necrotic and viable areas in acute abdominal inflammation thereby limiting the spread of necrosis-associated proinflammatory mediators [22]. It has been also reported that externalized decondensed neutrophil chromatin occludes pancreatic ducts and promote pancreatitis. During inflammatory conditions neutrophils may enter in to the lumen of biliopancreatic ducts and form aggregates of NETs, which then obstruct secretory flow, and thereby drive focal pancreatitis and parenchymal remodeling depending on histone citrullination by peptidyl arginine deiminase-4 (PADI4) [23]. Neutrophils also play critical role in distant organ damage and typically result in acute lung injury (ALI) during severe acute pancreatitis [2]. Recent report indicates that during AP, neutrophils that are recruited to the pancreas may reverse migrate back into the circulation and further contribute to ALI. These reverse migrated neutrophils during ALI are controlled by junctional adhesion molecule-C (JAM-C), which is termed as reverse trans-endothelial migration (rTEM) of neutrophils [24].

Eosinophils

Eosinophils play key role in the mucosal immune system of the gastrointestinal tract during normal and inflammatory conditions [25]. In normal conditions, the mucosa of the digestive tract is the only organ harboring a substantial number of eosinophils, which, if needed, get activated and exert several effector and immunoregulatory functions [26]. Although, in healthy pancreas no baseline eosinophils are reported; however, in several cases the presence of induced eosinophils in the patients with pancreatitis are reported and the condition is termed as "Eosinophilic Pancreatitis" [27-29]. Most recently the detection of induced IL-5 has been reported in experimental model of chronic pancreatitis [30] that indicates eosinophils may be a critical immune cells in promoting pancreatitis pathogenesis. IL-5 is well known growth and differentiation factor for the development, differentiation and maturation of eosinophils [31,32].

Eosinophilic Pancreatitis

Eosinophilic pancreatitis (EP) is rarely occurring disorder and several reports indicate that eosinophilic pancreatitis is frequently diagnosed only after "false positive" pancreatic resection for suspected pancreatic tumor and it can mimic a pancreatic neoplasm [28,29,33]. Juniper in 1955 [34] has shown for the first time peripheral blood eosinophilia in chronic pancreatitis patient and then, several reports based on eosinophilic pancreatitis were published [35-38]. A study based on 122 patients with chronic pancreatitis revealed that 17.2 % (21 patients among 122) had eosinophilia [35]. Notably, the report indicates that mostly male patients were affected with disease compare to the female patients, which indicates that male is more prone to pancreatitis. Markedly, increased eosinophils numbers during chronic pancreatitis regularly developed in connection with severe damage to adjacent organs

and further suggest a possibility of correlation between elevated eosinophils level in pancreas and severe tissue injury during acute exacerbations of chronic pancreatitis [35]. Furthermore, a study by Wang and coworkers based on 180 CP patients revealed that 15.6% patients (28 patients) of chronic pancreatitis suffered from eosinophilia with 8.3:1 ratio of male to female patients. Hence, the occurrence of eosinophilia during the course of chronic pancreatitis may be critical for pancreatitis pathogenesis [1,36]. Occurrence of eosinophils was also found in autoimmune pancreatitis (AIP) and reports indicated that peripheral eosinophilia, allergic disorders and pancreatic eosinophil infiltration were found to be associated with AIP [37,38]. The diagnosis of eosinophilic pancreatitis is very important not only because it can mimic a pancreatic neoplasm, but also because it is associated with eosinophilic gastroenteritis and the potentially fatal hyper eosinophilic syndrome. EP is generally associated with a high IgE levels in serum, whereas patients with AIP have elevated IgG4 levels. Patients with AIP generally give positive test for autoimmune and antinuclear antibodies and have enlarged (sausage-like) pancreas, rather than enlargement of the pancreatic head or tail [39].

Mast Cells

Mast cells are the cells of hematopoietic origin and known to be main effector cells in various allergic responses [40]. Several studies have shown that activated mast cells are the important effector cells in the pathogenesis of lethal acute [41] and chronic pancreatitis [42]. During onset of AP, these activated mast cells causes endothelial barrier dysfunction in both, pancreas and distal organs/tissues, particularly in the lungs and colon and known to be a crucial cause of multiple organ failure [43]. Mast cells were found to secrete and respond to IL-33 in duct ligation-induced acute pancreatitis model and induced histamine level was also observed in the same animal model [44]. Mast cells perform a critical role in the pain of chronic pancreatitis in patients and report showed that the large numbers of mast cells had been accumulated in patients having painful chronic pancreatitis when compared with the patients with painless chronic pancreatitis [45]. Interestingly, a large number of degranulated mast cells were detected in the patient biopsies that show pancreatic fibrosis. The presence of activated mast cells during pancreatic fibrosis suggested that the activated mast cell-released chemical mediators that activates pancreatic stellate cells (PSCs) which are the crucial for the development of pancreatic fibrosis and leading malignancy [46]. Additionally, another report indicates that mast cells are not detected in acute pancreatitis; however their number increases in pancreatic ductal adenocarcinoma (PDAC) [47]. Therefore, an utmost need to develop a better understanding on the role of mast cells and released biological mediators, which perturb other immune cells during the pathogenesis of acute and chronic pancreatitis.

Monocytes and Macrophages

Monocytes are a type of white blood cells with amoeboid shape and granulated cytoplasm. The most striking property of monocytes is, its capability to differentiate into macrophages and myeloid lineage dendritic cells [48]. In addition to neutrophils, monocytes also play crucial role in the pathogenesis of acute pancreatitis [49]. During initiation of acute inflammation, pancreatic acinar cells secretes several pro-inflammatory cytokines (IL-1, IL-6, TNF-α) [1,2,50,51] and chemokines such as monocyte chemotactic protein (MCP)-1 [52,53]. TNF-α and MCP-1 help to recruit the monocytes at the site of inflammation that further amplify the inflammatory signals by producing other cytokines [50,52,53]. Further report indicates that TNF-α-dependent regulation of Ly-6C (hi) monocytes has critical role in severity of acute pancreatitis in mice [54]. It was found that NF-kβ and p38 MAPK signaling has been operated in activation of monocytes/macrophages that might play a major role during disease pathogenesis [51].

Recent report has shown that silencing of cystathionine-gamma-lyase gene in monocytes/macrophages protects acute pancreatitis in mice [55]. Further, the macrophages that are derived from monocytes during inflammatory responses have an important role in antigen presentation, phagocytosis and immunomodulation via secretion of pro-inflammatory cytokines. Macrophage migration inhibitory factor (MIF) play a critical role in acute pancreatitis [56]. The pre-treatment with anti-MIF antibodies [56] or macrophage-depleting agent i.e. clodronate liposomes [57] improved survival of rodent models with acute pancreatitis. Two types M1 and M2 macrophages are reported [58,59], in which M2 macrophages are also known as activated macrophages that are found to be involved in promoting pancreatic fibrosis via IL-4 and IL-13 mediated signaling pathways [30]. Expression of area-specific M2-macrophage phenotype was also reported in rat inflammatory monocytes in duct-ligation pancreatitis model [60]. Patients with chronic pancreatitis with local inflammation have high risk for pancreatic cancer and the involvement of macrophages were reported in pancreatic acinar-to-ductal metaplasia (ADM). This ADM-promoting effect has been found dependent upon numerous macrophage-derived soluble mediators, especially TNF-α and CCL5/RANTES, that mediates its action via NF-Kβ to promote epithelial cell proliferation and matrix metalloproteinase 9 (MMP-9)-mediated remodeling of the extracellular matrix [61]. Interestingly, anti-inflammatory macrophages were reported to activate invasion in pancreatic adenocarcinoma by increasing the expression of MMP-9, disintegrin and metalloproteinase (ADAM) 8 [62]. Recently, the role of activated legumain, a lysosomal cysteine protease, was identified in macrophages that are involved in progression of pancreatitis. Moreover, the presence of legumain-expressed- macrophages in regions of acinar-to-ductal metaplasia (ADM) suggests that this lysosomal cysteine protease may have a critical role in reprogramming events that lead to inflammation-induced pancreatic cancer [63]. However, the role of monocytes/macrophages is still largely unknown and not explored well during the pathogenesis of pancreatitis that need further immense effort to unravel their role in pancreatitis, pancreatic fibrosis and malignancy.

T lymphocytes

T lymphocytes have been well reported in the pathogenesis of acute [64-67] as well as chronic pancreatitis [68-73]. The role of various T cell subsets in acute pancreatitis was reported that includes soluble interleukin-2 receptor (sIL-2R), soluble CD8

(sCD8) and soluble CD4 (sCD4). In the early phases of acute pancreatitis serum level of sCD8 and sIL-2R were significantly increased compare to normal patients; whereas, sCD4 serum levels were significantly decreased in acute pancreatitis patients [64]. In contrast, CD4+ T cells are recruited during acute pancreatitis and play a pivotal role in the development of tissue injury during acute experimental pancreatitis in mice [65]. Further, it has been also reported that $CD4^+$ T cells are the main source of IL-22 in pancreatic tissues from healthy mice; however during acute pancreatitis the number of these IL-22 producing $CD4^+$ T cells were decreased. This finding indicates that IL-22 producing $CD4^+$ T cells may have a protective role in experimental model of acute pancreatitis [66].

Furthermore, a study also suggested that the reduction of peripheral blood $CD4^+$ T cells is associated with persistent organ failure in acute pancreatitis [74]. Recently, increased activated effector T cells phenotyped by $CD4^+CD25^+CD127^{high}$ have a significant negative correlation with multiple organ failure in acute pancreatitis and show significant association between patient with low natural killer cells at admission and secondary infection in AP [75].

The patients with chronic pancreatitis have increased numbers of central memory T cells [72]. Several reports have shown the presence of different subsets of T lymphocytes in chronic pancreatitis is critical in cell-mediated pancreatitis pathogenesis [68,69]. In addition, $CD8^+$ $CD103^+$ T cells subset analogous to intestinal intraepithelial lymphocytes, were found infiltrated in the pancreas in chronic pancreatitis, pointing out the role of CD8+ $CD103^+$ T cell subsets as a first-line defense against damaging epithelial events in chronic pancreatitis [69]. The disease-specific regulatory T-cell responses were observed in chronic pancreatitis [73]. Interestingly, pancreatitis-specific IL-10 responses were facilitated by IL-10 (+) IFN-γ (-) FoxP3 (+) regulatory T cells, which were expanded in the blood, bone marrow, and pancreatitis lesions [73]. These findings indicate the existence of different T lymphocytes subsets during the progression of pancreatitis pathogenesis suggesting the role of T cells in the disease pathogenesis.

Dendritic Cells

Dendritic cells (DC) are the antigen-presenting cells in the immune system and have been arisen as crucial immune cells in inflammatory responses. During exposure to any inflammatory stimuli, these immature DCs get-up-and-go for both adaptive and innate immune responses [76,77]. The role of DCs has been reported to promote pancreatic viability in mice with acute pancreatitis and serve as a protective role during experimental acute pancreatitis [78]. Additionally, inhibition of MyD88 surprisingly accelerates the pancreatic tumor progression by augmenting DCs capacity to generate intra-pancreatic inflammation via induction of Th2-deviated $CD4^+$ T cells [79]. Hence, it seems that DCs have different role such as avoiding inflammation in AP, but also have augmenting inflammatory responses that lead to pancreatic neoplasia. Therefore, the role of DCs in pathogenesis of acute and chronic pancreatitis needs more investigations.

Critical pro-inflammatory cytokines and chemokines in pancreatitis

Inflammation of pancreas leads pancreatitis and it is tightly regulated by interwoven network of several cytokines and chemokines such as Tumor necrosis factor (TNF-α), interleukin (IL)-1, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-13, IL-18, and IL-33 and secreted from injured pancreatic acinar cells during acute and PSCs during chronic pancreatitis [1,80]. TNF-α is a pleiotropic cytokine and a key regulator of other pro-inflammatory cytokines. A number of studies have shown that TNF-α plays a critical role in pancreatitis pathogenesis and makes significant contribution in amplification of pancreatic inflammation [81-84]. However, increased levels of IL-1, IL-1 receptor (IL-1R) and IL-1β were also reported in acute pancreatitis [85-89]. IL-2 is recognized as central to normal immunologic function and its production was found decreased in experimental acute pancreatitis [90].

Additionally, soluble IL-2 receptor has been discovered as new biomarker for autoimmune pancreatitis [91]. A most recent study have shown that pharmacologic inhibition of IL-4/IL-13 in human ex vivo studies as well as in cerulean induced mouse chronic pancreatitis model, decreases pancreatic alternatively activated macrophages and reduces pancreatic fibrosis and suggesting that IL-4/IL-13 axis is critically involved in pancreatitis pathogenesis [30]. In the same study, induced IL-5 level was also observed by using ultrasensitive luminex assay indicating the role of IL-5 in the pathogenesis of pancreatitis [30]. IL-6 is another central cytokine involved in inflammation and immune responses. The role of IL-6 was found in acute pancreatitis and chronic pancreatitis and IL-6 mediates its action via Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway [92]. Available reports have shown that patients with pancreatitis have high serum levels of IL-6 as compared to healthy individuals [93]. The abnormal expression and deregulation of IL-6 in acute pancreatitis suggested that IL-6 may serves as a valuable early marker for pancreatitis. IL-8, a chemokine (C-X-C motif) ligand 8 or CXCL8, acts as a potent chemo-attractant to recruit neutrophils [14,15] during inflammatory responses and increased level of IL-8 was found in a patient with aggravation of pancreatitis indicating that IL-8 might also play an important role in pancreatitis pathogenesis [94].

However, systemic complications of acute pancreatitis were found associated with the higher level of IL-8 [50] and further, induced level of IL-8 was reported in a pancreatitis patient. These reports suggest that IL-8 plays important role in the pathogenesis of pancreatitis [94]. IL-18 is a member of IL-1 family cytokine and implicated in numerous aspects of the innate and adaptive immune system, with some analogy to IL-1β [95]. Further, evidences reveal that IL-18 is also induced in the blood of acute [96] as well as chronic pancreatitis patients [97,98]. Additionally, higher serum IL-18 was observed during mild and severe forms of acute pancreatitis compared to normal patients [99]. IL-33, also a member of the IL-1 superfamily of cytokine [100], activate

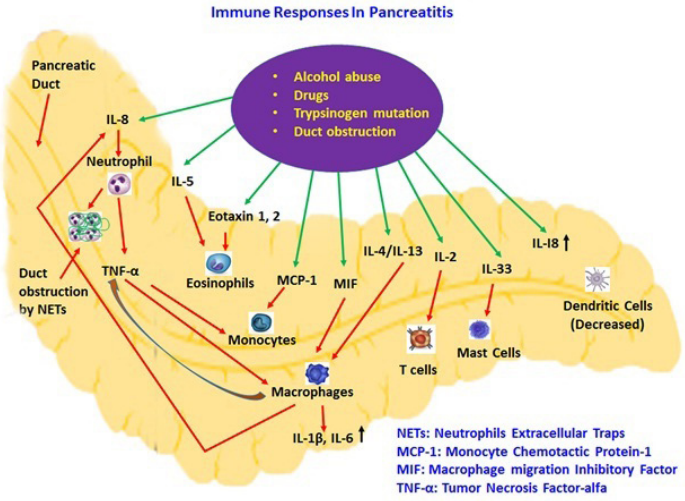
acinar cell mediated pro-inflammatory pathways to exacerbate inflammation in acute pancreatic mice [44]. Therefore, ample of investigations suggest crucial role of IL-33 in the pathogenesis of chronic pancreatitis and possibly pancreatic cancer [101,102].

Additinally, various chemokines are known to involve in pancreatitis such as monocyte chemotactic protein (MCP)-1 and macrophage migration inhibitory factor (MIF) that play important role in recruitment of monocytes and macrophages during pancreatitis [56,57]. Macrophage MIF is mainly secreted from monocytes, macrophages, T cells, and epithelial cells [103] and mediates its pro-inflammatory action by Toll-like receptor 4 (TLR4), resulting in the production of many pro-inflammatory cytokines, such as IL-6, IL-1β, IL-8, TNF-α [104]. MIF is evolving as a critical molecule for acute pancreatitis and pre-treatment with anti-MIF antibodies, improved the survival of rats with AP [56]. Furthermore, increased MIF levels were reported in the serum of severe acute pancreatitis as compared to normal individuals [56]. Other chemokines such as CXCL8 (IL-8) in human as well as CXCL1 (cytokine-induced neutrophil chemoattractant-1; CINC-1) in rodent are known to serve as chemoattractant for recruitment of neutrophils during inflammation [14,15]. Recently, it has been shown that CXCL4 (platelet factor 4) is one of the most abundant chemokine in platelets, and found to be involved in platelet-dependent accumulation of neutrophils via generation of CXCL2 in AP [16].

Eotaxin-1 and Eotaxin-2 are well known eosinophil-specific chemokines and are responsible for the recruitment of eosinophils [105-108]. Our unpublished data indicates that eosinophil active chemokines eotaxin-1 and eotaxin-2 are increased in the pancreas of cerulein-induced experimental chronic pancreatitis. These results indicate the induced levels of eotaxins serve as chemoattractant to recruit eosinophils at the site of chronic inflammation in pancreas. It is well know that eosinophils are the source of TGF-β1 that play critical role in development of fibrosis [109]. Hence, the role of eosinophils during pancreatitis pathogenesis and fibrosis cannot be ignored and need further attention of physicians and scientists.

Conclusion

The search for a specific therapy to treat pancreatitis remains the paramount goal of the current pancreatitis based research. Limited information is known about the role of several molecular immune cell mediators involved in pancreatitis, associated fibrosis and pancreatic malignancy that need further attention to explore their importance in progression of pancreatitis pathogenesis. The current review provides a comprehensive understanding and crucial role of complex interwoven network of various immune related cell types such as neutrophils, eosinophils, mast cells, T cells, dendritic cells, pro-inflammatory cytokines (TNF α, IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-13, IL-18, IL-33) and chemokines (MCP-1, MIF, CXCL-8, CXCL-1, Eotaxin-1, Eotaxin-2) in the development of pathogenesis of acute and chronic pancreatitis. Bridging the gap from bench to bedside, we provided the updated information of several immune cell types that might be useful for scientists and physician to focus on the role of particular cell types and their associated mediators in pancreatitis pathogenesis. We hope that our and others ongoing research will provide more insight and necessary motivation to create progress to acquire adequate understanding to discover an effective and efficient diagnostic and



therapeutic interventions in the treatment of pancreatitis. Below, a summarized diagrammatic figure of our current understandings of immune pathways involved in the pancreatitis pathogenesis is presented.

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