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TOPIC HIGHLIGHT

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Immunomodulatory therapies for acute pancreatitis

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Abstract

It is currently difficult for conventional treatments of acute pancreatitis (AP), which primarily consist of anti-inflammatory therapies, to prevent the progression of AP or to improve its outcome. This may be because the occurrence and progression of AP, which involves various inflammatory cells and cytokines, includes a series of complex immune events. Considering the complex immune system alterations during the course of AP, it is necessary to monitor the indicators related to immune cells and inflammatory mediators and to develop more individualized interventions for AP patients using immunomodulatory therapy. This review discusses the recent advances in immunomodulatory therapies. It has been suggested that overactive inflammatory responses should be inhibited and excessive immunosuppression should be avoided in the early stages of AP. The optimal duration of anti-inflammatory therapy may be shorter than previously expected (< 24 h), and appropriate immunostimulatory therapies should be administered during the period from the 3rd d to the 14th d in the course of AP. A combination therapy of anti-inflammatory and immune-stimulating drugs would hopefully constitute an alternative to anti-inflammatory drug monotherapy. Additionally, the detection of the genotypes of critical inflammatory mediators may be useful for screening populations of AP patients at high risk of severe infections to enable the administration of early interventions to improve their prognosis.

Key words: Pancreatitis; Immunomodulatory therapy; Systemic inflammatory response syndrome; Immunosuppression; Immunostimulation

Core tip: In light of the complex immune system alterations that occur in acute pancreatitis (AP), it is necessary to develop more individualized interventions for AP patients by using immunomodulatory therapy instead of inflammatory drug monotherapy. We first suggest how we could monitor the immune status of these patients and identify optimal treatment methods. We also demonstrate for the first time that the detection of the genotypes of critical inflammatory mediators may be useful for screening populations of AP patients at high risk of severe infections.

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INTRODUCTION

Acute pancreatitis (AP) is a common acute abdominal disease. Despite advances in treatment, the mortality rate of severe acute pancreatitis (SAP) remains as high as 10%-30%, and multiple organ dysfunction is the main

cause of death[1-3].

Currently, conventional treatments for AP include fluid infusion, inhibition of pancreatic secretion and organ support. However, fluid resuscitation cannot prevent pancreatic necrosis[4,5]. In addition, the inhibition of pancreatic secretions has always been considered one of the most important strategies for treating AP. Research has shown that cell apoptosis or necrosis occurs in AP patients, that the zymogen granules of acinar cells decrease in number and that pancreatic exocrine functions are inhibited[6]. Under such conditions, the inhibition of exocrine pancreatic function cannot prevent the progression of AP or improve its outcomes[6,7]. Because AP consists of chemical inflammation, the prophylactic use of antibiotics cannot lower the incidence of infection in a necrotic pancreas or the mortality of AP[8-10]. Although organ support and symptomatic treatment may help patients survive multiple organ failure[11,12], there is still a lack of effective treatment for AP.

Until now, conventional treatments for AP have mainly been anti-inflammatory therapies. However, their effects have not proven to be as satisfactory as expected[4]. In fact, numerous studies have shown that a variety of inflammatory cells and cytokines are involved in the occurrence and progression of AP, which comprises a series of complex immune events[13]. A thorough understanding of the AP immune response and its mechanism can aid in the development of better AP treatment strategies.

AP IMMUNE RESPONSE (INFLAMMATORY RESPONSE AND IMMUNE SUPPRESSION)

The onset of AP generally includes the following immunological stages: systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS) and mixed anti-inflammatory response syndrome (MARS)[4,14-16]. In light of the complex immune system alterations that occur during the different phases of AP, a more individualized approach to AP, such as the use of immunomodulatory therapy, may be beneficial.

SIRS

Following stimulation by various pathogenic factors, trypsin in the pancreatic acinar cells is prematurely activated due to neutrophil involvement[17]. This process is closely related to the following pathophysiological processes: high pancreatic duct pressure, the flow of Ca^{2+} into the pancreatic acinar cells and the activation of transcription factors, such as nuclear factor-κB (NF-κB)[6,12,18]. NF-κB is a core molecule of the innate immune response. The amplification of inflammatory signals generated by NF-κB is able to produce a large number of inflammatory factors, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and monocyte chemotactic protein (MCP)-1[19]. In the presence of these cytokines and chemokines, more neutrophils and lymphocytes gather in the pancreas and intestinal tracts, thus amplifying the inflammatory response[20]. When these pro-inflammatory cytokines are released into the blood, the inflammation is no longer confined to the pancreas, and, consequently, SIRS develops. The activated neutrophils and monocytes are then able to release proteases and oxygen free radicals. These inflammatory mediators can then cause damage to the vascular endothelial cells, increases in vascular endothelial permeability and the accumulation of a large amount of fluid in the tissue. As a result of these processes and other microvascular dysfunctions, tissue hypoxia and significant organ dysfunction develop[16].

In addition, intestinal ischemia-reperfusion during AP can significantly upregulate the expression of pattern recognition receptors, such as toll-like receptors (TLRs), in the intestinal mucosa, potentially leading to an overactive intestinal mucosal immune response and the rapid progression of AP[21]. Animal experiments have shown that TLR4-deficient mice rarely develop SAP[22]. Furthermore, TLR4 gene polymorphisms have been found to be associated with susceptibility to severe infections in AP patients[23].

CARS

With the release of pro-inflammatory cytokines, anti-inflammatory cytokines are produced in the body. The outcome of this disease depends on the balance between the inflammatory and anti-inflammatory responses. When the anti-inflammatory response is strong enough, patients may recover. On the contrary, when the anti-inflammatory response is not sufficiently strong, an excessive inflammatory response can lead to early organ dysfunction and SAP. During periods of overactive compensatory anti-inflammatory responses, the following changes may occur in AP: anergy in lymphocytes, thymus and spleen atrophy and a decrease in the number of peripheral lymphocytes (mainly the T lymphocytes), which could be associated with a depletion of lymphocytes or with lymphocyte apoptosis[13,24-27]. The abovementioned changes during immunosuppression are closely related to infection in the late stage of SAP[28].

In addition to lymphocyte-related defective defense systems in AP, mononuclear cell dysfunction may occur, which is characterized by a significant decrease in the expression of human leukocyte antigen (HLA-DR) and the synthesis of pro-inflammatory cytokines (*e.g.*, TNF-α)[16]. The expression of low-density HLA-DR in mononuclear cells indicates an impaired antigen-presenting function. Mentula *et al*[29,30] reported that reduced expression of HLA-DR in monocytes in early SAP most likely predicted the occurrence of a secondary infection and fatal complications in AP. HLA-DR expression can be detected by flow cytometry within 30-60 min; therefore, it can be used as a routine test to identify the immune status of AP patients and to predict the outcomes of AP[13].

Furthermore, intestinal immune function can be impaired in early AP, manifesting as damage to the integrity

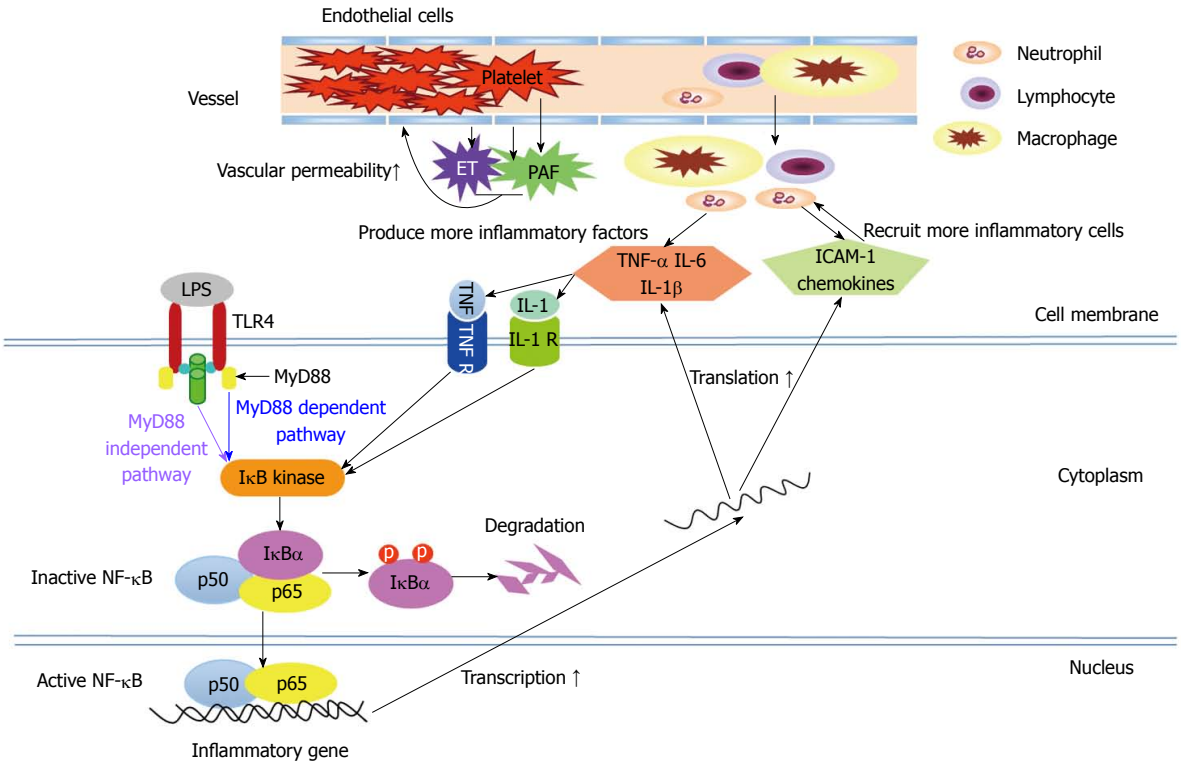

Figure 1 Schematic presentation of the pathways involved in the inflammatory response during acute pancreatitis. Following lipopolysaccharide (LPS) stimulation, the inhibitors of κB (IκB) kinase are activated *via* the toll-like receptor 4 (TLR4)-myeloid differentiation factor 88 (MyD88)-dependent (blue) or -independent pathway (purple). Thereafter, IκBα is rapidly phosphorylated by IκB kinase and then degraded. This process allows nuclear factor-κB (NF-κB) to translocate into the nucleus and to increase the transcription of several important inflammatory genes, such as the genes encoding tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), adhesion molecules and chemokines. The up-regulation of these inflammatory mediators, in turn, either leads to further IκB kinase activation or mediates the migration of the inflammatory cells to the site of inflammation, thus amplifying the inflammatory response. Meanwhile, platelet-activating factor (released from active macrophages, endothelial cells or platelets) and endothelins (released from endothelial cells) are involved in the increased vascular permeability and extravasation of inflammatory cells. TNF R: Tumor necrosis factor receptor; IL-1 R: Interleukin-1 receptor; ICAM-1: Intercellularadhesionmolecule-1; PAF: Platelet-activating factor; ET: Endothelin.

of intestinal mucosal barriers, decreased levels of immune cells and the absence of secretory immunoglobulin A (sIgA) in the intestine. These events may in turn cause translocations of intestinal bacteria and endotoxins, as well as infectious complications[31].

MARS

SIRS, MARS and CARS are traditionally thought to appear successively in AP. MARS is regarded as a transient dynamic balance in the transition from SIRS to CARS. However, increasing evidence has revealed that there is no distinct boundary between SIRS and CARS and that CARS also occurs in the early stages of sepsis or SAP[14,28]. Therefore, MARS cannot be a transition period from SIRS to CARS; instead, it may constitute an independent reaction in tandem with an excessive inflammatory response and immune suppression in early SAP[4,14-16].

ANTI-INFLAMMATORY THERAPIES

In AP, the overactivity of pro-inflammatory cells and factors may aggravate local inflammation in the pancreas, facilitating the development of SIRS. Anti-inflammatory factors will not work effectively when their levels are below those of the pro-inflammatory factors[32,33]. Theoretically, the modulation of immunocytes and inflammatory mediators may be able to prevent overactive immune reactions and to alleviate inflammatory injuries; this hypothesis has been gradually confirmed by accumulating animal experiments and clinical trials over the past 20 years. Blocking these inflammatory pathways (Figure 1), moderately and at the appropriate time, may be an effective treatment for AP. However, the inflammatory reaction involves numerous factors and cells. Thus, treatments targeting only certain factors or cells may be unable to terminate the entire overactive inflammatory reaction on their own.

NF-κB

NF-κB, a vital transcription factor, is activated early in the course of AP and regulates the transcription of many genes involved in inflammatory responses, such as TNF-α, IL-1β and IL-6[18] (Figure 1). It has been found that the inhibition of NF-κB activity with amobarbital, a NF-κB essential modifier binding domain peptide, or pyrrolidine dithiocarbamate (NF-κB activity inhibitor) attenuated AP-associated injuries in the pancreas and lungs. Currently, these results are only based on animal studies[34-36].

Table 1 Clinical trials of lexipafant in acute pancreatitis

Ref.	Study design	Severity of AP	No.	Interval	Dosage and administration	Major variables	Outcomes
Kingsnorth *et al*[74], 1995	Multi-center double-blind RCT	Mix	83	< 48 h	60 mg/d, *i.v.*, × 3 d	Organ failure OFS IL6, IL8	Positive
McKay *et al*[75], 1997	Multi-center double-blind RCT	APACHEII > 5, Glasgowscore ⩾ 3, and C-reactive protein ⩾ 120 mg/L	50	< 72 h	100 mg/d, *i.v.*, × 7 d	OFS Systemic complications Mortality	Positive
Johnson *et al*[76], 2001	Multi-center double-blind RCT	APACHEII > 6	290	< 72 h	100 mg/d, *i.v.*, × 7 d	Systemic sepsis Pseudocysts New organ failure. Mortality	Positive in systemic sepsis and pseudocysts

AP: Acute pancreatitis; No.: Number of patients; Interval: Time interval between AP onset and the initiation of octreotide treatment; RCT: Randomized controlled trial; Mix: Mixture of APACHEII < 8 and APACHEII ⩾ 8 acute pancreatitis patients; *i.v.*: Intravenous infusion; OFS: Organ failure score; IL: Interleukin; APACHE: Acute Physiology and Chronic Health Evaluation scale.

TNF-α

TNF-α is a monocyte-derived pro-inflammatory cytokine. In AP, TNF-α was found to contribute to pancreatic acinar cell death and to the expression of other pro-inflammatory factors, such as IL-1 and IL-6[37,38] (Figure 1). Animal studies have shown that TNF-α blockade with anti-TNF-α antibodies or soluble TNF-α receptors was able to decrease the severity of AP and reduce the associated mortality rate by prohibiting the effect of TNF-α[39-43]. In addition, several case reports have demonstrated that infliximab (monoclonal anti-TNF-α antibody) was effective in AP-complicated acute Kawasaki or active Crohn's disease and had a preventive effect on AP in a patient with recurrent acute exacerbation of chronic pancreatitis[44,45].

IL

Various pro-inflammatory interleukins, such as IL-1β, IL-6, IL-8 and IL-18, are involved in the inflammatory responses associated with AP[46-51]. Animal studies have suggested that the inhibition of pro-inflammatory interleukins with antibodies (*e.g.*, anti-IL-6 receptor antibody or anti-IL-8 antibody), receptor antagonists (IL-1 receptor antagonist) or biosynthesis inhibitors (IL-1-converting enzyme inhibitor) ameliorated pancreatic and lung injuries in AP and reduced the associated mortality rate[46,52-56].

During the overactive inflammatory reactions of AP, the anti-inflammatory cytokine IL-10 is unable to inhibit the inflammatory reactions effectively, as its serum level is far below that of the pro-inflammatory factors, such as TNF-α[32,33]. In animal experiments associated with AP, exogenous IL-10 or supplementation with its effective fragment (IT9302), IL-10 gene transfer and insulin-like growth factor administration were each reported to result in the downregulation of serum TNF-α levels, the alleviation of pancreatic injury and a decrease in death rates by increasing the circulating levels of IL-10 or its effective fragment[57-63]. In clinical trials, there were conflicting results regarding the ability of IL-10 to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis[64-66]. Different inclusion criteria and follow-up times may be responsible for the controversy. Nevertheless, persistent elevation in circulating IL-10 levels has been found to be one of the causes of immunosuppression in some AP patients[67].

Although the effectiveness of anti-inflammatory therapies targeting IL has been confirmed by many animal experiments, only treatment with IL-10 has been investigated through clinical trials. Larger randomized clinical trials (RCTs) are required to assess the safety and efficacy of these therapies.

Platelet activating factor

Platelet activating factor (PAF), a biologically active phospholipid that is released from macrophages, endothelial cells and platelets, has been shown to induce neutrophil-platelet aggregation and to increase vascular permeability[68] (Figure 1). Lexipafant, a PAF antagonist, is able to inhibit the inflammatory response and to ameliorate the severity of pancreatitis-associated intestinal and lung damage in experimental models of AP[69-73]. Several large-scale RCTs have also indicated that lexipafant led to significant decreases in mortality and the incidence of systemic complications of AP[74-76] (Table 1). The recommended administration of lexipafant is intravenous infusion at a dose of 100 mg/d for 7 d within 72 h after AP onset[74,75]. However, a phase Ⅲ clinical trial indicated that lexipafant had no effect on new organ failure or death rates in AP[76].

Endothelin

Endothelins (ETs: including ET-1, ET-2 and ET-3) and their receptors (ET_A and ET_B) mediate the vasoconstriction response and maintain vascular tension[77]. It has been found that elevated plasma endothelin-1 levels are associated with low perfusion and pancreatic necrosis in AP[78,79]. Currently, it remains controversial whether ET receptor antagonists have beneficial effects on pancreatic perfusion and the mortality of AP[80-86]. However, studies have involved only animal experiments, and no relevant

Table 2 Clinical trials of octreotide in acute pancreatitis

Ref.	Study design	Severity of AP	No.	interval	Dosage and administration	Major variables	Outcomes
Wang *et al*[89], 2013	Prospective RCT	P-SAP; SAP	P-SAP: 236 SAP: 136	< 48 h	50 μg/h, continued *i.v.*, × 3 d + 25 μg/h, continued *i.v.*, × 4 d, or 25 μg/h, continued *i.v.*, × 7 d	APACHE II, SIRS score, and MOF score Local complication IL6, TNF-α	Positive at higher dosage
Yang *et al*[90], 2012	Multi-center RCT	MAP	161	< 48 h	50 μg/h, continued *i.v.*, × 3 d	APACHE II and MOF score Local complication IL6, TNF-α	Positive
Nikou *et al*[91], 2004	Prospective RCT	MAP	36	< 12 h	200 or 500 μg, *i.h.*, 3 times/d × 5 d	IL-6, C-reactive protein	Positive IL-6 outcome at higher dosages
Beechey-Newman[93], 1993	Prospective case-control study	MAP	19	N	250 μg, *i.h.*, then 0.5 μg/kg per hour, continued *i.v.*, × 10 d	Biochemical and physiological parameters	Positive in serum calcium, albumin, hematocrit, hemoglobin, PaO2
Binder *et al*[94], 1994	Prospective trial	Mix	8	N	100, 200 or 500 μg, *i.h.*, 3 times/d × 10 d	Complications	Positive at two higher dosages
Paran *et al*[95], 1995	Multi-center RCT	MAP	38	N	100 μg, *i.h.*, 3 times/d × 14 d	Organ dysfunction Local complications Length of hospital stay Mortality	Positive in organ dysfunction and length of hospital stay
Fiedler *et al*[96], 1996	Prospective case-control study	SAP	39	N	100 μg, *i.v.*, 3 times/d × 10 d	Organ dysfunction Mortality	Positive
McKay *et al*[97], 1997	Multi-center RCT	Mix	58	N	40 μg/h, continued, *i.v.*, × 5 d	Complications Mortality	Negative
Karakoyunlar *et al*[98], 1999	Prospective controlled study	Mix	43	N	250 μg/h, continued *i.v.*, × 2 d	Biochemical, physiological and radiological changes Mortality	Positive outcomes for serum amylase levels, pancreatic edema and earlier return to oral intake
Paran *et al*[99], 2000	Case-controlled study	Mix	50	N	100 μg, *i.h.*, 3 times/d, × 14 d	Organ dysfunction Local complications Length of hospital stay Mortality	Positive in organ dysfunction, length of hospital stay and mortality
Nikou *et al*[100], 2001	Prospective RCT	Mix	120	N	100, 200 or 300 μg, *i.h.*, 3 times/d, × 7 d	Duration of pain Organ dysfunction Local complications	Little benefit only at two higher dosages

AP: Acute pancreatitis; No.: Number of patients; Interval: the time interval between AP onset and the initiation of octreotide treatment; RCT: Randomized controlled trial; MAP: Mild acute pancreas; SAP: Severe acute pancreas; Mix: Mixture of MAP and SAP; P-SAP: Predicted SAP; N: Not mentioned; *i.h.*: Subcutaneous infusion; *i.v.*: Intravenous infusion; APACHE: Acute Physiology and Chronic Health Evaluation scale; SIRS: Systemic inflammatory response syndrome scale; MOF: Multiple organ failurescale; IL: Interleukin; TNF-α: Tumor necrosis factor-α; PaO2: Arterial oxygen partial pressure.

clinical studies have been completed to date.

Somatostatin

Somatostatin (SST), a multifunctional neuropeptide, is mainly released from sensory nerve endings and gastrointestinal neuroendocrine cells. Accumulating evidence has suggested that SST causes a significant anti-inflammatory effect in AP, in addition to its potential roles in inhibiting exocrine pancreatic function and regulating the tone of the sphincter of Oddi[6]. Our previous animal experiments demonstrated that SST could relieve inflammatory injuries by blocking the TLR4-myeloid differentiation factor 88 (MyD88)-dependent and -independent pathways (Figure 1), as well as by inhibiting the activity of intestinal mucosal mast cells[21,87,88]. Over the past two years, our clinical studies have indicated that plasma SST levels decreased within 48 h after AP onset, along with increased plasma levels of IL-6 and TNF-α[89,90]. Thus, an early replacement of exogenous SST or its analogue, octreotide, may be beneficial for patients with AP. Our recent prospective RCTs have shown that octreotide administration attenuated SAP to some extent and prevented the development of SAP in obese patients and other patients with predicted SAP by raising their plasma SST levels and decreasing their circulating levels of TNF-α and IL-6[89-91]. However, the effect of SST or octreotide on AP remains controversial[92-100]. Different timings, doses or durations of octreotide administration may contribute to these disputed results (Table 2). More research is needed to fully understand the roles of SST and octreotide in AP and to identify the optimal treatment timing and dosage.

Immune cells and related factors

In AP, immune cells (macrophages, monocytes, neutrophils and lymphocytes) migrate to the sites of inflammation and release pro-inflammatory cytokines and chemokines with the aid of chemokines and adhesion

molecules, which recruit even more immune cells, aggravating the inflammation[13]. There is increasing evidence that inhibiting the activation and migration of immune cells may have a therapeutic effect on excessive inflammatory responses[20,101-103].

Macrophages are one of the major classes of immune cells involved in the pathogenesis of AP. They mainly present as M1 macrophages to release pro-inflammatory cytokines and to aggravate pancreatic and systemic inflammation[101,102]. In an *in vitro* study, IL-4 and IL-13 were able to convert M1 macrophages into M2 macrophages, which have an anti-inflammatory role. However, these cytokines failed to show similar results *in vivo*[101]. In addition, hemin and gadolinium chloride were able to attenuate the inflammation and AP-associated organ injuries in rats by inhibiting the pro-inflammatory effects of macrophages[102,103]. Although there is no related clinical trial, the results from the above animal studies may provide a new direction for the development of immunomodulatory therapy for AP[102,103].

Chemokines and their receptors contribute to the migration of leukocytes to areas of injury and the development of inflammation[104]. Chemokines can be broadly divided into CXC and CC subgroups. In the CXC subgroup, the first two cysteine residues (C) out of four are separated by another amino acid (X), whereas in the CC subgroup, the first two cysteine residues are adjacent[104,105]. Many animal experiments on AP have revealed that the blockage of chemokine synthesis (monocyte chemotactic protein-1 or fractalkine) or neutralization of chemokines with antibodies (anti-cytokine-induced neutrophil chemoattractant antibodies or anti-CC receptor 5 ligand antibodies) was able to relieve inflammatory reactions, increasing the survival rates[104-109]. In addition, the inhibition of combined chemokines (CXC or CC) and their receptors was also found to have a similar therapeutic effect on AP[110-112]. However, those results have not been confirmed by clinical trials.

Adhesion molecules are glycoprotein molecules that are located on the cell surface and are involved in binding to other cells or the extracellular matrix. Intercellular adhesion molecule-1 (ICAM-1) is one of the adhesion molecules expressed on endothelial cells; it mediates the adhesion and migration of immune cells, facilitates leukocyte infiltration and exacerbates systemic inflammatory reactions[3,83,113-118]. Studies using animal models of AP have shown that ICAM-1 antibodies attenuate inflammatory cell infiltration and pancreatic and lung injuries[83,114-116,118]. Unfortunately, there are no relevant clinical research data currently available.

IMMUNOSTIMULATORY THERAPIES

In the late stages of AP, a decreased number of lymphocytes can lead to impaired cellular and humoral immune function, including the inability to release cytokines and reduced ratios of $CD4^+/CD8^+$ T cells and Th1/Th2 helper T cells[28,119]. These changes, together with monocyte dysfunction, will most likely render the host susceptible to infection and death due to pathogenic invasion. Therefore, immunostimulation targeting $CD4^+$ cells, Th1 cells and monocytes may be effective for treating or preventing infectious complications of SAP. Monitoring immune cells and cytokines could be useful for predicting the prognosis of AP[119,120].

Restoring the balance in number and function of immune cells

It has been found that a reduction in the circulating $CD4^+$ T cell levels and the $CD4^+/CD8^+$ ratio may be partly responsible for the development of immunosuppression in SAP[121]. The application of thymosin alpha 1 showed a protective effect against SAP in rats, improving their survival rate by restoring serum $CD4^+$ T cell levels and the $CD4^+/CD8^+$ ratio[122]. Moreover, an imbalance between Th1 and Th2 cells was also found to be associated with the pathogenesis of immunosuppression in SAP, which included deficiencies in the number and function of Th1 cells and a large number and hyperfunctionality of Th2 cells[123,124]. Many studies have revealed that the granulocyte-macrophage colony-stimulating factor (GM-CSF) and/or interferon-γ (IFN-γ) have been able to restore the balance between Th1 and Th2 to some extent, based on *in vitro* and *in vivo* experiments associated with AP[122,125,126]. However, clinical studies supporting these findings remain sparse.

Additionally, monocyte dysfunction may result in AP-associated immunosuppression, including impaired antigen presentation capacity (marked by reduced HLA-DR expression) and insufficient synthesis of pro-inflammatory cytokines[127]. The administration of IFN-γ or GM-CSF was reported to raise the HLA-DR expression levels on monocytes and to enhance their capacity for TNF-α production in septic patients[128,129]. The only related RCT in the past five years also showed that the subcutaneous injection of GM-CSF (4 mg/kg per day) for 8 d was safe and effective for restoring monocytic immunocompetence and shortening the course of sepsis-associated immunosuppression[130]. GM-CSF or IFN-γ administration *in vitro* was able to upregulate HLA-DR expression and the TNF-α production of monocytes from SAP patients[127]. It has been suggested that combination therapy of GM-CSF and IFN-γ is able to completely reverse monocyte dysfunction[127]. To date, GM-CSF and IFN-γ have been widely used in the treatment of sepsis. More research is needed before GM-CSF and IFN-γ can be used in patients with AP-associated immunosuppression.

Restoring intestinal immune function

Intestinal immunosuppression may occur in early SAP (within 24 h after AP onset) and is characterized by a significant decrease in sIgA secretion and in the number of $CD4^+$ T lymphocytes in the intestinal mucosa, which is one of the most important causes for bacterial and endotoxin translocation[31]. Restoring intestinal immune function as early as possible may represent a promising

treatment to prevent infectious complications in SAP. In animal experiments on SAP, oral supplementation with arginine, glutamine and probiotics increased the number of $CD4^+$ T lymphocytes and sIgA levels in the intestine and circulation[31,131]. Furthermore, clinical trials have reached similar conclusions. Early enteral nutrition (within 48 h after admission) has been suggested to cause an increase in serum IgG levels and HLA-DR expression in T lymphocytes, thus reducing the incidence of multiple organ dysfunction syndrome, SIRS and pancreatic infection[132].

For patients with AP-associated immunosuppression, proper immunostimulation may alleviate the disease and prevent serious complications[130,132]. However, those results are mainly based on animal or *in vitro* studies. More large-scale RCTs are needed to evaluate the safety and efficacy of immunostimulatory therapies for AP-associated immunosuppression.

CLINICAL STRATEGIES FOR IMMUNOMODULATION IN AP

As mentioned above, different treatment regimens should be administered to AP patients according to their different immune statuses. However, it is currently unclear how the immune status of patients can be monitored to identify the optimal treatment timing. Genetic testing for gene polymorphisms in certain inflammatory mediators can be used to screen high-risk AP patients for severe infection, thus preventing severe infections[23,133,134].

Immune state monitoring of AP patients and interventional window

Clinical trials have shown that peripheral blood lymphocyte levels are significantly reduced to approximately 67% of the lower limit of normal within 24-72 h after a SAP attack[28,135]. This reduction may be associated with the depletion of lymphocytes, lymphocyte apoptosis or gut associated lymphocyte homing[13,24-27,136]. During the same period, peripheral blood $CD4^+$ T cell levels, the ratio of $CD4^+/CD8^+$ T cells and the ratio of Th1/Th2 helper T cells all significantly decreased[27,28,123,124,137]. Moreover, the antigen-presenting function of monocytes was also impaired (characterized by low HLA-DR expression) within 24-72 h after SAP onset[27,30,138]. It has been reported that a continuous decline of the above indicators from the 7th to the 14th d in the course of AP could predict a higher risk of infectious complications[27,28,30,123,124,138-140].

Many of the findings in the literature have revealed that the serum levels of pro-inflammatory cytokines (*e.g.*, IL-8, TNF-α, IL-6, IL-2, IL-12 and IFN-γ)[67,123,124,137,138,141-143] and anti-inflammatory cytokines (*e.g.*, IL-10 and IL-4)[67,123,124,138,141] were significantly elevated within 12-72 h after a SAP attack; thereafter, the shared pattern diverged. Retrospective studies in the past two years have suggested that the serum TNF-α, IL-6, IL-12 and IFN-γ levels gradually decreased in the 3rd-5th d after the onset of SAP[67,137]. In addition, the serum IL-10 and IL-4 levels of SAP patients with infections showed a continuous upward trend from the 3rd d to the 14th d after a SAP attack, whereas the anti-inflammatory cytokine levels of patients without infections declined continuously[67]. Despite certain shortcomings, serum cytokine levels remain one of the most important rapid indicators of a patient's immune status[120].

Monitoring the levels of immune cells and cytokines could enable the early detection of the immune suppression state over the course of SAP, and their appropriate modulation could be expected to reduce the incidence of infection and death.

In addition, clinical research completed during the past year showed that the overexpression of the factor-associated suicide (Fas) ligand on T lymphocytes in SAP patients resulted in the excessive apoptosis of T lymphocytes and a sharp drop in $CD4^+$ T cells, thus inducing immune suppression and sepsis[27]. Fas expression on T lymphocytes in SAP patients was transiently reduced within 48 h after AP onset but continuously increased within 8 d thereafter[124]. Therefore, for AP patients with continuously high expression of Fas for 10 d after AP onset, appropriate immune stimulation may improve the immune suppression state.

The interventional window for AP mentioned in the previous studies refers to the timing of anti-inflammatory therapy. Many researchers have found that this window usually arose between 12-18 h and 2-3 d after the onset of AP[16]. However, accumulated evidence has indicated that the timing for both anti-inflammatory and immune stimulation therapies should be considered. Thus, according to the above data, the duration of anti-inflammatory therapy may be shorter than expected (< 24 h), as immunosuppression can occur within 24 h after SAP onset[27,28,30,67,123,124,137-140], whereas appropriate immune stimulation therapy should be administered during the period between the 3rd and 14th d in the course of AP[27,28,30,67,123,124,137-140]. Nevertheless, the optimal interventional window of AP needs to be defined by further prospective studies.

Combination of anti-inflammatory and immune-stimulating therapies

Many factors are involved in the pathogenesis and progression of AP. The studies available on monotherapies for a certain factor did not yield the desired results. Thus, increasingly more investigators have begun to focus on multi-drug combination therapies for AP. Their studies have confirmed that a multi-drug combination is more effective than monotherapy. These therapies have comprised either the combination of various types of anti-inflammatory drugs[144,145] or a combined drug treatment for immunosuppression[127]. Currently, there are no published reports on the combination of anti-inflammatory and immune-stimulating therapies for AP, although this topic holds great promise as a new approach to AP immunotherapy.

AP populations at high risk of severe infections

Genetic polymorphisms of certain inflammatory mediators were found to be closely related to infections in AP

patients. It has been reported that AP patients with TLR4 Asp299Gly mutations were prone to necrosis and infection of the pancreas[23] and that SAP patients carrying the IL-10-1082G[133], TNF2 and TNFB2 alleles[134] were highly susceptible to septic shock. Therefore, the detection of these genotypes could be helpful in screening high-risk AP populations for severe infections. These findings suggest that we may be able to develop more successful interventions for those patients in the future, potentially preventing more severe infections.

CONCLUSION

In summary, immunomodulatory therapy will hopefully improve the outcomes of AP. In the course of AP, it is necessary to monitor the indicators related to immune cells and inflammatory mediators and to develop more successful and individualized interventions for AP patients using immunomodulatory therapies. During the early stages of AP, treatment should include the inhibition of the overactive inflammatory responses while avoiding excessive immunosuppression to maintain normal immune function and to reduce the incidence of infectious complications and organ failure. Furthermore, the duration of anti-inflammatory therapies may be shorter than previously expected (< 24 h), whereas appropriate immune stimulation therapy should be administered between the 3rd and14th d of the AP disease course. The combined therapy of anti-inflammatory and immune-stimulating drugs may represent an alternative to anti-inflammatory drug monotherapies. Finally, the detection of the genotypes of critical inflammatory mediators would facilitate early interventions in AP populations at high-risk for severe infections to improve their prognosis.

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