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Effect of continuous renal replacement therapy on serum levels of inflammatory cytokines/interleukin-17 in severe acute pancreatitis

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ABSTRACT

Despite continuous investigations in the diagnosis and treatment of severe acute pancreatitis (SAP), this disease still remains a critical condition with a mortality rate of up to 35%. The pathophysiology of SAP involves an important inflammatory reaction of the pancreas (mediated by inflammatory cytokines and immune system activation), causing severe local tissue damage as well as important systemic imbalances. IL-17 is an inflammatory mediator that have a pivotal role in SAP evolution, generating multiple interactions between inflammatory cytokines and significantly influencing the immune system response. Consequently, continuous renal replacement therapy/CRRT was added to the conventional therapy, leading to improved treatment results. This review aims to evaluate the involvement of Interleukin 17 in the diagnosis, pathogenesis and evolution of SAP, as well as the role of CRRT in reducing elevated serum levels of IL-17. As a conclusion, CRRT is a promising method to eliminate cytokine mediators from the blood, thus leading to a reduction of both pancreatic/peripancreatic tissue damage and systemic imbalances in severe acute pancreatitis, being strongly correlated with better therapeutic outcomes.

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Introduction

Acute pancreatitis (AP) is an inflammatory condition of the pancreas that can present different degrees of manifestation, being one of the most common acute abdominal disorders and a frequent condition in digestive pathologies requiring hospitalization [1]. The prevalence rate of AP is continuously increasing globally (food factors, lifestyle, etc.), having an extensive geographical distribution [2]. Considering the different degree of severity of the disease, AP is clinically divided into mild, medium and severe forms or, depending on the type of inflammation, interstitial, edematous and necrotizing AP forms [3].

Approximately 80% to 85% of patients have mild AP (MAP), while nearly 15% to 20% of patients develop sever forms of AP (SAP), followed in some patients by organ failure and complications, in some cases the disease progressing to death. The incidence rate of SAP is increasing annually, with a mortality rate of approximately 17% [4].

Prevalence and etiology vary in different countries, being dependent on data reporting techniques, diagnostic criteria, existing medical facilities and regional risk factors. Almost 20-30% of patients suffering from AP subsequently experience a relapse, while approximately 10% develop chronic pancreatitis. Alcohol, smoking, diabetes, gallstones, and obesity represent the main risk

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factors for AP. A new meta-analysis displayed that obesity (BMI> 30) is associated with a high risk of developing SAP. Diabetes increases the risk of AP approximately 1.5-3 times compared to the healthy population [5,6].

Currently, the APACHE score (which can quantify the severity of SAP quite well) is generally used in patients investigated and diagnosed in the ICU-admitted patients [7]. With the progress of imaging technology, a significant role in establishing the diagnosis and evaluation of SAP's severity and local complication brings the Balthazar CT score. The MODS score may better show the degree of interference with the body's vital organs and can be used as an important indicator in determining the outcome of patients [8].

Discussions

New insights in SAP pathogenesis; IL-17 involvement

AP is a leading cause of mortality and is frequently associated with systemic manifestations, usually related to a poor prognosis. Various cytokines contribute to pancreatic tissue destruction that generate local injury [9].

SAP is a specific type of AP characterized by a severe inflammatory reaction. Pancreatic protease activation mobilizes and releases inflammatory cytokines. An intense inflammatory response exacerbates overcompensation and the reaction of the immune system and augments systemic infection risk. Inflammatory mediators participate in promoting the incidence and evolution of SAP. The activation of natural killer (NK) cells and T lymphocytes is responsible for tumor necrosis factor (TNF- α) [8].

Acute pancreatitis (AP) is related to tissue damage due to several harmful cellular events [8]. From the first activation of enzymes and the implication of the immune system in a systemic inflammatory response and organ failure, SAP has significant mortality and a poor prognosis [10].

Over the last years, immune system activation has been recognized as a regulator and a trigger of inflammatory damage in the pancreas, altering the degree of pancreatic tissue deterioration, which ultimately causes organ failure. AP conduce to the activation of leukocytes and a high amount of neutrophil at the site of the inflammation, delivering proinflammatory cytokines, like different types of interleukins, cachexin (tumor necrosis factor, TNF), polypeptide growth factor-TGF and procalcitonin [11].

Its management may necessitate the collaboration of various specialties (gastroenterology, internal medicine, anesthesiologists, and surgery) to provide the best/customized therapeutic approach to each patient, so that every possible complication can be avoided or treated accordingly. For this reason, a common evaluation method is essential to establish the diagnosis, local and systemic complications, to appreciate the degree of severity which is useful to ensure the best standard of treatment [5].

IL-17 is an inflammatory mediator that can play an essential role in AP. Remarkably, IL-17 significantly influences the immune response and generates interactions between various inflammatory cytokines in the AP-related microenvironment [11].

Innovative observations into AP pathophysiology have confirmed the immune reactions' significance on AP's inflammatory evolution. Previous studies have demonstrated that the inherited immune system is vital in mediating the progression of AP. Several types of granulocytes, like neutrophils, platelets, leukocytes, macrophages, and dendritic cells, represent the base for the pathogenesis and progression of AP. T cells are also present in the place of inflamed pancreatic tissue and innate immune cells. The decrease in the degree of immune reactivity develops as a consequence of T cells apoptosis, generating a disruption of defense mechanisms in the course of systemic inflammation. At the same time, cellular damage induced by pancreatic self-digestion may cause the aggregation of CD4+ T helper cells delivering IL-17 and provoke an inflammatory reaction characteristic of this disease. Recruitment of different immune cells will create an additional injury to acinar cells, simultaneously diversifying proinflammatory cytokines releasing [11].

IL-17 is an essential proinflammatory cytokine that originated from T helper 17 (Th17) cells and natural killer (NK) cells [12]. The central role of IL-17 is to mediate reactions to pathogens and symbioses of different targets, all of which balance the immune system’s inflammatory response [13]. Furthermore, its potential function in adjusting the immune response is to regulate cytotoxic and tolerant immune profiles, resulting in acute injury [11].

Considering its great prognostic significance and quick availability, IL-17 has become recognized as an encouraging reference indicator among single predictive markers, reaching validity for AP outcome prediction [11].

The IL-17 family represents a multi-functional mediator that comprises six categories (from IL-17A to IL-17F), being recognized for its essential role in psoriasis and rheumatoid arthritis. In the last decade, many studies have described the importance of IL-17 in the origin of autoimmune disorders, inflammation, cancer, or even COVID-19 [14]. Related to pancreatic illness, IL-17A may directly injure acinar cells and recruit neutrophils and diverse immune cells, hence worsening pancreatitis [15].

Studies have reported that IL-17A balances the transcription of proinflammatory cytokines in acute inflammatory diseases. So far, scientists have established the correlation between IL-17 and AP and propose that IL-17 is a predictive indicator for AP outcome and connects with the degree of organ failure. In some studies, the serum level of IL-17 correlates with the severity of AP and is a valuable prognostic factor in evaluating disease advancement in AP patients. Compared to healthy patients, the same AP patients

had a substantial increase in serum IL-17 during the first 24 hours. In a prior study, researchers presented that high serum levels of IL-17 represent an independent risk factor for adverse outcomes in SAP. This could also be associated with excessive bacterial infections. In addition, IL-17 could be used as a predictive factor for the duration of hospitalization, organ dysfunction, and mortality in SAP patients after CRRT [16,17].

The evolution of AP is characterized by inflammation and edema, followed by necrosis of pancreatic tissue and extrapancreatic organ involvement. Apoptotic death suggests the ability of acinar cells to recombine their genetic program after the initial stage of mild AP, and necrosis is the most important mechanism of SAP cell death. Naturally, acinar cells synthesize and deliver cytokines and chemokines that stimulate other immune cells, like neutrophils and macrophages. Afterwards, an uncontrollable inflammatory episode inside acinar cells progresses to systemic inflammatory response syndrome (SIRS), contributing to the high prevalence rate of unsatisfactory outcomes [16,17].

Pancreatic acinar cells and pancreatic stellate cells (PSCs) can generate inflammatory cytokines. Injured acinar cells mobilize inflammatory macrophages to deliver IL-1β and IL-6 to recruit CD4+ T cells within pancreatic tissue. CD4+ T cells transform into Th17 cells to generate IL-17, which works on IL-17 receptor-positive cells to deliver different inflammatory mediators aggravating AP.

Additionally, neutrophils and macrophages lead to intra-acinar cellular protease activation and necrosis of the acinar cells, which have an essential role in the severity of AP [18]. The inflammatory and immune activation of AP is considered to be represented by neutrophil invasion and the production of different proinflammatory molecules. IL-17A enhances neutrophil invasion in sepsis, thus alleviating bacterial clearance [19]. Neutrophil expenditure assays indicate that neutrophils are essential boosters of pancreatic cell necrosis and suppress acinar cell apoptosis during AP. Therefore, IL-17A can augment the inflammatory cascade during AP by mobilizing neutrophils and macrophages to the injured area, which is partly responsible for AP's severity. Neutrophil extracellular traps (NETs), the following bactericidal action of neutrophils, stimulate pancreatic tissue damage and are very important in the pathophysiological processes of developing AP. Reviews have demonstrated that IL-17A is raised during the primary step of AP and causes pancreatic damage with acinar cell necrosis [20]. Mainly, IL-17A analogues also injure acinar cells directly and trigger these cells to produce inflammatory cytokines and chemokines, intensifying the torrent of AP. The aggregation of inflammatory molecules is culpable for acinar cell necrosis followed by multiple organ dysfunction [21].

According to the preceding literature, IL-17 induces many acute inflammatory diseases, but the exact mechanisms of its action are not understood. IL-17 is related to various cell types, works on several cellular tasks in tissue and immune cells, and is essential in innate and adaptive immunity [11]. The pharmacological stoppage of the IL-17 signaling pathway can have limited results in treating AP. Lowering the release of IL-17A or expressly blocking IL-17A receptors in various manners may offer a promising treatment for pancreatitis [15].

In the first step of infection or inflammation, IL-17 stimulates proinflammatory mediators to release, intensifying inflammatory reactions. IL-17 acts on other cytokines to mobilize tissue-infiltrating neutrophils and facilitates eliminating invading pathogenic bacteria. Being an initiator, IL-17 still participates in the inflammation mediated by T cells. IL-17 directly encourages inflammatory reactions or indirectly promotes the production of IL-6 through stabilizing IL-6 mRNA. In this manner, the mixture of biomarkers will aid physicians in developing and improving the clinical treatment of SAP.

Deterioration of intestinal barrier function is a detrimental issue in AP, which causes the shift of intestine germs and endotoxin. Excessive mobilization of inflammatory cytokines throughout AP is the leading cause of intestinal barrier damage. Disturbance to the intestinal barrier is connected with intestinal microcirculation interruption, the extreme release of inflammatory mediators, intestinal epithelial cell injury, and intestinal microorganism disturbance. As an intensifying element of the inflammatory reaction, new research has demonstrated that high levels of IL-17 in AP are detrimental to preserving intestinal barrier capacity and epithelial cells. IL-17 acts at mucosal junctions, such as the intestine epithelial wall, holding intact natural interface and causing antimicrobial peptides to stimulate attack by intestinal bacteria. Moreover, IL-17 causes intestinal wall edema and damage to the mucosal epithelial barrier through the movement of Th17 cells in the gut. A new study showed that IL-17 induces close contact expression via the ERK-MAPK signaling pathway to modify intestinal permeability. In addition, the level of serum IL-17 is nearly attributed to bacterial excess, revealing that the overproduction of IL-17 destroys intestinal barrier capacity, leading to organ failure [22].

IL-17A is an essential factor in mucosal monitoring and barrier stability by being partly responsible for generating antimicrobial elements needed to contain pathogens [22]. IL-17A promotes a suitable immune response to fight local bacteria in the intestines through diverse mechanisms, improving intestinal IgA responses and the apparition of epithelial cell-related native immune receptors, similar to Toll-like receptors (TLRs) and antimicrobial molecules [23]. The different commensal microbiota populations inside the gastrointestinal tract adjust the aggregation of proinflammatory and anti-inflammatory immune cells.

After all, intestine dysbiosis promotes alterations in immune cell action. Dysbiosis of the intestinal microbiota is partly responsible for the extreme release of inflammatory mediators prevalent in the evolution of AP [24]. Pathogenic bacteria, such as Escherichia Coli and Enterococcus, are overexpressed in PA showing a conclusive correlation, while beneficial bacteria, such as Bifidobacterium, Lactobacillus and Bacteroides, showed a trend of underexpression. Intestinal Th17 cells are activated by particular microbes, like Escherichia coli and Bifidobacterium [25].

Bifidobacterium and Lactobacillus suppress the expression of IL-6 and IL-17 while promoting protein production for the essential tight junctions [26]. Besides consolidating the gut epithelial barrier, the microbiome regulates the immune system, too, and transfers benefits to the host. Metabolites from the microbiota preserve intestinal homeostasis and the pathogenesis of inflammation by modulating IL-17 during AP [11]. Fecal microbiota transplantation and probiotics, prepared to inverse microbial disturbances and reestablish a more solid structural condition, can bring encouraging insights into inflammatory and immune reaction structures, facilitating the healing of AP patients.

Therapeutic implications of IL-17 and the beneficial role of CRRT in SAP management

Supplementary to conventional supportive treatment, medication therapy aiming at immunomodulation has accomplished encouraging results. The recent data from clinical trials using anti-IL-17 agents provided solid evidence for applying IL-17 signaling in the pathophysiology of inflammatory disorders and the excellent utilization of these agents in AP treatment. In AP, a torrent of reactions begins with releasing endogenous particles due to tissue injury and leukocyte activation. Regarding the above affirmations, such an approach may be a good therapeutic strategy capable of modulating the cascade response described [11,27].

Inhibition of IL-17A and its receptor or concurrent inhibition of IL-17A and IL-17F are partly responsible for disrupting signaling pathways that are essential for AP progress, outcome, and expansion. Subsequently, biologics aiming IL-17 serve for sudden and dramatic systemic manifestations during SAP. IL-17 could provide a deeper approach of SAP and represent an innovative immuno-therapy for AP by targeting the Th17 cell/IL-17 immune axis [11].

The conservative therapy of acute pancreatitis mainly decreases pancreatic fluid secretion and reduces the pancreas's self-digestion. This approach frequently involves fasting and liquid restriction, gastrointestinal decompression, and treatment with somatostatin and its analogues. Fluid resuscitation, suppressing gastric acid secretion, enteral nutrition, and antibiotics for infections are required to prevent organ failure [2]. However, a few data show that a significant decline in mortality or morbidity does not follow prophylactic antibiotic treatment in patients with AP. As a result, usual prophylactic antibiotics are no longer used for all patients suffering from AP. Antibiotics remain the first option only for infectious SAP therapy.

With the advancement of specific therapy, continuous renal replacement therapy (CRRT) has developed into one of the newest renal replacement therapy techniques. In SAP, the electrolytic balance must be ensured and the acid-base level of the blood and the waste of endotoxins and inflammatory mediators in the blood must be adjusted, in order to protect the endothelial cells from aggression and, at the same time, to regulate the severely affected immune function. For this reason, CRRT is not exclusively applied in acute and chronic renal failure, but can also be successfully used as a treatment for SAP [28,29].

CRRT represents the blood purification method that continuously and gradually eliminates water and solutes through extracorporeal circulation to supply renal function. Its application area is no longer restricted to kidney illness and is used to treat non-renal diseases like pancreatitis. Recent studies show that early CRRT can lower the mortality rate of SAP patients [30-32].

The method by which CRRT treatment can reduce the severity of disease progression in patients with PAS remains the long-term modulation of inflammation and endotoxins from the blood, ongoing immune adjustment, and increasing the body's ability to control inflammation [33-35].

Compared to the conventional treatment and CRRT, Gao et al. discovered that IL-17 displayed a continuous decline at 6, 12, and 24 hours following CRRT and was substantially diminished compared to traditional therapy at various time points [36]. Dai published that earlier and greater levels of IL-17 influenced the prolonged period of hospital stay and the evolution towards organ failure and death, probably due to a disruption of intestinal barrier capacity [37]. High-volume hemofiltration (HVHF) improved the Th17/Treg imbalance during SAP. These alterations indicate that CRRT is vital in the incidence and advancement of eliminating excess inflammatory cytokines in SAP patients. Consequently, these data indicate the clear clinical/pathophysiological implication of IL-17 in AP, such that its therapeutic targeting may therefore improve treatment outcomes in SAP [38].

Conclusions

From the discovery of Th17 cells, the mediator IL-17 has experienced a boost in research and clinical investigations. According to previous literature data, IL-17 leads to many severe inflammatory diseases, but the exact mechanisms involved are not entirely explained. IL-17 is related to various cell types and is very important in native

and adaptative immunity, working on different cellular tasks in tissues and immune cells. In AP, dysregulated mediators are numerous, and IL-17-targeted therapy appears to be promising.

Continuous venovenous hemofiltration (CVHV) removes IL-17 and excessive proinflammatory mediators from the serum, restoring both intestinal barrier function and diminishing systemic reactions.

As a final conclusion, CRRT is a promising method of eliminating cytokine mediators from the blood, thus leading to a reduction of local tissue damage in severe acute pancreatitis.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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