THE ROLE OF CYTOKINES IN IMMUNOPATHOGENESIS OF ACUTE PANTHEATITIS (review article)

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Acute pancreatitis (AP) remains one of the most common pathologies of the digestive organs with an ambiguous prognosis (19, 18), and ranks third in the structure of surgical diseases after acute appendicitis and acute cholecystitis (6, 8).

AP is an aseptic inflammation of the demarcation type, which is based on necrosis of the acinar cells of the pancreas and enzymatic aggression with subsequent expanding necrosis and dystrophy of the gland, in which damage to surrounding tissues and distant organs, as well as systems and the addition of a secondary purulent infection is possible (*15).* **To date, acute pancreatitis remains one of the most pressing problems in abdominal emergency surgery (*1)* .**

According to WHO, there is a tendency towards an increase in the number of patients with AP in young and middle age, which is often associated with unfavorable ecology, living conditions, the frequency of cholelithiasis , obesity and alcohol abuse (*5, 18).* **Despite successful achievements in improving the methods of treating acute pancreatitis, the overall mortality rate in its mild forms is 3.9 to 21%, and in severe forms it reaches 70%. Fatal outcome in patients with acute infected pancreatitis occurs within the first day due to progressive toxic shock and the development of multiple organ failure, or later, as a result of the formation of purulent-septic complications (*3.54).***

According to the 2012 revision of the Atlanta classification, AP develops in two phases (*20).* In the early phase, which usually resolves by the end of the first week, systemic abnormalities are secondary to local inflammation of the pancreas. As the disease progresses, generalized inflammation occurs, defined as the systemic inflammatory response syndrome (SIRS). If SIRS persists , there is

an increased risk of organ failure and local complications. Determining the duration of organ failure is important. If it resolves within 48 hours, it is called "transient organ failure"; if it persists for more than 48 hours, it is called "persistent organ failure". When organ failure affects more than one organ, it is called multiple organ failure (MOF) or multiple organ dysfunction syndrome (MODS) *(20,55).* The late phase is characterized by persistent systemic signs of inflammation or local complications. At this stage, the immune system is suppressed, making the pancreatic tissue more susceptible to infection due to translocation of intestinal bacteria. The resulting sepsis and multiple organ failure are the major causes of late complications and mortality (*28,57).* According to this classification, the following are distinguished: acute edematous (interstitial) pancreatitis, sterile and infected pancreatic necrosis, which are links in a single pathogenesis (*12).*

The transition of acute pancreatitis from one type to another is determined by the initial severity of the patient and the volume of destruction, leading to the development of severe risk factors (*4, 9, 10, 11, 45, 48).* According to severity, mild, moderate and severe forms are distinguished, which are determined by the development of SIRS, complications and the severity of multiple organ dysfunction according to the SOFA scale (*14).* In severe AP, the local inflammatory process intensifies and spreads through the bloodstream throughout the body, leading to a systemic inflammatory response (*35,56).* A detailed assessment of the severity and prediction of the outcome of OP are the fundamental principles of an adequate choice of conservative therapy and timely surgical tactics (*2).*

Numerous studies have been published on the pathogenesis of AP; however, the exact mechanism of this pathology remains unclear (*44).* Even when several mechanisms for the pathophysiological process of AP have been proposed, none of them is completely informative (*53).*

Premature activation of trypsin is the most widely accepted theory as the underlying mechanism initiating autodigestion of pancreatic tissue and

subsequently local and systemic inflammatory processes. The initial events of AP occur in acinar cells, which can act as pancreatic inflammatory cells (*23).* An excessive inflammatory response is a common aspect of these mechanisms. This process is characterized by the release of pro- and anti-inflammatory cytokines and other inflammatory mediators that attract and activate neutrophils, monocytes, and lymphocytes, as well as adhesion molecules and oxygen free radicals, leading to mitochondrial dysfunction and microcirculatory injury in the pancreas (*44 , 50 , 55 , 54).*

In AP, a wide range of changes in homeostatic parameters of the body are determined (*13).* It is well known that as a result of tissue damage and/or infection, a complex sequence of reactions unfolds in the human body aimed at preventing further destruction, isolating and destroying the pathogen, activating reparative processes and restoring the original homeostasis (*16)* . Considering that the pathogenesis of the disease is directly related to the cytokine response of the body, it is proposed to determine the concentrations of proinflammatory and antiinflammatory mediators. An increase in the levels of both types of cytokines occurs early and persists for several days in the systemic circulation. High concentrations of IL -1β, IL -6, IL -8, IL -10, IL -12, TNF-α indicate a severe course of AP, although they cannot be predictors of a fatal outcome in a particular patient (*30, 41; 49; 32).*

Cytokines are a family of low-molecular proteins (16-25 kDa) secreted by many cells, including macrophages and monocytes. They are regulatory mediators of the immune response, acting both on the cells that produce them and on nearby cells. A distinction is made between: interleukins (IL) , which in turn are subdivided into proinflammatory (IL -1, IL -8, etc.) and anti-inflammatory (IL -4, IL -10, IL -14, IL -18, etc.); interferons (IFN) (-α, -β, -γ) - with pronounced antiviral action; tumor necrosis factors (TNF) (-α and -β) - cytokines with cytotoxic and regulatory action; chemokines - chemoattractants for leukocytes; growth factors and some others (*17).* All cytokines exert their effects through specific cell surface receptors. Most cytokines have pleiotropic activity and

exhibit multiple functional effects on multiple target cells. Although cytokines induce a “beneficial” inflammatory response to limit tissue damage, excessive production of these proinflammatory agents can be even more dangerous than the initial stimulus *[52]*. The term “ cytokine storm” has no precise definition but refers to a particular type of uncontrolled immune response.

The cytokine storm in AP is a potentially fatal immune response consisting of a positive feedback loop between cytokines and immune cells. When the immune system fights infectious agents, cytokines signal immune cells such as T cells and macrophages to move to the site of infection. Additionally, cytokines activate cells, stimulating them to produce more cytokines. The cytokine storm has the potential to cause significant tissue and organ damage. These facts explain the mechanism by which the release of large amounts of cytokines contributes to the progression of severe SIRS in AP (*7)*.

Today, it is known that the leading role in the pathogenesis of AP is played by inflammatory mediators: proinflammatory cytokines such as IL -1, IL -6, IL -8 and tumor necrosis factor (TNF -α), as well as cyclooxygenase and other mediators (*43)*. The results of their influence are increased vascular permeability, leukocyte migration, local tissue damage, generalization of the inflammatory reaction, damage to the organs of natural detoxification with the development of multiple organ failure (*21)*.

Tumor necrosis factor (TNF)-α is an important inflammatory cytokine that participates in the pathogenesis of AP by directly damaging acinar cells and leading to necrosis, inflammation, and edema (*22)*. The main producers of TNF-α are monocytes and macrophages, but it is also secreted by neutrophils, endothelial and epithelial cells, eosinophils, mast cells, B and T lymphocytes when they are involved in the inflammatory process. It activates endothelial cells, stimulates angiogenesis, enhances migration, and activates leukocytes. This cytokine, which is the first to be released, is a major mediator of immune responses (*21)*. TNF-α expression in the pancreas increases with the onset of AP. *El - Ashmawy et al* . (*26)* conducted a study on a mouse model of L-arginine-

induced pancreatitis to investigate the underlying molecular mechanisms of AP. They confirmed that the concentration of TNF-α in the pancreas was markedly increased after L-arginine administration. This may be due to the excessive formation of reactive oxygen species (ROS), which activate nuclear factor kappa B (NF- κB) followed by the activation of various inflammatory cytokines, especially IL-1β and TNF-α. TNF-α receptor levels, indicators of TNF-α activity, were found to be elevated in patients with severe AP, and TNF-α blockade reduced mortality and alleviated experimental AP (*39).*

Interleukin (IL) -1 is well known as an integral early component of the acute inflammatory process (*41).* IL -1β is a secretory cytokine that acts both locally and systemically. IL -1 is produced by many cells in the body. Its main sources in the body are monocytes and macrophages, as well as Langerhans cells , Kupffer cells in the liver, endothelial cells, fibroblasts, keratinocytes , microglial cells , natural killers, neutrophils, T-lymphocytes other than T-helpers, dendritic cells, etc. *Hartman H . et al .* (*29)* in their study assessing the severity of AP found that IL-1 levels predicted severe AP at admission with the same accuracy as IL-6 (82% vs 88%, respectively), and that IL-1 receptor antagonist had the best accuracy among various markers including IL-6 and CRP during the first 48 h. At 48–72 h, IL-1 levels were found to predict pancreatic necrosis with 88% accuracy, and the IL-1:IL-1 receptor antagonist ratio could identify septic complications with 72% accuracy. (22 *)*

Interleukin (IL) -6 is the main stimulator of protein synthesis in the acute phase in the liver and is the main mediator in the synthesis of fibrinogen, CRP and hepcidin . IL-6 is synthesized by macrophages, endothelial cells, fibroblasts soon after stimulation by microbial products. The role of IL-6 in early and accurate prediction of the severity of AP has been confirmed by numerous studies (*34, 40). Soyalp , M. et al .* (*48)* found that elevated IL-6 levels increased according to the severity of pancreatitis, suggesting that IL-6 may act as a prognostic tool for AP. IL-6 has the best sensitivity and specificity for the early assessment of severe AP among various proinflammatory and antiinflammatory

cytokines. However, IL-6 assay has a significant drawback in that its serum concentration decreases very quickly under certain conditions (*34)*. In the Garipati studies Sathyanarayan et al (2007) found that elevated IL -6 levels are a prognostic factor for organ failure and severe pancreatitis, and also indicate its pathophysiological significance in AP (*27).*

Among all cytokines, Interleukin (IL)-8 stands out in the pathophysiology of AP, as its level has been shown to be significantly elevated during the development of AP and its level has been reported to be associated with the severity of AP (*36).* Interleukin (IL)-8 is a member of the chemokine family CXC , which mediates recruitment polymorphonuclear neutrophils, basophils, eosinophils and lymphocytes into the foci of inflammation. IL -8 acts as a neutrophil activator and chemoattractant. Several studies have shown promising results in the early prediction of severe AP . *Rau B et al* . (*42)* confirmed the role of IL-8 in monitoring major complications in patients with necrotizing pancreatitis with multiple organ failure. Various studies have confirmed that IL-8 levels increase in the first 24 hours after the onset of symptoms, and a rapid decrease after 3–5 days is a good marker of multiple organ failure and death from sepsis in patients with AP (*25).*

In studies of the role of TNF-α, IFN-γ, IL-1, IL-2, IL-4, IL-6, IL-8 in predicting acute destructive pancreatitis, Salienko S.V. established that from the first day of development of acute destructive pancreatitis, several parallel and interdependent processes are observed: formation of pancreatic necrosis (superantigen) with development of blockade of a full-fledged immune response against the background of hyperproduction of cytokines (especially IL-8 and TNF-α) causing a number of symptoms of endotoxicosis , as well as participating in the genesis of multiple organ failure and early deaths. The author came to the conclusion that if the ratio of cytokines is assessed, then during this period a deficiency of IL-2 and a relative insufficiency of IFN-γ are revealed, which predetermines disorders of the cell-mediated immune defense system. It was also revealed that along with the continuing increase in the values of the pool of

proinflammatory cytokines, there is a rapid increase in the concentration of anti-inflammatory IL-4 in the blood serum, leading, on the one hand, to the suppression of macrophage activity and the secretion of IL-1, TNF-α, IL-6, and, on the other hand, to an increase in the cytotoxic activity of macrophages, inducing massive cell apoptosis (*16)* .

chemoattractant protein 1 (MCP-1 or CCL2) is a prototypical inflammatory chemokine that targets monocytes, T lymphocytes, and other cells expressing the CC chemokine receptor (CCR2) (*24)* . Notably, MCP-1 not only provides chemotactic signals for the recruitment of monocytes from the bloodstream into tissues, but is also responsible for monocyte activation and the induction of the respiratory burst. In fact, increased expression of MCP-1 has been detected during acute and chronic pancreatitis in both animal models and human tissues, suggesting a contribution of this chemokine to the pathogenesis of mononuclear infiltration (*46 , 31)* . However, MCP-1 is only one of several chemokines whose expression is increased in pancreatitis, and evidence for its pathogenic role was lacking.

Ohmoto K et al , when comparing clinical and laboratory data , found that the serum IL-6 level showed a significant correlation with markers of the severity of acute pancreatitis, indicating that IL -6 is a useful indicator of the severity of this disease. The IL -10/ IL -6 ratio was significantly lower in patients with severe acute pancreatitis, indicating the prevalence of a proinflammatory response in these patients. However, in patients receiving continuous regional arterial infusion of a protease inhibitor and antibiotics, the IL -10/ IL -6 ratio in patients with severe acute pancreatitis was significantly increased *(38).*

Since the discovery of Th17 cells, the cytokine IL-17 has become the subject of increasing attention and discovery. According to the literature, IL-17 is involved in many acute inflammatory diseases. IL-17 acts on a number of cellular targets in tissues and immune cells and plays a vital role in innate and adaptive immunity (*17)* . Dysregulation cytokine systems are commonly involved in AP, and targeted therapy of IL-17 is of great importance. Inhibition of IL-17A and its

receptor or simultaneous inhibition of IL-17A and IL-17F contributes to the interruption of signaling pathways important for the development and maintenance of AP. Accordingly, biologics that act on IL-17 contribute to the rapid and dramatic manifestation of systemic symptoms during AP. *Thomson J.-E. et al* in a study on IL -17 in predicting the severity of AP found that the average concentration of IL-17A on days 7, 9, 11 and 13 in patients with mild and severe AP did not show statistically significant differences between the groups (*51)* .

Hanna Sternby et al, in a comprehensive study of IL 1β, IL -6, IL -8, IL -10, IL -12, IFN -γ and TNF -α, the differences between severity groups, the prognostic ability of biomarkers and the association with severe disease were analyzed, which established a clear change in IL -1β, IL -8, IL -10 and IL -6 during the first 48 hours after the onset of AP. At the same time, IL-1β and IL-6 were associated with severe disease, but the prognostic ability of the studied biomarkers is low (*29).* Also, a synchronous study of the early dynamics of proinflammatory cytokines IL -6, IL -8, IL -18 and TNF -α on the 1st, 2nd and 14th days in 60 patients substantiated the use of these markers as prognostic factors for the development of organ failure in patients with the first attack of AP (*37).*

Thus, the study of the role of pro- and anti-inflammatory cytokines in AP plays a certain role in the pathogenesis of the development and course of this disease. This area of scientific research is certainly one of the promising areas for solving the indicated problem and requires further development, in connection with which the study of the cytokine profile, its relationship, changes in various courses and treatment remains an urgent problem.

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