ejpmr, 2023, 10(12), 246-251

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

THE SIGNIFICANCE OF IMMUNE RESPONSE MEDIATORS IN THE DEVELOPMENT OF ACUTE PANCREATITIS (REVIEW ARTICLE)

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Article Received on 16/10/2023 **Article Revised on 06/11/2023** **Article Accepted on 26/11/2023**

ABSTRACT.

Background: The article deals with the main issues of etiology, pathogenesis, classification, clinic, diagnosis and treatment of acute pancreatitis, taking into account of the participation of the immune system, namely the cytokine system in the development of acute pancreatitis.

KEYWORDS: acute pancreatitis, immunity, cytokines.

Acute pancreatitis (AP) remains one of the most common pathologies of the digestive system with an ambiguous prognosis[19, 18], and ranks third in the structure of surgical diseases after acute appendicitis and acute cholecystitis.[6, 8] OP is an aseptic inflammation of the demarcation type, which is based on necrosis of the acinar cells of the pancreas, and enzymatic aggression, followed by 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] Until now, acute pancreatitis remains one of the most urgent problems in abdominal emergency surgery.[1]

According to the WHO, there is a trend towards an increase in the number of young and middle-aged patients with AP, which is often associated with unfavorable ecology, living conditions, the incidence of obesity, and alcohol abuse.[5, 18] Despite the successful achievements in improving the methods of treatment of acute pancreatitis, the overall mortality in its mild forms is 3.9 to 21%, and in severe forms it reaches up to 70%. Lethal outcome in patients with acute infected pancreatitis occurs during 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]

According to the Atlanta classification revised in 2012, AP develops in two phases.[20] In the early phase, which usually ends by the end of the first week, systemic disturbances are secondary to local inflammation of the pancreas. As the disease progresses, a generalized inflammation occurs, defined as 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 an organ failure affects more than one organ, it is called multiple organ failure (MOF) or multiple organ dysfunction syndrome (MODS).[20] The late phase is characterized by persistence of systemic signs of inflammation or local complications. During this stage, the immune system is suppressed, making the pancreatic tissue more susceptible to infection as a result of translocation of intestinal bacteria. The resulting sepsis and multiple organ failure are subsequently major causes of late complications and mortality.[28] According to this classification, there are: acute edematous (interstitial) pancreatitis, sterile and infected pancreatic necrosis, which are links of a single pathogenesis.[12]

The transition of acute pancreatitis from one type to another is due to 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, a mild, moderate, and severe form is distinguished, which are determined by the development of SIRS, complications, and the severity of multiple organ disorders according to the SOFA scale.[14] In severe AP, the local inflammatory process intensifies and spreads through the bloodstream throughout the body, which leads to a systemic inflammatory response.[35] A detailed assessment of the severity and prediction of the outcome of AP are fundamental principles for an adequate choice of conservative therapy and timely surgical tactics.[2]

Numerous studies of the pathogenesis of AP have been published; however, the exact mechanism of this pathology remains unclear.[44] Even when several

mechanisms of the pathophysiological process of OP are proposed, none of them is completely informative.[53]

Premature trypsin activation is the most widely accepted theory as the underlying mechanism for initiating pancreatic tissue autodigestion and subsequently local and systemic inflammatory processes. The initial events of AP occur in acinar cells, which can act as inflammatory cells in the pancreas.[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 damage in the pancreas.[44, 50, 55, 54]

In AP, a wide range of changes in the homeostatic parameters of the body is determined.[13] It is well known that as a result of damage and/or infection of tissues in the human body, a complex sequence of reactions unfolds aimed at preventing further destruction, isolating and destroying the pathogen, activating reparative processes, and restoring the initial homeostasis.[16] Given that the pathogenesis of the disease is directly related to the cytokine response of the body, it is proposed to determine the concentrations of pro-inflammatory and anti-inflammatory mediators. Elevations of both types of cytokines occur early and persist 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 lethal outcome in a particular patient.[30, 41; 49; 32]

Cytokines are a family of low molecular weight proteins (weight 16-25 kDa) that are secreted by many cells, including macrophages and monocytes. These are regulatory mediators of the immune response, acting both on their producing cells and on adjacent cells. There are: interleukins (IL / IL), which, in turn, are divided into pro-inflammatory (IL-1, IL-8, etc.) and anti-inflammatory (IL-4, IL-10, IL-14, IL-18, etc.).); interferons (IFN / IFN) (-α, -β, -γ) - with a pronounced antiviral effect; tumor necrosis factors (TNF) (-α and -β) - cytokines with cytotoxic and regulatory effects; chemokines - chemoattractants for leukocytes; growth factors and some others.[17] All cytokines realize their effects through specific cell surface receptors. Most cytokines have pleiotropic activity and show multiple functional effects on a variety of target cells. Although cytokines elicit a “beneficial” inflammatory response to limit tissue damage, overproduction of these pro-inflammatory 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.

Cytokine storm in AP is a potentially fatal immune response consisting of positive feedback between cytokines and immune cells. When the immune system fights infectious agents, cytokines signal immune cells such as T-lymphocytes and macrophages to head to the site of infection. Additionally, cytokines activate cells, stimulating them to produce even more cytokines. A cytokine storm has the potential to cause significant tissue and organ damage. These facts explain the mechanism by which the release of a large amount of cytokines contributes to the progression of severe SIRS in AP.[7]

It is known that inflammatory mediators play a leading role in the pathogenesis of AP: pro-inflammatory 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 an increase in vascular permeability, migration of leukocytes, local tissue damage, generalization of the inflammatory response, damage to the organs of natural detoxification with the development of multiple organ failure.[21]

Tumor necrosis factor (TNF/TNF)-α is an important inflammatory cytokine that is involved in the pathogenesis of AP, directly damaging acinar cells and leading to necrosis, inflammation, and edema.[22] The main producers of TNF-α, monocytes and macrophages, also secrete 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 the main mediator of immune responses.[21] The expression of TNF-α in the pancreas increases with the onset of AP. El Ashmawy et al.[26] conducted a study in a mouse model of pancreatitis caused by L-arginine to study the main molecular mechanisms of OP. They confirmed that the concentration of TNF-α in the pancreas was markedly increased after administration of L-arginine. This may be due to the overproduction 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 have been found to, indicators of TNF-α activity, are increased in patients with severe AP, and blockade of TNF-α reduces mortality and facilitates the course of experimental AP.[39]

Interleukin (IL/IL)-1 is well known as an integral early component of an 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, except for 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 on

admission with the same accuracy as IL-6 (82% versus 88%, respectively), and that the IL-1 receptor antagonist had the best accuracy among various markers, including IL-6 and CRP, within the first 48 hours. After 48–72 h, IL-1 levels were found to predict pancreatic necrosis with an accuracy of 88%, and the ratio of IL-1:IL-1 receptor antagonists could identify septic complications with an accuracy of 72%.[22]

Interleukin (IL/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, and fibroblasts shortly after being stimulated 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 levels of IL-6 increased in line with the severity of pancreatitis, suggesting that IL-6 may act as a predictive tool for OP. IL-6 has the best sensitivity and specificity for early assessment of severe AP among various pro-inflammatory and anti-inflammatory cytokines. However, the analysis of IL-6 has a significant drawback, which consists in the fact that its concentration in serum decreases very quickly with certain activities.[34] In studies by Garipati Sathyanarayan et al (2007), it was found that an elevated level of IL-6 is a prognostic factor for organ failure and severe pancreatitis, and also indicates its pathophysiological significance in AP.[27]

Among all cytokines, Interleukin (IL/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 CXC chemokine family that mediates the recruitment of polymorphonuclear neutrophils, basophils, eosinophils, and lymphocytes to inflammatory sites. IL-8 acts as a neutrophil activator and as a 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 the prediction of acute destructive pancreatitis, Salienko S.V. found that from the first day of development of acute destructive pancreatitis, several parallel and interdependent processes are observed: the formation of pancreatic necrosis (superantigen) with the development of a 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, and also involved in the genesis of multiple organ failure and early deaths. The author came to the conclusion that if we evaluate the ratio of cytokines, then during this period there is a deficiency of IL-2 and a relative deficiency of IFN-γ, which predetermines violations of the cell-mediated immune defense system. It was also found that, along with a continuing increase in the values of the pool of pro-inflammatory 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, on the other hand. – to an increase in the cytotoxic activity of macrophages, induction of massive cell apoptosis.[16]

Monocyte chemoattractant protein 1 (MCP-1 or CCL2) is a prototype 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 to tissues, but is also responsible for monocyte activation and induction of a respiratory burst. In fact, increased expression of MCP-1 has been found during acute and chronic pancreatitis both in animal models and in 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 that are upregulated in pancreatitis, and evidence for its pathogenic role was lacking.

Ohmoto K et al, when comparing clinical and laboratory data, found that serum IL-6 levels showed a significant correlation with markers of 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 a predominance of the pro-inflammatory 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 object of increasing attention and discovery. According to the literature, IL-17 causes 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 of cytokine systems is usually included in OP, and targeted therapy with 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 and important for the development and maintenance of AP. Accordingly, biologics that act on IL-17 contribute to the rapid and abrupt onset of systemic symptoms during AP. Thomson J.-E. et al in a study of 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 reveal statistically significant differences between groups.[51]

Hanna Sternby et al, in a comprehensive study of IL1β, IL-6, IL-8, IL-10, IL-12, IFN-γ, and TNF-α, analyzed differences between severity groups, predictive capacity of biomarkers, and association with severe disease 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 a severe course of the disease, but the predictive ability of the studied biomarkers is low.[29] Also, a synchronous study of the early dynamics of pro-inflammatory cytokines IL-6, IL-8, IL-18 and TNF-α on days 1, 2 and 14 in 60 patients substantiated the use of these markers as prognostic factors for the development of organ failure in patients with the first attack. OP.[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 cure of this disease. This area of scientific research is certainly one of the promising areas for solving this problem and requires further development, and therefore the study of the cytokine profile, its relationship, changes in various courses and treatment remains an urgent problem.

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