REVIEW

ICAM-1 and Acute Pancreatitis Complicated by Acute Lung Injury

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Summary

One of the most common complications of acute pancreatitis is acute lung injury, during which intercellular adhesion molecule-1 (ICAM-1) plays an important role by participating in leukocyte adhesion and activation as well as by inducing the "cascade effect" of inflammatory mediators, pulmonary microcirculation dysfunction and even acute respiratory distress syndrome, multiple organ failure or death. Although it is generally believed that the modulatory mechanism of ICAM-1 during this process is associated with the activation of nuclear transcription factor kappa B which is mediated by IL-1, IL-6, IL-18 and oxygen free radical, etc., further studies are still required to clarify it. Since the upregulation of ICAM-1 expression in the lung during acute lung injury is one of main pathogeneses, the early detection of the ICAM-1 expression level may contribute to the prevention and treatment of acute lung injury. Moreover, reducing pulmonary ICAM-1 expression levels through treatment with anti-ICAM-1 monoclonal antibody (aICAM-1) and antagonists of the neurokinin 1 receptor, etc., should have a positive effect on protecting the lungs during acute pancreatitis. This review aims to further clarify the relationship between ICAM-1 and acute pancreatitis complicated by acute lung injury, and therefore provides a theoretical basis for the formulation of corresponding therapeutic measures in clinical practice for acute pancreatitis.

Introduction

Severe acute pancreatitis is a commonly encountered and frequently-occurring disease, which does harm to the pancreas as well as other organs. Multiple organ dysfunction syndromes and multiple organ failure are believed to be the main reasons for high mortality (11.8-25% [1, 2]) in severe acute pancreatitis. In particular, acute lung injury and acute respiratory distress syndrome are the most common complications during the first week after the onset of acute pancreatitis and mortality can reach 60% [3].

At present, effective therapeutic methods on preventing and treating acute pancreatitis complicated by acute lung injury are still vague, and the pathogenesis is not clear yet. Some reports have indicated that intercellular adhesion molecule-1 (ICAM-1) plays an important role in the development and progression of acute pancreatitis complicated by acute lung injury, and the severity of the lung injury correlates well with the expression levels of ICAM-1 protein [4, 5, 6]. In this paper, we review the advances in research in this field.

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Abbreviations LFA-1: lymphocyte function-associated antigen-1; Mac-1: macrophage antigen-1; NK1R: neurokinin-1 receptor; PPAR: peroxisome proliferator- activated receptors-gamma

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1. Overview of ICAM-1

ICAM-1, a single-chain transmembrane glycoprotein with a molecular weight of 80-110 KDa, consists of five Ig-like domains, a hydrophobic transmembrane domain and a short cytoplasmic C-terminal domain [7]. Its ligand includes lymphocyte function- associated antigen-1 (LFA-1) and macrophage antigen-1 (Mac-1) [8]. Under physiological conditions, ICAM-1 is expressed at a low level in endothelial cells and epithelial cells [9, 10] or constitutively on the surface of alveolar cells [11], providing the underlying molecular basis for cell recognition, activation, proliferation, differentiation and motility, and thereby helping to stabilize the internal environment of the body. Moreover, ICAM-1 also plays a key role during pathological conditions, such as inflammatory reaction etc. [12, 13]. For these reasons, a comprehensive and objective understanding of ICAM-1 is needed.

2. ICAM-1 Expression and the Factors Influencing ICAM-1 Expression

2.1 Mechanism of ICAM-1 Expression

Experimental studies concerning acute pancreatitis have shown that an infusion of trypsin into the lungs

can significantly upregulate the expressions of both membrane-bound ICAM-1 (mICAM-1) and soluble ICAM-1 (sICAM-1) proteins [14], and the use of a urinary trypsin inhibitor is obviously capable of downregulating the expression of ICAM-1 [15], suggesting that trypsin is an initial provocative factor for the expression of ICAM-1. At present, it is generally believed that the upregulation of ICAM-1 expression is associated with enhanced transcription of the ICAM-1 gene which might be activated by nuclear transcription factor kappa B (NF-kappa B) [16], although the precise mechanism is not entirely clear. NF-kappa B is a member of the Rel protein family and is maintained in the cytoplasm as an inactivated trimer complex through binding to the inhibitory protein I-kappa B under normal circumstances [17]. When acute pancreatitis complicated with acute lung injury occurs, inflammatory mediators gathering in the lungs can induce, through signal transduction systems, the phosphorylation of I-kappa B and its dissociation from NF-kappa B which subsequently translocates into the nucleus, binds to the promoter of the ICAM-1 gene and stimulates its transcription [18].

2.2 Influencing Factors of ICAM-1 Expression

The "cascade effect" of inflammatory mediators during acute pancreatitis could lead to the release of a large number of inflammatory mediators and various active substances into the blood, which subsequently enter into the lungs through the circulatory system and thereby result in lung injury and regulate the expression of ICAM-1. The main influencing factors of ICAM-1 expression include the following.

2.2.1 Tumor Necrosis Factor-alpha (TNF-alpha)

TNF-alpha, mainly produced by mononuclear cells, is not only capable of directly killing cells but is also capable of promoting the production of other cytokines [19], thus participating in the systemic progression of diseases from local stages. The content of TNF-alpha in serum increases significantly when acute pancreatitis complicated by acute lung injury occurs [20, 21]. For this reason, serum TNF-alpha concentration is considered to be an early parameter for reflecting the severity of acute pancreatitis. Some experimental results have shown that the binding of highly expressed TNF-alpha to TNF receptor (TNFR) is able to promote NF-kappa B-mediated ICAM-1 expression [22, 23], and the activation of NF-kappa B can in turn enhance the transcription of TNF-alpha gene, thereby forming a positive feedback loop which is able to amplify the early inflammatory signal and aggravate the initial inflammatory effect. In contrast, the soluble TNF receptor (sTNFR), as one of the ways of removing the TNF receptor [24], is able to inhibit the response of cells to TNF-alpha, thereby exerting a negative regulatory role and, to a certain extent, antagonizing ICAM-1-mediated lung injury.

2.2.2 Interleukin (IL) Family

Interleukins are important cytokines which play important roles during acute pancreatitis complicated by acute lung injury by means of stimulating the activation of leukocytes and the release of toxic substances, etc. [25, 26]. It has been proven that the expression levels of IL-1 and IL-6 have a good correlation with the expression levels of ICAM-1 in the lungs during acute pancreatitis [27, 28, 29]. Recently, some researchers have found that the expression levels of IL-18 are significantly elevated in patients with acute pancreatitis; IL-18 can promote the expression of ICAM-1 [30, 31, 32]; there exists a mutual induction between the expression of IL-18 and those of IL-1 and TNF-alpha, and IL-18 is involved in the functional failure of distant organs. The mechanism with which IL-18 exerts its functions must still be elucidated. Furthermopre, IL-10 is considered to be capable of inhibiting the synthesis of a wide variety of pro-inflammatory cytokines [33, 34] and of perhaps having a negative regulatory effect on ICAM-1. In short, ILs play a dual role in the regulation of ICAM-1. During acute pancreatitis, persistent inflammatory stimulation enables the positive feedback to be dominant and, therefore, the injurious effect is more obvious.

2.2.3 Other Influencing Factors

Some protein kinase C (PKC) isoforms, such as effectors of G-protein-coupled receptor systems, are also involved in NF-kappa B activation upon receiving extracellular stimuli [35]. Some studies have indicated that this activation is associated with mitochondrial reactive oxygen species (mROS) which are regulated by protein kinase C isoforms [36], and Ca^{2+} plays a key role during this process. Therefore, calcium antagonists should be effective in reducing ICAM-1 expression. Furthermore, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2) are also considered to be directly related to the development of acute pancreatitis complicated by acute lung injury [37]. During these processes, the enhancement of NF-kappa B activity is the key point [22, 38, 39] since NF-kappa B can be synergistic with ICAM-1 expression in the lungs or on the surface of endothelial cells. As we know, reactive oxygen species (ROS) can promote the expression of ICAM-1 as well. The activated polymorphonuclear (PMN) leukocytes may be an important source of ROS which contributes to the massive expression of ICAM-1 on the surface of endothelial cells [40]. Interferon-gamma (INF-gamma) is one of the regulators of inflammation, and its upregulated expression is noted during respiratory distress syndrome complicating acute pancreatitis [41, 42]. It is generally believed that interferon-gamma is relevant to the development of acute pancreatitis. However, a recent study shows that inflammatory reaction in mice

with defects of INF-gamma expression is more severe than that in wild-type mice, suggesting that INF-gamma may function by means of suppressing the activity of NF-kappa B [43], although this result still needs to be verified.

3. Roles of ICAM-1 During Acute Pancreatitis Complicated by Acute Lung Injury

3.1 Inducing the Emigration and Recruitment of Leukocytes

The recruitment of leukocytes (mainly PMN) in the lungs plays a central role during acute pancreatitis complicated by acute lung injury [44]. A variety of adhesion molecules are involved in the adhesion to endothelial cells, migration through vascular endothelium and gathering in the lungs of PMN leukocytes [45, 46]. When PMN leukocytes are activated by IL-1, platelet-activating factor (PAF) or mast cells [47, 48], the expression of LFA-1 on the surface of PMN leukocytes is enhanced. The configuration change of the extracellular receptor-binding domain of LFA-1 is the key to the stable adhesion of PMN leukocytes. Cascade reactions induced by LFA-1 through binding to ICAM-1 can cause the structural rearrangement of PMN leukocytes, which subsequently migrate to inflammation sites in the presence of chemotactic factors and are enriched there [49]. In contrast, this phenomenon is not pronounced in mice with defects of ICAM-1 expression [50]. These results indicate that it is of great significance for ICAM-1 to mediate the adhesion and recruitment of PMN leukocytes, suggesting that ICAM-1 can be chosen as a target for treatment. Through blocking the binding of ICAM-1 to its ligands, it is expected that a better interference to the adhesion and migration of leukocytes would be achieved.

3.2 Promoting the Activation of Leukocytes

After PMN leukocytes adhere and bind to target cells, a relatively compact and stable micro-environment is formed, thus providing a necessary condition for toxic mediators to exert toxic action against target cells. The binding of ICAM-1 to Mac-1 and LFA-1 can further induce the expression of the latter on the surface of PMN leukocytes, and thereby promote PMN leukocytes to release hydrogen peroxide (H_2O_2) and a variety of pro-inflammatory cytokines [51, 52, 53]. Once inflammatory injury occurs, pulmonary epithelial cells and capillary endothelial cells will release a large number of blood coagulation-promoting substances which can cause platelet aggregation [54], and then promote an increase of pulmonary vascular resistance and permeability as well as interstitial pulmonary edema [55] and acute lung injury. These results demonstrate that the injuries of the lungs and other organs during acute pancreatitis are due to the activation of leukocytes. Although ICAM-1 is involved in the activation of PMN leukocytes, it is not the trigger factor. Therefore, inhibiting the expression of ICAM-1 is not capable of completely blocking the activation of PMN leukocytes. Nevertheless, this inhibition may exert a positive effect in protecting lung injury caused by PMN leukocytes and delay the progression of the illness.

4. Expression Levels of ICAM-1 and the Diagnosis and Treatment of Acute Pancreatitis Complicated by Acute Lung Injury

4.1 Diagnostic Significance

Due to the particular physiological structure of the lungs, they are usually the first target of attack when multi-organ dysfunction complicating acute pancreatitis occurs. It is reported that about 48.3% of acute pancreatitis patients suffer from pulmonary disease, and part of them die from acute lung injury [56]. Therefore, it is of great practical significance to better predict acute lung injury and reduce its incidence rate. Through detecting the changes of serum ICAM-1 contents in 34 cases of patients with acute pancreatitis, some researchers have hypothesized that ICAM-1 can be used as an early marker in the diagnosis of lung injury [57]. If corresponding therapeutic measures are taken as soon as possible on the basis of early diagnosis through detecting ICAM-1, the therapeutic effect will certainly be superior to that achieved by conventional treatment. Currently, some researchers have attempted to conduct clinical studies on the classification of acute pancreatitis by standardizing the expression levels of ICAM-1 [58] since they believe that the extent and manner of the increase in blood sICAM-1 content in patients with acute pancreatitis are correlated with the severity of the disease. Although we also believe that the expression levels of ICAM-1 have significance in the classification of acute pancreatitis complicated by acute lung injury, further studies are still needed to verify this.

4.2 Therapeutic thoughts and Approaches

Since the precise mechanism underlying the development of acute pancreatitis complicated by acute lung injury has not yet been completely clarified, supportive therapy (for example, application of antibacterial drugs or nutritional support etc.) is generally used in the treatment of acute lung injury except when clear indications for surgery are clinically observed. However, these therapeutic measures are not able to fundamentally solve all the problems. Therefore, the exploration of new therapeutic strategies and approaches has become one of the focal points of the study. Some scholars have found that abnormal expressions of adhesion molecules, such as ICAM-1, during acute pancreatitis occur after the appearance of cytokines, and neutrophil infiltration and organ injury often occur after the upregulation of ICAM-1 expression. Therefore, they think that cell adhesion can be blocked by treatment [59]. For these reasons, studies on adhesion molecules have become a new breakthrough point. At present, many therapeutic approaches aimed at changing the expression levels of ICAM-1 have been proposed, including the following:

4.2.1 Treatment with Monoclonal Antibodies

The literature has shown that treatment using membrane-bound ICAM-1 as a target can effectively reduce lung injury [60], and better therapeutic effects can be achieved by using anti-ICAM-1 monoclonal antibody (aICAM-1) in the treatment of various types of acute lung injury in animal models [61]. If aICAM-1 is applied in the early stage of acute pancreatitis, better protection for the pancreas and lung functions is observed [62]. The underlying mechanism may be mainly associated with the inhibition of ICAM-1-mediated adhesion and infiltration of PMN leukocytes as well as the decrease in the expression of active substances, such as inflammatory mediators, etc. In addition, aICAM-1 is also able to lessen myeloperoxidase (MPO) and downregulate the expression of nitric oxide synthase-2 mRNA (NOS-2 mRNA) [63], thus ensuring the functional and structural stability of endothelial cells and exerting a positive influence on the protection of pulmonary microcirculation. However, it should also be noted that the long-term use of ICAM-1 antibodies may give rise to autoimmune diseases. Moreover, considering that this practice can only mitigate the disease, the popularization of ICAM-1 antibodies is still an issue open to question.

4.2.2 Treatment by Inhibiting NF-kappa B Activation

It is obvious that NF-kappa B plays a critical role in the expression of ICAM-1. Therefore, research on the use of NF-kappa B inhibitor to alleviate inflammation response has become a hotspot [64, 65, 66]. Calpain I inhibitor and pyrrolidine dithiocarbamate (PDTC) are antioxidants which are potent inhibitors of NF-kappa B. Calpain I inhibitor and pyrrolidine dithiocarbamate (PDTC) can lessen lung injury in rats with acute pancreatitis, decrease the activation of NF-kappa B as well as the expression of ICAM-1 protein [67, 68, 69], and can retain the soakage of inflammatory cells and mitigate the microvascular impairment of the lungs, which reduces the incidence rate of pneumonedema [70]. After Hietaranta *et al*. [71] first reported that MG132, a prosome inhibitor, could depress the activation of NF-kappa B in acute pancreatitis, some researchers demonstrated that MG132 also had the effect of protecting lung tissue in rats with acute pancreatitis [72, 73, 74] which may be associated with the function of inhibiting NF-kappa B activation. The use of the NF-kappa B inhibitor may be considered as another effective path in the treatment of acute pancreatitis complicated by acute lung injury, and associated clinical research is required.

4.2.3 Treatment Through Activating Peroxisome Proliferator-Activated Receptors-gamma (PPAR-gamma)

A large number of studies have shown that, for acute pancreatitis or for chronic pancreatitis, the use of thiazolidinediones, pioglitazone and rosiglitazone, etc. [75, 76, 77] can antagonize the expression of TNF-alpha and ICAM-1, and delay the progression of acute pancreatitis. Utilizing PPAR-gamma gene knockout mice, some researchers have proven that the functions of the above-mentioned drugs are mediated by PPAR-gamma [78]. Therefore, it is believed that PPAR-gamma agonists are able to effectively protect the lungs and reduce the expression of the ICAM-1 protein. The action mechanism of PPAR-gamma agonists is also associated with suppressing the activities of transcription factors NF-kappa B and activator protein-1 [79, 80, 81]. At present, the study of PPAR-gamma agonists in the treatment of acute pancreatitis complicated by acute lung injury is quite limited, although it has good prospects.

4.2.4 Other Therapeutic Strategies and Approaches

Neuropeptides, such as substance P (SP), can stimulate elevated expression of ICAM-1 in human skin capillary endothelial cells [82]. When neurokinin-1 receptor (NK1R) antagonists are used to treat acute pancreatitis mice, RT-PCR results reveal that the expression levels of ICAM-1 mRNA in the lungs in the study group are significantly lower than those in the model control group. Moreover, pathological changes in mice in the study group are also milder than those in the model control group [83]. Although the mechanism by which NK1R antagonists act on acute pancreatitis complicated by acute lung injury is not entirely clear, what is certain is that this practice is less likely to inhibit the activation of ICAM-1 and NF-kappa B. It has been proven that NF-kappa B activation happens prior to the transcription of ICAM-1 and NK1R mRNAs [84]. Thus, it is difficult to achieve a therapeutic effect on acute lung injury by antagonizing NK1R.

Conclusions

To sum up, ICAM-1 plays an extremely important role during the whole development process of acute pancreatitis complicated by acute lung injury, including the adhesion and activation of leukocytes and pulmonary vascular endothelial cells. The usage of aICAM-1, PPAR-gamma agonists, NF-kappa B inhibitor and antagonists of neurokinin 1 receptor, etc. should have a positive effect on reducing the expression of ICAM-1 in lungs during acute pancreatitis. Well-designed clinical and experimental research should be done. With the gradual elucidation of the regulatory mechanism of ICAM-1 and the pathogenic mechanism of acute lung injury, together with in-depth pharmacological research, and the diversification of treatment means, it is believed that the incidence rate of the disease will be reduced and the prognosis of acute pancreatitis patients will be significantly improved.

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