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Review Article

Inhibition of metalloproteinases in therapy for severe lung injury due to COVID-19

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ABSTRACT

Since its first appearance in December 2019 in the Chinese province of Wuhan, COVID-19 has spread rapidly throughout the world and poses a serious threat to public health. Acute respiratory failure due to widespread lung inflammation progress to acute respiratory distress syndrome (ARDS) with an altered pulmonary and alveolar function that can lead to disability, prolong hospitalizations, and adverse outcomes.

While there is no specific treatment for severe acute lung injury (ALI) and ARDS due to the COVID-19 and the management is mostly supportive, it is very important to better understand the pathophysiological processes activated by the inflammatory mediators such as cytokines and metalloproteinases with the aim of their subsequent inhibition in the course of the complex treatment.

Herein, we will discuss the pathophysiological mechanisms of ALI/ARDS, with a focus on the pivotal role played by matrix metalloproteinases (MMP) and the kinin-kallikrein system (KKS), and the effects of the possible pharmacological interventions.

Aprotinin is a nonspecific protease inhibitor especially of trypsin, chymotrypsin, plasmin, and kallikrein, and it is many years in clinical use. Aprotinin inhibits the release of pro-inflammatory cytokines and involved in the process of glycoprotein homeostasis. Experimental data support that the use of aprotinin to inhibit MMPs and KKS may be a new potential approach to the treatment of ALI / ARDS.

Contents

1. Introduction

The current treatment of COVID-19 disease is mostly supportive, and respiratory failure due to ALI/ARDS is the leading cause of death [1].

In a recently published large cohort study from the Chinese Centre for Disease Control and Prevention that enrolled >70,000 patients with COVID-19, >44,000 of them showed a mild to critical severity range illness with the overall case-fatality rate of 2,3% and the highest up to 49% among

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critical cases [2]. Recently published studies from China regarding the epidemiological and clinical characteristics of patients with COVID-19 disease revealed a wide difference (from 17 to 67%) in the incidence of ARDS with a mortality rate of up to 52,4% [3–6].

According to the recent US Centre's for Disease Control and Prevention (CDC) statistics since mid-March, the fatality rates in the US from COVID-19 was highest in patients aged ≥85, ranging from 10% to 27%, followed by 3% to 11% among persons aged 65–84 years, 1% to 3% among those aged 55–64 years and < 1% among persons aged 20–54 years [7].

Significant progress has been made recently in understanding the epidemiology, pathogenesis, and treatment of ALI and ARDS. However, more efforts are needed to further reduce mortality and morbidity from these diseases. Since ALI/ARDS are so common in the United States and around the world and the rapid and widespread of the COVID-19 has only aggravated the existing problem, ALI/ARDS is still an unresolved medical issue. In other words, new treatment modalities should be developed to further improve the clinical outcomes [8].

In this review, we will discuss the pathophysiological mechanisms of ALI, with a focus on the pivotal role of matrix metalloproteinases and the kinin-kallikrein system in this process. We will also review, whether aprotinin, as a nonspecific protease inhibitor, be useful in treating ALI.

2. The pathophysiological mechanism of acute lung injury

In Covid-19 infection, epithelial damage is the initial event and hallmark of the acute lung injury that initiates a cascade of local and/or systemic processes leading to diffuse lung parenchymal damage [9,10]. The focal airway inflammation produces an elevation of proinflammatory cytokines and other inflammatory mediators and an over-expression of nuclear factor kappa B [11,12]. These mediators activate alveolar macrophages and neutrophils, which release oxygen radicals and proteolytic enzymes and produce further lung tissue damage. Indeed, increased pulmonary vascular permeability caused by activated neutrophils, oxygen radicals, and proteases seem the fundamental cause of ALI [13].

Neutrophils are the prototypic cells of the immune system with their primary function of host defense and eradication of invading microbial pathogens [14]. These functions are accomplished by activation of immune receptors, such as toll-like receptors and other recognition receptors [15,16]. An important component of this process is the differentiation and activation of T helper lymphocytes of the Th1 and Th2 phenotypes with overproduction of their cytokines including IL-3, IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 [17].

Increased levels of cytokines are a usual finding in the sputum of patients with acute inflammatory lung processes [18–20]. IL- 13 and IL- 6 from activated mast cells play an important role in various inflammatory lung diseases and induced matrix contraction [21–23]. IL-13, as well as a vascular endothelial growth factor, are known as potent mediators of tissue fibrosis and key regulators of the cellular matrix [24,25].

Mild cases of COVID-19 sometimes are rapidly turning into severe cases, with lower respiratory tract infections. This may be due to the “cytokine storm”. Cytokine storm is a group of disorders representing a variety of inflammatory etiologies known as systemic inflammatory response syndrome, cytokine release syndrome, macrophage activation syndrome, and hemophagocytic lymphohistiocytosis [26].

A cytokine storm is the overproduction of immune cells and their activating compounds - cytokines, often associated with the release of activated immune cells into the lungs. Resulting pneumonia and fluid accumulation can lead to respiratory failure and may be contaminated with secondary bacterial pneumonia. All of the above increase the risk of patient morbidity and mortality [27–31].

Matrix metalloproteinases (MMP) are part of a family of proteolytic zinc enzymes. Till recently, more than twenty types of MMP have been recognized. They play a pivotal role in normal physiological conditions such as embryogenesis, proliferation, angiogenesis, cell motility, wound healing, degradation of the extracellular matrix, and in the different pathological states [32].

Proinflammatory cytokines induce MMP over-expression and increase their activity thereby participating in airway remodeling [33–36]. MMPs secreted at sites of lung inflammation in the extracellular matrix that lead to release bioactive chemokines with inflammatory properties [37]. Every type of MMP, and fluctuation in their levels, play a specific role in different lung disease [38]. For example, MMP-12 (macrophage elastase) can regulate the extracellular matrix component elastin and is involved in the tissue remodeling process [39,40].

Studies on the involvement of MMP in the pathological processes during ALI / ARDS have been found in the literature since the early 1990s. Nevertheless, research efforts failed to lead to effective pharmacotherapy. Previously published works are devoted to the role of MMP in the destructive pathologies of the lungs without considering their function in the process of tissue repair, which was demonstrated in later studies [41–43].

Nonspecific inhibition of MMP has been shown to limit lung damage. This suggests that there is a potential pharmacotherapeutic strategy for treating early ALI / ARDS with drugs that are non-specific MMP inhibitors. Nonspecific inhibition of MMPs can have multiple effects on other cellular processes and inflammatory mediators involved in lung damage. In clinical practice doxycycline and tetracyclines, such as COL3 and CMT, are the most commonly used non-specific MMP inhibitors [44].

Further investigations are required to fully understand the role of MMPs in the pathogenesis of ALI/ARDS. These data are necessary to determine what type of metalloproteinases should be inhibited, at which stage of the disease, and what MMPs level may be optimal for the restoration of the abnormal collagen.

3. Involvement of the kinin- kallikrein system in the pathophysiology of inflammation

Kinin-kallikrein system (KKS) plays an important and even critical role in human physiology. Tissue kallikreins are a family of extracellular serine proteases participating in complex proteolytic cascades, physiological functions, and various pathological processes [45]. KKS is responsible for the release of the vasoactive pro-inflammatory neurotransmitter bradykinin (BK). BK is a pro-inflammatory peptide, potent vasodilator, leading to stable fluid accumulation in the interstitium. KKS is involved in the pathogenesis of inflammation, hypertension, endotoxemia, and coagulopathy. In all these cases the elevated level of BK is a hallmark [46]. Schapira M. et al. reported the activation of human plasma KKS in patients with ARDS [47].

The kinin's level in the inflammatory environment is markedly increased. Thus, bradykinin (BK) can play an important role in initiating and maintaining pathophysiological changes that occur in the lungs. Experimental trials on animals with ARDS demonstrated the beneficial effects of selective kinin receptor antagonists and provided convincing evidence of the key role of kinins in the respiratory tract pathophysiology [48].

COVID-19 may predispose to venous and arterial thromboembolism due to the inflammatory process, hypoxia, immobilization, and diffuse intravascular coagulation. In a recently published study, Klok et al. enrolled 184 ICU patients with COVID-19 to evaluate the incidence of the composite outcome of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism. They reported about 31% incidence of thrombotic complications [49].

Deep vein thrombosis (DVT) followed by pulmonary embolization may result from increased thrombolysis and/or activation of KKS in plasma. KKS activation leads to the generation of BK and tissue plasminogen activator (tPA), two factors involved in ensuring smooth blood flow through the arterial system. Thus, inhibition of kallikrein may be a possible therapeutic target, given the effect of kallikrein on the plasma production of bradykinin [46].

4. Aprotinin- possible therapeutic way to treat ALI/ARDS?

Aprotinin is a monomeric polypeptide and it is derived from bovine lung tissue. It was initially named kallikrein inactivator and isolated from the cow parotid gland in 1930. In 1964 it was purified from bovine lung tissue. Aprotinin acts as a nonspecific serine protease inhibitor - especially trypsin, chymotrypsin, plasmin, and kallikrein [50]. The antikallikrein action of aprotinin leads to the inhibition of factor XIIa formation, inhibition of the intrinsic pathway of coagulation, fibrinolysis, thrombin generation, and to the attenuation of the pro-inflammatory response [51].

Aprotinin inhibits proinflammatory cytokine release and maintains glycoprotein homeostasis. In platelets, aprotinin reduces glycoprotein loss, while in granulocytes it prevents the expression of pro-inflammatory adhesive glycoproteins [52].

The systemic inflammatory response is a common phenomenon that occurs in most patients undergoing coronary artery bypass graft (CABG) surgery. Acute activation of the complement system, as well as activation of the coagulation and fibrinolytic systems lead to multiorgan inflammatory damage. Using aprotinin, as a nonspecific serine protease inhibitor, not only decreases the bleeding tendency but may also attenuate the systemic inflammatory response as well [53].

In the study of Tain-Yen Hsia et al. aprotinin more effectively reduced the levels of MMPs and cytokines than tranexamic acid in infants after cardiac surgery [54].

Aprotinin is approved by the US Food and Drug Administration (FDA) as an agent that effectively prevents blood loss and transfusion during coronary artery bypass graft surgery [51].

In 2007 the drug use was temporarily discontinued due to increased risk of complications and death after Bayer Health Care has published the follow-up study [55]. Moreover, in a randomized controlled study, Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) Fergusson et al. reported a higher mortality rate in the aprotinin-treated patients. However, the subsequent analysis identified methodological research flaws making the findings of the cardiovascular risks from the BART study controversial [56]. In 2012 the European Medicines Agency (EMA) scientific committee reinstated its previous view regarding aprotinin and has recommended it for further use [57]. Since that time the Nordic Group became a distributor of aprotinin [58].

Nevertheless, we do not recommend to use aprotinin for treatment COVID-19 induced ALI/ARDS in patients after CABG, acute coronary syndrome, cerebrovascular events, renal failure, or concomitant use of aminoglycosides.

Since deep vein thrombosis (DVT) is a known complication in hospitalized patients with COVID-19 disease [59], we recommend using Clexane (Enoxaparin sodium) twice daily injections of 100 IU/kg (1 mg/kg) simultaneously with the aprotinin treatment.

In a small experimental study of Svartholm et al., the authors used aprotinin on laboratory pigs with septic shock. They concluded that aprotinin attenuated the effects on coagulation, fibrinolytic systems, and cardiopulmonary hemodynamic, seriously impaired due to septic shock [60].

Anderson et al. used sulfur mustard to induce oxidative and inflammatory lung injury in rats with further treatment with aprotinin, ilomastat, or trolox. Aprotinin effectively prevented the increase in total protein and IL-1 alfa levels in bronchial lavage fluid. Moreover, aprotinin maximally reduced histopathological findings. These results suggest that therapy with aprotinin may reduce the inflammatory response during experimental lung damage [61].

Currently, there is no clinical evidence supporting the use of aprotinin in COVID-19 patients. Therefore, further clinical studies should be conducted to verify it's effectiveness in patients with COVID 19.

5. Conclusion

The pathophysiological mechanism of ALI/ARDS includes a cascade of local and systemic responses with activation of numerous proinflammatory cytokines and mediators. Between them, matrix metalloproteinases and kinin-kallikrein system play a pivotal role in the pathological process. Overexpression of MMPs leads to destructive tissue injury and tissue remodeling. Experimental data suggest that MMPs may be a new potential target for therapy of ALI/ARDS. Aprotinin as a nonspecific protease inhibitor is many years in clinical use. It does not only decrease the bleeding tendency by inhibition of the kinin-kallikrein system but also attenuated systemic inflammatory response due to decreased level of inflammatory cytokines and MMPs. Based on these data, we think that aprotinin may be a potential therapeutic agent in the complex treatment of ALI and a good area for further investigations and clinical trials.

Conflict of interest

The authors declare that they have no competing interests.

Author Agreement

both authors have seen and approved the final version of the manuscript.

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