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REVIEW

The role of soluble urokinase-type plasminogen activator receptor (suPAR) in multiple respiratory diseases

Ummugulsum Can

Konya Education and Research Hospital, Department of Biochemistry, Konya, TURKEY

Correspondence: Ummugulsum Can
E-mail: cangulsum@yahoo.com
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Serum soluble urokinase-type plasminogen activator receptor (suPAR) is a glycoprotein secreted during infections and inflammation [1]. Urokinase-type plasminogen activator (uPA) is secreted by polymorphonuclear neutrophils (PMN) and macrophages; then uPA binds to membrane urokinase-type plasminogen activator receptor (uPAR) [2]. suPAR is formed by cleaved from the uPAR [2]. suPAR is expressed in various cell types, such as macrophages monocytes, endothelial cells and neutrophils [3]. suPAR can be potentially cause or modulate various diseases in patients with cancer, various infectious and inflammatory diseases (including infections with human immunodeficiency virus (HIV), tuberculosis, liver fibrosis and inflammatory bowel disease) [2, 3]. suPAR can convert plasminogen to plasmin, which degrades fibrin, activates matrix metalloproteases and mediates proteolysis of extracellular matrix proteins during cellular invasion [4]. suPAR modulate the functions of integrins (including activating intracellular signals, monocyte chemotaxis, cell adhesion and proliferation) [4, 5]. So suPAR contributes to cell adhesion, migration, proliferation inflammation, chemotaxis, proteolysis, immune system activation, tissue remodeling and signal transduction [5, 6]. Several studies have identified that suPAR level is a important marker in patients with various diseases and associated with a poorer outcome in a range of non-infectious and infectious diseases [2]. Biomarkers of lung disease are required to aid diagnosis, define clinical phenotypes and monitor the response to existing and new therapeutic strategies. Our review aims to explore the potential of suPAR as a general marker in the diagnosis, prognosis and follow-up of therapy of lung disease.

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Introduction

Associated with the activation of the immune system, soluble urokinase-type plasminogen activator receptor (suPAR) has been commenced to be used as a potential biologic marker of diseases in recent years [1, 2]. Increased suPAR levels were observed in autoimmune diseases, various forms of solid tumors, such as nonsmall cell lung cancer, various infectious and inflammatory diseases including human immunodeficiency virus (HIV), tuberculosis, arthritis, pneumococcal and streptococcus pneumonia, bacteraemia and sepsis [2-4]. So, high suPAR levels are of a vital importance in prediction in the diagnosis and course of these diseases [2].

Previous data assert that suPAR in circulation may play a significant role in various respiratory diseases. Our review aims at investigating the potential role of suPAR as an effective marker on the diagnosis and prognosis in lung diseases through the understanding of biochemical and molecular mechanism in the effect of suPAR.

The main components of urokinase-type plasminogen activator (uPA) system, including uPA urokinase-type

plasminogen activator receptor (uPAR) and urokinase-type plasminogen activator inhibitor (PAI-1), are important constituents of activated immune system and inflammation [5, 6]. uPAR (CD87) is a cysteine-rich, glycosylphosphatidylinositol (GPI)-anchored cell membrane protein [7, 8]**.** uPAR is on the outer parts of several cell types, such as monocytes and macrophages, polymorphonuclear neutrophils, vascular endothelial, smooth muscle and epithelial cells [7, 8]**.** uPAR protein is composed of three different sites, called D1, D2 and D3 between the amino and the carboxy termini of molecules, each including a preserved organization of disulfide bonds and separated by among short linker arrays [7, 9]. suPAR arises from proteolytic cleavage of the GPI anchor by various proteases, is released from cell membrane-bound uPAR and determined in bodily fluids, such as blood, urine and pleural [1,9]. The release of suPAR is influenced by various immune and inflammatory effectors, such as bacterial products, cytokines and growth factors [10]. suPAR has been observed to increase during the tumor growth and metastatic tumor dissemination [10]. When uPA is bound to it, uPAR catalyzes cell surface plasminogen into plasmin [11], activating a proteolytic cascade including matrix metalloproteinases (MMP), such as MMP-2 and MMP-9 [12], and breaks down fibrin and other the extracellular matrix (ECM) constituents [9]. The system of uPA-uPAR/plasmin is of a vital importance while regulating MMP-1 and TNF-α, cytokines associated with inflammatory responses by activated monocytes and highly effective on pericellular and ECM proteolyses [7, 11]. The system of uPA-uPAR/plasmin initiates many intracellular signaling pathways, such as PI3-kinase/Akt p38MAPK and Erk1/2 [13], resulting in such outcomes as tissue remodeling, adhesion chemotaxis, proliferation, cell migration, coagulation, fibrinolysis, complement activation and apoptosis [2, 3] through binding the ECM adhesive protein vitronectin and various integrins [7, 13, 14] in both normal and disease states [9, 12]. suPAR has direct chemotactic characteristics [1], which may ease the recruitment of inflammatory cells, such as neutrophils and monocytes, and the mobilization of hematopoietic stem cells [2]. As different from suPAR, uPAR has an interaction with G-protein coupled receptors so as to signal in cells via intracellular kinases and integrins (primarily α3β1 and α5β1), and so influences the cell adhesion and migration [1, 9]. The mechanism activating uPA system was found in various airway inflammation and pulmonary diseases such as adult respiratory distress syndrome, idiopathic pulmonary fibrosis and asthma [4].

We demonstrated that serum suPAR may be of a crucial role in the inflammation of chronic obstructive pulmonary disease (COPD), and such an increase may be particularly effective on patients in stages III and IV of Global Initiative for Chronic Obstructive Lung Disease (GOLD). The levels of serum suPAR and plasma fibrinogen may be beneficial in the assessment of stable COPD [15]. Other researchers also emphasize that suPAR has a significant influence on lung diseases. Wang *et al.* [16] found that the markers of active epithelial-mesenchymal transition (EMT) and existence of uPAR were highly elevated in the small airway epithelium of patients with COPD than those of controls and also witnessed a significant association of uPAR with vimentin expression in the small airway epithelium. These researchers proposed that elevated uPAR in the small airway epithelium of COPD patients is responsible for active EMT process, and so uPAR is associated with airflow restriction, as well. They found a considerable inverse relationship between FEV1% and uPAR expression ($r=-0.564$, $p< 0.01$**)**. In another study performed by Wang *et al.* [17], it was also determined that uPAR is an important factor in the development of COPD via 203 differentially regulated genes. This study on gene profiling also indicated uPAR is expressed as an increased staining for uPAR protein in the airway epithelium of patients with airflow restriction. It was put forth that uPA and uPAR are potential markers in monitoring COPD treatment. In their study, Stewart *et al.* [9] determined the following: multiple uPAR isoforms are present in the lung and immune cells; uPAR expression is cell specific; uPAR is related to an asthma susceptibility gene; and, the evidence shows that uPAR could be seen as increased in pulmonary diseases such as COPD and asthma. Kucharewicz *et al.* [18] found that uPAR has a potential and inducing effect on tissue remodeling and may be a predictor influencing the decrease in the function of lungs based on the effect on ECM remodeling, proliferation and migration of different cell types. In a study by Barton *et al.* [19], plasma urokinase plasminogen activator receptor (PLAUR) single nucleotide polymorphisms (SNPs) were reported to be tied to PLAUR levels and to affect the decline of FEV1 in asthma, backing up the hypothesis that PLAUR is responsible for chronic changes in the airways. It is also known that PLAUR is a novel therapeutic marker while treating asthma. Chu *et al.* [20] showed that uPAR has a high rate of expression in lung epithelium of severe to fatal asthma cases. In another study by Xiao *et al.* [21], increased rates of uPAR and PAI-1 levels were encountered in the sputum of COPD patients, and such an increase was reported to be extremely associated with lung function and interleukin-8 levels. It was reported that suPAR is increased in the sputum in such pulmonary diseases as asthma, COPD and cystic fibrosis. In a study performed by Brooks *et al.* [22], lower molecular weight structures of uPAR were demonstrated to be in peripheral neutrophils, while higher molecular weight structures are seen more frequently in lung eosinophils. Bdeir *et al.* [23] found that mice lacking uPA have an impaired capacity to lyse pulmonary microemboli. uPA mediates endogenous fibrinolysis in the pulmonary microvasculature. $uPAR^{-/-}$ mice

showed a marked impairment in pulmonary fibrinolysis throughout the experimental period. These data indicate that uPA contributes to endogenous fibrinolysis in the pulmonary vasculature. Takahaski *et al*. [24] found that pulmonary microvascular cells produce abundant uPA and less tPA in culture, compared with other sources of endothelium. Backes *et al*. [1] found that high suPAR levels are detected in lung-lavage fluid in burnt patients with inhalation trauma and correlated with pulmonary inflammation and coagulation, except for fibrinolysis. suPAR levels in lungs could be beneficial in the diagnosis of burnt patients, while systemic suPAR levels may have a prognostic benefit. In a study performed by Zhang *et al*. [5], it was found that uPA, uPAR and PAI-1 are at a significantly higher rate in lung cells and pulmonary macrophages in patients with COPD than those of controls, and significant inverse correlations were observed between lung function, and uPA, uPAR and PAI-1. This study also demonstrated that the system of uPA is seen at different levels in lung tissues of COPD patients from those of control smokers and nonsmokers. There are significant correlations between uPA system, and lung function, the degree of small airway fibrosis and emphysema. uPA system may be of a vital importance in the development of COPD by inducing both inflammation and tissue remodeling, including parenchymal destruction and small airway fibrosis. Gyetko *et al*. [25] found that uPA is in need of lung inflammatory response to *C. neoformans.* uPA Deficiency leads to insufficient cellular recruitment, uncontrolled infection and death. Another study performed with mice by Gyetko et al. [26] concluded that lymphocyte proliferative responses are decreased when uPA is absent, and the mice may not yield protective T1 cytokines, leading to impaired antimicrobial activity. This novel study demonstrates that uPA is an important modulator of immune responses *in vivo*. Gyetko *et al*. [27] also performed another study and revealed that uPAR is essential to recruit neutrophils into lungs in response to *P. aeruginosa pneumonia*, and that this mechanism is independent of uPA. Additionally, they also showed that uPAR and CR3 show an action via a common mechanism during the neutrophil recruitment to lungs in response to *P. Aeruginosa.* Beck *et al*. [28] concluded that deleting uPA gene inhibits the clearance of *P. carinii* and decreases the recruitment of inflammatory cells. Thereby, uPA is a considerable contributor to the network of inflammatory events in the clearance of *P. carinii*. Against opportunistic pathogens, uPA plays a key role in pulmonary host defense. Simon *et al*. [29] found that epithelial uPA with fibrinolytic activity has a significant role in COPD. Wasswa-Kintu *et al*. [30] asserted that uPA system of uPA, uPAR and PAI-1 is extremely responsible for the pathogenesis of lung cancer, a frequent comorbidity in COPD patients. Montuori *et al*. [31] found that an increase in uPA system is associated with lung cancer progression, metastasis and poor prognosis. Zhang *et al*. [32] found that the activity of fibrinolysis system was injured progressively by the upregulation of PAI-1 activity and the downregulation of uPA activity. In a study by Rijneveld *et al*. [33], it was determined that mice deficient in uPAR are more sensitive to pneumococcal pneumonia owing to an inhibition of neutrophil recruitment into the inflamed lung. uPAR is needed to recruit adequate neutrophils into alveoli and lungs during pneumonia led by *S. pneumoniae*.

suPAR is increased in active tuberculosis (TB) disease. suPAR levels are important in the course of TB treatment and become decreased to the level of non-infected individuals in those completing the treatment successfully [34]. Portelli *et al*. [35] reported that elevated serum levels of suPAR were identified in asthma and COPD cohorts, when compared to control subjects. Mardining *et al*. [36] showed that the mobilization of macrophages into bronchi increases suPAR levels. uPAR interacts with integrins and leads to the adherence and migration of monocytes. They also detected that suPAR levels in patients with from advanced lesions to moderate and minimal lesions showed no difference significantly. In a study by Stewart and colleagues [37], membrane urokinase plasminogen activator receptor (muPAR) was found to be the critical molecule affecting plasminogen system on the function of airway epithelial cells. These data suggest that uPAR is the main target in the treatment of such diseases as cancer and asthma to change epithelial cell function.

As a potential clinical marker, suPAR is known as a good candidate due to its high stability in plasma samples [4]. Biomarkers can be used in the diagnosis, follow-ups or prognosis of patients with a specific treatment as the early predictors of efficacy or of treatment toxicity. In pulmonary diseases, an ideal biomarker should be composed of diagnostic, prognostic and follow-up of treatment and be easily and rapidly available while using in daily clinical practice. suPAR is a relatively new nonspecific marker of inflammation. suPAR has lately been associated with the pathogenesis of lung disease.

This systematic review shows that systemic levels of suPAR are elevated in lung diseases, and the number of publications related to critically lung diseases still remains low. We consider that suPAR will play a role in the enlightenment of the progression, prognosis and mortality of lung diseases and the link between the molecular mechanisms and the inflammatory process. Further studies are needed to determine whether suPAR could be used while monitoring the treatment and guiding therapeutic decisions.

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