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The role of cathepsin S in the pathophysiology of bronchial asthma

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ABSTRACT

To date, the study of the role of proteases in the pathogenesis of various diseases remains relevant. The variety of cathepsin functions is associated with the peculiarities of their localization, expression, and regulation, due to which cathepsins are involved in development of many pathologies. Dysregulation of proteases, their inhibitors, and substrates can lead to the development of multiple organ dysfunction.

The review presents data on the characteristics of the entire family of cathepsins and cathepsin S, in particular. The pathophysiological role of cathepsin S in the formation of bronchopulmonary pathologies, as well as in bronchial asthma is described, and intra- and extracellular implementation mechanisms are considered. The authors believe it is this enzyme that could be targeted in targeted asthma therapy to prevent airway wall remodeling at the earliest stages of the disease. The literature search was carried out in the search engines Medline, eLibrary, Scopus, the Cochrane Library, and RSCI.

Keywords: cathepsin S, bronchial asthma, pathophysiology, proteases, airway remodeling

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Роль катепсина S в патофизиологии бронхиальной астмы

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РЕЗЮМЕ

До настоящего времени сохраняет свою актуальность изучение роли ферментов – протеаз в патогенезе различных заболеваний. Многообразие функций катепсинов обусловлено особенностями их локализации,

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экспрессии и регуляции, благодаря чему они принимают участие в развитии многих патологических процессов. Дисрегуляция активности протеаз, их ингибиторов и субстратов может привести к развитию полиорганных заболеваний.

В обзорной статье представлены данные о характеристике всего семейства катепсинов и катепсина S в частности; описаны его патофизиологические роли при формировании бронхолегочных патологий, а также при бронхиальной астме; освещены внутри- и внеклеточные механизмы реализации. Авторы считают, именно этот фермент может стать мишенью для таргетной терапии астмы с целью предотвращения ремоделирования бронхиальной стенки на самых ранних этапах заболевания. Поиск литературы осуществлялся в поисковых системах Medline, eLibrary, Scopus, The Cochrane Library, РИНЦ.

Ключевые слова: катепсин S, бронхиальная астма, патофизиология, протеазы, ремоделирование дыхательных путей

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Cathepsins are found in lysosomes of different cell types, including endothelial cells, vascular smooth muscle cells, and macrophages [1]. These enzymes are secreted as inactive forms (zymogenes) maturating due to a cascade of pathological chemical reactions. Their proteolytic activity partially depends on the balance between proteases and the endogenous inhibitor cystatin C [2]. Over the past two decades, scientists have revealed that it is cathepsins K, L, and S that are highly potent elastases in the cathepsin family [3]. Cathepsin S is able to destroy different components of the basement membrane. Apart from this, it has been demonstrated that it is cathepsin S that is involved in atherosclerosis, angiogenesis, inflammation, rheumatoid arthritis, chronic obstructive pulmonary disease, and bronchial asthma [4]. It is important to note that activity of proteases requires strict regulation, since disturbances in the close interaction between proteases, substrates, and inhibitors may promote progression of different pathologies: both multiple organ dysfunctions and disorders impairing a specific organ [5, 6].

GENERAL CHARACTERISTIC OF CATHEPSINS

International research performed over the past 60 years has demonstrated that proteases make a decisive contribution to the pathophysiology of pulmonary diseases. Initially, these molecules were known as enzymes cleaving the protein with a limited range of substrates [7]. However, modern data have shown that the variety of protease substrates and biological effects induced by their processing is enormous [8, 9].

The cathepsin molecules are a group of lysosomal enzymes, the proteolytic activity of which may manifest both in the intra- and extracellular space. All cathepsins fall into three protease families: serine proteases (A, G), aspartic proteases (D, E), and cysteine proteases (B, C, F, H, K, L, O, S, V, X, and W), amounting to 31%, 25%, and 4% from the total number of cathepsins, respectively [10]. The gene of cathepsin S was found in human chromosome 1q21, and, as all lysosomal cathepsins, it is translated into a prezymogen before transition to the mature and active state [11, 12]. These enzymes are participants of such physiological processes as food digestion, blood clotting, and bone resorption. They are also directly associated with pathogenesis of diseases of almost all organs and systems in the body [8, 12]. The diversity of functions and properties of cathepsins is explained by the specifics of their localization, expression, and regulation.

The ability to irreversibly cleave peptide bonds requires strict regulation of activity of these enzymes. All cathepsins manifest the highest activity in an acid environment particularly characteristic of lysosomes [8, 10]. Moreover, it is known that in-

flammation as a non-specific physiological process is accompanied by development of acidosis, which may lead to an increase in protease activity in the extracellular space. Apart from that, the ability of certain cathepsins to retain proteolytic activity in a neutral environment broadens the spectrum of their activity. Thus, it is known that cathepsins K and H retain activity at pH = 7.4, and the optimal pH for cathepsin S is 6.5 [10, 12]. The regulation of cathepsin synthesis may be carried out at the transcriptional, translational, posttranslational, and epigenetic levels [10]. In particular, methylation of CpG islands, as an example of epigenetic regulation, is typical of cysteine cathepsins [10].

It is important to note that the activity of proteases is strictly regulated by the tissue cytokine profile [5]. The release of active molecules of cathepsin S takes place under the influence of many regulating factors, including such proinflammatory molecules as interleukin (IL)-1β, IL-4, IL-13, and tumor necrosis factor (TNF) α [12]. Disturbances in the close interaction of the studied enzymes with their substrates and inhibitors may promote activation of pathological cascades and progression of different pulmonary diseases, including such mucosal inflammatory diseases as cystic fibrosis, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis (IPF), as well as secondary bacterial infections [13].

It is an important observation that some proteases have limited expression in the body, which defines the specificity of their functions. For example, cathepsin K is specifically localized in osteoclasts, while cathepsins E and S are localized in immune cells [14].

In order to understand the disease pathogenesis, it is also important to know which protein is the substrate in the specific situation. Depending on the cathepsin localization, it is possible to suggest the presence of one substrate or another. Cathepsins are known to possess high collagenolytic and elastolytic activity that plays a special role in tissue remodeling [15].

SPECIFICS OF CATHEPSIN S, ITS ROLE IN BRONCHOPULMONARY PATHOLOGY

In the human body, a large volume of cathepsin S is localized in smooth muscle cells, macrophages, and dendritic cells, which allows for local degradation of the basement membrane and elastic layer in the bronchial and vascular wall. The launch of a cascade of lysosomal pathophysiological reactions activates wall remodeling in small bronchi and progression of atherosclerotic changes in the intima. Activation of the vascular and bronchial endothelium results in deterioration of the comorbid patient's condition, which makes it relatively difficult to determine the primary pathology leading to clinical exacerbation [16].

Studies register a higher level of cathepsin S and its activity in the bronchoalveolar lavage fluid of COPD patients compared with healthy individuals [17]. Apart from that, cathepsin S is a potent elastin-destructing proteinase, which participates in adaptive immune responses. Analysis of COPD pathogenesis in mouse models showed that cathepsin S contributes to damage to pulmonary interstitium and development of pulmonary hyperinflation through destruction of elastic fibers in the lung tissue [18, 19].

Cathepsin S is especially relevant in the context of pulmonary pathology, since its ability to potentiate elastase activity and inactivate protective proteins in the airways induces extracellular matrix remodeling and impairs mucus secretion in a wide pH range. Respiratory acidosis or alkalosis, characterised by alteration of partial pressure of CO_2 in arterial blood due to the change in alveolar ventilation, and, as a result, insufficient removal of CO_2 from the blood are often revealed in such diseases as pneumonia, bronchial asthma, COPD, and adult respiratory distress syndrome [20].

In diseases with high neutrophil counts, registered in patients with bronchopulmonary pathology, a frequent imbalance between proteases and their inhibitors (neutrophil elastase, α_1-antitrypsin, secretory leucoprotease inhibitor, and elafin) is found [6, 21, 22]. The reactions emerging during the antiprotease overload lead to chronic inflammation in the airways determined by mucociliary clearance dysfunction, extracellular matrix remodeling activation, and a decrease in the susceptibility threshold to secondary bacterial infection [23].

INTRACELLULAR FEATURES IN MECHANISMS OF CATHEPSIN S ACTION

Cathepsin S plays an important role in various intracellular processes, including proteolysis and

formation of the immune response mediated by the major histocompatibility complex class II (MHC II) [24]. Biochemically, cathepsin S also differs from many members of the cathepsin family in its ability to retain activity in neutral pH [25].

Upon delivery of the antigen to the endolysosomal pathway, the invariant chain (Ii) of the MHC II is cleaved with formation of a fragment of class II-associated invariant chain peptide (CLIP), which allows for subsequent binding of the exogenous antigen. The proteolytic cleavage of Ii is catalyzed by active cathepsin S and other proteases. The CLIP fragment is then cleaved, moving to the plasma membrane of the antigen-presenting cell to activate CD4+T lymphocytes. Cathepsin S-mediated cleavage of Ii is of key significance not only for the presentation but also for the activation of mobility of dendritic cells [26].

CATHEPSIN S IN THE CONTEXT OF BRONCHIAL ASTHMA PATHOGENESIS

Extracellular cathepsins directly participate in activation of extracellular matrix remodeling through degradation of structural components of the latter: collagen and elastin [27]. The representative of the protease family under study is also noted to possess elastolytic and collagenolytic properties, which makes it possible to consider its elevated expression as a predictor of pulmonary dysfunction development [28, 29].

Studies have shown that patients with bronchial asthma (BA) undergoing therapy with systemic glucocorticoids (GCs) have lower serum level of cathepsin S [30]. Polymorphisms in the molecular structure of the enzyme may define susceptibility of patients to BA development and severity of its progression [31].

The results obtained using animal models have also shown the association between the expression of the protein and allergic BA pathogenesis, as well as atopy in general. High levels of cathepsin S are registered in modeling of eosinophilic inflammation in the airways. The knockout of cathepsin S or preventive introduction of its inhibitor leads to a decrease in the bronchial wall inflammation and limitation of eosinophilia in the bronchoalveolar lavage fluid [32].

Elevation of cathepsin S level leads to skin itching and atopic dermatitis in mice due to binding of protease-activated receptors, such as PAR-2 and PAR-4. Activation of PAR-2-induced maturation of dendritic cells and subsequent differentiation of CD4+T-cells lead to an increase in skin inflammation and chronic scratching of the defects. It is by no means unimportant that the volumes of expired air in the studied mice with allergic BA were significantly lower than those of the control group. This facilitates proteolytic activity of cathepsins, including cathepsin S. Therefore, this enzyme may be associated with inflammation, atopy, and susceptibility to BA and dermatitis [33].

Due to its key role in the antigen presentation pathway, cathepsin S may potentially promote progression of asthma [34]. This thesis is confirmed by a number of preclinical models: the profiles of antigen expression in BALB/c and C57BL/6J mice infected with ovalbumin (OVA), a classical mouse model of allergic pulmonary inflammation, have shown that the expression of the cathepsin S gene were elevated by 4.0 and 3.2 times, respectively [35]. A study researching levels of the protein revealed an increase in cathepsin S in the bronchoalveolar lavage fluid after infecting mice with OVA [36]. Apart from that, treatment of wild-type mice with a reversible inhibitor of cathepsin S reduced inflammation in the OVA-infected mice compared with the levels in the cathepsin S knockout model, which highlights the pharmaceutical ability of protease in this disease [37].

CLINICAL APPLICATION

Considering the whole variety of processes emerging at the molecular level, cathepsin S performs extracellular and intracellular functions that may impact on many physiological changes in the lung tissue and, most importantly, define the trend of pathological and chemical processes in disease progression [38]. A number of recent theoretical studies as well as studies based on mouse models indicate the potential of the enzyme as a predictor of lung tissue deformation and irreversible airway remodeling [39].

Therefore, these features underline the fact that cathepsin S is an ideal target for disease treatment: its strict therapeutic inhibition must minimize the potential adverse effects [40]. Moreover, its higher stability in neutral pH compared with the other members of the cathepsin family highlights its

increased potential for participation in extracellular proteolytic activity [36].

It has been shown that preventive dosage of the irreversible inhibitor of cathepsin S decreases pulmonary eosinophilia in mice, which confirms the hypothesis that inhibition of the enzyme before inflammation in the airways is beneficial in lung tissue diseases. Additionally, foreign studies have shown that the studied molecule participates in later manifestations of the allergic reaction [41].

Our improved understanding of the structure and activity of cathepsin S will lead to explanation of the immunological role of the protein and determination of the therapeutic strategy – extracellular inhibition of cathepsin S aimed at preventing wall remodeling in small bronchi at the earliest stages.

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Kraposhina A.Yu. – conception and design, analysis and interpretation of the data. Sobko E.A. – substantiation of the manuscript, critical revision of the manuscript for important intellectual content. Demko I.V. – final approval of the manuscript for publication. Kazmerchuk O.V. – conception and design. Kacer A.B. – analysis and interpretation of the data. Abramov Yu.I. – analysis and interpretation of the data.

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