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UDK: 616.24-006:612.017.1

SIGNIFICANCE OF OXIDATIVE STRESS MARKER IN BRONCHOPULMONARY PATHOLOGY

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XULOSA

Ushbu sharhning mavzusi Kloto oqsili (KO) va uning bronxopulmonal patologiyaning rivojlanishidagi roli. Kloto oqsili qarishga qarshi protein bo'lib, organizmda ko'p funktsiyalarga ega. Kloto yetishmovchiligi insonning qarishida va xususan, qarish bilan bog'liq ko'plab kasalliklarda rol o'ynaydi. Ma'lumki, Kloto protein darajasi yoshga qarab kamayadi. Bundan tashqari, Klotoning giperfosfatemiya, surunkali buyrak kasalligi, ko'plab yurak-qon tomir kasalliklari, neyrodegenerativ kasalliklar, bir nechta saraton, o'pka fibrozi, o'pkaning surunkali obstruktiv kasalligi (O’SOK), suyak kasalliklari va diabet bilan aloqasi turli mualliflar tomonidan bildirilgan. Bugungi kunga kelib, nafas olish tizimining fiziologiyasi va patologiyasida Kloto oqsilining rolini o'rganishga bag'ishlangan nisbatan kam tadqiqotlar mavjud, ammo so'nggi yillarda bu sohaga qiziqish ortdi. Ushbu sharh maqolasida biz ushbu sohadagi so'nggi yutuqlarni umumlashtirishni, Kloto oqsilining O’SOK va bronxial astma (BA) kabi patologiyalarning rivojlanishiga qo'shgan hissasini muhokama qilishni va kelajakdagi tadqiqotlar istiqbollarini belgilashni maqsad qilganmiz.

Kalit so'zlar: *Kloto oqsili, fibroblast o'sish omili (FGF), bronxopulmonal patologiya, O’SOK, bronxial astma.*

РЕЗЮМЕ

Предметом данного обзора является белок Клото (КЛ) и его роль в развитии бронхолегочной патологии. Белок Клото является антивозрастным белком и выполняет в организме множество функций. Недостаточность Клото, по-видимому, играет определенную роль в старении человека и, в частности, во многих заболеваниях, связанных со старением. Известно, что уровень белка Клото снижается с возрастом. Кроме того, различными авторами сообщалось о связи Клото с гиперфосфатемией, хроническими заболеваниями почек, множественными сердечно-сосудистыми заболеваниями, нейродегенеративными заболеваниями, несколькими видами рака, легочным фиброзом, хронической обструктивной болезнью легких (ХОБЛ), заболеваниями костей и диабетом. На сегодняшний день исследований, посвященных изучению роли белка Клото в физиологии и патологии дыхательной системы относительно немного, но интерес к данному направлению за последние годы возрос. В этой обзорной статье мы стремимся обобщить последние достижения в этой области, обсудить вклад белка Клото в развитие таких патологий, как ХОБЛ и бронхиальная астма (БА) и наметить перспективы для будущих исследований.

Ключевые слова: *белок Клото, фактора роста фибробластов (FGF), бронхолегочная патология, ХОБЛ, БА.*

Klotho protein is an anti-aging protein and has many functions in the body. It is encoded by the Klotho gene, which was first identified in mice in 1997 [1]. The gene received its name in honor of the Greek goddess of fate Clotho spinning the thread of life.The Klotho gene produces two molecules: a membrane-bound form and a circulating form of the Klotho protein. Membrane bound form of Klotho is a coreceptor for fibroblast growth factor 23 (FGF23) [2], and the circulating form is a soluble endocrine mediator with many functions [3]. Klotho deficiency appears to play a role in human aging and, in particular, in many diseases associated with aging. Klotho protein levels are known to decline with age. IN2022year Espuch-Oliver et al. published reference values for this protein for the first time [4]. As it turns out, the age-related decline in serum CL levels appears to be similar in both men and women. Notably, a recent study of American adults found that low serum Klotho levels

correlated with increased mortality from various causes [5]. Klotho has also been reported by various authors to be associated with hyperphosphatemia, chronic kidney disease, multiple cardiovascular diseases, neurodegenerative diseases, several types of cancer, pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), bone diseases and diabetes.

Klotho protein and its functions. Klotho protein is a paracrine and endocrine hormonal factor with an anti-aging effect in many human organs, which has 3 subfamilies: α-klotho, β-klotho and γ-klotho [6]. α-Klotho is highexpressedin the brain, liver and kidneys, β-Klotho is predominantly expressed in the liver, γ-Klotho is expressed in the skin [7]. Recent work also documents CL expression in circulating peripheral blood cells [8]. If no subfamily is specified, the word "Klotho" usually refers to the α-Klotho subfamily, since α-Klotho was discovered before the others [9]. It is known that destruction of the Klotho gene leads to premature multiple organ degeneration and death [11], while overexpression increases lifespan [10]. Members of the Klotho family are important components of the endocrine fibroblast growth factor (FGF) receptor complexes because they are required for the high-affinity binding of FGF19, FGF21, and FGF23 to their cognate FGF receptors (FGFRs). Together, these proteins form a unique endocrine system that controls numerous metabolic processes in mammals. FGF19 is a satiety hormone that is secreted in the intestine upon food intake and binds the β-Klotho–FGFR4 complex in hepatocytes, promoting metabolic responses to feeding. In contrast, under fasting conditions, the liver secretes the fasting hormone FGF21, which induces metabolic responses to fasting and stress responses through activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system after binding to the β-Klotho–FGFR complex in adipocytes and the suprachiasmatic nucleus, respectively. Finally, FGF23 is secreted by osteocytes in response to phosphate and binds to αKlotho–FGFR1c complexes, which are most abundantly expressed in the renal tubules, to regulate mineral metabolism by causing increased phosphate excretion (phosphaturic effect), regulating vitamin D metabolism, and increasing calcium reabsorption [11]. Klotho has significant effects on several biological processes associated with aging and disease. Independent of FGF23, Klotho can inhibit at least four pathways that have been linked to aging in different ways. Klotho blocks or inhibits transforming growth factor β (TGF-β), insulin-like growth factor 1 (IGF-1), nuclear factor κB (NF-κB) and Wnt/β-catenin through the following mechanisms: 1) it binds to the TGF-β receptor β (TβRII component) to block the action of TGF-β; 2) it inhibits the activation of the NF-κB inflammasome pathway by preventing nuclear translocation of the active form; 3) it enhances signaling in the Nrf2 pathway; induces several antioxidant enzymes and inhibits NF-κB; 4) it blocks the transmission of signals from the IGF-1 receptor; it increases FoxO activation and antioxidant responses; 5) it also blocks the activation of the Wnt pathway by binding to soluble Wnt ligands [12]. Considering the fact that all of the above signal transduction pathways are involved in the pathogenesis of many different diseases, the ability of the Klotho protein to inhibit them determines the following functions of this protein: antioxidant and anti-inflammatory activity of Klotho, participation in the prevention of chronic fibrosis, protective effect against cardiovascular diseases, anticancer (tumor suppressor) activity, metabolic regulatory functions related to diabetes mellitus, anti-apoptotic and anti-aging functions (preservation of stem cells), protection against neurodegenerative diseases (Alzheimer's disease, etc.).

Klotho protein in the respiratory tract. A recent study revealed the absence of endogenous Klotho expression in the lungs [13]. Like the myocardium, the lungs rely heavily on circulating Klotho for airway maintenance and protection rather than on their own expression of this protein [13]. The lack of native local production of Klotho does not diminish its biological importance in lung homeostasis or contradict the body of literature overwhelmingly supporting Klotho as essential for lung health. Given the ongoing physicochemical insults imposed on the lungs, it is not surprising that local endogenous cytoprotective mechanisms must be supplemented by circulating factors such as renal-derived Klotho to counteract the toxicity of whole-body waste products carried by the blood and passing through the lungs. Circulating Klotho protects the alveolar endothelium and quickly penetrates the septum to reach the epithelium [14]. Klotho may promote the synthesis and release of NO, thereby enhancing the vasodilatory capacity of blood vessels and airways, protecting against oxidative stress and preserving endothelial function [36]. In lung epithelial cells, Klotho activates the Nrf2 network of antioxidant proteins to reduce cell damage [15]. It has also been shown in vitro and ex vivo that overexpression or supplementation of α-Klotho regulate mucociliary clearance by increasing airway surface fluid volume, improving the activity of large conductance calcium-activated potassium channels, and downregulating IL-8 [16]. In two mouse models, α-Klotho attenuated pulmonary fibrosis by suppressing TGF-β-induced fibroblast activation and extracellular matrix production, as well as by down-regulating vascular endothelial growth factor and TGF-β1/Smad3 signaling [17,18]. Circulating Klotho levels inversely correlate with local oxidative DNA damage in the lungs [19]. It turned out that homozygous hypomorphic mice with αKloto deficiency die at the age of 8-12 weeks. Their lungs are friable, with enlarged air spaces and increased apoptosis [20].These mice exhibit reduced numbers of hematopoietic stem cells and cytoprotective molecules [21], which indicates a decrease in reparative and regenerative capacity. Hemizygous mice deficient in circulating α-Klotho also show age-related oxidative damage and increased air space [15], increased lung compliance and increased apoptosis [22]. In addition, acquired deficiency of circulating α-Klotho, such

as in kidney disease, has been shown to predispose to secondary lung injury [19] and exacerbates concomitant hemodynamic, metabolic and pro-inflammatory factors contributing to pulmonary dysfunction. The same results were obtained in a rat model of renal ischemia-reperfusion injury [23] and severely reduced plasma Klotho levels in which acute lung injury developed rapidly [19]; replenishment of circulating Klotho alleviated pulmonary complications regardless of the severity of kidney damage [19].Thus, as renal α-Klotho production declines with age or disease, an imbalance is created between pulmonary toxin delivery and cytoprotective capacity, predisposing to lung degeneration and dysfunction. Local or systemic diseases, such as diabetes mellitus and cardiovascular disease causing renal failure, further reduce α-Klotho synthesis and accelerate widespread age-related organ degeneration in the lungs, which in turn is associated with physiological changes that lead to decreased function lungs, decreased regeneration and repair, altered airway remodeling, decreased innate and adaptive immune responses, and increased susceptibility to respiratory diseases [24–26]. In addition, it should be noted that primary acute or chronic lung diseases can also secondarily impair kidney function and reduce circulating Klotho levels, thereby exacerbating lung degeneration in a vicious cycle. Thus, circulating delivery of Klotho to the lungs is a likely mechanism for pulmonary and renal crosstalk and explains an important aspect of the interdependence between these two organs. Summarizing all of the above, we can come to the conclusion that a decrease in renal Klotho synthesis, associated with age or pathologies, increases the susceptibility of people to lung damage and, as a consequence, to the development of various bronchopulmonary pathologies [19].

Klotho protein in bronchopulmonary pathology: COPD, asthma. To date, there is a relatively small number of epidemiological and clinical studies devoted to studying the role of Klotho in the pathogenesis of bronchopulmonary pathologies. But the data available from the studies indicate a connection between this protein and pathologies of the respiratory tract. Diseases of the bronchopulmonary tract that occur with obstructive syndrome, such as COPD and asthma, are among the most widespread pathologies of the modern world and their burden on global health is great. COPD is a heterogeneous chronic inflammatory lung disease that manifests clinically later in life and can lead to significant morbidity and premature death [25]. COPD is a common disease in older adults, with cigarette smoking being the greatest risk factor for developing COPD in genetically susceptible individuals [27]. Interestingly, many of the anatomical and physiological changes observed in COPD, such as expansion of the air space resulting from loss of supporting tissue without destruction of the alveolar wall, have also been described in the lungs of nonsmokers of similar age, further illustrating that the aging process is a contributing factor. progression of the disease [25].α-Klotho knockout mice develop COPD and have increased IL-6 expression [28]. A recent study demonstrated for the first time FGF23-induced signaling in the bronchial epithelium and provided new insight into the opposing roles of FGF23 and Klotho in COPD. It has been demonstrated that 1) plasma FGF23 levels are increased in patients with mild to moderate COPD and an inflammatory phenotype with goblet cell hyperplasia, 2) exposure to cigarette smoke in combination with FGF23 induces IL-1β secretion from primary cultures of human bronchial epithelial cells in patients with COPD, 3) cigarette smoke induces an increase in FGFR4 and a decrease in Klotho expression, thereby causing activation of PLCγ/NFAT signaling and inflammation, and 4) the presence of soluble Klotho attenuates tobacco smoke-induced IL-1β secretion [28]. In another report, increased FGF23 levels in patients with COPD were associated with hypophosphatemia, but the mechanism of increased levels and the source of circulating FGF23 were not identified [29]. A recent study in a cohort of US adults found that higher serum α-Klotho levels were associated with a lower likelihood of airflow obstruction and higher pulmonary function scores in adults with and without airflow obstruction, and also with lower numbers of neutrophils and eosinophils in peripheral blood [thirty]. The same results were found in another earlier study of people with interstitial lung abnormalities, in which lower serum α-Klotho levels were associated with lower FEV1, FVC, and carbon monoxide diffusing capacity of the lungs [32]. Finally, the NHANES cross-sectional study, conducted a correlation analysis of serum Klotho levels and fractional exhaled nitric oxide (FeNO) in a sample of 6,527 individuals. They found a positive correlation between serum Klotho levels and FeNO, as well as measures of pulmonary function (FEV1, FVC, FEV25%-75%, FEV1/FVC) [37], which confirms the results of previous studies. Serum α-Klotho levels were also inversely associated with inflammatory biomarkers such as white blood cell count, CRP, and uric acid [33]. In addition, α-Klotho has been shown to play a role in the regulation of autophagy and cellular senescence in smokers [31]. As for bronchial asthma (BA), the role of the Klotho protein in the pathogenesis of this pathology has been studied even less. As we know, asthma is characterized by bronchospasm, airway obstruction and airway swelling. Structural changes, such as subepithelial collagen deposition, hyperplasia of goblet cells and mucous glands, and hypertrophy and hyperplasia of the smooth muscle layer of the airways, indicate that airway remodeling occurs in patients with bronchial asthma [34]. It is believed that the increased airway remodeling and inflammation that occurs in asthma may contribute to the accelerated decline in lung function. Age-associated impairments in innate and adaptive immune responses in the lungs also contribute to increased susceptibility of individuals to asthma exacerbation [25]. As it turns out, the Klotho protein is directly involved in the development of airway hyperresponsiveness. This is due to the fact that Klotho can inhibit the ICE-1 signaling pathway, which in turn leads to a decrease in prolifera-

tion and contraction of airway smooth muscle, a decrease in airway hyperresponsiveness and resistance [35]. In addition, Klotho's ability to inhibit signaling pathways such as Wnt/β-catenin and TGF-β1 has been shown to reduce pulmonary fibrosis in patients with asthma and improve lung function [28], and its ability to inhibit NF-κB nuclear translocation and downstream gene expression leads to suppression of the release of inflammatory mediators such as interleukin-6 and tumor necrosis factor-alpha, which in turn also reduces the level of airway inflammation in patients with COPD and asthma [38].

Thus, Klotho protein is a pleiotropic protein that may have antioxidant and anti-inflammatory properties both throughout the body and in the lungs in particular, but its role in airflow obstruction or lung function and obstructive diseases such as COPD and asthma, is largely unknown. Several experimental studies have shown that Klotho has an effect on lung health and is also involved in the development of bronchopulmonary tract pathologies. Given the plausible role of Klotho in mediating aging and inflammatory processes in the lungs, it can be concluded that higher serum Klotho levels would be associated with higher lung function scores, a lower likelihood of airflow obstruction, and lower levels of atopic and inflammatory markers. and, as a result, with a lower incidence of bronchopulmonary pathology.

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