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LUNGS AS A TARGET FOR VITAMIN D AND PHOSPHATONINES

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Abstract. Vitamin D axis — fibroblast growth factor 23 (FGF23) — the klotho protein plays an important role in ontogenesis and functioning of the respiratory system. There is evidence of the connection of vitamin D with phosphatonines — a complex of phosphatic substances that stimulates the withdrawal of phosphates through the kidneys. Vitamin D receptor (NDR) is found in animal models in virtually all lung cell types. In cells of the airway epithelium, there is not only HDR, but also enzymes that activate and degrade its metabolites. The involvement of vitamin D and the main components of the phosphatonin complex in inflammatory diseases of the respiratory system has been proven. Studying the actions of the $1,25(OH)_2$ — FGF23 — protein klotho system and the control capabilities of this system is key to the development of new therapeutic interventions in pulmonology.

Key words: *vitamin D; respiratory system; fibroblast growth factor — FGF; klotho protein; phosphatonins.*

ЛЕГКИЕ КАК МИШЕНЬ ДЛЯ ВИТАМИНА D И ФОСФАТОНИНОВ

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Резюме. Ось «витамин D — фактор роста фибробластов 23 (fibroblast growth factor, FGF23) — белок klotho» играет важную роль в онтогенезе и функционировании дыхательной системы. Приведены доказательства связи витамина D с фосфатонинами — комплексом фосфатурических субстанций, стимулирующим вывод фосфатов через почки. Рецептор витамина D (ВДР) на моделях животных обнаружен практически во всех типах клеток легкого. В клетках эпителия дыхательных путей существует не только ВДР, но и ферменты, осуществляющие активацию и деградацию его метаболитов. Доказано участие витамина D и основных компонентов комплекса фосфатонинов в воспалительных заболеваниях дыхательной системы. Изучение действий системы «$1,25(OH)_2$ — FGF23 — белок klotho» и возможностей управления этой системой является ключом к разработке новых терапевтических вмешательств в пульмонологии.

Ключевые слова: *витамин D; дыхательная система; фактор роста фибробластов — FGF; белок klotho; фосфатонины.*

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Vitamin D is mainly involved in maintaining phosphorus and calcium homeostasis. However, modern research has revealed it also effects on a number of cellular processes including cell proliferation, differentiation, wound healing, repair and regulatory systems, immunity and inflammation. The active metabolite of vitamin D, 1,25-dihydroxyvitamin D (1,25$(OH)_2$), is known to promote mucosal barrier integrity, destroy pathogens (via induction of antimicrobial peptides), and modulate inflammation and immune responses.

INTRODUCTION

The vitamin D — fibroblast growth factor 23 (FGF23) — klotho protein axis is well known for its role in maintaining phosphorus and calcium homeostasis [1]. The airway mucosa is an important site of local synthesis, degradation and signaling of 1,25$(OH)_2$. The expression of vitamin D receptor by different cell types in the lung and the fact that these cells respond to vitamin D or can locally produce vitamin D, proves that the lungs represent a target for vitamin D action [2]. Vitamin D deficiency is associated with various diseases, including chronic inflammatory lung diseases, namely asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD) [3–5]. Animal model studies have shown that maternal vitamin D deficiency can impair lung development, structure, and function in offspring; it is hypothesized that maternal serum 25(OH)D levels are important for healthy fetal lung development. It may be relevant because associations have been found between the reduced pulmonary function in children and the development of COPD later in life [6]. In addition, 25(OH)D circulating in the mother's body influences the gut microbiota and therefore may indirectly modulate immune responses in the lung via the gut-lung axis [7]. These observations suggest an important role for vitamin D during fetal and postnatal lung maturation and dempnstrate that adequate levels of 25(OH)D may contribute to protection against childhood asthma and, possibly, COPD in older age.

In 1994, the existence of a complex of phosphaturic factors (phosphatonins) was described. They cause phosphate loss by the kidneys. The currently known phosphatonins include fibroblast growth factor (FGF23), matrix extracellular phosphoglycoprotein (MEPE), secreted frizzled related protein 4 (sFRP4), and fibroblast growth factor 7 (FGF7) [8]. The close relationship and mutual influence of phosphatonins and vitamin D have been proven. The role of these metabolites in the pathogenesis of a number of diseases, primarily renal, cardiovascular, and pulmonary diseases, is being intensively studied.

A complex of phosphaturic proteins, the *phosphatonins*, downregulate phosphate balance through direct inhibition of its reabsorption in the proximal tubule and indirectly through suppression of 1,25$(OH)_2$ production in the kidney. There are four components included in the phosphatonin group, FGF23 is the best studied.

FGF23 is predominantly expressed in bone (osteocytes and osteoblasts). FGF23 production is stimulated by multiple factors, including high dietary or serum phosphate levels, parathyroid hormone (PTH), 1,25$(OH)_2$, calcium, iron deficiency, erythropoietin, metabolic acidosis, and inflammatory cytokines. In order to effect phosphorus balance FGF23 requires the co-receptor α-klotho, which is mainly produced in the kidney and the parathyroid gland. As for the kidney, klotho is expressed in distal tubules and less abundantly in proximal tubules. α-klotho is a transmembrane protein that exists both in a membrane-bound form acting as a co-receptor for FGF23 and in a secreted soluble form found in the blood, exerting endocrine and paracrine actions in distant organs [9]. Excessive FGF23 causes hypophosphataemia by decreasing NaPi transport activity and suppressing 1,25$(OH)_2$ production, whereas FGF23 deficiency causes hyperphosphataemia and elevates 1,25$(OH)_2$ levels. α-klotho functions as a co-receptor for FGF23; its production is increased in response to elevated 1,25$(OH)_2$ levels. This protein causes phosphaturia by inhibiting the renal NaPi-IIa transporter [10]. The function of fibroblast growth factor FGF23 is far beyond its canonical function as a regulator of mineral metabolism. FGF23 is implicated in the pathogenesis of several diseases, including chronic complications associated with kidney disease, cardiovascular disease, and obesity-related disorders [11]. The presence of four FGF receptor isoforms in the lung and the ability of FGF23 to stimulate lung cells support the concept that the lung is a target for FGF23, whereas the contribution of klotho remains to be clarified [12].

Matrix extracellular phosphoglycoprotein MEPE administered intraperitoneally causes hyperphosphaturia and hypophosphataemia in mice. MEPE inhibits phosphate uptake by human proximal tubule epithelial cells *in vitro*. In addition, MEPE in-

hibits bone mineralization in vitro. Mice with zero MEPE show increased bone mineralization [13].

In experiments on opossums, *secreted Frizzled related protein 4 (sFRP4)*, has been shown to inhibit sodium-dependent phosphate transport by reducing NaPi-2a content in the brush border membrane of proximal tubules and on the surface of renal epithelial cells. Generally, although sFRP4 dramatically alters phosphate transport in the kidney and possibly the physiology of $1,25(OH)_2$, most data indicate that it plays a minor role in the regulation of phosphate homeostasis [14].

Fibroblast growth factor 7 (FGF7) reduces sodium-dependent phosphate transport in opossum kidney epithelial cells and enhances phosphaturia in rats. A recent study showed that low serum FGF7 levels were observed in children with hypophosphatasia and hyperphosphatemia [15].

VITAMIN D AND PHOSPHATONINS IN RESPIRATORY SYSTEM CELLS

The presence of vitamin D receptor (VDR) in animal models can be detected in the last stages of pregnancy and after birth in practically all types of lung cells — on airway epithelial and smooth muscle cells, on type 2 alveolar cells, on alveolar macrophages, on fibroblasts, as well as on blood cells, including neutrophils, monocytes, NK cells, eosinophils, T- and B-lymphocytes, and mast cells [16]. Recently, it was shown that VDRs are localized in apical bronchial epithelial cells and are completely absent in basal epithelial cells and in vascular endothelial cells [17]. Studies have established the influence of genetic polymorphisms of VDR (BsmI, FokI, TaqI, ApaI) which amplify the risk of development of chronic allergic lung diseases and COPD. At the same time, the study of phenotypic influence of FokI polymorphism of VDR gene on the course of chronic nonspecific lung diseases (CNLD) in children showed no statistically significant association [18].

Due to the presence of the CYP27B1 enzyme, the active form of vitamin D ($1,25(OH)_2$) is synthesized in airway epithelial cells, in stimulated macrophages, and in B-lymphocytes. Restriction of endogenous formation of $1,25(OH)_2$ is apparently accomplished by the presence of the enzyme CYP24A2 in some cells, which converts the active form of vitamin D to the inactive form. CYP24A2 is found in type 2 alveolar cells, in airway epithelial cells; its inactive form has been detected in alveolar macrophages [12].

FGF23 is expressed in adult mouse and human lung tissue [19, 20], although the cell types that produce FGF23 have not yet been identified. There is no consensus on the presence of α-klotho in lung tissue. In humans, this protein is distributed along the airway epithelium [21]. A recent study using specific antibodies showed that the lungs do not endogenously express native α-klotho protein, but rather obtain it from the bloodstream [22].

The currently available information on the nature of the effect of vitamin D, FGF23 and α-klotho on various processes in the lung is presented in Table 1.

Table 1. Overview of the Actions of Vitamin D, FGF23, and α-klotho in the Lung (adopted from [16])

Таблица 1. Роль витамина D, FGF23 и α-klotho в различных процессах, связанных с легкими (адаптировано из [16])

Process	Vitamin D	FGF23	α-klotho
Fetal development	Lung maturation	Structural integrity	Structural integrity "Anti-senescence"
Innate/adaptive immunity	Positive modulation	Not known	Not known
Infection	Modulation phagocytosis Antibacterial Antiviral Antimicrobial	Not known	Not known
Inflammation	Anti-inflammatory	Pro-inflammatory	Anti-inflammatory
Oxidative stress	Antioxidant	No action	Antioxidant
Remodeling/damage	Antifibrotic Antiproliferative Antiprotease	Antifibrotic	Antifibrotic
Epithelial barrier	Maintenance integrity	Not known	Not known

ROLE OF VITAMIN D AND PHOSPHATONINS IN THE DEVELOPMENT OF LUNG IN ONTOGENESIS

The fetus does not produce 25(OH). 25(OH) passes through the placenta. The placenta absorbs 25(OH) by endocytosis. An important component of calcium homeostasis during pregnancy is calcitonin. It promotes transcription of the CYP27B1 gene and may therefore be a key determinant of placental vitamin D metabolism. 25(OH) is transformed into both inactive 24,25-dihydroxyvitamin D_3 and active 1,25-dihydroxyvitamin D ($1,25(OH)_2$) in the placenta, consequently, these metabolites release into both maternal and fetal circulation [23]. Vitamin D supply to the fetus does not solely depend on maternal vitamin D status but on placental functioning as well.

Transfer of 25(OH) through the placenta mainly occurs during the last trimester, meaning that preterm newborns are particularly at risk of vitamin D deficiency.

The effect of low maternal vitamin D levels during pregnancy and its role in fetal lung development and maturation, as well as susceptibility to lung disease in the postnatal period, is currently being investigated. This issue is very relevant as hypovitaminosis D is common in pregnant women and newborns.

The presence of VDR in fetal lungs during the last quarter of pregnancy and the activation of vitamin D regulatory enzymes just before birth confirm the potential role of vitamin D in the late stage of normal fetal lung development [24]. The appearance of VDR during gestation coincides with the time of the onset of type 2 pneumocyte differentiation and the beginning of surfactant secretion, typical signs of lung maturation. In vitro studies on fetal rat lung cultures and freshly isolated cells have shown that exogenous $1,25(OH)_2$ accelerates functional maturation of type 2 pneumocytes by decreasing their glycogen content and increasing surfactant synthesis and secretion. Type 2 alveolar cells were actually identified as specific targets for $1,25(OH)_2$ during fetal lung maturation, as these cells responded to exogenous $1,25(OH)_2$ by increasing VDR expression. Fetal lung fibroblasts do not express VDR, but they are able to convert $25(OH)D_3$ to $1,25(OH)_2$, unlike type 2 alveolar cells [12].

Several studies have shown that maternal vitamin D deficiency during pregnancy is associated with postnatal lung function impairment after birth [25], in particular with an increased risk of asthma. Moreover, low levels of 25-hydroxyvitamin D in cord blood of preterm newborns have been associated with an increased incidence of respiratory infections in infancy [26]. However, these data require verification. The association between vitamin D administration during pregnancy and the risk of bronchial asthma in born children was not confirmed at 6-year follow-up [27]. In a study to determine the association of vitamin D levels with endogenous microbial peptides (cathelicidin LL-37 and HBD-2) in congenital pneumonia in preterm newborns, it was shown that low vitamin D concentration may be associated with congenital pneumonia. Vitamin D levels may also predict the need for artificial ventilation and the duration of hospitalization for congenital pneumonia in preterm newborns [28].

It is not known whether fetal lungs can be a target for FGF23. However, experimental data do not allow us to deny the role of FGF23 and klotho in lung development. Indeed, mice lacking FGF23 develop emphysema that appears as early as 3 weeks of age and resembles emphysema found in an aged population, consistent with the premature aging phenotypes in these mice. Vitamin D has been shown to partially mediate this process. The first signs of emphysematous in homozygous mutant klotho (KL-/-) mice began to appear at 4 weeks of age and progressed with age until premature death at 8 to 10 weeks of age. Taken together, these data indicate that FGF23 plays an important role in premature lung aging and that klotho gene expression is important for maintaining lung integrity in the postnatal period [12].

ROLE OF VITAMIN D AND PHOSPHATONINS IN RESPIRATORY SYSTEM PATHOLOGY

The production of biologically active $1,25(OH)_2$ is tightly regulated to maintain optimal levels of calcium (Ca^{2+}) and phosphate (PO_4^{2} — PO_4^{2}) for bone mineralization, whereas locally produced (autocrine) $1,25(OH)_2$ in mucosal tissues, and signal transduction may be increased or decreased under the influence of inflammatory mediators, pathogens or inhaled toxins [29]. It may be important since the airway mucosa of patients suffering from chronic inflammatory lung disease is constantly exposed to these factors [30].

The anti-inflammatory effects of vitamin D in the lungs have been proven by studies on cells derived from animals and from human lavage fluid *in vitro*. After dendritic cells, alveolar macrophages, epithelial and smooth muscle cells of

the airways were affected by various stimuli, they reduced the production of proinflammatory cytokines and chemokines under the influence of vitamin D. Anti-inflammatory contribution of vitamin D *in vivo* have been proven in animal models. Vitamin D deficiency aggravates and prolongs lung inflammation, increases amounts of neutrophils in bronchoalveolar lavage after inoculation with *Aspergillus fumigates* [31], as well as with exposure to cigarette smoke [32]. The fact that intratracheal administration of vitamin D in mice had a more pronounced anti-inflammatory effect than oral administration seems to be practically important [16].

The role of FGF23 in the development of lung inflammation and the anti-inflammatory properties of α-klotho are reflected in few studies. Plasma FGF23 levels are elevated in lung diseases characterized by chronic inflammation, such as cystic fibrosis [33] and COPD [34].

Patients with COPD had elevated plasma FGF23 levels which coincided with high levels of inflammatory cytokines in lung and plasma and positively correlated with serum IL-6 levels. However, FGF23 levels were not correlated with disease severity. The authors attribute it to a "burnout" when the residual mass of viable pulmonary epithelium, which serves as a target for FGF23/klotho action, decreases. Thus, changes in the FGF23/klotho correspondance may serve as a marker of the disease, but to a less extent as a marker of its severity [35].

In patients with cystic fibrosis, elevated plasma FGF23 levels were combined with TGF-β-mediated airway inflammation. The proinflammatory role of FGF23 in lung disease can be considered proven; meanwhile there is evidence that klotho has anti-inflammatory activity. Overexpression or supplementation of klotho was able to reduce IL-8 secretion induced by TGF-β and FGF23 in bronchial epithelial cells of cystic fibrosis patients. Blocking klotho in bronchial epithelial cells resulted in increased formation of inflammatory cytokines such as IL-6, IL-8 and MCP-, which points to a role of endogenous klotho in human bronchial inflammation [33].

The klotho protein provides a protective effect against chronic inflammation and therefore may slow the progression of lung diseases characterized by chronic inflammation. This is proved by the following facts. Patients with idiopathic pulmonary fibrosis or COPD have low plasma levels of soluble klotho and high levels of FGF23[34]. α-klotho secretion is decreased after exposure to cigarette smoke on bronchial epithelial cells derived from COPD patients [21, 35]. The expression of α-klotho is reduced in the lungs of healthy smokers compared to nonsmokers [21], as well as in primary interstitial lung fibroblasts from patients with idiopathic pulmonary fibrosis [34]. A significant association between serum klotho level (s-klotho) and well-known biomarkers of inflammation — uric acid, C-reactive protein, leukocyte number and average platelet volume have been found. The correlation between uric acid and s-klotho was the strongest among four markers. The level of s-klotho implies a general inflammatory status; therefore, s-klotho serves as a potential biomarker that inversely correlates with inflammatory conditions [36].

The antibacterial properties of vitamin D have been demonstrated in several studies showing its ability to participate in the destruction of Gram-negative bacteria (untyped *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Bordetella bronchiseptica*) in respiratory epithelial cells [37].

Vitamin D can enhance antimicrobial defense by stimulating the production of antimicrobial peptides such as cathelicidin (LL-37). These antimicrobial peptides contain a vitamin D-sensitive element in the promoter region of their genes and are activated upon vitamin D stimulation. Several *in vitro* studies have confirmed that vitamin D enhances cathelicidin expression in human bronchial epithelial cells (NHBE, 16HBE) derived from donors and COPD patients [38], as well as in alveolar macrophages from smokers and nonsmokers [39]. These data indicate that bacterial or viral infection in lung tissue is probably a potential target for vitamin D, which may contribute to pathogen elimination and reduction of an inflammatory response. No studies could be found to answer the question whether infection in the respiratory system could be a target for FGF23 or klotho.

Some *in vitro* and *in vivo* studies have shown that vitamin D can influence oxidative stress in the lungs. A mouse model of asthma demonstrated that vitamin D normalizes elevated levels of malonic dialdehyde and reduces superoxide dismutase and glutathione activities to control levels. It also increases levels of NF-E2-related factor 2 (Nrf2), a cellular sensor of oxidative stress associated with transcriptional activation of antioxidant response element genes. Moreover, Vitamin D reduces oxidative DNA damage and regulates cellular apoptosis [40]. FGF23 itself is not

involved in protection against oxidative stress, unlike α-klotho, which can directly protect human lung epithelial cells (A459 and primary alveolar type I cells) from oxidative damage and apoptosis induced by hyperoxia and phosphotoxicity by reducing lipid and protein content [41].

Vitamin D probably plays an important role in maintaining the epithelial barrier integrity in the lung. Studies on the bronchial epithelial cell line 16HBE showed that vitamin D is able to counteract cigarette smoke-induced epithelial barrier breakdown by preventing a decrease in transepithelial electrical resistance, increased permeability, and degradation of E-cadherin and β-catenin [42]. It is indicative that vitamin D also increases the expression of transmembrane conductance regulator in human bronchial epithelial cells in cystic fibrosis. This effect was also observed after local administration of vitamin D in vivo by intranasal administration to mice [43]. Whether FGF23/klotho can affect the integrity of the lung epithelial barrier remains to be elucidated.

CONCLUSIONS

Vitamin D is essential for the development of the respiratory system during gestation. Vitamin D has mainly beneficial effects on the lung in the postnatal period, they include immunomodulatory, anti-inflammatory, anti-infectious and antioxidant effects, as well as maintenance of airway structure and epithelial barrier integrity. One of the aspects that is still poorly understood is the ability of some lung cells to respond to exogenous vitamin D and/or to produce active vitamin D. More research is needed, since local direct administration of active vitamin D could enhance the beneficial effects in the respiratory pathology.

In vitro and animal studies show that FGF23 acts as a deleterious agent, increasing inflammation in a variety of chronic lung diseases. Many of these effects are counterbalanced by klotho, which clearly protects the lung from inflammation, oxidative stress, and apoptosis. Studying the "$1,25(OH)_2$ — FGF23 — klotho" system and its possibilities to control this system may be a key to the development of new therapeutic interventions in pulmonology.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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