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Characteristics of matrix metalloproteinases and their role in embryogenesis of the mammalian respiratory system

Charakterystyka metaloproteinaz macierzy zewnątrzkomórkowej i ich rola w embriogenezie układu oddechowego ssaków

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Summary: The human respiratory system appears as an outgrowth from the ventral wall of the primary foregut and its development includes a series of subsequent processes, dependent on the interactions between endothelial cells, respiratory epithelium and extracellular matrix (ECM). These interactions determine the acquisition of normal structural and functional features of the newly created tissues. The essential role in the morphogenesis of the respiratory system is performed by matrix metalloproteinases (MMPs). MMPs are endopeptidases containing zinc ion in their active center, necessary for the processes of hydrolysis of peptide bonds of substrates. The production of MMPs takes place in most connective tissue cells, leukocytes, macrophages, vascular endothelial cells as well as in neurons, glial cells and in tumor cells. Like other proteolytic enzymes, MMPs are produced and secreted in the form of inactive pro-enzymes, and their activation occurs in the extracellular space. MMPs perform both physiological and pathological functions during tissue modeling and their role in embryogenesis is based on the regulation of angiogenesis processes, stroma formation and cells migration. This article aims to characterize, discuss and demonstrate the activity and the role of MMPs in the subsequent stages of respiratory development.

Keywords: **matrix metalloproteinases, stromelysin-1, tissue inhibitors of metalloproteinases, lung development, respiratory system**

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Abbreviations: **cAMP** – cyclic adenosine monophosphate, ***CAs*** – catecholamines, **CXCL 8** – chemokine (C-X-C motif) ligand 8, **DPPC** – dipalmitoylphosphatidylcholine, **ECM** – extracellular matrix, E**GF** – endothelial growth factor, **EGF-r** – receptor of endothelial growth factor, **EMMPRIN** – extracellular matrix metalloproteinase inducer, **FGF** – fibroblast growth factor, **GPI** – glycosylphosphatidylinositol, **IFN-β** – β-interferon, **IL-1β** – interleukin 1β, **IL-4** – interleukin 4, **IL-6** – interleukin 6, **IL-10** – interleukin 10, **IκB-α** – inhibitor of nuclear factor kappa B alpha, **LPS** – lipopolysaccharide, **LAP** – latency associated protein, **MMPs** – matrix metalloproteinases, **mRNA** – messenger RNA, **MT-MMPs** – membrane-type-MMPs, **NF-κB-α** – nuclear factor kappa B alpha, **PC** – phosphatidylcholine, **PDGF** – platelet derived growth factor, **PG** – phosphatidyl glycerol, ***PI*** – phosphatidylinositol, **RA** – rheumatoid arthritis, **TGF-β** – transforming growth factor β, **TIMPs** – tissue inhibitors of matrix metalloproteinases, **TK** – tyrosine kinase, **TNF-α** – tumor necrosis factor-α, **VEGF** – vascular endothelial growth factor, **VEGF-r** – receptor of vascular endothelial growth factor.

INTRODUCTION

The first enzyme from the group of matrix metalloproteinases (MMPs) was discovered in the tadpole tail more than 50 years ago. Until now, more than 20 enzymes from the MMPs group have been recognized. They play a role in initiating and regulating inflammatory processes and carcinogenesis, and also play a significant role in embryogenesis and the maturation of organs, including lungs [21, 25, 70].

In human pathophysiology, the most important role is played by gelatinases, MMP-2 and MMP-9 and their tissue inhibitors (TIMPs) – TIMP-1 and TIMP-2. Other MMPs, like stromelysin-1, referred to as MMP-3, are involved in the activation of gelatinases and regulate their biological activity. The main substrate of gelatinases is type IV collagen, which is an important component of the basal membrane of the vascular endothelium.

Local degradation of the basal membrane is necessary in the migration of cells into and out of the vascular bed. The possible results of this process may be the formation of tumor metastases, propagation of the inflammatory process and the regulation of embryogenesis [9, 16, 21, 26].

At each stage of lung development, the differentiation of individual elements of the respiratory system is dependent on the interaction between endothelial cells and respiratory epithelium and extracellular matrix (ECM). These interactions enable the acquisition of normal, both structural and functional, features by the lung-forming tissues. They are largely dependent on the activity of MMPs, which play an important role in the morphogenesis of not only the lungs, but also all tissues of the developing organism [36, 72].

CHARACTERISTICS OF MATRIX METALLOPROTEINASES

Biochemically, MMPs are endopeptidases that act mainly extracellularly, containing in their structure active zinc ions. They also have the ability to hydrolyse all the proteins of ECM and perform an important function in its physiological and pathological modeling. The production of MMPs takes place in most connective tissue cells, leukocytes, macrophages, vascular endothelial cells as well as in neurons, glial cells and in tumor cells [21, 25, 70].

The constant components of MMPs are the following: a propeptide (whose task is to inhibit catalysis by blocking the active center of the enzyme) and a catalytic domain with zinc ion, allowing hydrolysis of peptide bonding of substrates [49]. Other elements, such as the hinge region or the hemopexin-like domain, do not appear in all MMPs [53].

The regulation of MMPs activity, present in the extracellular space, is under constant control by TIMPs, creating non-covalent complexes in the ratio 1:1 with MMPs and block the attachment of substrates [14, 25]. The most important role in mammalian physiology and pathology is attributed to TIMP-1, TIMP-2 and TIMP-3 [15].

TIMP-1 has the ability to inhibit most MMPs; however, it has the most significant effect on MMP-3 and MMP-9. The weakest affinity is demonstrated for MT-MMPs [76]. It has the structure of an alkaline glycoprotein with a molecular mass of 28 kDa and consists of 184 amino acids. It is composed of two domains, one of which is the N-terminal domain, which has the ability to bind to the active center of MMPs [62]. The structure of TIMP-1 is coded by the gene located on the X chromosome (Xp11.23-11.4), and the possible variability of its molecular weight depends on the amount of carbohydrate moieties. TIMP-1 has an inducible expression mechanism [4]. Erythropoietin, TNF-a, IL-1ß and such growth factors as epithelial (EGF) and platelet-derived (PDGF) have stimulating effects on its synthesis [15]. Factors that induce TIMP-1 expression also include TGF-ß, which undergoes a TIMP-1 inhibitory effect by negative feedback, whereby TIMP-1 limits the effect of TGF-ß on its own expression [76]. The essential function of TIMPs is to inhibit the activity of MMPs by forming non-covalent bonds with them. TIMP-1 binds with both the latent and the active form of MMP-9 [14, 15]. It has been shown that TIMP-1 stimulates erythropoiesis through direct effects on erythropoietic cells [34]. TIMP-1 also has, independent of the inhibition of MMPs, a stimulating effect on cell division occurring in keratinocytes, chondrocytes, fibroblasts, epithelial cells and tumor-transformed cells [76]. The effect of TIMP-1 on the CD63 receptor, located on the surface of cells, has antiapoptotic effects [76].

TIMP-2 is a soluble protein consisting of 194 amino acids with a molecular weight of 21 kDa. Unlike TIMP-1, TIMP-2 is constitutively expressed [50]. In its structure, it contains

two domains common to all TIMPs family proteins, i.e. a C-terminal domain, responsible for combining an inhibitor with a hemopexin-like MMP fragment, and an N-terminal domain that binds to the active center of MMPs. It does not contain carbohydrate moieties in its structure [7]. TIMP-2 has the ability to bind with both the active and inactive forms of MMP-2 and exerts an activating action on pro-MMP-2. In *in vitro* studies, TIMP-2 blocks the activity of both MMP-9 and MMP-2 [69]. Studies demonstrate the effect of TIMP-2 on the induction of mitogenesis dependent on the growth factors, probably by affecting membrane receptors and inducing the secondary transmitters, such as adenosine monophosphate (cAMP) and tyrosine kinase (TK) [46, 50].

TIMP-3 is an insoluble protein with a molecular weight of 30 kDa, which is present in the ECM. It has an N-terminal domain, but, characteristically, it has no C-terminal domain. Its structural homology between TIMP-1 and TIMP-2 is small, 37% and 42%, respectively [71]. TIMP-3 has the lowest of all TIMPs inhibitory activity for MMP-2, -3, -7 and -9 and has anti-angiogenic activity, limiting the ability of vascular endothelial cells to migrate, and activity enhancing their apoptosis [18, 71]. The proapoptotic effect of TIMP-3 is probably related to the stabilization of the cell structure of the Fas receptor and TNF-a. TIMP-3 has an inducible expression mechanism [23, 83]. By inhibiting the activity of most collagenases, gelatinases and matrilysines, TIMP-3 also plays an important role in controlling the ECM degradation that occurs during lung development [35].

The regulation of biological activity of MMPs is analogous to the regulation of the activity of other proteolytic enzymes. The activity depends on the following: gene transcription, TIMPs activity and proenzyme activation. The ability to initiate the expression of MMPs is demonstrated by many biological factors, among which IL-1ß, TNF-a, interleukin 6 (IL-6), CXCL-8, lectin and the extracellular inducer MMPs (EMMPRIN) are distinguished [79]. Expression of MMP-9 is reduced by interleukin 4 and 10 (IL-4, IL-10), interferon-ß (IFN-ß), glucocorticoids and retinoids [68]. The synthesis of MMP-3 increases in the presence of bacterial lipopolysaccharide (LPS), while it decreases as a result of inhibited activity of the nuclear NF-kappa-B type α transcription factor (NF-κB-α) via its inhibitor (IκB-α), demonstrating the type of expression similar to MMP-1 [65].

Expression of MMP-9 occurs in leukocytes, fibroblasts, keratinocytes, vascular endothelial cells, microglial cells and dendritic cells, as well as in tumor cells, showing an inducible expression [45]. MMP-2 expression is present in smooth muscle cells and microglia, adipocytes, astrocytes, macrophages and vascular endothelial cells, and is characterized as constitutive expression [55, 74]. MMP-3 is synthesized in neutrophils, vascular endothelial cells, astrocytes, and neurons, and it is subjected to constitutive or inducible expression, depending on the cell type [60].

MMPs are secreted in the form of inactive proenzymes into the extracellular space [67]. Gelatinase activation may

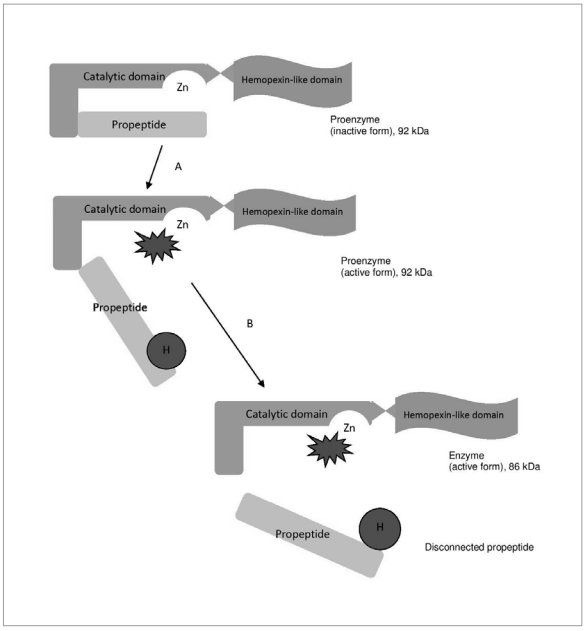

Fig. 1. Diagram of the structure and activation of the MMP proenzyme (on the example of MMP-9). The domains present in the gelatinases are: propeptide, a catalytic domain with a zinc atom (Zn), a hinge region and a hemopexin-like domain. A – non-proteolytic activation using, for example, mercury (Hg) compounds or some denaturing compounds. During this process, there is no disconnection of the propeptide (no change in mass in relation to the proenzyme). If the propeptide activating agent is removed, the propeptide rejoins the active site preventing catalysis ("cysteine switch"). B – proteolytic activation involves the detachment of the propeptide. It is an irreversible process associated with a reduction in the mass of the enzyme by the mass of the propeptide

take place in two stages. The first step takes place according to the principle of a "cysteine switch," it is reversible and does not involve a permanent detachment of the propeptide [28, 43, 45]. This process also takes place during the in vitro experiments, causing the formation of MMPs with a mass equal to proenzymes to exhibit catalytic activity [48, 81]. The second step in the activation of MMPs is the irreversible process of detachment of the propeptide, which is catalyzed by proteolytic enzymes. As a result, it reduces the molecular weight of the enzyme by the mass of the propeptide [61]. The activation of pro-MMP-9 is performed *in vitro* in the presence of MMP-2, -3, -10, -13 and cathepsin G, α-chymotrypsin and trypsin [41]. The activation of pro-MMP-3 is mediated by plasmin, whereas in vivo activation of pro-MMP-2 is a complex process involving the interaction of a proenzyme with the cell surface, where the MMP-14/TIMP-2 complex or the 1-ß integrin receptor influences directly the pro-MMP-2 activation [45 ,47]. Due to the presence of zinc atoms in the active center, MMPs activity may be blocked by chelating agents as well as by tetracycline antibiotics and hydroxyamates [52, 80].

MMPs are similar to each other, both functionally and structurally, but the differences between them have become the basis for the isolation of smaller groups such as collagenases, gelatinases, stromelysines, matrilysines,

membrane type MMPs (MT-MMPs) and other MMPs, not qualified for previous groups [25].

COLLAGENASES (MMP-1, -8, -13, -18)

From the structural point of view, collagenases contain the hemopexin domain connected to the catalytic domain. They have the ability to degrade almost all subtypes of collagen and aggrecan, fibronectin and entactin [54]. They are characterized by a significant capability for hydrolysis of superhelix of collagen at about ¾ chain length, or more precisely, between Gly775 - Ile776 α1 chain and Gly775- Leu776 2 [1].

GELATINASES (MMP-2, -9)

The name "gelatinases" is derived from their ability to catalyze the degradation of gelatin, which is a partially denatured collagen [8]. The molecular weight of latent form MMP-2 (pro-MMP-2) is 72kDa, whereas the mass of pro-MMP-9, which is a glycoprotein, is 92kDa [68, 87]. The molecular weights of proteolytically activated enzymes are 66 kDa and 86 kDa for MMP-2 and MMP-9, respectively. Gelatinases have additionally a hydrophobic fragment resembling the structure of fibronectin, involved in combining the enzyme with gelatin, and MMP-9 also has a small domain resembling V-type collagen [49].

An important substrate of gelatinases is type IV collagen, which is a part of the basal membrane of the vascular endothelium. Owing to its ability to degrade, gelatinases are involved in the migration of cells from and into the vascular bed. In addition, gelatinases sequester fibronectin, elastin, laminin and aggrecan. MMP-2 and MMP-9 have the ability to proteolytic activation of proinflammatory cytokines, such as interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α) and chemokine CXCL-8 [68]. This feature, together with the possibility of degradation of proteins that are part of the basal membrane of endothelium, contributes to the fact that gelatinases are mediators of inflammatory reactions.

STROMELYSINES (MMP-3, -10, -11)

MMP-3 resembles gelatinases with its structure. In addition to the constant elements typical of all MMPs, the enzyme has a hemopexin-like domain along with the hinge region [85]. The list of MMP-3 substrates is similar to gelatinases substrates, including many ECM proteins [45]. MMP-3 may activate other pro-forms of MMPs, i.e. pro-MMP-1, -3, -7, -8, -9, -13; therefore, the presence of MMP-3 affects the increase of the extracellular protein degradation rate not only by MMP-3 alone, but also by activating, for example, pro-MMP-9. Some studies indicate the presence of MMP-3 substrates also within the cytoplasm and cell nucleus, indicating the possible role of the enzyme in apoptotic processes, the regulation of gene expression and cytoskeleton modeling [16].Currently, MMP-10 does not have a specific characterization. It is known that it shows an 85% similarity to MMP-3 in the amino acid composition of the catalytic domain and has a similar substrate spectrum. It has an effect on the development and maturation of the skeletal system and plays a role in angiogenesis [6]. MMP-11 has little activity against ECM molecules [63]. The gene coding for MMP-11 is located on the 22nd chromosome, while the genes encoding MMP-3 and MMP-10 are located on the 11th chromosome. MMP-11 in its structure, on the C-terminal fragment of the propeptide, has a furin recognition motif RX (R/K) R, which makes it able to be activated intracellularly [92]. The MMP-11 isoform of 40 kDa molecular weight (β-stromelysin-3), which is located in the placenta cells, is devoid of pro-domains and signal peptides. So far, the biological function of this enzyme has not been discovered [64].

MATRILYSINES (MMP-7, -26)

Matrilysines, also called endometalloproteinases, are the smallest group of MMPs. From the structural point of view, they lack the hemopexin domain. Their catalytic activity includes the degradation of fibronectin, fibrinogen, as well as collagen type IV. They are a marker of the level of malignancy of lung and breast tumors in humans and a rapid increase in their expression positively correlates with the tumor's ability to form metastases [11, 32, 53]. MMP-7 has a proven role in the pathophysiology of atherosclerosis and heart failure, by its enzymatic destabilization of atherosclerotic plaque [91].

MEMBRANE TYPE OF MMPS – MT-MMPS (MMP-14, -15, -16, -17, -24, -25)

MT-MMPs include a group of enzymes structurally and functionally linked to cell membrane elements, some of which are macromolecules belonging to type I membrane proteins (MMP-14, MMP-15, MMP-16, MMP-24), while others, such as for example, MMP-17 and MMP-25 are proteins associated with glycophosphatidylinositol (GPI). MMP-14 plays a significant role in the process of angiogenesis, while other enzymes, besides MMP-17, are essential in the activation of MMP-2 [91].

OTHER MMPS (MMP-12, -19, -20, -21, -28)

This group includes enzymes that, based on their structure and their biological functions, have not been classified in other groups. Some of them, such as enamelysin (MMP-20), are necessary in the process of embryogenesis of tooth enamel. The inhibition of the activity of enamelysin in the early stages of development may result in congenital enamel hypoplasia [56]. MMP-19 has been detected in synovial vessels affected by the inflammatory process in the course of rheumatoid arthritis (RA) [17], whereas epilysin (MMP-28) present in keratinocytes is attributed to the hemostasis process [58].

MAMMALIAN RESPIRATORY SYSTEM DEVELOPMENT AND THE ROLE OF METALLOPROTEINASES

Stages of mammalian respiratory system development

Table 1. Matrix metalloproteinases, their substrates and tissue inhibitors [15, 82, 91, 93]

Matrix metalloproteinases	Name	Substrates	Dominant types of tissue inhibitors
MMP-1	collagenase 1	collagen type I, II, III, V, VII, VIII, X gelatine, entactin, aggrecan	TIMP-1, TIMP-3
MMP-2	gelatinase A	collagen type I, IV, V, VII, X, XI, XIV, gelatine, elastin, fibronectin, laminin, aggrecan	TIMP-2, TIMP-3, TIMP-4
MMP-3	stromelysin 1, proteoglycanase	collagen type III, IV, V, IX, X, XI, elastin, laminin, fibronectin, aggrecan, gelatine, proMMP-1, -8, -9	TIMP-1, TIMP-3
MMP-7	matrilysin, metalloendopeptidase	collagen type IV, X, gelatine, laminin	TIMP-1, TIMP-3
MMP-8	collagenase 2	collagen type I, II, III, V, VII, VIII, X, proteoglycans, fibronectin	TIMP-3
MMP-9	gelatinase B	collagen type IV, V, VII, X, XIV, gelatine, aggrecan, elastin, entactin, fibronectin	TIMP-1, TIMP-2, TIMP-3, TIMP-4
MMP-10	stromelysin 2	collagen type III, IV, V, gelatine, casein, elastin, laminin, aggrecan, fibronectin	TIMP-1, TIMP-2
MMP-11	stromelysin 3	collagen type IV, fibronectin, laminin, aggrecan, casein, gelatine	TIMP-1, TIMP-2, TIMP-3
MMP-12	elastase, macrophage metaloelastase	collagen type IV, elastin, gelatine, fibronectin, vitronectin, laminin	TIMP-3
MMP-13	collagenase 3	collagen type I, II, III	TIMP-1, TIMP-2, TIMP-3

The human respiratory system appears to be an outgrowth from the ventral wall of the primary foregut. When the embryo is about 4 weeks old, the respiratory diverticulum appears, which then widens longitudinally and forms two tracheoesophageal ridges [22, 89].

The endodermal lining of the tracheoesophageal ridges creates tracheal and bronchial glands and the epithelium of larynx, trachea, bronchi, bronchioles and alveolus. Subsequently, tracheoesophageal ridges fuse to form the tracheoesophageal septum and then the trachea and lung buds, which at the beginning of the 5th week of development, are divided into 2 endodermal bronchial buds and, penetrating into the pericardioperitoneal canals, they form two pleural cavities. By dividing the right bronchial bud into three main bronchi and the left bronchial bud into the two main bronchi, three right lobes and two left lobes of lungs are formed, respectively [22, 75, 78, 89].

The primary bronchi undergo dichotomous division, which results in segmental bronchi that are subject to further division. Up to the 24th week of fetal life, there are 17 divisions of the bronchial tree, which, after additional 7 divisions occurring after birth, assumes the final shape [75].

Lung development occurs essentially in 5 stages that can overlap slightly. Stage 1 – the embryonal phase lasts from the 4th to the 6th week of development, and includes the formation and maturation of the tracheoesophageal ridges until the bronchopulmonary segments of the lung are formed. Stage 2 – the pseudoglandular phase lasts from the 6th to the 16th week of development, includes the dichotomous division of the primary bronchi. Around the 6th week of intrauterine life, the main and segmental bronchi are shaped, while around the 7th week, pulmonary blood vessels are shown along the bronchi. Breathing movements are evident around the 8th week of intrauterine life [10, 20, 37, 75, 78]. Stage 3 – the tubular phase lasts from the 16th to 27th week of pregnancy, is characterized mainly by intensive development of pulmonary blood vessels, which is accompanied by the development of bronchioles, alveolar ducts and pneumocytes type I and II. Around the 24th week of fetal life, the synthesis of surfactant by type II pneumocytes begins. There is an intensive proliferation of the bronchial epithelium and respiratory muscle cells from the endoderm. At this stage of lung development, limited gas exchange is already possible [10, 20, 37, 78]. Stage 4 – the saccular phase begins at the 28th week of fetal life, lasts up to the 36th week of gestational age. This stage includes the formation of terminal sacs and intensive development and maturation of type II pneumocytes, in which between the 28th and 32nd week of pregnancy the most intense synthesis of surfactant occurs.

The blood-air barrier becomes thinner as a result of thinning of the respiratory epithelium, thus creating increasingly better conditions for gas exchange [10, 20, 37, 90]. Stage 5 – the follicular phase lasts from the 36th week of fetal life up to the age of 8 years. After delivery, the first air inhalation is accompanied by the expansion of the primitive alveoli and their transformation into mature alveoli. The lungs of the newborn consist of approximately 50 million alveoli, the number of which increases systematically to reach the final amount of about 300 million at the age of 8 years [40, 75, 84].

The development of fetal lungs depends on many factors, both physical and biochemical. Adequate space in the uterine cavity, proper production of amniotic fluid, stimulation of breathing movements and proper tension of the

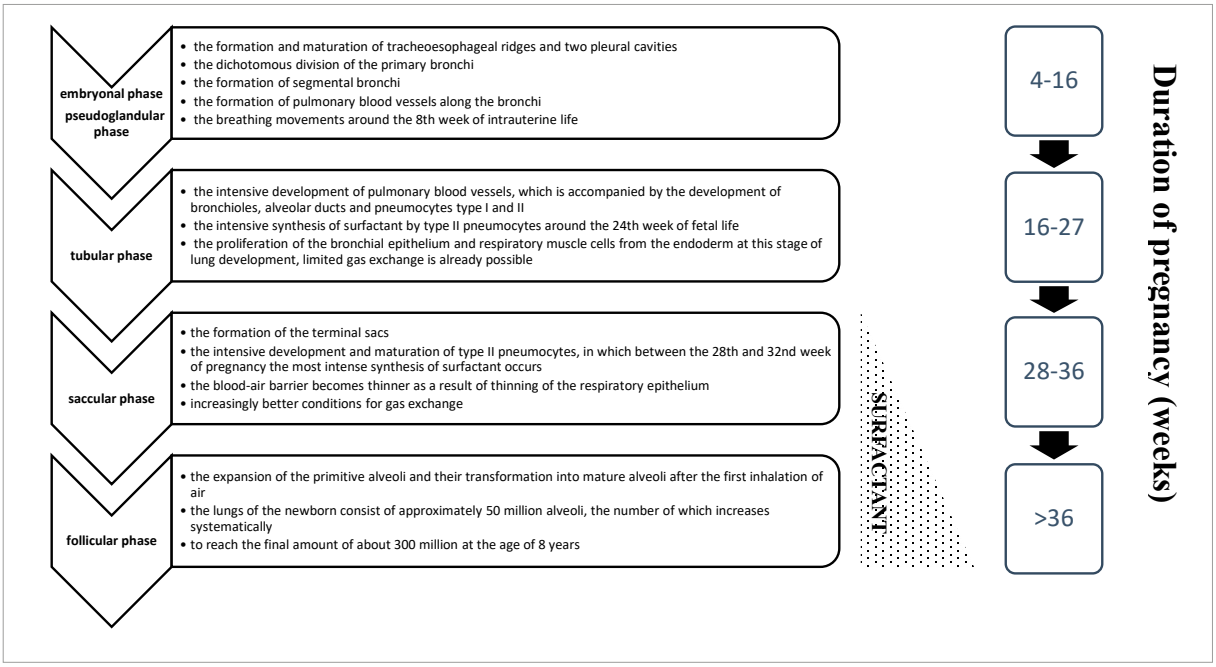

Fig. 2. Stages of human respiratory system development

alveolar wall appear to be the key physical factors [42]. The ability of alveoli to maintain normal tension depends to a large extent on the surfactant produced by type II pneumocytes. The surfactant consists of about 70% phospholipids, about 10–20% proteins and about 10% fat. The main phospholipids that make up the surfactant include phosphatidylcholine (PC), phosphatidylinositol (PI) and phosphatidylglycerol (PG). PC is about 60% weight of surfactant and is mainly found in it as dipalmitoylphosphatidylcholine (DPPC). Among the surfactant proteins, the essential role is attributed to the Sp-A protein, and to a lesser extent to the Sp-B, Sp-C and Sp-D proteins. Surfactant proteins are designed to regulate the metabolism of phospholipids by modifying and stimulating their adhesion to alveolar walls and they perform immune functions, by neutralizing bacterial and viral factors [10, 20, 37, 86].

In the second half of pregnancy, increasing the number of α- and ß-adrenergic receptors in the lungs results in greater response to catecholamines (CAs) in the stimulation of the surfactant secretion. The increase in the number of adrenergic receptors in the lungs is stimulated by estrogens, thyroid and adrenal cortex hormones [2, 7, 19, 27, 39].

The role of MMPs in the development of the mammalian respiratory system

During lung development, the expression of MMPs in various elements of the respiratory system is diversified, and their activity during development phases is clearly variable. Studies of lung morphogenesis, performed on albino rabbits fetuses and experimental sheep, revealed clear differences in the expression and activity of MMPs in the pseudoglandular, tubular, and follicular phase, also in the first days after birth [30, 31].

The inhibition of MMPs during the development of the respiratory system may result in the inhibition of dichotomous division of the bronchi and bronchioles, which proves the important role of MMPs in morphogenesis [36]. A study conducted using an exogenous inhibitor of MMPs with broad spectrum - GM6001 showed that high concentrations of the inhibitor inhibit the maturation of the fetal bronchial tree, whereas lower concentrations of the inhibitor did not show any inhibitory effect [61].

In the examined animal models in the pseudoglandular phase, immunological reactions using specific antibodies showed the presence of MMP-9 only in epithelial cells, MMP-2 in epithelial cells and the cells of mesenchymal origin. MMP-14 was detectable in epithelial cells, whereas TIMP-2 was found in epithelial cells, mesothelial cells and mesenchymal-derived cells. The immunoexpression of type IV collagen was found in epithelial cells, endothelium, basal membrane cells as well as in smooth muscle cells [31]. In the tubular phase, MMP-1 and MMP-9 were detected mainly in epithelial cells, whereas MMP-2 was found in both epithelial cells and mesenchymal cells. MMP-14 was detected in epithelial cells of the primitive alveoli whose slow differentiation begins at this stage of embryogenesis. The expression of MMP-14 was significantly less pronounced in the epithelial cells that form primary bronchioles. TIMP-2 was detected mainly in epithelial cells, but only in some cells of mesenchymal origin. Type IV collagen was detected mainly in the basal membranes of the primitive alveoli, while the tested peri-glandular tissue was significantly poorer in collagen [29, 31]. The follicular phase was characterized by a significant activity of MMP-1 and MMP-9 in type II pneumocytes and epithelium of the bronchioles and bronchi. MMP-9 reactions were also found in alveolar macrophages. MMP-2, like TIMP-2, was detected

in epithelial cells of bronchi and bronchioles, type II pneumocytes, vascular endothelium and in some mesenchymal cells [31, 47]. The immunoreactions typical of MMP-14 were very intense in type II pneumocytes, less intense in type I pneumocytes and in the epithelial cells of bronchi and bronchioles. The messenger RNA (mRNA) of MMP-9 was detected in macrophages, type II pneumocytes and bronchial epithelial cells on the 29th day of the intrauterine life of a rat fetus [77].

The studies of gelatinases activity showed the dominant activity of isoforms of 68 kDa and 62 kDa, which corresponds essentially to the latent and active form of MMP-2. The value of MMP-2 (active form) to pro-MMP-2 (latent form) tested on the 23rd day of intrauterine life was close to 1.0 and clearly increased as fetal maturation continued, in favor of the active form of MMP-2, indicating its important role in the maturation and remodeling of the rat fetal respiratory system [57]. The activity of the 92 kDa isoform, corresponding to the inactive form of MMP-9 (pro-MMP-9), was detected in fetal rat lungs on the 26th day of intrauterine life and did not significantly differ in later stages of development. At each stage of fetal development, the activity of MMP-14 was detected, and it was systematically increased in the further stage of morphogenesis [77].

In studies conducted on the development of mice lungs, no MMP-3, MMP-9, MMP-10 and TIMP-1 were detected at any stage of fetal life. Expression of MMP-2 and MMP-14 decreased with the age of the fetus, while MMP-21 was transiently expressed during morphogenesis, with the peak of growth approximately on the 11th day of intrauterine mice life, which could be associated with the development of the nervous system. MMP-15 and MMP-20 showed relatively constant expression during fetal mouse development, which slightly increased in the final stages of pregnancy [36, 57, 66].

During the pseudoglandular phase of the lung development, at the stage of bronchiolar development, distinct expression of MMP-1, MMP-9, TIMP-1, TIMP-2 and TIMP-3 was observed in epithelial cells of the human fetus. It is worth mentioning that MMP-1, MMP-2, TIMP-2 and TIMP-3 were derived exclusively from vascular endothelial cells [36, 44, 59].

In the light of the conducted research, the development of the respiratory system and its reconstruction during intrauterine life are regulated by TGF-ß, which is a strong inhibitor of MMPs in physiological conditions. In rat fetal lungs, suppression of MMP-1 expression and increased expression of TIMP-1 have been shown in fibroblasts of the maturing rat fetal, which is caused by TGF-ß1 and TGF-ß3. However, no inhibitory effect of TGF-ß on the expression of MMP-2 has been demonstrated [36, 88]. Increased TIMP-1 expression in fibroblasts of rat fetal may result in suppression of elastin degradation and, thus facilitating the development of the bronchial tree [12].

The low oxygen tension in the lung tissue inhibits the activity of MMP-2, which in turn leads to the acceleration of maturation and division of the bronchi. The reduction of MMP-2 activity as a result of hypoxia is inherently associated with the inhibition of tenascin C degradation, an important component of ECM [38]. Tenascin is a glycoprotein that determines the mutual cell-cell and cell-stromal interaction. In mammals, four tenascin isoforms, designated as X, C, R, Y, are distinguished. Genes encoding individual tenascin isoforms are expressed at different stages of fetal life, regulating the processes of adhesion and proliferation of specific cell types. Tenascin X is mainly found in muscle, skin and nervous tissue, tenascin R is found only in the nervous system, whereas tenascin C is an important component of the walls of blood vessels and lungs [24, 38]. The inhibition of MMPs activity by TGF-ß and increased expression of tenascin C as a result of inhibition of MMP-2 activity by low oxygen tension seem to be one of the key mechanisms in the process of primary bronchial division and the formation of main and segmental bronchi [36, 38].

In the tubular phase, in which intensive pulmonary vascular development occurs and the capillary network is formed around the developing alveolar ducts, the human lungs clearly express MMP-1 and MMP-9 [10, 20, 36, 37].

Experimental inhibition of MMPs during embryogenesis results in significant disturbances in the maturation and differentiation of the respiratory structural elements. In mice fetal with low MMP-14 activity, there was a clear reduction in the pulmonary alveolar surface by about 40% compared to fetuses with normal MMP-14 activity. Differences were also observed in the diameter of the alveoli and total lung weight. Low activity of MMP-14 also resulted in pulmonary hypoplasia and more frequent pleural defects, while the diameter of the alveoli was 46% lower compared to fetuses with high MMP-14 activity [5]. In a mouse fetus with normal MMP-14 activity, the alveolar pores showed a fluctuation of 5-20 µm, while the low activity of MMP-14 was closely related to significantly smaller alveolar pores of Kohn studied using the electron microscope, and their reduced amount [5]. This clearly indicates the important catalytic role of MMP-14 in the reconstruction of stroma and the formation of alveolar pores. MMP-14 possesses the ability to activate pro-MMP-2 to the active form; therefore, the mechanisms leading to the induction of MMP-14 expression, including EGF interaction on the cell, indirectly affect the activity of MMP-2 in the lungs [30].

The effect of MMPs on angiogenesis in developing lungs

MMPs are also involved in the development of blood vessels in the pulmonary microcirculation. This process depends on the mutual interaction of many growth factors, among which the most important role is played by fibroblast growth factor (FGF) and VEGF and its receptor (VEGF-r) [3, 13, 51]. The release of growth factors from the ECM takes place mainly in the mechanism of matrix degradation by MMPs, whereas FGF and VEGF can stimulate the expression

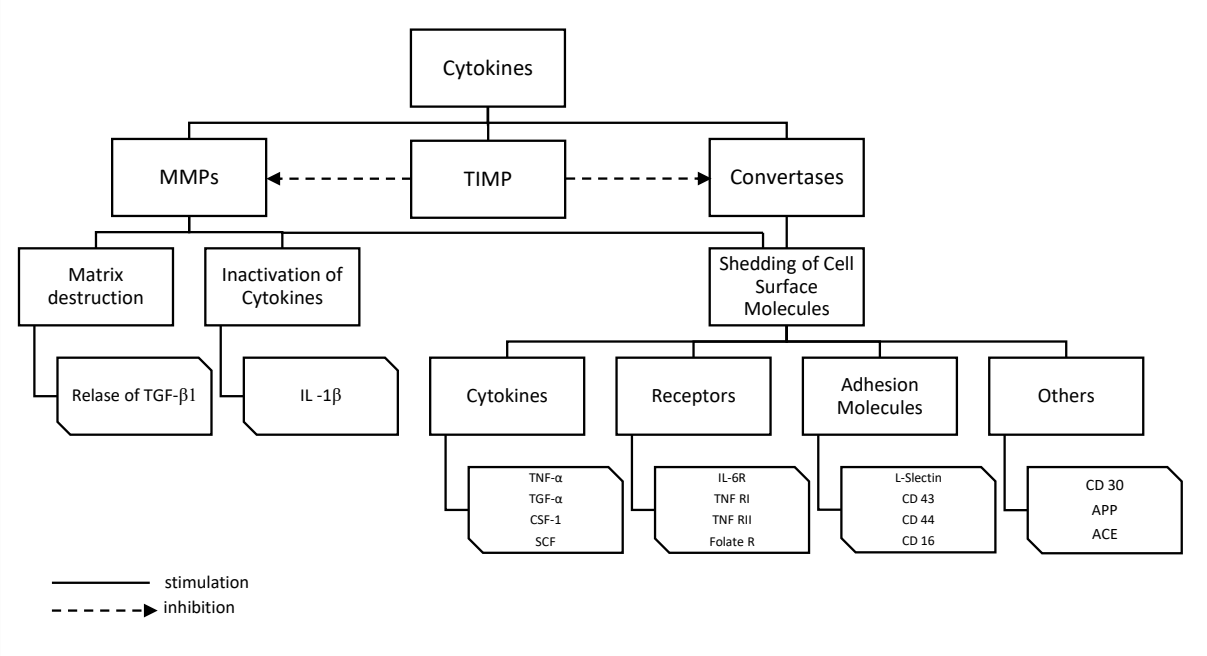

Fig. 3. The mutual interactions of MMPs, TIMPs and cytokines

of MMPs, which in turn stimulates the angiogenesis process. In comparison to mice in which MMP-9 activity was detectable, in experimental mice with no MMP-9 expression found in the fetal life, disturbances and a significant delay in angiogenesis were observed. On the other hand, adult mice had a well-formed network of pulmonary blood vessels, which probably indicates the existence of compensatory mechanisms depending on other forms of MMPs [36]. The activity of MMPs in the lungs of the developing fetus may also have an inhibitory effect on the maturation of the pulmonary circulation. The degradation caused by MMPs of several ECM components, which include type IV, XV and XVII collagen, as well as plasminogen and thrombospondin, results in the production of bioactive fragments inhibiting the process of blood vessel differentiation, which proves the regulatory role of MMPs over the course of angiogenesis in developing lungs [36, 73].

In the last stage of lung development, the formation of alveoli and intense maturation of the pulmonary vascular network is observed. This process depends on intensive ECM reconstruction and epithelial cell differentiation [10, 20, 37]. It is emphasized that MMP-14 plays a vital role in the process of pulmonary alveolar maturation. In mice deficient in this enzyme, a defective alveolarization was observed, and the air areas in the lungs were increased at the expense of the disappearance of interstitial connective tissue. This problem is probably related to disturbances in the maturation of the capillary network of alveoli and damage to the alveolar ducts, which also proves the important role of MMP-14 in the process of angiogenesis [66].

The main role in the regulation of MMP-14 expression in the lungs of the maturing fetus is attributed to EGF and its receptor-specific ligands (EGF-r), which exhibit both autocrine and paracrine effects on differentiating respiratory cells. In the lung fibroblasts of mice deficient in EGF-r, significantly fewer MMP-14 mRNA molecules were observed, which in turn was associated with significantly lower activity of MMP-2 in the examined tissues. Also, the disturbances of neovascularization processes, important from embryogenesis point of view, were observed. They result in the impairment of bronchioles differentiation and alveolar ducts, which suggests the important role of EGF-γ and its ligands in the regulation of MMP-14 expression and its influence on angiogenesis [44].

The regulatory role of EGF in the process of angiogenesis is inextricably linked to the stimulation of MMP-3 expression, whose main role in the maturing of fetus lungs is the degradation of ECM components such as collagen, thrombospondin, laminin, which, as mentioned earlier, results in the creation of bioactive fragments with potential effects inhibiting the process of differentiation of blood vessels [4, 33].

CONCLUSION

In this paper, the characteristics of MMPs, their structure, mechanisms of activation and role in the development of respiratory system of mammals were briefly discussed. It should be noted that each stage of development of the respiratory system depends on many coordinated physiological processes, among which physical and biochemical factors play a significant role, such as the correct amount of amniotic fluid, normal volume of the uterine cavity, fetal breathing movements, normal surface tension of alveoli depending on the presence of surfactant as well as the activity of adrenocortical hormones, thyroid and estrogen, which influence the increase of the number of α- and β-adrenergic receptors in the fetal lungs, especially in the

second half of pregnancy, thereby increasing the local response to CAs in the stimulation of surfactant secretion.

A significant role in the process of respiratory maturation in the fetus is played by elastin, FGF, VEGF, PDGF (mainly its αα, ββ, αβ isoforms), TGF-β1, TGF-β2 and EGF as well as MMPs, mainly MMP-7, MMP-8, MMP-9, MMP-2 and MMP-14, responsible for the activation of pro-MMP-2 in vivo. As proved above, MMP-14, whose expression is largely regulated by EGF, participates in the physiological processes of cell migration, remodeling of the stroma, vascularization and repair processes. MMP-9 plays a role in remodeling the respiratory system at every stage of lung development, showing clear expression in epithelial cells, type II pneumocytes and in pulmonary macrophages.

In the rat fetal, MMP-9 activity was observed from the 26th day of intrauterine life and no significant changes were observed during further stages of development, which may indicate a relatively constant activity of MMP-9 during particular stages of respiratory development. The role of MMP-2 in the course of embryogenesis of the respiratory system is most likely associated with the reconstruction of the respiratory system, leading to the formation of alveolar ducts and terminal sacs, as well as the differentiation of type II pneumocytes, responsible for the synthesis of surfactant. Given the fact that the expression of MMP-2 is not induced by pro-inflammatory cytokines and is of constitutive nature, it is highly probable that the structural and functional changes of the respiratory system that it catalyzes during fetal development are associated with physiological, genetically determined regulation of its expression.

In summary, the important role of MMPs in the development of the respiratory system should be emphasized almost at every stage of embryogenesis, including ECM modeling as well as repair processes, which protect the lungs against excessive connective tissue proliferation and pathological fibrotic processes.

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