

REVIEW / PRACA POGLADOWA

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ANGIOGENESIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

ANGIOGENEZA W PRZEWLEKŁEJ OBTURACYJNEJ CHOROBY PŁUC

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S u m m a r y

Angiogenesis is a very important process that occurs in both physiological and pathological states. The new blood vessels formation is characteristic for cancers, ischemic diseases and inflammatory diseases. The process is controlled by factors that stimulate and inhibit neovascularization. The next stages of the neovascularization are known as well as the role of the extracellular matrix, cells and cytokines/factors growth modulating this process. The cells of the endothelium and proangiogenic factors are the most important. The endothelial progenitor cells (EPCs), which origin from bone marrow, are the cells involved in angiogenesis. VEGF is the most important factor of the first

stages of new blood vessels formation; it is responsible for EPCs recruitment from bone marrow and their collecting in ischemic tissue.

Many researches that determine pathogenetic factors of the chronic obstructive pulmonary disease as its aim are conducted because of the frequency of appearing of this disease. The attempts to get to know the vascularization in COPD pathogenesis are made; however, published results may be ambiguous. More studies are needed for the explanation of the angiogenesis mechanism. Understanding it could be helpful in preparing more effective COPD therapy.

S t r e s z c z e n i e

Angiogeneza to ważny proces zachodzący w wielu stanach fizjologicznych i patologicznych. Formowanie się nowych naczyń krwionośnych jest charakterystyczne szczególnie dla chorób nowotworowych, niedokrwienych i zapalnych. Proces ten przebiega pod wpływem czynników stymulujących oraz hamujących neowaskularyzację. Znane są kolejne etapy naczyniotworzenia oraz rola macierzy pozakomórkowej, komórek oraz cytokin/czynników wzrostu modulujących ten proces. Wśród nich najważniejsze są komórki śródbłonka oraz czynniki proangiogenne. Komórki zaangażowane w angiogenezę to przede wszystkim progenitory śródbłonka (EPCs), które wywodzą się ze szpiku kostnego. VEGF jest najważniejszym czynnikiem początko-

wych etapów tworzenia nowych naczyń, jest odpowiedzialny za uwalnianie niedojrzałych komórek śródbłonka (EPCs) ze szpiku i ich gromadzenie w miejscu niedokrwienia.

Ze względu na dużą częstość występowania przewlekłej obturacyjnej choroby płuc prowadzonych jest wiele badań mających na celu określenie czynników patogenetycznych tego schorzenia. Podejmowane są też próby poznania procesu nowotworzenia naczyń w etiopatogenezie POChP, jednakże wyniki opublikowanych badań bywają często niejednoznaczne. Konieczne są więc dalsze prace wyjaśniające mechanizm angiogenezy. Ich zrozumienie pozwoliłoby w przyszłości zaproponować nowe skuteczniejsze metody leczenia POChP.

Key words: angiogenesis, chronic obstructive pulmonary disease (COPD), pro- and antiangiogenic factors, vascular endothelial growth factor (VEGF), endothelial progenitor cells (EPCs)

Słowa kluczowe: angiogeneza, przewlekła obturacyjna choroba płuc (POChP), czynniki pro- i antyangiogenne, naczyniowo-śródbłonkowy czynnik wzrostu (VEGF), komórki progenitorowe śródbłonka (EPCs)

INTRODUCTION

Angiogenesis occurs as new blood vessels formation by sprouting from already existing vessels. The new blood vessels are rarely formed during postnatal life. Blood vessels proliferation takes place in pathological states, especially cancerous, ischemic and inflammatory processes. Neovascularization is the main vascular response to hypoxia and inflammation. Hypoxia and inflammation are the factors that initiate the process of the blood vessels formation by proangiogenic factors genes activation [1, 2]. The endothelial cells play the crucial role in angiogenesis. It has an ability to produce various cytokines, adhesion molecules, growth factors, vasoactive peptides, proteolytic enzymes (metalloproteinases) and plasminogen activators [3, 4].

New capillaries' building is a multistage process. The relaxation of blood vessels (by nitric oxide) is the preliminary signal that activates angiogenesis cascade. After that the endothelial cells are activated, basement membrane and extracellular matrix are degraded. Next, the endothelial cells proliferate and form blood vessels tube that with time becomes covered with basement membrane, muscular coat and tunica adventitia [1]. Finally, new three-dimensional mature structure is formed which supplies surrounding tissues with blood. This process is controlled by two groups of factors (mediators) that act opposingly: stimulating blood vessels formation (proangiogenic factors) and inhibiting this process (angiogenesis inhibitors). The normal, healthy body maintains a balance of angiogenesis mediators (with angiosuppression majority); it ensures the stability of the blood vessels. Neovascularization is stimulated by environmental factors, oncogenes and cytokines. Hypoxia is the strongest inducer of the angiogenesis [1, 5].

PRO- AND ANTIANGIOGENIC CYTOKINES

The cytokines that stimulate angiogenesis include direct and indirect proangiogenic markers. The first of them stimulate the endothelial cells to migration and proliferation, influence the increase of blood vessels permeability and pericytes mobilization, they also activate the proteolytic enzymes of the extracellular matrix [1].

The direct proangiogenic group of markers consists of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and hepatocyte growth

factor (HGF). The indirect proangiogenic markers stimulate appropriate cells to production and secretion direct markers by paracrine mechanism. It includes: interleukine 6 (IL-6), interleukine 8 (IL-8), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF- β). Angiopoietins are the other group of the factors stimulating angiogenesis; angiopoietin 1, angiogenin 1, angiogenin 2, angiothrombin. The factors that make the degradation of the extracellular matrix (such as proteolytic enzymes) take part in angiogenesis process too.

The roles of the antiangiogenic factors are the inhibition of the endothelial cells proliferation and its inactivation, the inhibition of the signal transduction, cells migration and the inhibition of the precursors of the endothelial cells formation. This group includes: angiostatin, endostatin, tumor necrosis factor alpha (TNF- α), interleukine 10 (IL-10), interleukine 12 (IL-12) [1, 5, 6].

COAGULATION FACTORS

Coagulation system also takes part in regulating angiogenesis process too. Antithrombin is a strong inhibitor of the coagulation. The platelets secrete many factors that stimulate (VEGF, bFGF, HGF, PDGF) and inhibit (PF4, thrombospondin, TGF- β 1) neovascularization. Heparin may modulate angiogenesis: low molecular weight heparin inhibit the process, however, large fractions stimulate the process [7].

THE MECHANISM OF THE VEGF ACTION

Many factors take part in neovascularization; however, VEGF, bFGF and angiogenin 2 play the main role. Vascular endothelial growth factor is the strongest activator of the physiological and pathological angiogenesis [6, 7]. It is secreted by the endothelial cells, immunological and cancerous cells; it is stored and transported in the blood by leukocytes and platelets. VEGF is released in hypoxia conditions as the effect of the hypoxia-inducible factor action. IL-6, IL-8, endothelin and calcium ions increase VEGF secretion [8]. VEGF acts by receptors that are localized on the endothelial cells and causes the increase of blood vessels permeability, proliferation, migration and finally new blood vessels formation. VEGF may influence the endothelial cells thanks to cooperation with the endothelial receptors VEGF-R1 and VEGF-

R2. Besides the induction role of VEGF in angiogenesis, it plays an important role in maintaining the normal structure of the new blood vessels as a stimulating factor of the type I and type II collagen synthesis. It is also an activator of the antiapoptotic trails in the endothelial cells that contributes to vessels wall stabilization. This process acts by the activation of the proteins from the bcl-2 family by VEGF. Vascular endothelial growth factor takes direct part in neovascularization by the activation of the cancerous cells to proliferation in auto and paracrinic way causing growth and proliferation of the tumor [2, 5, 7].

ENDOTHELIAL PROGENITOR CELLS

In many diseases with inflammatory etiology, the endothelial cells (ECS) damage takes place. In the endothelium we can distinguish three groups of cells: endothelial cells (ECS), circulating endothelial cells (CECs) that shed off the vessels wall as the result of damaging the wall and circulating endothelial progenitor cells derived from bone marrow (EPCs). Progenitor cells come into existence thanks to diversifying of the CD34+cells that reside in bone marrow. EPCs determine a little percentage of circulating cells in blood vessels. In healthy people EPCs constitute about 0,002% of all mononuclear cells of the blood. CD34, CD133 (AC133), VEGF-R2 (KDR, Flk-1) are their main antigens.

Numerous factors may lead to EPCs mobilization from bone marrow and its coming into circulation from where it migrates to a place of injury in the circulatory system. The factors are hypoxia, erythropoietin, many cytokines, and growth factors: VEGF, SDF-1, SCF, G-CSF, GM-CSF and medicines are these factors. Circulating progenitor cells are detected by monoclonal antiendothelial antibodies against CD133 antigen. Their levels are determined by immunomagnetic isolation technique or more sensitive flow cytometry. Many reports have pointed at the great changeability (decreasing) of these cells in patients with various diseases or with risk factors of these diseases only. Their influence on EPCs may be explained by progenitor's involvement in keeping the continuity and the relevant functional efficiency of the endothelium. Whereas the risk factors contribute to damage of the vessels wall, circulating endothelial progenitor cells are the endogenous repairing mechanism for the endothelium that functions incorrectly. On that account, the consideration of the

pro- and antiangiogenic factors in the context of the behavior of endothelial progenitor cells is necessary for the evaluation of the angiogenesis in pathological and physiological states. The studies about migration, invasion EPCs into the new blood vessels structure during angiogenesis and about precise moment of the EPCs transformation to mature endothelial cells have been taken [9, 10].

ANGIOGENESIS IN PHYSIOLOGICAL AND PATHOLOGICAL STATES

Angiogenesis, as a physiological process, is necessary for normal development, growing and organism maturation. An intensification of the angiogenesis is observed during embriogenesis, the endometrium tissue evolution and wound healing. The physiological balance between pro- and antiangiogenic factors causes angiogenesis to be stopped rapidly, while pathological process extends for months or years and becomes a continuous and uncontrolled process [1, 2]. Neovascularization is an important element of many diseases pathogenesis, mainly inflammatory diseases and cancers. It has been affirmed in connective tissue diseases (psoriasis), gastroenterological affection (non-specific intestines inflammation), cardiological (ischemic heart disease), diabetes (retinopathy) and cancers [11].

INFLAMMATION AND HYPOXIA PARTICIPATION IN COPD PATHOGENESIS

Chronic obstructive pulmonary disease is a state where deterioration of air flow in respiratory tract because of the changes in bronchi (chronic inflammation) and alveoli (emphysema) takes place. Smoking is the main reason of morbidity. Tobacco smoke and toxic substances included in it activate inflammatory process in lungs that contributes to emphysematous destruction of the structure and resilience alveoli and bronchofibrosis and bronchiostenosis. It causes difficulty in breathing and remaining of air in inflated lungs [12]. Chronic inflammation, impairing gases diffusion in lungs, leads to ischemia. Both, chronic inflammation and hypoxia are strong stimulus for new blood vessels formation. Hypoxia not only activates angiogenesis, but also is responsible for tissue remodeling [1]. In COPD the changes in bronchioles vascularization are rather not observed, but the changes in pulmonary arteries are

demonstrated: pulmonary hypertension and endothelium dysfunction that contributes to synthesis disorder and inflammatory mediators' secretion [13].

At present, chronic obstructive pulmonary disease is known as chronic inflammatory process including not only lungs, but also taking part in pathologies development such as: metabolic syndrome or cardiovascular diseases [12]. The inflammation is a response for the antigen action that increases blood supply, vessels permeability and intensifying leucocytes migration through the endothelium. If elimination of the antigen does not occur, the chronic inflammatory response will develop. It is initiated and supported by T lymphocytes, plasmatic cells, macrophages and neutrophiles observable in cytological view [1, 2].

The inflammatory process leads to reconstruction and respiratory tract stricture and loosing flexibilities of pulmonary tissue. An enzymatic balance disorder (protease-antiprotease), oxidative stress and incoming infections take a huge part in COPD pathogenesis. In histopathological researches metaplasia and hyperplasia of the bronchi mucous membrane, thickened internal layer, increasing fibrosis and excess of smooth muscles are observed. Chronic inflammatory process taking place in bronchi and pulmonary tissue in patients with COPD is subject to a folded control of cytokines mutually influencing one another. Their excess is released from cells forming inflammatory swelling (macrophages, neutrophiles, T lymphocytes, eosynofiles, NK cells) and under the influence of its mediators. Macrophages secrete proinflammatory mediators, chemotactic factors for lymphocytes and elastolytic enzymes, stimulate neutrophiles for serine proteases secretion, release colony stimulating growth factors: granulocytes and macrophages. Neutrophiles secrete interleukin 8 (IL-8) influencing neutrophiles respiratory tract migration. Respiratory epithelium under the influence of tobacco smoke releases VEGF, TNF- α , TGF- β , IL-1 β , GM-CSF, IL-8 and reactive oxygen species. The increasing lymphocytes CD8+ and CD4+ in lymphocytes population contributes to cytolysis and apoptosis of the respiratory epithelium by perphorynes, gransim-B and TNF- α release. What is more, in COPD increasing expression of proinflammatory cytokines such as IL-6, IL-10, IL-12, IL-13 is observed. The precise role of the individual cytokines still has been unknown. There are many hypotheses about answering the question: which cells initiate and next support inflammatory process in

respiratory tract during COPD. The parallel course of fibrosis and elastolysis in lungs of patients with COPD seem to depend on preferential increase in expression of the elastolytic enzymes or growth factors in various areas of the pulmonary tissue [14, 15, 16].

ANGIOGENIC FACTORS IN COPD STUDIES

Current knowledge about angiogenesis is very wide, especially as far as cancers are concerned. There are a few reports about neovascularization in COPD, the published results are often ambiguous.

The cellular and tissue material taken from patients with COPD have been used in experimental researches so far. Immunohistochemical techniques, the latest techniques of the molecular biology and immunoenzymatic tests have been used for evaluation of the neovascularization degree and activity. The evaluation of the proangiogenic cytokines concentration was measured in serum, plasma and urine, however, the expression of these cytokines and their receptors were determined in the tissues materials. The density of the microvessels was evaluated in histological preparations knowing the surface antigens of the endothelium. The number of the circulating endothelial progenitor cells (EPCs) was measured by tricolor flow cytofluorimetry [17, 18].

Vascular endothelial growth factor (VEGF) was the most frequent subject of the scientists' interest in works about angiogenesis mechanism in chronic obstructive pulmonary disease. The published results of the immunohistochemical studies have shown increased VEGF concentration and its receptors in bronchi tissue of the former smokers with or without COPD. The VEGF expression was significantly higher in patients with COPD than in others, that may suggest the activation of the angiogenesis process in patients with obturative respiratory tract [8, 9, 20]. The cells containing VEGF were found in smooth muscles of the hypertrophic artery in patients with emphysema. The VEGF expression was observed on the macrophages surface located in the alveoli walls of the patients with emphysema, however, similar findings were not observed in healthy people [15].

On the other hand, the published results of the other studies have shown that the VEGF concentration in sputum and biopate of the patients' lungs with COPD were essentially lower compared to healthy volunteers. These studies need to be extended and confirmed, however, their preliminary results let to put the

hypothesis that in COPD angiogenesis process is inhibited and degree of the VEGF expression in respiratory system may determine the stage of the disease progression. In other authors' opinion, the decreased VEGF expression and its receptors is involved with the atrophy of the epithelium cells and the endothelial cells of the damage of bronchioles walls and alveoli. It was claimed that the apoptosis of the microvessels walls could precede emphysema development and could be connected with loosing signal transduction by one of the VEGF receptors located on the endothelial cells. Kasahara et al. and Yasuda et al. studying the role of VEGF and its receptor VEGF-R2 in emphysemal lung tissue have shown that decreasing of expression and activity of these factors precedes emphysema induced apoptosis development. It was affirmed that apoptosis may be one of the lungs destruction mechanisms leading to emphysema development, especially in smokers [20, 21].

The cooperation of the bronchi epithelium cells and endothelium cells seems to be especially important in COPD. Studying VEGF expression on the surface of cultured human bronchi cells, it was affirmed that VEGF as the strong factor of the growth and permeability appeared in the epithelium as the effect of its destruction or reparation. The authors demonstrated that the VEGF expression in cultured epithelium cells had been increasing under the influence of TGF-1 β and hypoxia. These results show the part of the bronchi epithelium in the endothelium proliferation [22].

The paper of Krasnowska et al. demonstrated a higher number of the circulating endothelial cells in blood patients with COPD compared to the control group [4]. The interpretation of this paper is difficult because of the lack of similar findings in the available literature. It is unknown if the endothelial cells were progenitor cells or shed-off cells. In the first case, this observation could be interpreted as the mechanism of new blood vessels formation, however, the presence of the shed-off cells would show the apoptosis process. It seems that more light on this problem could be shed by studies with exact definition: if the patient was in a stable or intensified COPD stage, exact evaluation of the kind of the circulating endothelial cells (progenitors or shed-off cells) and also simultaneous study of the angiogenic factors (VEGF, VEGF-R1, VEGF-R2) and proapoptotic factors (p53 gen). Palange et al. studies have demonstrated that in patients with chronic obstructive pulmonary disease the number of the

circulating cells CD34+ and endothelial progenitor cells is 3-fold lower compared to the control group and is correlated with the stage of the disease progression [23]. It was affirmed that the number of the endothelium precursors in peripheral blood was inversely proportional to the number of the cardiovascular disease risk factors. Decreased EPCs level in patients with stable coronary artery disease (CAD) is connected with death risk. In patients with COPD during the progression of the disease, the circulating EPCs level was importantly higher than in patients with CAD, healthy smokers and no-smoking people. The stimulation of the VEGF explains the reached results [24].

Higher proangiogenic interleukines: IL-6 and IL-8 were observed in the induced sputum and bronchoalveolar lavage fluid (BALF) patients with COPD compared to the healthy group of smokers and non-smokers [19, 25]. It proves the stimulation of the endothelial cells chemotaxis, proliferation and migration. Although it was affirmed that IL-6 caused growth of the VEGF mRNA level and intensified the endothelium cells migration, some authors classify this interleukin to angiogenesis inhibitors [20, 26].

The literature data shows significant role of TGF- β 1 in macrophages and mastocytes migration to the respiratory endothelium of patients with COPD. TGF- β 1 concentration in bronchioles and alveoli epithelium patients with COPD was higher than in healthy smokers. TGF- β 1 production was significant higher in patients with pulmonary emphysema compared to healthy people [27].

In patients with COPD higher TNF- α concentration in serum, sputum and bronchial biopates was affirmed than in healthy smokers and non-smoking people. The knowledge about TNF- α role in angiogenesis process is limited. The reports are ambiguous and it appears that in various conditions this factor may act as inhibitor or stimulator of blood vessels formation. The stimulating role is concerned with activating proangiogenic genes such as VEGF, FGF, IL-8 and their receptors, while inhibiting role manifests as blanking signaling cascade of these factors and inhibitors angiogenesis activation. Among patients with COPD one may observe the difficult for explaining loss of weight. It is suggested that TNF- α is responsible for the cachexy in these patients. It induces losing skeletal muscles proteins and activates apoptosis of the muscles cells [1, 2, 19].

Angiogenesis and the circulating endothelial precursors are currently the aim of many studies which might enable us to know new markers and molecular mechanisms of the chronic inflammatory process underlying the COPD base. Literature analysis about the role of the inflammatory process and hypoxia in pathogenesis of the angiogenesis process in COPD demonstrates the various views about this subject that different findings show. Among the results testifying angiogenesis process activation, the studies about impaired angiogenesis have been found. In some papers the attention was paid to the apoptosis part in COPD pathogenesis.

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Received: 6.12.2011

Accepted for publication: 4.09.2012

