УДК 616.15-07+616-001/.009
DOI: 10.56871/UTJ.2025.71.27.005

РОЛЬ ФАКТОРОВ РОСТА В РАЗВИТИИ РАЗЛИЧНЫХ ЗАБОЛЕВАНИЙ

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Для цитирования: Иманвердиева Н.А. Роль факторов роста в развитии различных заболеваний. University Therapeutic Journal. 2025;7(1):49–58. DOI: https://doi.org/10.56871/UTJ.2025.71.27.005

Поступила: 31.10.2024 ***Одобрена: 24.11.2024*** ***Принята к печати: 01.12.2024***

РЕЗЮМЕ. В настоящее время достаточно активно исследуются состояния и факторы, провоцирующие и отягощающие течение патологических процессов, анализируется их роль в патогенезе заболеваний и влияние на клеточный и гуморальный иммунитеты. Работы, направленные на выявление клинико-диагностических и прогностических значений ростовых факторов для повышения эффективности оказания медицинской помощи пациентам данного профиля и снижения степени тяжести заболеваний, показывают необходимость и актуальность их реализации. Для нормального функционирования тканей необходима регулярная доставка кислорода к ней кровеносными сосудами, во избежание гипоксических проявлений, однако в понимании того, как формируются кровеносные сосуды, сфокусирована большая часть исследовательских усилий в последнее десятилетие. Обеспечение кислородом тканей и органов кровеносными сосудами определяет их реактивность в патологических условиях. Таким образом, адекватность ангиогенеза играет ключевую физиологическую роль в поддержании гомеостаза тканей организма, особенно в коже, где репарационные и биологические процессы тесно связаны с процессами образования и развития новых микрососудов. Несмотря на то что к настоящему времени накопилось большое количество молекулярно-генетических, иммунологических исследований, посвященных роли семейства вазоэндотелиального (VEGF) и эпидермального (EGF) факторов роста в развитии различных патологических процессов, многие аспекты влияния этих факторов и взаимодействия между собой требуют дальнейшего изучения, что позволит оказывать прецизионное воздействие на любой сложный патологический процесс. В статье рассмотрены вопросы, связанные с ролью вазоэндотелиального и эпидермального факторов роста в развитии различных заболеваний, патогенез которых связан с патологическим ангиогенезом.

КЛЮЧЕВЫЕ СЛОВА: ангиогенез, вазоэндотелиальный фактор роста, эпидермальный фактор роста

THE ROLE OF GROWTH FACTORS IN THE DEVELOPMENT OF VARIOUS DISEASES

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For citation: Imanverdiyeva NA. The role of growth factors ın the development of varıous dıseases. University Therapeutic Journal. 2025;7(1):49–58. (In Russian). DOI: https://doi.org/10.56871/UTJ.2025.71.27.005

Received: 31.10.2024 ***Revised: 24.11.2024*** ***Accepted: 01.12.2024***

ABSTRACT. Currently, conditions and factors that provoke and aggravate the course of pathological processes are being actively studied, their role in the pathogenesis of diseases and

the impact on cellular and humoral immunity are analyzed. Work aimed at identifying clinical, diagnostic and prognostic values of growth factors to improve the effectiveness of medical care for patients of this profile and reduce the severity of diseases, show the need and relevance of their implementation. For normal tissue functioning, regular oxygen delivery to it by blood vessels is necessary to avoid hypoxic manifestations, but most of the research efforts in the last decade have been focused on understanding how blood vessels are formed. Providing tissues and organs with oxygen by blood vessels determines their reactivity in pathological conditions. Thus, the adequacy of angiogenesis plays a key physiological role in maintaining tissue homeostasis, especially in the skin, where reparative and biological processes are closely related to the processes of formation and development of new microvessels. Despite the fact that by now a large number of molecular-genetic, immunological studies have been accumulated on the role of the family of vasoendothelial (VEGF) and epidermal (EGF) growth factors in the development of various pathological processes, many aspects of the influence of these factors and the interaction with each other require further study, which will allow for a precise impact on any complex pathological process. The article discusses issues related to the role of vasoendothelial and epidermal growth factors in the development of various diseases, the pathogenesis of which is associated with pathological angiogenesis.

KEYWORDS: angiogenesis, vascular endothelial growth factor, epidermal growth factor

INTRODUCTION

Currently, the problem of diagnostics and treatment of diseases associated with disorders of angiogenesis and regenerative processes is acute. Along with the study of known etiopathogenetic factors, the study of clinical diagnostic criteria and features of the course of these diseases is of particular interest. The main diagnostic laboratory indicators, as a rule, are the indicators of clinical and biochemical blood tests, but the attention of researchers is drawn to the study of various molecular peptide factors involved in the development of angiogenic and endothelial disorders [1–2].

The purpose of this review is to summarize data on the study of cellular and molecular mechanisms of angiogenesis in health and pathology.

SOME ASPECTS OF THE PHYSIOLOGY OF ANGIOGENESIS

It has been established that physiological angiogenesis is caused by the equilibrium activity of its stimulators (vasoendothelial factor, angiogenin, transforming factor, interleukin-8, etc.) and inhibitors (endostatin, thrombospondin, angiostatin, VEGFR-1, vasostatin, etc.) [3]. Chronic hypoxia is considered the main trigger of angiogenesis, which activates angiogenic impulses through a number of cytokines and growth factors. The main effect of the impulses is directed at endothelial cells, as a result of which they migrate beyond the basement membrane and take direct part in the formation of vascular tubes [4, 5].

The main role in the process of formation and development of new blood microvessels belongs to angioblasts, the functional activity of which is manifested under the influence of vascular endothelial growth factor (VEGF), which acts as a chemoattractant. It has been proven that VEGF is produced by various cells (macrophages, fibroblasts, lymphocytes, osteoblasts, keratinocytes, etc.). The main function of VEGF is the induction of division of vascular epithelial cells [6–8].

VEGF exists in several isoforms, for which the spectrum of biological activity has been proven — VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor. Thus, VEGF-A at the early stages of the organism development functions as a stimulator of proliferation and migration of endothelial cells. It is a key regulator of angiogenesis, inhibits apoptosis of endothelial cells and participates in the regulation of vascular wall permeability, thus providing angioprotective effect [9, 10]. The angiogenic role of VEGF-B has been proven only in the vascular network of the myocardium, however, this variant of the endothelial factor is also synthesized in large quantities in the nervous tissue, where it prevents neuronal apoptosis and provides neuroprotective effect. Its role is being studied in connection with the possibility of using it in the treatment of Alzheimer's disease. It has been established that the function of VEGF-C and VEGFD is to regulate embryonic lymphogenesis in the lung tissue. The functional activity of the VEGF isoform depends on the type of tyrosine protein kinases (TPK) receptors (VEGFR-1, -2 and -3). There is evidence that activation of different VEGFR receptors causes opposite physiological effects [11].

THE ROLE OF ENDOTHELIAL GROWTH FACTOR IN THE FORMATION OF INDIVIDUAL PATHOLOGICAL CONDITIONS

Along with the physiological role in the processes of vessel formation, VEGF occupies one of the leading places in the development of various diseases, the mechanism of formation of which is associated with pathological angiogenesis. A striking example is the development of such conditions as retinopathy, atopic dermatitis, rheumatoid arthritis, malignant neoplasms, psoriasis, endometriosis, etc., which are accompanied by increased angiogenesis. A decrease in the intensity of angiogenesis is observed in gastric ulcer and duodenal ulcer, osteoporosis [12–14]. It has been established that such pathological processes as inflammation, ischemia, atherosclerosis lead to reinduction of VEGF expression. VEGF-C and VEGF-D are synthesized by cells of the heart, muscles, ovary, and small intestine. Their high expression leads to the development of malignant tumors of the hematopoietic system and is a marker of tumor metastasis [15, 16].

It has been established that VEGF can directly affect immune cells, namely dendritic cells, T cells, regulatory T cells, and myeloid-derived suppressor cells. VEGF can alter the process of differentiation of myeloid progenitors into endothelial cells. VEGF can affect the expression of endothelial cells by decreasing the expression of vascular cell adhesion molecule-1 (VCAM-1), which plays an important role in the apoptosis of antitumor T cells. In addition, high levels of VEGF in the tumor microenvironment can additionally stimulate the proliferation of myeloid-derived suppressor and regulatory T cells that express VEGFR [17].

Currently, there are active studies on the effect of VEGF on the development of cardiovascular diseases. It has been established that high levels of VEGF-A are observed in the serum and blood plasma of patients with acute myocardial infarction, which correlates with the level of interleukin (IL)-18, a cytokine that induces VEGF expression. Since high levels of this factor in these patients lead to neovascularization of the ischemic lesion, VEGF-A levels have prognostic significance [18].

It has been established that the VEGF level also changes in atherosclerosis, performing a dual function. On the one hand, the VEGF level has a beneficial effect, protecting endothelial cells by enhancing the expression of anti-apoptotic proteins and nitric oxide (NO) synthesis, and on the other hand, it acts as an inducer of re-endothelialization and restoration of damaged endothelium. However, there is evidence that VEGF-A promotes monocyte adhesion, enhances endothelial permeability and expression of adhesion protein and monocyte chemoattractant protein-1 (MCP-1), which triggers the development of atherosclerotic damage to the vascular endothelium [19, 20].

It has been shown that the concentration of VEGF synthesized by alveolar epithelial cells, bronchial epithelial cells, smooth muscle cells, fibroblasts and alveolar macrophages increases under hypoxia under the influence of hypoxia-inducible factor (HIF-1α). This causes inflammatory changes in the respiratory epithelium, leading to the development of various lung diseases: pulmonary hypertension, chronic obstructive pulmonary disease, asthma, fibrosis and lung cancer.

VEGF-A has also been shown to affect other cell types, including neurons. VEGF-A promotes neuronal survival in experimental stroke and excitotoxicity models, exerting a neuroprotective effect. VEGF accelerates neuronal development and the growth of dendrites and axons. In addition, VEGF regulates the functions of neuronal membrane ion channels and alters nerve excitability. Increased VEGF-A levels have been shown to induce neurogenesis in the subventricular zone, lateral ventricles, and subgranular zone of the dentate gyrus [21, 22].

Overexpression of endothelial growth factor has been shown to enhance not only neurogenesis, but also migration of newly formed neurons to the peri-infarction cortex, which may be important for rapid neuronal recovery in the stroke site. Studies have shown that VEGF may play an important role in neural plasticity in the healthy brain, as well as in the reconstruction of neurovascular units and neural recovery in cranial injuries [23–25]. Researchers have established high reactivity of retinal neurons and glial cells under ischemic conditions, associated with increased VEGF production, which is accompanied by increased inflammation characterized by leukostasis, accumulation of macrophages, activation of the intercellular adhesion molecule-1 (ICAM-1), and an increase in prostacyclin, which subsequently leads to the destruction of the hematoretinal barrier. It is noted that patients with macular edema, the most common cause of vision loss in patients with diabetic retinopathy, have higher levels of VEGF, ICAM-1, IL-6, and MCP-1 compared to patients without diabetes [26, 27].

It is known that a significant decrease in VEGF is observed in kidney pathologies asso-

ciated with a chronic decrease in blood flow, including renovascular and chronic kidney disease of various etiologies, as well as progressive glomerulopathy. It has been proven that in an experimental model of chronic kidney disease, subcutaneous injection of VEGF contributed to the preservation of the structure and density of the microvascular epithelium, which subsequently stabilized kidney function and weakened the progression of the disease [28–31].

It has been established that elevated VEGF levels are characteristic of the progression of musculoskeletal diseases. Intra-articular administration of VEGF has shown that it causes changes in the joint characteristic of osteoarthritis: a decrease in the level of proteoglycans, calcification and degradation of articular cartilage, bone sclerosis, the formation of osteophytes and synovial hyperplasia. Injection of VEGF into the temporomandibular joint in mice is accompanied by progressive cartilage degeneration and subchondral bone lesions. The pathological role of VEGF in the development of musculoskeletal diseases emphasizes the relevance of developing therapeutic approaches based on blocking VEGF signaling pathways and angiogenesis [32].

The involvement of VEGF in the development of the tumor process has been proven, and tumor cells express VEGF receptors. Studies have shown that tumor progression is based on the ability of VEGF to enhance immunosuppression by inhibiting the development of cytotoxic T lymphocytes and dendritic cells, increasing the proliferation of immunosuppressive regulatory (Treg) and myeloid suppressor cells (MDSC). Expression of VEGF-A and VEGFR-2 microRNAs increases in most human tumors, correlating with tumor recurrence, metastasis, and poor prognosis [33, 34].

The importance of VEGF in the development of various pathological processes is also manifested in the pathogenesis of dermatological pathology. The most striking example of a disease with increased secretion of VEGF is atopic dermatitis (AD), the main histological signs of which are intercellular edema of the epidermis and pronounced perivascular infiltration of the skin by lymphocytes, monocytes/macrophages, and dendritic cells. The chronic form of dermatitis is characterized by epidermal hyperkeratosis, acanthosis, and papillomatosis, which is accompanied by increased angiogenesis.

It has been established that angiogenic factors, such as prostaglandin E2, adenosine, etc., play a significant role in the induction of VEGF-A and VEGF-B expression in human mast cells. It has been established that the course of urticaria is associated with neovascularization and elevated levels of vascular markers. Studies have shown that with this pathology, the levels of VEGF-A and VEGF-C in the blood plasma are significantly elevated and correlate with the severity of the disease [12, 35].

It has been established that exacerbation of psoriasis is accompanied by an increase in the concentration of such angiogenic mediators as VEGF, HIF-1α, tumor necrosis factor (TNF), bFGF (basic fibroblast growth factor), Ang (Angiogenin) and Tie-2 (tyrosine-kinase transmembrane receptor), IL-8 and IL-17. Most of them are secreted by mast cells, macrophages and neutrophils. Angiogenesis of psoriatic lesions is characterized by significant vasodilation and increased vascular permeability due to the presence of a single- or multilayer basement membrane and endothelial fenestration. The level of VEGF-A expression in patients with psoriasis correlates with the severity of the disease [5, 36].

Along with the above-described angiogenic dermatoses, lichen planus deserves attention. It has been established that the course of this disease is accompanied by impaired microcirculation and the development of hypoxia, against the background of which the secretion of proinflammatory cytokines (TNFα, IL-1) increases, resulting in the induction of VEGF. Pathophysiological changes in the skin during the development of lichen planus are caused by hypersecretion of VEGF in the upper part of the spinous and granular layers, the level of which correlates with the density of microvessels in the papillary layer of the dermis [6].

EPIDERMAL GROWTH FACTOR AND ITS ROLE IN THE DEVELOPMENT OF CERTAIN DISEASES

In recent years, active research has been conducted on the physiological activity of epidermal growth factor (EGF) and its role in the development of various pathological processes. EGF is identified in significant quantities in blood, urine, cerebrospinal fluid, saliva, etc. EGF stimulates proliferative processes in fibroblasts, renal epithelial cells, glia, thyrocytes, etc. EGF induces regenerative processes by increasing the production of cytokines and intracellular active oxygen species [37].

It has been proven that EGF exhibits protein kinase activity, playing a decisive role in the pathogenesis of many types of cancer. It has now been proven that EGF causes cell malignancy by inducing the expression of the protooncogenes *c-fos* and *c-myc*. It has been noted that in 40%

of cases of malignant tumors of the digestive and genitourinary systems, mammary glands, and lungs, there is an increase in EGF secretion [38, 39]. The role of EGF in the genesis of tumor diseases has been studied in detail. It has been established that an increased level of EGF contributes to the development of various types of cancer.

To date, three signaling systems have been studied that activate EGF receptors, resulting in tumor growth stimulation. The first pathway is associated with the activity of phosphatidylinositol 3-kinase, which activates the Akt protein, which leads to the suppression of apoptosis; the second is due to the activation of cell cycle proteins; the third is due to the phosphorylation of phospholipase, stimulating the rearrangement of actin molecules.

Recent results have shown that the EGF level is significantly reduced in the cerebrospinal fluid and spinal cord of patients with multiple sclerosis. At the same time, the introduction of EGF to laboratory rats with chemically induced allergic encephalomyelitis prevents demyelination and inflammatory reactions in the central nervous system (CNS) [40].

Experiments have shown that EGF significantly reduces the expression of luteinizing hormone mRNA, increases the expression of growth hormone mRNA, α- and β-somatolactin [41].

It has also been proven that EGF is involved in the pathogenesis of schizophrenia. In an experiment, rodents were given EGF subcutaneously with subsequent study of neurobiological reactions. EGF penetrates well through the blood-brain barrier and leads to persistent dopaminergic disorders characteristic of schizophrenia in rodents. Animals that received EGF neonatally demonstrated persistent hyperdopaminergic abnormalities in the nigro-pallido-striatal system. In addition, low plasma EGF levels are a diagnostic sign of cognitive decline in Alzheimer's and Parkinson's diseases [42].

Currently, the role of EGF in the skin is of particular interest. EGF is widely expressed in normal skin tissues, such as the epidermis, sebaceous and eccrine glands, and dendritic cells. EGF activation results in increased keratinocyte proliferation by inducing downstream signaling, phosphoinositide 3-kinase and mitogen-activated protein kinase pathways [2].

EGF inhibition increases the expression of the cyclin-dependent kinase inhibitor p27KIP1, which initially leads to keratinocyte cell cycle arrest in the G1 phase and ultimately to disruption of epidermal barrier formation. Blockade of EGF signaling affects cytokine secretion, resulting in increased levels of β-chemokines, monokine, interferon (IFN)-γ, fractalkine and decreased IL-8 levels. Inhibition of EGF activity also increases the expression of IFN-α and -β. EGFR signaling enhancement plays an important role in the anti-apoptotic processes of keratinocytes and dendritic cells. Inhibition of EGFR leads to negative consequences for the skin: acute inflammatory reactions and apoptosis, skin atrophy, telangiectasia and increased photosensitivity [2, 43–44].

Thus, the adequacy of angiogenesis plays a key physiological role in maintaining the homeostasis of body tissues, especially the skin, where reparative and biological processes are closely related to the processes of formation and development of new microvessels.

Violation of the regulation of angiogenesis underlies the pathogenesis of many diseases, including dermatoses. The sequence of angiogenesis stages is determined by many proangiogenic growth factors. The main ones are VEGF, which exerts its effects through receptors (VEGFR-1, VEGFR-2, neurophilin-1 and neurophilin-2), and EGF — through tyrosine kinases human epidermal growth factor receptor (HER)-2 and HER-1 [40]. The HER-1 and HER-2 receptors play an important role in the regulation of cell proliferation and survival. After binding to the appropriate ligand and dimerization, they are activated and induce transduction of the mitogenic signal to the cell nucleus. As a result of their inhibition, the normal functioning of the cell is disrupted and the formation of malignant transformation is initiated.

CONCLUSION

Currently, conditions and factors that provoke and aggravate the course of various pathological processes are being actively studied, their role in the pathogenesis of diseases, the impact on cellular and humoral immunity are analyzed. Work aimed at studying the role of growth factors in increasing the effectiveness of medical care proves the need and relevance of such research.

For normal tissue functioning, regular oxygen delivery through blood vessels is necessary, so a significant part of research efforts in the last decade has been focused on studying the mechanisms of angiogenesis. Providing tissues and organs with oxygen by blood vessels determines their reactivity in pathological conditions. Adequacy of angiogenesis plays a key physiological role in maintaining homeostasis of body tissues, especially in the skin, where reparative and biological processes are closely related to

the processes of formation and development of new microvessels.

Despite the fact that by now a large number of molecular-genetic and immunological studies have been accumulated, devoted to the role of the VEGF and EGF families in the development of various pathological processes, many aspects of the influence of these factors on the body and their interactions with each other require further study. New data in this area in the future will allow for precise impact on various pathological processes.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Автор прочитал и одобрил финальную версию перед публикацией.

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Автор заявляет об отсутствии внешнего финансирования при проведении исследования.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

Competing interests. The author declares the absence of obvious and potential conflicts of interest related to the publication of this article.

Funding source. This study was not supported by any external sources of funding.

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