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REVIEW ARTICLE

An Overview of Angiogenesis and Chemical and Physiological Angiogenic Factors: Short Review

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KEYWORDS

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ABSTRACT: Angiogenesis refers to the formation of new blood vessels from existing ones, which can occur in both physiologic and pathologic conditions. Lack of tissue oxygen is the main stimulator of angiogenesis accompanied by increasing in HIF-1α-(hypoxia-inducible factor-1α) expression as a nuclear transcription factor. Other factors such as VEGF (vascular endothelial growth factor), FGF2 (fibroblast growth factor2), and TGF (transforming growth factor) are involved in angiogenesis, too. To control diabetes and tumoral disease, abnormal angiogenesis inhibition can be useful besides stimulation that can be helpful in cardiovascular disease. In this study, we have reviewed the mechanisms and stimulators of angiogenesis and its influential factors. The most important angiogenic factors are MMP, Ang, FGF, and VEGF. Ang is not directly involved in the process of angiogenesis but sometimes destabilize the arteries. In contrast to angiostatin, endostatin TIMP and TSP1 act as the most important angiostatic factors. Many attempts have been made to identify the mechanisms and factors involved in this process but angiogenic inhibitors that inhibit the growth of cancerous masses or tumors in the body have not yet been adequately investigated

INTRODUCTION

Angiogenesis refers to the formation of new blood vessels from existing vessels. This phenomenon is seen in pathophysiological conditions such as retinopathy, diabetic nephropathy, and hypertension and tumor growth and occurs in physiological conditions, in wound healing, ovulation and menstrual cycles [1]. The most important stimulus for angiogenesis is tissue hypoxia, which is associated with increased expression of Hypoxia Inducible Factor-1α, a nuclear transcription factor. Vascular endothelial growth factor (VEGF), Fibroblast growth factor (FGF-2) and Transforming growth factor (TGF) are the most important angiogenic factors. Angiogenesis strategy entails inhibition of abnormal angiogenesis in diabetes and tumor and its stimulation in heart disease or vascular

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disease [2, 3]. Thus, the process of creating new blood vessels from the existing vascular system begins. In this process, the main cells become involved with the endothelial cells, which cover all the blood vessels and account for the true nature of the capillaries.

To form new blood vessels, endothelial cells must first be removed from their fixed location by decomposing the basement membrane. Endothelial cells then migrate to an angiogenic stimulus, such as that released from activated lymphocytes. Endothelial cells proliferate to provide the necessary number of cells to build a new vessel, and eventually the endothelial cells are placed in a three-dimensional tubular structure [4]. To explain the mechanism of angiogenesis in detail, it should be noted that initially a large number of endothelial cells within the capillary are selected to initiate angiogenesis. These cells, which are called tip cells, act as guide cells reacting with the VEGF-A gradient, which specializes in migrating them to the growing capillaries. Angiogenic stimulus causes a major change in the tip cell phenotype. They acquire properties such as invasion and migration ability, as well as activate cell surface or secreted proteases for partial destruction of their adjacent basement membrane. During embryonic development, tip cell selection is monitored by Notch receptors and their trans-ligands (D114 Dll4 = Delta like ligand) [5]. When VEGF affects endothelial cells, it activates D114 expression and Notch receptors. In response to VEGF action, tip cells germinate toward the VEGF gradient and are regulated for capillary growth [6]. In this review, angiogenesis, angiogenic stimulators, angiogenic factors, and angiogenesis mechanism are discussed.

Angiogenic stimulators

One of the causes of increased angiogenic factors is angiogenic stimuli. These stimuli are a set of factors that stimulate and form new blood vessels. The most important of these factors are hypoxia, adenosine, lactate, hemodynamic forces, metabolites, vasodilators, muscle contraction, various strains and tumors [7]. Resistance training leads to an increase in hypoxia and a significant increase in the protein and mRNA of HIF hypoxia factor, which is expressed in a variety of mammalian tissues, especially skeletal muscle. HIF leads to transcription of the VEGF gene [8]. Exercise also results in higher mRNA and VEGF protein expression [9]. Vascular dilation activates growth factors, especially VEGF, by producing and increasing nitric oxide. It also causes the expression of basal fibroblast growth factor from vascular endothelial cells, which ultimately leads to increased FGF. Strength training is associated with cyclic and static stretching and leads to increased angiogenic factors [10].

One of the stimulators that are often addressed with respect to improving exercise capacity or performance as a result of exercise is increasing capillary density Muscle oxygen uptake increases several times during exercise, and it is necessary for the bed of local vessels to direct a large amount of blood to active tissues to meet this main need of active muscles. A wider capillary network usually increases the uptake of metabolism and delays muscle fatigue. Increasing capillary density by increasing the level of diffusion, increasing the time of exchange between blood and tissue and reducing the distance of diffusion causes more free fatty acids to be called from adipose tissue and more muscle fibers to have access to fatty acids [11].

Another stimulant to increase VEGF is adenosine. Adenosine is a product of ATP metabolism. Significant amounts of adenosine are produced in the absence of oxygen or muscle contraction. Various researches have shown that increased adenosine dilates muscle blood vessels, promotes energy balance, increases the expression of growth factors, increases the proliferation and migration of endothelial cells, and ultimately the formation of blood vessels in various tissues. The angiogenic response in hypoxia is mediated by adenosine. In this regard, in the study of Emami et al., which examined the effects of endurance training on tissue VEGF levels in mice with tumors, after 8 weeks of training, VEGF levels increased in mice with breast cancer and the tumor volume in these mice increased, significantly. After 8 weeks of aerobic exercise caused a significant increase in the rate of angiogenic factors in women with breast cancer. Yang et al. also studied the effect of 3 weeks of endurance training on

mice with breast cancer and the results showed that aerobic exercise increases VEGF in mice with breast cancer [11, 12].

Mechanisms and chemical and physiological factors of angiogenesis

Angiogenic factors are also the factors that are directly or indirectly involved in the formation of new capillaries and contribute to the formation and development of blood vessels, so that the lack of any of these factors disrupts the process of capillary formation and development. Vascular endothelial growth factor (VEGF), Fibroblast growth factor (FGF-2), and Transforming growth factor (TGF) are the most important angiogenic factors involved in the proliferation and migration of endothelial cells and smooth muscle cells, and recruitment of the Pre sits play a major role in the process of angiogenesis and arterio-laryngitis [2, 3] (Table 1).

Table 1. The most important chemical and physiological factors of human affecting angiogenesis

Factor	Action
Resistance training	Leads to an increase in hypoxia and a significant increase in the protein and mRNA of HIF hypoxia factor, which is expressed in a variety of mammalian tissues, especially skeletal muscle. HIF leads to transcription of the VEGF gene [14-20].
Increasing capillary density	Increasing capillary density by increasing the level of diffusion, increasing the time of exchange between blood and tissue and reducing the distance of diffusion causes more free fatty acids to be called from adipose tissue and more muscle fibers to have access to fatty acids [7-12].
Adenosine	Increased adenosine dilates muscle blood vessels, promotes energy balance, increases the expression of growth factors, and increases the proliferation and migration of endothelial cells, and ultimately the formation of blood vessels in various tissues [7, 15].
Lactate	Lactate facilitated NF-κB translocation to induce increased transcription of VEGF and bFGF [31-34].
Angiovitine 1	Angiovitine 1 stabilizes the arteries by affecting the binding molecules and increasing the interaction between endothelial and mural cells and mobilizing pericytes [32-34].
Angiovitine 2	Angiovitine 2 stimulates vascular growth by reducing the interactions of endothelial cells and pre-endothelial cells, and degrading extracellular matrix [5, 6 and 9].
Vascular endothelial growth factor (VEGF)	VEGF enhances the survival, survival, and survival of all early stages by increasing the regulation of anti-apoptotic components, DNA synthesis, basement membrane degradation, and phosphorylation of intercellular endothelial components and tight attachments, respectively [5-12].
Transforming growth factor (TGF)	Unlike VEGF, which performs its angiogenic functions independently, beta-transforming growth factor (TGF-β) indirectly shapes its angiogenic effects [22-30].
Matrix metalloproteinases (MMPs)	MMPs play a vital role in capillary network development and angiogenesis, as well as migration, proliferation, and degradation of the endothelial cell matrix More production and stimulation of anti-angiogenic factors than angiogenic factors leads to a decrease in the process of angiogenesis and thus stops growth [35-41].

VEGF

Vascular endothelial growth factor (VEGF) is the most important angiogenic factor of vascular endothelial growth. It is a secretory protein with a molecular volume of 35 to 45 kDa that is mainly secreted by endothelial cells, smooth muscle, tendons, platelets, thymus and skeletal muscle. Angiogenic factor has five isoforms, PDGF, A, B, C, and D Isoforms A and B are mostly used to make blood vessels and isoforms C and D are used to make lymphatic vessels. The strongest and most active isoform is VEGF-A (13). VEGF enhances the survival, survival, and survival of all early stages by increasing the regulation of anti-apoptotic components, DNA synthesis, basement membrane degradation, and phosphorylation of intercellular endothelial components and tight attachments, respectively [14, 15].

VEGF is secreted from endothelial cells, smooth muscle cells, platelets, thymus and tumor cells in response to ischemia/hypoxia stimulators, stress milk (frictional force due to blood colliding with endothelial cells), metabolites such as adenosine and lactate, vasodilators such as nitric oxide, adipokines such as visfatin and leptin, and reactive oxygen species [15].

Hypoxia, which is a hallmark of the tumor, is the main cause of VEGF secretion. This stimulation promotes the

growth, migration and survival of endothelial cells, resulting in further expansion of the vascular network and growth. VEGF causes endothelial cells to germinate from the anterior vessel. Evidence is available that points to the role of MMPs in separating smooth muscle cells from the extracellular matrix, which allows cells to migrate. The activity of MMPs is temporary and transient and is essential for the processes of angiogenesis and wound healing. MMPs also play an important role in the growth and development of axons in the central nervous system [16]. The results show pathological processes, control of MMPs and VEGF has been removed and the production increases, resulting in the exacerbation of inflammatory diseases such as cancer of different types [17]. MMP-9, MMP-2 have the highest R&D in the MMPs. MMPs-2 in fibroblasts are present, endothelial and monocyte cells, and MMP-9 ocular, hepatocytes, O, T, and ocular and peripheral ocular [18, 19]. Thus, MMPs and VEGFs play a vital role in capillary network development and angiogenesis, as well as migration, proliferation, and degradation of the endothelial cell matrix more production and stimulation of anti-angiogenic factors than angiogenic factors leads to a decrease in the process of angiogenesis and thus stops growth [20].

TGF-β

TGF-β mRNA is increased in adult adipocytes and vascular stromal cells of adipose tissue in obese mice [21]. Unlike VEGF, which performs its angiogenic functions independently, beta-transforming growth factor (TGF-β) indirectly shapes its angiogenic effects [22, 23]. The TGF-β gene has a special element for stress milk in its promoter region. Therefore, it can be expected that in response to the increase in milk, the stress resulting from the binding of blood flow to endothelial cells increases with TGF-β expression In this regard, increased expression of TGF-β after one hour of passive hyperperfusion has been reported [24]. The amount of TGF-β is present and is proportional to the increase in the number of coronary arteries [25]. FGF: So far, 20 fibroblast growth factors (FGF) and four different tyrosine kinase receptors have been identified. Acidic FGF-1 and alkaline FGF-2 are among the first growth factors known to stimulate angiogenesis [26]. FGF2 and FGF1 contain endothelial cells, fibroblasts, and many other cells [27]. In the process of angiogenesis, FGF2 stimulates the synthesis of proteases such as collagenase and urokinase-type plasminogen activator (uPA) and integrin to form new capillaries [21]. FGF is involved in angiogenesis, wound healing and embryonic development. FGFS plays a key role in the processes of proliferation and differentiation of a wide range of cells and tissues. Decreased FGF reduces muscle mass, resulting in muscle weakness and ultimately physical disability [28]. Since angiogenesis and increased blood flow within the tumor are essential for tumor growth, regular exercise can cause competition among the skeletal muscles of the tumor to receive blood [29]. The inherent hypothesis states that during exercise of active muscles, the distribution of blood, oxygen, and nutrients is disputed [30].

Angiopoietin

Angiopoietin (Ang): 1, 2, 3, and 4 are paracrine growth factors that act specifically on endothelial cells. Angiopoietin 1 is secreted by vascular smooth muscle cells and increases the germination of endothelial cells. Angiopoietin 1 stabilizes the arteries by affecting the binding molecules and increasing the interaction between endothelial and mural cells and mobilizing pericytes. Angiopoietin 2 stimulates vascular growth by reducing the interactions of endothelial cells and pre-endothelial cells, and degrading extracellular matrix [31]. The site where angiopoietin 1 binds to its receptor, namely, Tie2, stabilizes endothelial cells by recruiting pericytes. In contrast, Ang2 in the presence of VEGF causes the separation of binding between endothelial cells and smooth muscle cells and therefore provides the context for migration of endothelial cells [32, 33]. Angiopoietins, as with VEGFs, have endothelial cell-specific mitogens, ie, they have Tie2 on the endothelial cells [34].

Matrix metalloproteinases

Germination and capillary division require extracellular matrix degradation and capillary basement membrane proteins. This mechanism is accomplished by matrix metalloproteinases (MMPs) [35]. MMPs are endopeptidases from the large family of proteases that play a vital role in regulating adhesion, proliferation, and differentiation of endothelial cells, resulting in the formation of new capillaries [36, 37]. In this regard, MMP inhibition reduces new capillary growth and destruction of the basement membrane. MMPs that enter the bloodstream also secrete growth factors and cytokines involved in the process of angiogenesis from their own process and activate them [38].

Endostatin: Endostatin is one of the most important angiostatic factors, which is a fragment isolated from collagen XVIII [39, 40]. This inhibitory factor is produced by various tissues in the body. The inhibitory mechanisms of endostatin are such that this factor binds to the angiogenic factor VEGF and inhibits its function, thus preventing endothelial cell proliferation. Endostatin also prevents the destruction of the capillary basement membrane, which ultimately prevents the migration of endothelial cells. In fact, endostatin inhibits the growth of the capillary network by inhibiting the proliferation and migration of endothelial cells [41].

Angiostatic factors

Angiostatic factors: Angiostatic factors prevent the occurrence of angiogenesis. The importance of these factors is more apparent in pathophysiological conditions such as cancer. Now, if activity or exercise is considered as a stimulus to increase these factors, it can be hoped that regular activity or exercise will prevent the growth of cancerous mass or tumor in the body. In this regard, it was first shown in 2007 that under normal conditions, there is a shift between the factors involved in angiogenesis and angiostatic factors [40].

Angiostatin is a component of the plasminogen protein [41]. Angiostatin is produced following the action of tissue plasminogen activator on plasminogen and its conversion to plasmin with the participation of serine proteinases and metalloproteinases. Angiostatin inhibits angiogenesis by preventing the destruction of the basement membrane and preventing the proliferation and migration of endothelial cells. Angiostatins only prevent angiogenesis of pathological conditions but have no effect on physiological angiogenesis [42].

Relationship between angiogenesis and some diseases

Angiogenesis and hypertension

Structurally, hypertension increases the wall thickness of the arterioles and increases the ratio of wall thickness to the lumen of the artery and changes their components. The number of capillaries and Arteries also decreases [43, 44]. There is growing evidence that hypertension is associated with an inadequate, incomplete, and ectopic response to angiogenic growth factors. It is also possible that angiogenesis and arteriogenesis are suppressed during the progression of hypertension so that capillary density decreases in these patients [43]. Conversely, long-term and effective antihypertensive treatment increased capillary density. In a study using a tyrosine kinase receptor inhibitor, VEGF was reported as a side effect of hypertension [45]. A contradictory finding that has been proven in recent studies on hypertension is that there are high levels of angiogenic growth factors in this disease [46, 47]. Possible mechanisms involved in increasing angiogenic factors in this disease include tissue ischemia, increased vascular traction, endothelial damage by hypertension, decreased clearance of these factors and compensatory responseIt is also possible that endothelium in hypertensive patients at the cellular or post-receptor level is resistant to angiogenic factors and does not respond adequately to these factors. Defects in the VEGF-related signal cascade have also been reported [48]. Anti-hypertensive therapies appear to normalize unregulated

angiogenic markers and restore normal ability for angiogenesis.

Angiogenesis and diabetes

Diabetes and other chronic diseases are largely the result of reduced physical activity due to lifestyle changes. Diabetes mellitus is a chronic metabolic disease characterized by high blood glucose levels and insufficient secretion or insulin dysfunction. One of the hallmarks of type 2 diabetes is insulin resistance, which in addition to impairing glucose metabolism, appears to cause endothelial dysfunction through increasing fat and insulin and oxidative stress, which is why the prevalence of cardiovascular disease is comparatively higher in diabetics than in the general population [49]. Diabetes has chronic effects on the structure and function of blood vessels in various tissues, which are observed in small vessels (including retinopathy, neuropathy and nephropathy) and large vessels (including peripheral vascular disease and cardiovascular disease) [50]. In general, diabetes is a contradictory disease in terms of vascular system and angiogenesis, because in organs such as the kidneys and eyes, it increases angiogenesis and inhibits it in the heart and peripheral arteries. Therefore, the term *paradox of angiogenesis* in diabetes refers to the simultaneous presence of pro- and anti-angiogenic conditions in this disease [51]. Numerous factors are involved in stimulating angiogenesis, including nitric oxide and vascular endothelial growth factor (VEGF), which reduce their production and biological activity in diabetes [52]. Based on empirical evidence, the ability to repair tissue through angiogenesis, which requires the presence of VEGF, is impaired in conditions such as aging and diabetes [53].

Angiogenesis and tumor

A tumor is able to grow and survive if adequate nutrients and oxygen as well as blood flow reach that area of the tumor, which is facilitated by the angiogenesis of the tumor cells [54]. Malignant tumors increase disproportionately in blood vessels that help them grow, and eventually, with the expansion of the vascular system, the tumors become aggressive and enter other tissues, which are called metastasis [55]. Therefore, the angiogenic power of malignant tumors are directly related to the strength of tumor metastasis [56, 57]. Angiogenic factors are released by tumor cells into the environment and stimulate different types of cells, especially endothelial cells in the capillaries adjacent to the tumor. Eventually, these cells break down the basement membrane and enter the extracellular matrix, and migrate to the tumor cells [58]. Some vascular factors, such as VEGF1, which is an angiogenic factor, as well as hypoxic conditions, may facilitate metastatic conditions [59].

Angiogenesis and ovulation

In the ovary, angiogenic factors increase the permeability of blood vessels and support the process of cavity formation and the antral follicle itself to reach the stage of ovulation. Important factors in angiogenesis, which are present in the ovarian tissue or reach it through the bloodstream, include the growth factor of FGF-2 (Fibroblast Growth Factor-2), VEGF and ANPT: Angiopoietin and Endothelin-1. Among these three factors, ANGII, FGF-2 and VEGF are the most important [60]. Therefore, the establishment of blood flow in the tissues as soon as possible leads to the stimulation and activation of angiogenic factors and are important in maintaining the follicular reserves of the ovaries. In angiogenesis-deficient mice, the number of primary follicles and ovary was severely reduced [61]. While its overexpression caused the growth of ovary and reduced apoptosis of granulosa cells of antral follicles. This improves the folliculogenesis pathway [62].

Angiogenesis and embryo formation

Fetal blood vessels are formed through both vasculogenesis and angiogenesis. In the fetus, endothelial cells that make up blood vessels and hematopoietic tissues develop simultaneously. In the early stages of embryonic development, angioblasts are derived from the lateral plate

of the mesoderm and the cardiac crescent, and a number of them migrate into the brain. A number of cells also accumulate inside the endocardium of the primitive heart tube. Other angioblasts form a network of endothelial cells at the base of the heart tube that fuse with the vitelline duct, allowing blood cells to flow from the yolk sac into the fetus. In addition, endothelial cells that directly surround the mesenchyme form visceral arteries by angiogenic invasion to tissues. Finally, angiogenesis is stimulated by both endoderm and ectoderm and eventually causes the development of various embryonic organs [63, 64].

Angiogenesis and ulcers

At the site of the wound, the damaged cells secrete substances that lead to narrowing of the arteries and thus prevent bleeding at the site, which continues with the activation of the coagulation response and the formation of fibrin filaments. In fact, coagulation is an active repair signal that leads to the recruitment of monocytes to the wound site one day after the onset of injury Platelets begin to secrete TGFs-converting growth factor, fibroblast growth factor (FGFs), and platelet-derived growth factor (PDGFs), which stimulate cells to grow and proliferate. Moreover, the role of macrophages is to clean the injury site through micropores and secretion of cytokines and growth factors. At the end of the third day and the inflammatory response, the leukocytes migrate from the wound site and, if infected, return to the wound site. The proliferation phase begins on the fourth day of the injury, and the skin reproduction and collagen repair begin on the fourth day of the injury. Fibroblasts migrate and proliferate into the wound after macrophages pass through the site of injury Fibroblasts proliferate through a variety of mechanisms that begin with the secretion of insulin-like growth factor TGFβ and PDGF from platelets and continue with cytokines secreted by macrophages. Fibroblasts are also argued to secrete IGF-1. Epidermal growth factor EGF migrates through the bloodstream to the affected area. First, type 2 collagen is made and replaced by type 1 collagen. In the final stage of repair, the evolution of collagen fibers continues [65].

Angiogenesis and ischemic heart disease

Myocardial ischemia is one of the diseases that lead to, anxiety, heart attack, and cell damage [66, 67]. The most effective clinical treatment for these patients is treatment that restores normal blood flow to the heart [68]. High-speed angiogenesis begins after each ischemic event [69] and several factors, including VEGF, play a role [70]. VEGF is the most important factor involved in the process of angiogenesis [71], which plays an important role in angiogenesis following myocardial infarction [72]. The expression of VEGF is increased in myocardial ischemia in patients with myocardial infarction [73]. Tissue hypoxia is one of the factors that stimulate the expression of VEGF. With increasing metabolism, oxygen decreases and tissue hypoxia develops. Hypoxia is involved in the pathology of heart disease and can also produce various signals to stimulate angiogenesis [74, 75]. There are a variety of chemical compounds in medicinal plants that can probably be used to treat diseases or physiological activation of the body due to their active ingredients and medicinal and antioxidant compounds [76-88].

CONCLUSIONS

Angiogenesis is an important process in physiological and pathophysiological conditions such as tumor growth, diabetes, endometriosis and ischemic heart disease. The most important angiogenic factors are MMP, Ang, FGF, and VEGF. Ang is not directly involved in the process of angiogenesis, but sometimes destabilize the arteries. In contrast to angiostatin, endostatin TIMP and TSP1 act as the most important angiostatic factors. Many attempts have been made to identify the mechanisms and factors involved in this process, but angiogenic inhibitors that inhibit the growth of cancerous masses or tumors in the body have not yet been adequately investigated.

Conflicts of interest

The authors declared no competing interests.

ETHICAL CONSIDERATION

Ethical issues (including plagiarism, data fabrication, double publication and etc.) have been completely observed by author.

Authors' contribution

All authors contributed equally to the manuscript.

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