Review Article

Investigating Mechanisms and Causes Related to Angiogenesis: A Review

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Abstract

The increasing resistance of cancers to common treatments has caused researchers to make more efforts to discover and identify new anticancer agents. Excessive use of chemical drugs increases the resistance of cancer cells, and as a result, treatment measures fail due to a decrease in the response level of these cells to the drug. Therefore, it is extremely important to study drugs that are more effective and have fewer side effects. Angiogenesis is a new treatment method that has been studied recently due to the high importance of this treatment method and the efficiency of this method in the treatment of some diseases, including all types of tumors. There are many hopes for the use of this method. It has created an effective method. Among the most important potential advantages of this method in cancer treatment, we can mention the absence of cell resistance problems, easy access to intravascular targets, as well as the wide scope of using this type of strategy to treat many types of diseases related to angiogenesis. Therefore, the use of different angiogenesis models and the development of these models can be very important for the treatment of all types of cancer and other diseases. In this review article, various dimensions of the angiogenesis process and the mechanisms and factors related to it, as well as the studies surrounding them, have been discussed.

Keywords: Angiogenesis, Anti-cancer agents, Angiogenic factors, Angiogenesis inhibitory

Introduction

The first system that develops in the embryonic gastrula stage is the cardiovascular network [1]. The vascular system of the body is the result of the blood vessel network that is created during the embryonic period during vasculogenesis. The initial endothelial cell organization that leads to the blood vessel's creation is called vasculogenesis, and there is no other vascular system before it. During this process, blood vessels proliferate and join together in a primary vascular network called the capillary network [1-4].

Angiogenesis is the development and growth of novel blood vessels by the endothelial cells sprouting of existing vessels. Dr. Hunter in 1787 used this term for the first time for the new blood vessels formation from previous vessels. During embryonic stages, both processes are involved in blood vessel formation, but in adults, blood vessels are formed only by angiogenesis.

Under normal conditions, angiogenesis involves the controlled blood vessel formation from existing vessels. This process is the basis of multiple physiological processes such as wound healing, placenta formation, and fetal growth. During the normal formation of novel blood vessels, which is associated with a controlled order, endothelial cells receive a stimulating massage from angiogenesis and secrete special enzymes such as matrix metalloproteinases and heparinase, which digest the extracellular matrix. This results in the breakage of the tight connections through endothelial cells. Thereafter, endothelial cells can move and advance from the newly created organized, spaces and differentiate to form new capillary tubes [1, 5].

In many severe cases of diseases, the body loses control of pigmentation. In diseases such as cancer, age-related degeneration of moles, psoriasis, and endometriosis, when diseased cells abnormally produce several angiogenic factors such as hepatocyte growth factor and VEGF, these factors inhibit the impact of natural inhibitors such as angiostatin. They cover thrombospondin and aldostatin and as a result, premature (excessive) angiogenesis happens. In general,

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How to cite this article: Davidescu L, Precup AI, Fodor R, Ilias TI. Investigating Mechanisms and Causes Related to Angiogenesis: A Review. Arch Pharm Pract. 2024;15(1):47-52. https://doi.org/10.51847/QO4iMf1QmE

there are more than 70 other diseases such as asthma and obesity that are related to excessive angiogenesis [6-8]. Also, today it is believed that solid tumors (such as prostate, lung, colon, uterus, breast, brain, and bladder) and soft tumors (increased bone marrow density in patients with acute leukemia, myeloma, and myeloid) have angiogenesis potential and are dependent on angiogenesis for the growth of invasion and metastasis [9-12].

Due to the importance of the pigmentation process in the development of diseases related to it, in this review article, various dimensions of the angiogenesis process and the mechanisms and factors related to it, as well as the studies surrounding them, have been discussed.

Mechanism of Natural Angiogenesis

Normal angiogenesis is related to the coordination of multiple independent processes. To form novel blood vessels, mural cells initially move from the branch of the existing vessel. Vascular destabilization by angiopoietin-2 switches endothelial cells from a stable nonproliferative state to a proliferative phenotype. After that, vascular permeability increases through VEGF. At this stage, matrix compounds and proteases are leaked from the endothelial cells and the vessel wall begins to multiply. Following proliferation, endothelial cell migration occurs. After that, tube-like structures are shaped, and blood can flow. The proliferation of mesenchymal cells induces and migrates along novel vessels, then differentiates into mature pericyte cells. Strengthening the cell-cell interactions and the precise construction of the new matrix is the apple of the stability of the new vessel [13].

Angiogenesis and Cancer

In 1971, Folkman proposed for the first time the hypothesis that the growth of tumors depends on pigmentation. Later research showed that the metastasis and growth of tumors depend on the new vessels creation and the nutritional needs of the tumor. Until the 1960s, scientists believed that tumor cells secreted substances that dilated blood vessels, thus providing food for tumor growth. However, today it is believed that tumor cells secrete substances that cause the sprouting of previous vessels and angiogenesis [14-16]. Therefore, the continued growth of the primary neoplasm is related to the adequate blood supply to that area. The process of shaping new vessels, i.e., angiogenesis, allows tumors to develop more than 1 to 2 cubic millimeters [17].

Except for benign tumors that have little angiogenesis and their growth rate is slow, malignant tumors have many vessels and their growth is fast. Increased vasculature likely increases tumor cell invasion by spreading to other organs and entering the bloodstream. Studies have also shown that the vascular system formation in cancer is directly dependent on the power of tumor metastasis [18, 19].

Angiogenic factors are created by tumor cells in the environment and stimulate various types of normal cells. This particular stimulation includes the endothelial cells adjoining the tumor. These cells decompose their basement membrane and migrate towards the mass of tumors using separating from the neighboring cells and entering the extracellular matrix. But the cell division also happens in the bud and with the increase in the migration of endothelial cells, a string is shaped from these cells and the inter and intracellular basement membrane evolves and they form a tubular structure. Then these tubes are connected and form the structure of new vessels, which are finally connected to the blood circulation system. The capillary network is created in the tumor mass and can extend to expand as a result. Oncogenic alters and tumor cells hypoxia may play a role in the induction and expansion of angiogenesis using angiogenic factors [20, 21].

Induction of Angiogenesis in Tumors

Hypoxia is among the factors that induce angiogenesis. Several angiogenic compounds such as Interleukin-1 (IL-1β), Tumor necrosis factor (TNF), Vascular endothelial growth factor (VEGF), and Fibroblast growth factor (FGF) are induced by hypoxia. In soft tissue sarcoma and human cervical cancer, the hypoxia presence before treatment increases the likelihood of metastasis to distant sites. In addition, the tumor area presence or high vascular density in prostate cancer and breast carcinoma has a bad prognosis. These findings show that hypoxia causes metastasis and activates angiogenesis. In conditions where there is oxygen around the cell, the Hypoxia-inducible factor (HIF) is hydroxylated and thus decomposed. While in the condition of lack of oxygen, this factor is not hydroxylated and stable and moves to the nucleus and induces efficient factors in angiogenesis.

Oncogenic transformations of tumor cells may play a role in the induction and expansion of angiogenesis by angiogenic factors. Mutations in oncogenic genes H-ras, Kras, V-src, and V-raf induce VEGF expression. Also, a mutation in the suppressor gene TP53 (Tumor protein 53) leads to a decrease in the production of trospondin (TSP) and an increase in the VEGF expression, and as a result, angiogenesis is activated. Other angiogenic growth factors including TGF-α and β are increased by ras mutant and cause the activation of angiogenic growth factor stimulating areas [22, 23].

Mechanism of Tumor Angiogenesis

Tumors can prepare the blood supply they need in multiple ways. During a process similar to normal angiogenesis, a tumor may distort the blood vessels' shape. In addition, tumor cells can develop around the existing vessels and do not need novel angiogenesis at first [24].

In addition, tumor-induced vessels form a tube-like structure for the metabolite delivery, they are ultrastructurally abnormal. several inactive pericytes are contracted and

expanded and become permeable because of the presence of pores and cell gaps and the absence of a complete basement membrane [25]. Tumor vessel walls may be composed of both endothelial types and tumor tubules. These abnormal structures show the pathological nature of tumor stimulation. However, their support cell growth ability is related to the physiological mechanisms of angiogenesis that they use.

Angiogenesis Inhibitors

In addition to several factors that stimulate physiological and pathological angiogenesis, factors inhibiting this process have also been identified. More than 40 endogenous inhibitors of angiogenesis are classified into 4 general categories.

Interferons

INF-α, β, δ interferons are in a group secreted from glycoproteins. This group of compounds was initially noticed because of their antiviral impacts [26]. Endogenous angiogenesis inhibitors were initially determined by identifying INF-α with the capability to restrain chemotaxis of endothelial cells in vitro [27].

Recent studies indicate the anti-angiogenic effects of interferons in vivo and it has been shown that INF-α inhibits angiogenesis [28]. Also, the ability of interferons to downregulate FGF-related mRNA levels in breast, kidney, bladder, and prostate cancer cells has been proven [29]. Researchers have approved the application of interferon-alpha in the adjuvant setting for melanoma treatment when the nodes of lymph are caught or the disease is at an advanced stage.

Because there is a possibility that alpha interferon has anti-angiogenic activity, its combination with anti-VEGF antibody or thalidomide may have synergistic activity [30].

Interleukins

Interleukins are proteins secreted by leukocytes that mediate a wide range of cell activity, including the activity and proliferation of lymphocytes to stimulate the release of immunoglobulin IgE through B cells [31]. The inhibitory role of 4-IL in the growth of tumors is also well-defined [32]. This compound directly inhibits some tumor cell proliferation or induces immune reactions against the tumor [33]. Inhibition of angiogenesis induced by bFGF in rat cornea is another anti-angiogenic impact of 4-IL.

The interesting thing is that interleukins such as IL-S, which have glutamic acid-leucine-arginine sequence at their amino end, strengthen the interleukins, and angiogenesis process without this sequence, such as 4-IL, restrain angiogenesis [34].

Inhibitors of Matrix Metalloproteinases (TIMPs)

The effect of matrix metalloprotease enzymes in the process of angiogenesis is very important. For the proliferating endothelial cell migration, the basement membrane and extracellular matrix should be digested. Furthermore, intercellular junctions must also be broken. This is done using the matrix metalloproteases family. Inhibiting their activity or secretion can cause tumor control in angiogenesis. TIMPs as inhibitors of metalloproteases inhibit both inactive and active forms of MMPs. TIMPs can inhibit the endothelial cell migration in the gelatin substrate [35].

Proteolytic Components

Several anti-angiogenic compounds are components of the larger protein digestion. Some of these fragments are derived from compounds of extracellular matrix, such as fibronectin or collagen, or their origin is enzymes such as 2-MMP and plasminogen. Endostatin and angiostatin are both part of this group.

Angiostatin is a 38 kDa component derived from plasminogen that strongly restrains the capillary endothelial cell growth [36]. A study shows that angiostatin intratracheal administration in mice inhibits tumor metastasis and angiogenesis [37].

Endostatin is a peptide with a weight of 20 kilodaltons, whose origin is collagen type 18. This compound has been identified as an inhibitory factor for the growth of endothelial cells, and similar to angiostatin, it has significantly inhibited angiogenesis in the chicken embryo model [38, 39].

The Relationship between Atherosclerosis and Angiogenesis

Due to the abnormal deposition in the interference of the extracellular matrix receiving oxygen, an atherosclerotic plaque suffers from hypoxia. This is an important driving force for the sprouting of vessels (angiogenesis). As revealed in human studies, there is a positive relationship between the atherosclerotic lesions development and the small vascular network development derived from the vasa vasorum. This implies that angiogenesis is the important process caught in atherosclerosis, which can be through plaque growth or contribute to its growth. These novel-formed capillaries (vasa vasorum) may be inclined to bleeding inside the plaque and thereby activate platelets and stimulate proliferation and vascular smooth muscle cell migration [40].

Pharmacological Strategies to Control Atherosclerosis and its Diagnostic Markers

A diagnostic strategy for positive intervention in atherosclerosis is to consolidate the atheroma (strengthen the fibrotic cap and decrease the lipid pool) instead of decreasing the lesion size. Plaque stabilization should prevent vascular events including stroke and myocardial infarction through non-invasive treatments instead of invasive strategies (bypass surgery, endarterectomy surgery, angioplasty).

The studies conducted so far have indicated the performance of conventional lipid-lowering treatments by HMG-CoA reductase inhibitors (statins) in reducing the inflammatory response in atheroma and also inhibiting the risk of acute coronary events. Because this issue is only associated with the improvement of narrow ducts, stains make the atheroma more resistant to rupture, and by having a small effect on reducing the size of platelets, they reduce the possibility of thrombosis of plaques. Today, several serum markers have been discovered to evaluate the absolute risk of acute coronary syndromes and Peripheral artery disease (PAD) in patients, including Intercellular Adhesion Molecule 1 (1-ICAM), serum amyloid A solution, fibrinogen, LDL inflammatory marker, hs-CRP and interleukin 6, and in addition to this, it is possible to predict the results obtained. Despite the major advances in our understanding of atherosclerosis and its consequences, today the need to devise other strategies for early diagnosis, effective treatment, and prevention of this vascular disease is felt to a great extent [41, 42].

Overlap between Atherogenesis, Arteriogenesis, and Angiogenesis

Many peripheral growth regulatory factors such as monocyte chemotactic protein- (MCP-1), FGF, TNF-α, and VEGF have concurrent atherosclerosis-inducing properties and vice versa. The same applies to cell populations such as monocytes, smooth muscle cells, and fibroblasts, which are the main factors involved in the inflammatory process, matrix changes, vascular structure remodeling, and new intima formation. This method of operation, which is called the Janus phenomenon, becomes important when we seek to find a suitable treatment to induce arteriogenesis and angiogenesis by inhibiting sclerosis. Therefore, understanding the complex molecular factors involved in these overlapping processes to clarify the nature and mechanism of different regulatory molecules is still considered a serious challenge [43-45].

Studying the Anti-Angiogenic Agents Role in Different Phases of Clinical Trials

Currently, more than 75 anti-angiogenic agents are under clinical trial studies. Most of them were in phase 1 or 2 of the trial and at least 12 of these agents entered phase 3 or completed it. A number of these agents have been confirmed for use in some pathophysiological or physiological conditions, such as Visudyne for treating muscle wasting and PDGF for wound healing. Theoretically, the use of antiangiogenic agents for cancer treatment has several potential benefits. These agents may have easier access to cells of endothelial compared to drugs that act directly on tumor cells and must penetrate large tumor volumes. Antiangiogenic drugs are unlikely to cause many of the standard chemotherapy agents unwanted toxicities. They may also prevent the mechanisms of tumor resistance. If the use of anti-angiogenic agents is successful, they may apply to many types of tumors and do not depend on the cell type or components that support the growth of cells within the tumor [46].

However, there are multiple obstacles to the use of the antiangiogenic drug in clinical trials. These situations include (1) determination of the appropriate dose from the first phase trials to advance to the next phases, (2) drug timing, (3) biological correlations, (4) appropriate use of these factors in the clinical environment, (5) how to combine these treatments with biological treatments, radiation therapy, and chemotherapy as best as possible, and (6) the required to calculate the angiogenesis index (adapted treatment). To overcome these problems, more preclinical tests and information from early clinical trials using antiangiogenic agents are necessary. In addition, the effect of matrix metalloprotease inhibitors (MMPI) on angiogenesis in humans is not known. MMPIs may affect cancer initially and not when the disease has reached advanced stages. On the other hand, because immune cells cannot attack tumors and destroy them, perhaps the use of MMPIs in this context also helps the immune system [47-50].

Conclusion

The increasing resistance of cancers to common treatments has caused researchers to make more efforts to discover and identify new anticancer agents. Excessive use of chemical drugs increases the resistance of cancer cells, and as a result, treatment measures fail due to a decrease in the response level of these cells to the drug. Therefore, it is extremely important to study drugs that are more effective and have fewer side effects. Angiogenesis is a new treatment method that has been studied recently due to the high importance of this treatment method and the efficiency of this method in the treatment of some diseases, including all types of tumors. There are many hopes for the use of this method. It has created an effective method. Among the most important potential advantages of this method in cancer treatment, we can mention the absence of cell resistance problems, easy access to intravascular targets, as well as the wide scope of using this type of strategy to treat many types of diseases related to angiogenesis. Therefore, the use of different angiogenesis models and the development of these models can be very important for the treatment of all types of cancer and other diseases. Many researchers around the world benefit from various models of angiogenesis to investigate this significant phenomenon and the agents affecting it.

ACKNOWLEDGMENTS: None
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: None
ETHICS STATEMENT: None

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