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Role of Angiogenesis in Oncology: A Deep Insight into the Mechanistic Aspect

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Abstract: Angiogenesis is the formation of a new vascular system from existing ones and its role in the body's natural physiological and pathophysiological mechanisms. It leads to the beginning and progression of several human problems such as cancer, inflammatory processes, atherosclerosis, and blinding eye diseases in pathologic form. Oncology studies have emphasized inhibiting angiogenesis may be a potential treatment option for some neoplastic diseases. Starting with angiogenesis development, its modulation is followed by vasculature signaling, and the mechanistic exploration of the new vascularisation process is focused on. This review article will focus on the phenomenon of an interface between cancerous cells and their nearby ecosystem, giving the impression of antiangiogenic. However, various anti-angiogenesis drugs that arrest tumor development might not be enough for the eradication of tumors. The blood vessels can also be remodeled by the development, multiplicity, and redundancy of other compensatory mechanisms. Henceforth, novel anticancer strategies will require the identification of broad-spectrum anti-angiogenesis targets and also establishing combination approaches involving antiangiogenic drugs and other anticancer regimes, such as chemotherapeutic agents that may play a vital role in cancer therapeutics.

Keywords: angiogenesis; cancer; anti-angiogenesis; pro-angiogenesis; endothelial cell; vascular growth factor; secondary metabolites.

1. Introduction

Blood vessels are necessary for fetal development, bodily growth, and wound repair. The processes of angiogenesis involve the formation of new blood vessels from pre-existing vessels, and they are essential for both physiological and pathophysiological biological activities [1]. Angiogenesis is a term derived from the Greek words "angio" (vessel) and "genesis" (appearance or birth) that refers to the development of new blood (hemangiogenesis) or lymph

(lymphangiogenesis) vessels from existing ones. While physiological angiogenesis occurs during embryogenesis, tissue regeneration, and the menstrual cycle, non-physiological angiogenesis occurs in non-cancerous pathologies like diabetes, ischemic retinopathy disorders, connective tissue illnesses, and psoriasis [2].

In a healthy individual, hemangiogenesis could be seen in tissue regeneration, where blood supply is restored to damaged tissues to only give oxygen and nutrients for physiological wound reconstruction. Histologic hemangiogenesis, on the other hand, occurs in a range of conditions such as cancer, inflammation, atherosclerosis, and blinding eye diseases and is characterized by the production of leaky, unstable blood arteries, which are sometimes paralleled by lymph vessels. To fulfill the requirement of nutrients and oxygen to carry out metabolic functions, tumors are required to create a blood supply like other normal organs [3]. Tumor angiogenesis thus becomes an essential step of blood vessel formation, invasion, and expansion in the tumor ecosystem, which is linked to tumor growth, recurrence, and metastasis. When the extracellular matrix creates significant components that support tumor growth, a malignant tumor growth-promoting cycle is formed [4].

2. Angiogenesis Process

The angiogenesis mechanism incorporates a variety of cells, accessible angiogenic agents, and molecules, and it is essentially comprised of the following specific sequential steps:
Proteolytic enzymes destroy outer membrane glycoproteins and other outer membrane proteins around the vasculature. They also activate and cause the migration of endothelial cells. This leads to the proliferation of vascular endothelial cells, which convert into a capsule-like structure, forming capillaries and progressing into new endothelium [5]. Usually, angiogenesis develops only during embryogenesis, the female ovulation cycle, and wound healing [6]. Unusual angiogenesis, on the other hand, is an essential cofactor and a fundamental process in cancer development.

2.1. Angiogenesis in normal cells.

In normal cells, there are two types of angiogenesis: sprouting angiogenesis and intussusception. Sprouting angiogenesis is most commonly responsible for vascular growth and is regulated by angiogenic growth factors expressed by hypoxic tissue. Intussusception, also known as splitting angiogenesis, occurs when a particular groove forms inside an existing vessel, inevitably splitting into two vessels. Chaining angiogenesis happens when vessel loops are inherently brought into the tissue. Both types play crucial roles in the regeneration and advancement of organ systems[7,8].

Angiogenesis is a multi-stage procedure encompassing a range of rapidly increasing factors, substrate compounds, and cellular components [9], as well as the effect of an angiogenesis trigger like oxygenation or inflammation [10]. The vascular system is formed either by "propagation" of neovascularization by vascular endothelium. The angiogenic mechanism includes the production of proteolytic enzymes, vascular endothelium cell migration, the formation of vascular tubes, the junction of newly established tubes, the manufacture of a new basal layer, and the incorporation of endothelium and keratinocytes, as shown in Figure 1 [1,2].

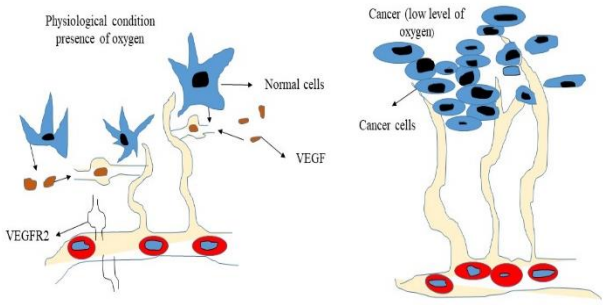

Figure 1. Tumor angiogenesis via degrading the extracellular matrix to trigger the signaling of angiogenic pathways.

2.2. Angiogenic stimulation.

When proteolytic enzymes activate endothelial cells, angiogenic stimuli are created, which break down both the basement layer and the perivascular extracellular matrix (ECM). Hence, primary sprouts are formed by the proliferation and migration of endothelial cells into the perivascular area. Following the creation of capillary loops from the lumination of these initial sprouts, a new inner membrane is synthesized, and blood vessels mature to become tube-like structures through which blood can flow [11].

2.3. Hypoxia and its role in tumor angiogenesis.

Excessive oxygen ingesting, dietary deficiency, and metabolic material buildup in cells can all contribute to an oxygen-deficient microenvironment unsuitable for cancer cellular activity [12]. Unlike normal cells, tumor cells can undergo metabolic reprogramming by altering the expression of glycolysis-related proteins under hypoxia and boosting glucose intake to promote growth [13]. Furthermore, hypoxia can affect the expression of EMT markers such as N-cadherin, E-cadherin, slug, snail, and vimentin, as well as enhance the synthesis of matrix metalloproteinases (MMPs), which promote the invasive metastasis [14,15]. HIF is widely expressed in the hypoxic tumor microenvironment and can bind effectively to the promoters of several pro-angiogenesis molecules, giving rise to transcriptional activation. Hypoxic cancer cells secrete the endothelial growth factor A (VEGFA), which initiates tumor angiogenesis by engaging VEGF receptor 2 (VEGFR2) expressed on the endothelial cells (ECs) of neighboring blood vessels [3]. The perception of hypoxia-induced angiogenesis and the allied hope for a new magical treatment [16] and also the hypoxia-inducible factor (HIF)-driven gene reprogramming [17], have chiefly contributed to the existing understanding of the determinants and biological significances of tumor hypoxia, promoting tumor angiogenesis (Figure 2). Recent research suggests that HIF-1 might enhance tumor angiogenesis in hypoxic circumstances by activating proangiogenic genes and inhibiting antiangiogenic genes [18].

Hypoxia can also enhance tumor angiogenesis by regulating the expression of certain extracellular matrix components (ECM). Hypoxia, for example, has been shown to increase MMP9 and MMP2, which are important components for tumor cell invasion and metastasis. [18–20]. Several elements in the tumor microenvironment and the hypoxic microenvironment can stimulate tumor angiogenesis (see Figure 2) [21].

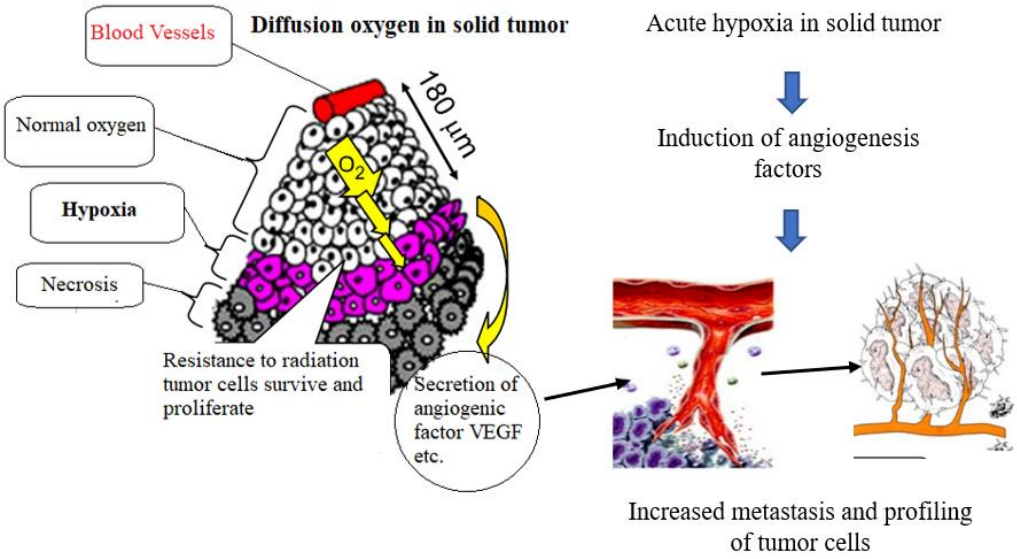

Figure 2. Hypoxia and tumor angiogenesis: During tumor growth, hypoxia causes angiogenesis. As the tumor grows, an oxygen gradient develops between the oxygen source and the tumor's periphery. As cells get closer to the blood supply, they detect hypoxia and produce angiogenic factors. Angiogenesis occurs as a result, and the tumor develops its blood supply independent of the original tissue.

3. Tumor Angiogenesis

Mostly, it is seen that the tumor initiates the process of tumor angiogenesis. When malignancy grows to a certain size, it turns out to be hypoxic and starts to secrete growth factors. The angiogenic growth factors bind to the receptor of endothelial cells of nearby blood vessels, resulting in the growth of new vessels that penetrate the tumor and support its increased growth. Endothelial cells (EC) make up small blood vessels, while pericytes (mural cells) [22]. Several stimulators and inhibitors control the process of angiogenesis. Fibroblast growth factor, granulocyte colony-stimulating factor, interleukin8, transforming growth factors alpha and beta, and vascular endothelial growth factor are angiogenic stimulatory growth factors. Angiostatin, interferons (alpha, beta, and gamma), endostatin, interleukin-12, and retinoids are all angiogenic inhibitors [22].

Chemicals like transforming growth factor-beta (TGF), platelet-derived growth factor (PDGF), angiopoietins (Ang), hepatocyte growth factor (HGF), hypoxia-inducible factor (HIF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and fibroblast growth factor (FGF) as well as matrix metalloproteinase (MMP (TNF) [23-27].

3.1. Angiogenic modulation for tumor vasculature.

The chemical signals induce blood formation, i.e., angiogenic stimulator, and another type of chemical signal is known as an angiogenesis inhibitor. These results either disrupt blood vessel formation or support the removal of existing vessels. Inhibitors promote several proteins that have been identified as angiogenic activators, including vascular endothelial growth factor (VEGF) – which affects permeability, basic fibroblast growth factor (bFGF, FGF2)-promotes proliferation and differentiation of endothelial cells and fibroblast, angiogenin, transforming growth factor

(TGF)- increase ECM production, tumor necrosis factor (TNF)-regulation of immune cells, platelet-derived endothelial growth factor (PDGF)-recruit smooth muscle cells, granulocyte colony-stimulating factor, placental growth factor (PGF)- trophoblast growth and differentiation, interleukin-8 (IL-8)- recruit of neutrophils and other immune cells to the infection site, hepatocyte growth factor, and epidermal growth factor [28]. In vascular homeostasis, it is very necessary to keep a balance between stimulators and inhibitors, and this balance is regulated. In the extracellular matrix (ECM), inhibitory factors are present. Small non-coding RNA molecules at a molecular level control angiogenesis, collectively called angiomas. AngiomiRs are comprised of proangiogenic miRs and antiangiogenic miRs [29]. "The term angiomiRs is adopted to name miRNA that regulates angiogenesis", which belongs to the miR-200 family [30]. miR-200b inhibits angiogenesis. When new vessel production is necessary, such as during wound healing, its effect is immediately reduced.

To control new blood vessel formation or angiogenesis, miR200b action is expressed as soon as the physiological demand subsides. Tissue hypoxia triggers epithelial cells to mesenchymal transition and modulates endothelial cell migration, which results in new vessel formation in response to the down-regulation of miR-200b [31]. This dysregulation of miR-200b contributes to oncogenesis and metastasis in some cancers, for example, lung cancer, breast cancer, etc [32].

3.2. Angiogenic signaling.

Generally studied antiangiogenic regulators include angiostatin, endostatin, tumstatin, platelet factor-4, interleukin (IL)-12, thrombospondin-1 (TSP-1), tissue inhibitors of metalloproteinases (TIMPs), and interferon-α, -β, and -γ. Various biological activities trigger this angiogenic switch. Activation of oncogenes or loss of tumor-suppressor genes that control the production of angiogenesis regulators, metabolic stress (hypoxia, low pH, or hypoglycemia), mechanical stress (pressure generated by proliferating cells), and the immune/inflammatory response (immune/inflammatory cells that have infiltrated the tissue) are important stimuli of angiogenic signaling and tend to cause tumor formation [33]. Hypoxia is the most common cause of primary factors that drive tumor angiogenesis, resulting in increased expression of VEGF and other angiogenesis stimuli. The cancerous cells seem to be an important cause of VEGFA and other proangiogenic mediators during the angiogenic switch; enrolled leukocytes increase VEGFA bio-availability and signaling [34]. Besides this, many signals arise from various tumor-associated stromal cells (TASCs) and the ECM through which they are set so that after the angiogenic switch is done, the resulting phases of tumor progression remain to assist the angiogenesis [35].

3.3. Tumour-associated stromal cells (TASCs).

Based on their origin, TASCs can be classified into two main categories. From the bone marrow, tumor-infiltrating cells of hematopoietic origin are enrolled in the tumor through the systemic circulation and include various leukocyte types and subtypes, such as monocytes and macrophages, neutrophils, lymphocytes, and their immature precursors. Bone marrow-derived endothelial or mesenchymal progenitors, which are non-hematopoietic, contribute to tumor angiogenesis. Tissue-resident cells, including vascular cells (endothelial cells and pericytes),

fibroblasts, adipocytes, and some tissue-resident leukocytes, such as mast cells and macrophages, are also involved [36].

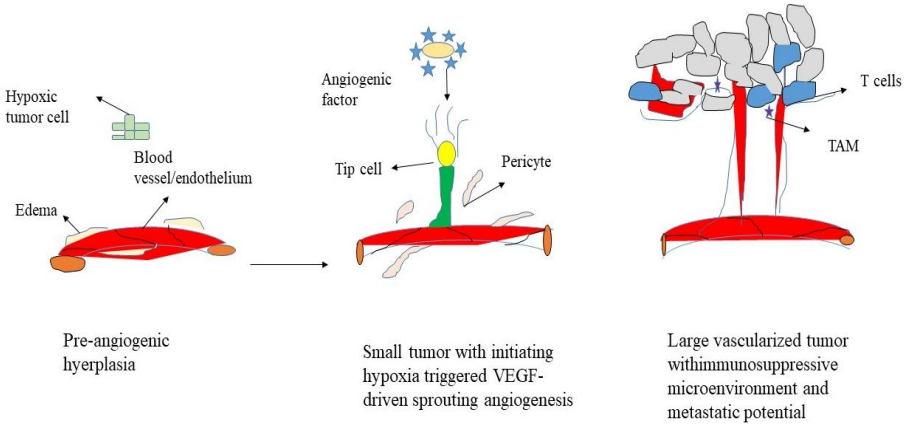

Figure 3. The "angiogenic switch" is initiated by hypoxic cells of the tumorous cell via growth factors, which stimulate adjacent endothelial cells of the microvasculature of the host/parental tissue in which they develop.

VEGFA soluble gradients persuade the configuration of motile ECs, called tip cells (as shown in figure 3), which break down the adjacent extracellular matrix (ECM) and lead to the development new vascular sprouts towards VEGFA. Tumor hypoxia reaction is two-fold: to decrease the hypoxia and enhance the perfusion, new blood vessels are formed, and the V of the tumor adapts to combat the cell death, and the tumor metabolism adapts to resist cell death and even preserve the production of cells in this antagonistic environment [37]. Hypoxia metabolic adaptation involves changes in the approach glucose is handled by cancer cells.

Hypoxia induced by a master transcription factor, namely, HIF1α, significantly raises the expression of various glycolytic enzymes that transform glucose into pyruvate and glucose transporters [38]. A rich source of energy and biosynthetic intermediates is provided by this metabolic reprogramming to the tumor cells when oxygen is in limited form. For the monocarboxylate transporter 4 (MCT4) and lactate dehydrogenase A (LDHA), HIF1α-mediated upregulation of the genes coding further assists an increased glycolytic flux upon hypoxia [39]. Specifically, pyruvate is transformed by lactate dehydrogenase A into lactate to certify NAD+ regeneration, while monocarboxylate transporter 4 favors the passive discharge of lactate out of cells along its concentration gradient [40]. The vascular basement membrane in tumors is commonly discontinuous and relatively allied with ECs and pericyte cells [41]. Chemoattractants for proangiogenic inflammatory cells, such as TAMs, are caused by the breakdown of the ECM [42].

4. Angiogenesis Mechanism in Cancer

Tumor angiogenesis research has progressed significantly in the nearly four decades since the studies established the field's foundations, allowing for collecting specific knowledge about the systems that drive pathological vascular proliferation.

In normal cells, all the vital functions are carried by the presence of oxygen; angiogenesis is regulated by oxygen tension. Different oxygen-sensing receptors, such as oxygen-sensitive

NADPH oxidases, endothelial nitric oxide synthase (eNOS), and heme-oxygenases, are present in endothelial cells (ECs) and smooth muscle cells (SMCs) [43].

Endothelial cell metabolism under aerobic circumstances, in which oxygen can be utilized to build either a sprout in vitro [44] or a vascular network *in -vivo* [45]. Tumor angiogenesis occurs when cells lack oxygen-carrying ability, resulting in hypoxic circumstances caused by oxygen deprivation in which hypoxic tumor cells (tumor cells that have been deprived of oxygen) will neither proliferate nor expand. Endothelial cells are highly active in growing cancers due to the discharge of many proteins, including EGF, estrogen, basic and acidic FGF, IL-8, prostaglandin E1, VEGF, and E2, TNF, which can activate endothelial cell growth and motility when antiangiogenic factor production is reduced [46, 47]. VEGF and bFGF growth factors are particularly significant in tumor angiogenesis [46]. In comparison to antiangiogenic therapy, vascular enhancement therapy is being researched to boost tumor blood supply and improve cytotoxic medication delivery to the target tissue [48].

The role of VEGF in angiogenesis is to exceed through a complex autocrine and paracrine signaling pathway; this signaling helps VEGF promote the cancer stem cells' functionality and the initiation of tumors [49]. Increased VEGF activates epithelial-mesenchymal transition (EMT), leading to tumorigenesis [50]. Due to this, complex interactions between the cell membrane, ECM, and biochemical regulatory signaling pathways are involved. As a result of EMT promoter cancer cell invasion of the basement membrane and cancer cell metastasis, phenotypic alterations occur [51]. EMT is also involved in producing proteolytic enzymes that break down the extracellular matrix, such as matrix metalloproteases and serine proteases, which are involved in extracellular matrix disintegration (ECM). Several routes influence endothelial cell (EC) survival and proliferation during EMT [52]. EMT-induced phenotypic changes promote cancer cell invasion of the basal layer, which leads to cancer cell metastasis. A complex interaction between the cell membrane, ECM, and intracellular regulatory signaling pathways results in cancer cell metastasis [53]. In cancer, homeostasis is disturbed between stimulatory and inhibitory factors that lead to a proangiogenic state [54], which causes relatively poor blood-supply hyperplasia converted to an uncontrollable new vessel formation that ultimately causes malignant tumor progression. The poor blood supply in tumor angiogenesis is one of the postulated mechanisms of resistance to chemotherapy due to the failure of adequate delivery of cytotoxic drugs to the tumor site [55].

VEGF exceeds angiogenesis during a complex autocrine and paracrine signaling pathway. In tumourigenesis, VEGF production is increased, which leads to the activation of epithelial-mesenchymal transition (EMT) [56]. EMT is involved in the formation of new vessels. [57]. Angiogenic growth factors like VGEF are the main angiogenic growth factor, and various other proangiogenic factors such as angiopoietin and MMPs in proliferation, migration, and breakdown of basement membrane degradation for activation of local EC so that tube formation, elongation, and remodeling takes place (Figure 4) [58]. In this newly formed vessel, the maturation of pericytes smooth muscle cells occurs at the end, which is associated with vasculature [59].

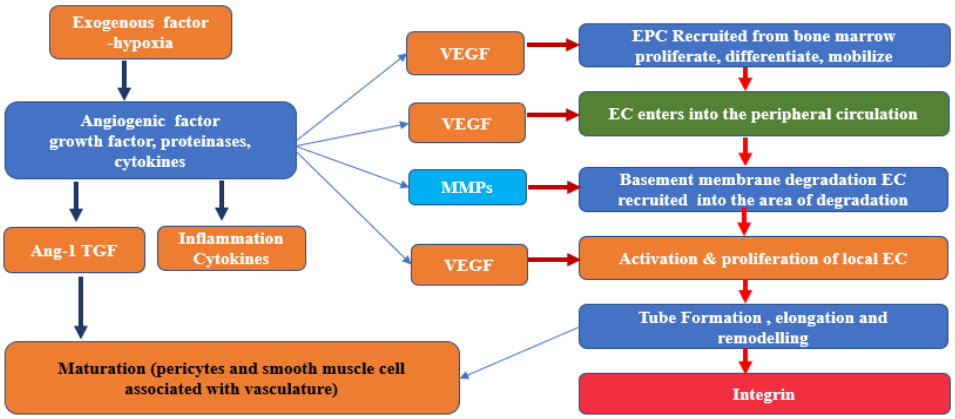

Figure 4. Growth factors VEGF play an important role in angiogenesis. Schematic representation of key VEGF/VEGFR signal transduction pathways.

4.1. Angiogenic switch.

Many endogenous inhibiting and stimulating factors have been identified that regulate the balance between the pro and antiangiogenic states. Angiopoietins are essential regulators of angiogenesis. Angiopoietins bind to the Tie-2 TK receptor on EC. Angiopoietins affect the function of the EC by interacting with other angiogenesis factors [60,61]. Apart from that, several angiogenesis promoters include a diverse spectrum of polypeptides, metabolites, and hormones that contribute to the formation of new blood vessels in both healthy and pathological conditions [60]. Conversely, a large spectrum of anti-angiogenetic factors prohibit the promoters from functioning. Extracellular matrix (ECM), basement membrane constituents, and proteolytic fragments are effective angiogenesis inhibitors [62]. Thrombospondin-1 (TSP1), a key glycoprotein present in the ECM, inhibits angiogenesis [49]. Another matrix-derived angiogenesis inhibitor is a collagen proteolytic product. Endostatin is the name given to XVII. Angiogenesis inhibitors include interferon-alpha and beta and angiostatin, a plasmin by-product [63,64]. Phytocompounds such as flavonoids, tannins, curcumin, resveratrol, and gallocatechin are naturally occurring angiogenesis inhibitors and anticancer properties [65].

Proangiogenic imbalance often arises at the genetic level due to oncogene activation or tumor suppressor gene inactivation. On the other hand, the cells' environmental variables include hypoglycemia, hypoxia, cellular nutrition shortage, and metabolic acidosis [66]. Angiogenic switches result from an imbalance between proangiogenic activators and inhibitors of angiogenesis activity because they include a variety of tasks, such as tumorigenesis. The tumor and inflammatory cells that penetrate the tumor determine this ratio [67].

4.2. Antiangiogenic therapies.

Antiangiogenic interventions may inhibit tumor cell nourishment by destroying existing tumor blood vessels and inhibiting the development of new blood vessels, hence reducing intravasation in primary tumors and blocking the angiogenic switch in metastasis [68]. Consequently, such treatments potentially regulate tumor blood vessels, improving hypoxia levels within the tumor microenvironment and, as a result, lowering the degree of malignancies and increasing the efficacy of antiangiogenic therapy[69,70].

4.3. Side effects in antiangiogenic therapy.

Normally, VEGF activates endothelial nitric oxide synthase (eNOS) and prostacyclin (PGI2) in vessel walls, resulting in vasodilation via the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) downstream pathways [71-74]. As VEGF stimulation is inhibited, the level of NO decreases, promoting vasoconstriction, increasing peripheral resistance, and eventually elevating blood pressure [75, 76]. Such as body processes, wound healing, blood pressure, kidney function, fetal development, reproduction, and increased risk of clots in the arteries resulting in stroke or heart attack [77, 78].

5. Angiogenesis Inhibitor for Cancer Therapy

Initially, it was hoped that cancer therapy acts on the cellular level, which includes inhibiting cancer cell proliferation, promoting apoptosis of cancer cells so that the necrosis of tumors, and blocking its metastasis. According to Harrison (1998), angiogenesis inhibitors are thought to prevent the creation of new blood vessels, which would slow but not stop the growth of tumors. Anti-angiogenesis monotherapies are, therefore, ineffective in people [79-81]. Angiogenesis inhibitors can be divided into two primary categories based on their broad scope.: Direct inhibitors facilitate targeting endothelial cells in the growing vasculature. Indirect inhibitors facilitate targeting either tumor cells or other tumor-associated stromal cells [82].

Direct angiogenesis inhibitors include angiostatin, endostatin, arrestin, canstatin, and tumstatin, which are released upon proteolysis of different ECM molecules and prevent vascular endothelial cells from proliferating and migrating in response to a variety of angiogenesis inducers such as VEGF, bFGF, IL-8, and PDGF [83-89]. Proangiogenic proteins that suppress angiogenesis indirectly, such as EGFR [87]. For instance, Ciardiello et al. investigated the antiangiogenic and antitumor activity of gefitinib (ZD1839; Iressa, a small molecule known as an EGFR tyrosine kinase inhibitor (TKI) in the human colon (GEO, SW480, breast (ZR-75-1 and MCF-7 ADR), ovarian (OVCAR-3), and CaCo2), and gastric (KATO III and N 87) cancer cells, that co-expressed TGF- and EGFR (proangiogenic factor) [90, 91].

The balance between proangiogenic and antiangiogenic forces will be restored through the reduction of vessel permeability and hypoxia, as well as the restoration of blood flow homogeneity and perivascular cell coverage. During hypoxia, cancer cells release angiogenic chemicals such as cytokines, bioactive lipids, growth factors, or matrix-degrading enzymes, which bind to a receptor on the vascular endothelium of neighboring blood vessels and induce the development of new vessels [75,76].

6. Summary

Several years after tumor angiogenesis was identified as a cancer characteristic, the therapeutic application of antiangiogenic treatments has reached a certain level of maturity. Specific angiogenic stimulators and inhibitors regulate angiogenesis, as angiogenic imbalances result in a variety of pathological conditions. VEGF, FGF, PDGF, Ang, HGF, and HIF are proangiogenic factors, while angiostatin and endostatin are antiangiogenic factors. Angiogenesis is required for tumor growth, wound healing, embryonic development, and other processes. Abnormal angiogenesis contributes to tumor survival, growth invasion, and metastasis. Potential

anticancer therapy includes the identification of proangiogenic molecules and the blocking of their activity. However, as the administration of antiangiogenic treatment could not eradicate the tumor, novel strategies are necessary to treat cancer efficiently. Based on this finding, a combination of therapy targeting various stromal components, as well as standard anticancer drugs, could be the key to slowing cancer progression.

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Conflicts of Interest

The authors state that there is no conflict of interest in the submission of this work.

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