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Review Article

Markers of Angiogenesis and Methodological Approaches to the Study of Angiogenesis

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Abstract

The creation of new blood vessels is referred to as angiogenesis. Endothelial cells, which line the inside wall of blood arteries, migrate, proliferate, and differentiate during this process. Chemical cues in the body influence the process of angiogenesis. This study intends to highlight the expression of various angiogenic indicators throughout various diseases, the involvement of pro-angiogenic and anti-angiogenic factors during angiogenesis, and the use of angiogenic inhibitors during antiangiogenic therapy, particularly in cancer.

Keywords: Angiogenesis, Angiogenesis Markers, Pro-Angiogenic Factors, Anti-Angiogenic Factors, Anti-Angiogenic Therapy

Introduction

Angiogenesis, or the formation of new blood vessels from pre-existing vessels that allow oxygen and nutrients to reach the body's tissues, is not only important during embryogenesis and wound healing, but it also plays a role in the pathogenesis of many diseases, including cancer, proliferative retinopathy, and chronic inflammatory conditions. Angiogenesis regulation is linked to disorders like rheumatoid arthritis, diabetes, atherosclerosis, and cancer. Angiogenesis is a tightly controlled process.

The sequence of events that leads to new vessel formation begins with endothelial cell activation by an angiogenic stimulus, which causes the basement membrane and extracellular matrix to breakdown; then, the endothelial cells migrate and divide, forming new vessels, which mature with basement membrane reconstruction as the final step in the sequenc [1].

Angiogenesis inducers include members of the vascular endothelial growth factor (VEGF) family, angiopoietins, transforming growth factors, platelet-derived growth factor, thrombospondin-1 (TSP-1), tumor necrosis factor-alpha (TNFα), interleukins, and members of the fibroblast growth factor family. Angiogenesis occurs when proangiogenic and antiangiogenic factors fall out of balanc [2].

Proangiogenic factors and Antiangiogenic factors

Classical and non-classical proangiogenic factors (PFs) that activate in tumors induce angiogenesis [3]. Proangiogenic factors (PF) are potential targets of antiangiogenic therapies (e.g. monoclonal antibodies). All PFs induce the overexpression of several signaling pathways that lead to the migration and proliferation of endothelial cells and pericytes contributing to tumor angiogenesis and survival of cancer cells [4].

Proangiogenic factors are classed as classical or non-classical angiogenic factors.

Classical proangiogenic factors
- Vascular endothelial growth factor (VEGF)
- Fibroblast growth factor-2 (FGF-2)
- Platelet-derived growth factor (PDGF)
- Platelet-Derived Endothelial Cell Growth Factor (PD-ECGF)
- Angiopoietins (Ang)
- Hepatocyte growth factor (HGF)
- Insulin-like growth factors (IGFs)

Non-classical proangiogenic factors
- Stem cell factor (SCF) Stem cell factor (SCF) is a GF overexpressed in various inflammatory diseases
- Tryptase. Tryptase is a preformed active neutral serine protease that is abundantly stored in the MC secretory granules.
- Chymase.

The main proangiogenic factors include VEGF and members of the angiopoietin family. Alternative splicing produces a variety of VEGF isoforms. The proliferation and migration of endothelial cells, as well as an increase in blood artery permeability, are all impacts of VEGF. VEGF binds to the VEGFR-1 and VEGFR-2 tyrosine kinase receptors, which are mostly produced by endothelial cells [5]. The most potent pro-angiogenic protein is vascular endothelial growth factor-A. It causes endothelial cells to proliferate, sprout, and form tubes.

Tie-2 is the receptor for angiopoietins [6]. Angiopoietin-1 promotes the development and stabilization of newly created vasculature by working in tandem with VEGF. Angiopoietin-2 is thought to be a natural angiopoietin-1 antagonist that makes endothelial cells more sensitive to the effects of VEGF.

Angiogenesis is significantly influenced by inflammatory mediators. Proangiogenic agents, such as VEGF or angiopoietins, upregulate many pro-inflammatory pathways, resulting in leukocyte recruitment, infiltration, and inflammatory mediator release [7]. The interaction of inflammation and angiogenesis is demonstrated by the ability of VEGF to drive T cells towards a T helper 1 phenotype by increasing IFN- and lowering IL-10 production [8].

Thrombospondins (TSP), angiostatin, and endostatin are the most important anti-angiogenic factors. TSP-1, -2, -3, -4, and TSP-5/COMP are now part of the TSP family. They carry out a variety of tasks by binding to matrix proteins, plasma proteins, and cytokines [9-12].

The involvement of proangiogenic and antiangiogenic factors in the angiogenesis process

Urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), and metalloproteinases (MMPs) act as proangiogenic factors during basement membrane disintegration, whereas tissue inhibitors of metalloproteinases (TiMPs) and Plasminogen Activator Inhibitor (PAI) act as antiangiogenic factors. During endothelial cell migration, vascular endothelial growth factors (VEGF-A, VEGF-B, VEGF-C, VEGF-D) behave as proangiogenic factors, while thrombospondin and angiostatin act as antiangiogenic factors. Platelet-derived growth factor (PDGF), platelet-derived endothelial cell growth factor (PDECGF), and fibroblast growth factor (FGF) all operate as proangiogenic agents during endothelial cell proliferation. Antiangiogenic factors such as endostatin and prolactin may be present. Proangiogenic factors such as angiopoietin 1, tumor growth factor (TGF-), epidermal growth factor (EGF), and angiogenin are involved in the formation of lumen-bearing cords. Antiangiogenic agents include interferons and angiopoietin 2 [4].

Angiogenic inhibitors during cancer treatment

Angiogenesis inhibitors are distinct cancer-fighting drugs in that they impede the formation of blood vessels that support tumor growth rather than tumor cell growth [13].

Angiogenesis inhibitors disrupt blood vessel creation at various stages in a variety of ways Some are monoclonal antibodies that identify and bind to VEGF selectively. The VEGF receptor cannot be activated when VEGF is coupled to these medications. Other angiogenesis inhibitors bind to VEGF and/or its receptor, as well as other receptors on endothelial cell surfaces and other proteins in downstream signaling cascades, and prevent them from acting. Some angiogenesis inhibitors are antiangiogenic immunomodulatory medicines (agents that stimulate or suppress the immune system) [13].

Angiogenesis inhibitors appear to be most effective when coupled with other medications in some malignancies. Angiogenesis inhibitors are given over a long period because they function by slowing or preventing tumor growth without destroying cancer cells [13].

Expression of different angiogenesis markers in various diseases. Expression of Angiogenesis Markers in Rheumatoid Arthritis (RA) and Cardiovascular diseases following Rheumatoid Arthritis.

Rheumatoid arthritis is an inflammatory and autoimmune illness. Uncontrolled cell division, an inflammatory condition, and the creation of new vessels are all features of RA, just as they are in cancer. The synovial membrane and tendons have an inflammatory infiltration, as well as synovial-membrane hyperplasia. The loss of function is caused by the destruction of cartilage and subchondral bone. The progression of chronic disease is aided by the proliferation of blood vessels. The synovial mass requires a considerable amount of nutrients and oxygen, and the enlarged vascular network allows inflammatory cells and pro-inflammatory cytokines easy access to the synovium. In addition to the growth in blood vessels, the location of blood vessels inside the synovium changes,

Hypoxia promoted by synovial proliferation, together with the release of pro-inflammatory factors, acts as a powerful proangiogenic stimulus. Hypoxia-inducible factor (HIF) is highly inducible by hypoxia and inflammatory mediators, promoting angiogenesis and contributing to the pathogenesis of RA [14]. HIF induces the expression of proangiogenic factors and stabilizes VEGF gene transcription.

The rheumatoid synovium expresses a variety of proangiogenic factors [15,16]. Some of these factors, such as FGF, PDGF, HGF, and EGF, are not specific to angiogenesis. Overexpression expression of angiogenesis factors, most prominently VEGF, angiopoietins -1 and -2, and the angiopoietin receptor, tie-2, is found in inflammatory joint disorders, including RA [17-22]. In addition, in the rheumatoid synovium, upregulation of adhesion molecules occurs and is reduced with treatment, most commonly TNF-antagonist therapy [18].

In vivo and in vitro, conventional DMARDs, as well as NSAIDs and glucocorticoids, have been demonstrated to have antiangiogenic effects. Proangiogenic mediator inhibition or the delivery of cytokines that typically inhibit angiogenesis, such as angiostatin and thrombospondin [23-28].

The risk of cardiovascular disease is increased in those with RA. Increased amounts of circulating inflammatory mediators in RA may promote endothelial cell activation and damage, contributing to endothelial dysfunction. Early-stage atheroma lesions are characterized by endothelial dysfunction. Atheroma development is strongly linked to abnormalities in arterial endothelial function. RA is linked to changes in endothelial cell morphology and function, as well as changes in the number and distribution of blood vessels [23].

Even in young patients with minimal cardiovascular risk factors, endothelial impairment has been found in early-stage RA [29]. Treatment increases endothelial function, particularly with TNF-antagonists [30-32]. Endothelial progenitor cells (EPCs) are responsible for the development of new blood vessels in adults, and their absence has been linked to poor cardiovascular outcomes. They are also a biological marker for vascular function and increased cardiovascular risk. EPC levels in the peripheral blood of patients with active RA are lower. In individuals with inactive illness or those using TNF blockers or glucocorticoids, EPC levels are within normal limits [33].

Angiogenesis markers during kidney diseases.
The influence of angiogenic factors and chronic kidney disease

Higher circulating VEGF-A and pentraxin-3 levels, as well as a lower angiopoietin-1/VEGF-A ratio, may be related to an increased risk of CKD due to the role of an angiogenic factor imbalance in the etiology of kidney disease. Angiopoietin-1 treatment reduced tubular damage in unilateral ureteral obstruction, lowered albuminuria in streptozotocin-induced type 1 diabetes [16], and stabilized peritubular capillaries in folic acid nephropathy, albeit with profibrotic and inflammatory effects. Angiopoietin-1 deficiency, along with microvascular stress, resulted in organ damage, increased angiogenesis, and fibrosis [22].

The findings on the connection between angiogenic factors and CKD in humans are somewhat inconsistent, most likely due to differences in sample size, research population, angiogenic factor sources, and covariables included in the studies. In a small cohort study, vascular endothelial growth factor (VEGF)-A predicted CKD progression in diabetic individuals [23]. However, another study found that VEGF expression was reduced in biopsied kidney tissue from diabetic nephropathy patients [20]. In dialysis patients, elevated soluble VEGF receptor-1 (sVEGFR-1) and decreased VEGFR-2 were related to mortality [24, 25]. Angiopoietin-1 regulates endothelial cell migration, adhesion, and survival, and co-expression of angiopoietin-1 and VEGF promotes angiogenesis [26].

In CKD patients, angiopoietin-1 levels are lower and angiopoietin-2 levels are higher [30,31]. Angiopoietin-2 [31-33] and angiopoietin-1 have been linked to subclinical CVD in CKD [33]. Angiopoietin-2 has been linked to an increased risk of death in CKD patients [30]. Pentraxin-3 can bind fibroblast growth factor-2 (FGF2) and operate as an FGF2 antagonist, inhibiting FGF2-dependent angiogenesis [32].

Angiogenesis Markers in Patients with Renal Cell Carcinoma Receiving Sunitinib Therapy

In patients with advanced renal cell carcinoma, sunitinib is a tyrosine kinase inhibitor (TKI) that targets tumor angiogenesis (RCC) [34].

Angiogenesis is critical in the development of renal cell carcinoma, and clear cell renal cell carcinoma (CCRCC). Because of their anti-angiogenic properties, VEGF-targeted treatments have been implicated in the management of RCC and CCRCC. These treatments have also been shown to improve the survival rate of individuals with advanced kidney cancer [35,36]. Abnormal VEGF expression in renal cell carcinoma correlates with advanced stage, high nuclear grade, and increased microvascular density.
A study evaluating the effect of anti-angiogenic medicines, such as bevacizumab, found that circulating VEGF levels were reduced [37].

PDGF is a powerful mitogen that has also been linked to tumor angiogenesis [38]. PDGF expression is controlled during hypoxia by hypoxia-inducible factor 1 (HIF1) and other HIF1-independent processes.

CA9 is an enzyme that is generally activated by HIF-1 during hypoxia. CA9 expression was found to be a favorable predictive factor in patients with metastatic clear-cell RCC [39]. CCND1 has been demonstrated to be a HIF2 downstream target and has been employed to detect HIF activation [40]. Angiogenesis indicators are useful in analyzing angiogenesis in tissue and the expression of angiogenesis markers is frequently enhanced in kidney tumors [41]. The majority of clear cell RCCs have mutations in the tumor suppressor gene VHL, which leads to increased expression of growth factors such as VEGF, platelet-derived growth factor (PDGF), insulin-like growth factor 2 (IGF2), and erythropoietin via downstream induction of transcription factors of hypoxia-inducible factor 1 (HIF) [42]. The constitutive overexpression of these genes is believed to enhance the pathophysiological development of RCC by causing excessive vascularization and the inappropriate activation of signaling pathways that lead to cell proliferation and apoptosis inhibition.

Sunitinib is a tyrosine kinase inhibitor that targets VEGFR1, VEGFR2, VEGFR3, and PDGFR/ [43]. Sunitinib has been shown in several clinical trials to be particularly effective against clear cell RCC [43,44]. This medication has been demonstrated to produce an objective response in roughly 30-40% of patients [38]. Importantly, sunitinib therapy has been proven to improve PFS.

The Relationship Between Angiogenesis Markers and Acute Kidney Injury and Mortality following Cardiac Surgery

Acute kidney injury (AKI) occurs in 5% to 42% of individuals after heart surgery. Severe or protracted AKI has been linked to an increased risk of death, as have end-stage renal disease and earlier stages of chronic kidney disease (CKD). Renal hypoxia caused by capillary rarefaction is thought to have a role in the pathophysiology of the AKI-to-CKD transition.

Before and after surgery, plasma concentrations of two proangiogenic markers (vascular endothelial growth factor A [VEGF] and placental growth factor [PGF]) and one antiangiogenic marker (soluble VEGF receptor 1 [VEGFR1]) were measured. After heart surgery, plasma VEGF concentrations decreased 2-fold, but PGF and VEGFR1 concentrations increased 1.5- and 8-fold, respectively.

High levels of pro-angiogenic markers, vascular endothelial growth factor A isoform (VEGF), and placental growth factor (PGF), in postoperative plasma, were independently related to a lower risk of AKI. High postoperative levels of an anti-angiogenic marker, soluble VEGF receptor 1 (sVEGFR1), also known as sFlt-1, on the other hand, were independently linked to an increased risk of AKI.

VEGF is a crucial growth factor for angiogenesis, playing an important role in endothelial survival, peritubular capillary maintenance, and interstitial matrix modeling [45,46]. VEGF is present largely in podocytes and the thick ascending limb, but it is also detected in proximal and distal tubules. VEGFRs (VEGFR1 and VEGFR2) are found in peritubular capillaries and glomerular capillary loops in endothelial cells. PGF is a proangiogenic chemical that stimulates the development of new blood vessels via the same receptor that VEGF does, VEGFR1. When sVEGFR1 attaches to VEGF or PGF, its activities are neutralized, and it acts as an antiangiogenic molecule [47].

VEGF production is enhanced in the presence of hypoxia via hypoxia-inducible factor-mediated transcriptional upregulation [40)], and it represents an adaptive mechanism that promotes repair. The loss of angiogenic factors, particularly VEGF, has been linked to capillary loss following AKI [48]. Tubulointerstitial fibrosis occurs in animal models after capillary loss, implying that hypoxia caused by capillary rarefaction hinders redifferentiation of regenerated tubules.

Upregulation of VEGF improves kidney function, and VEGF injection after ischemia-reperfusion injury reduces capillary rarefaction [49].

In addition, VEGF treatment during cardiopulmonary bypass protects kidney function by improving renal microcirculation via nitric oxide-mediated vasodilation and inhibiting neutrophil accumulation and leukocyte adhesion [50]. High plasma VEGF levels, on the other hand, have been linked to higher mortality in experimental sepsis models [51].

Whereas sFlt-1 or anti-VEGF antibody administration has been linked to lower mortality [52]. Similarly, elevated serum VEGF levels have been linked to an increased risk of AKI and death in individuals with influenza and acute respiratory distress syndrome [53].

Serum PGF levels were not observed to be significantly higher in AKI compared to controls in short cross-sectional research [54]. Furthermore, giving a single angiogenic agent may promote the growth of aberrant vasculature and produce inflammation, exacerbating hypoxia and tubulointerstitial fibrosis [45].

Anti-VEGF medications have been linked to the development of hypertension, proteinuria, and kidney injury in oncology. Similar results can be seen when sFlt-1 is administered during pregnancy.

Angiogenesis Markers' Impact on Cardiovascular Diseases.
01)Effect of glucose on VEGF expression:
Hypoglycemia enhances VEGF expression, which returns to normal after re-equilibration of the glucose concentration [55,56]. This is most likely caused by an increase in intracellular CA2+ levels in a glucose-depleted environment, which results in the activation of protein kinase C. This mechanism activates Angiopoiten-1, resulting in increased VEGF expression [57]. Not only does hypoglycemia promote VEGF expression, but so does hyperglycemia, both of

02)Inflammation
The presence of inflammatory cells such as macrophages and neutrophils is enough to cause angiogenesis. Following cardiac necrosis, an influx of inflammatory cells such as macrophages, monocytes, and platelets causes the release of cytokines capable of boosting the expression of fibroblast growth factor and vascular endothelial growth factor [58,59]. The vascular endothelial growth factor can activate and recruit additional macrophages to stimulate the inflammatory response and angiogenesis.

03)Angiogenic growth factors
The isolation of tumor factors that promote mitogenic activity in endothelial cells led to the discovery of angiogenic factors [60-62]. They are induced by a wide range of cells, and their functions include development and tumor angiogenesis. Angiogenic growth factors are so named because of their propensity to generate cell proliferation in vitro, which contributes to the process of angiogenesis in vivo, as evidenced by animal model studies. We shall discuss a few of these development factors briefly:

04)Fibroblast growth factor(FGF)
The first angiogenic growth factor found as a member of a family now consists of at least 20 compounds with significant mitogenic potentials, including some of the most potent angiogenic peptides [61-63]. Smooth muscle cells and vascular endothelial cells create them. The ability of the FGF family to interact with heparin-like glycosaminoglycan of the extracellular matrix is

one of its characteristics [64]. FGF-1 and FGF-2 are the two most studied isoforms[65-65].

05)Vascular endothelial growth factor (VEGF)
It was first isolated as a vascular permeability factor from tumor cell ascites [69]. It is currently recognized as a multifunctional peptide capable of promoting both in vivo and in vitro receptor-mediated endothelial cell proliferation and angiogenesis. It is essential for embryonic vascular development as well as adult pathophysiology. VEGF is a family of five members, and their action is mediated by three receptors (VEGFR)[70-73].

06)Placenta growth factor
It has limited angiogenic activity in vitro, although it appears that PLGF and VEGF co-express in vivo [74-76].

07)Angiopoietin
Angiopoietin1 (Ang1) is expressed in tissue near blood arteries, implying a paracrine method of action. Angiopoietin 2 (ANG2) is present at tissue remodeling sites [77-80].

08)VEGF receptors
The effect of VEGF on endothelial cells in humans is mediated by two membrane-spanning receptors, VEGFR1 and VEGFR2. Both receptors have strong VEGF affinity [81-83]. VEGFR1 promotes cell motility, has a function in blood vessel organization, and regulates monocyte and macrophage gene expression. While VEGFR2 is important in mitogenesis, endothelial cell differentiation, cell migration encouragement, and vascular permeability increase,

Expression of Tumor Angiogenic Markers During Tumor Growth.
VEGFs and their receptor VEGFR-2 (KDR) have a substantial impact on the process of angiogenesis, among other growth factors such as PDGFs, FGFs, and cytokines. After activation, KDR undergoes auto phosphorylation, which leads to endothelial cell proliferation, tumor angiogenesis, tumor development, and metastasis.

VEGFR-2 overexpression has been seen in a variety of cancers, including breast cancer, cervical cancer, non-small cell lung cancer, hepatocellular carcinoma, renal carcinoma, and others. Several VEGFR-2 inhibitors have been developed throughout the last decade. Angiogenesis suppression by VEGFR-2 inhibition is a new technique for developing selective and targeted anticancer medicines.

Many tumors rely on an angiogenic switch after reaching a diameter of 1–2 mm, making tumor angiogenesis one of the hallmarks of early malignancy [84]. As a result, the ability to visualize and quantify tumor angiogenesis may not only allow antiangiogenic treatment monitoring in cancer patients, but it may also be an elegant approach for screening and detecting cancer at an early, still curable stage, just after the angiogenic switch in tumor progression [85].

Several molecular angiogenic markers are overexpressed in tumors and may be exploited as early cancer detection targets. v3 Integrin, endoglin, and vascular endothelial growth factor receptor (VEGFR) 2 are three well-studied molecular indicators of tumor angiogenesis [86-88]. These angiogenic markers are seen on tumor vascular endothelial cells in a variety of solid tumors, including breast ovarian [88,89], and pancreatic cancer [90], and are thought to be key factors in tumor angiogenesis [89-93]. Integrin v3, a glycoprotein composed of a noncovalently bound subunit, forms a heterodimeric transmembrane receptor

for extracellular matrix components such as fibronectin, fibrinogen, von Willebrand factor, vitronectin, and proteolyzed collagen and laminin [94,95].

These extracellular matrix components stimulate signaling cascades that influence gene expression, cytoskeletal architecture, cell adhesion, and cell survival, causing tumor cells to become more invasive, migratory, and capable of surviving in a variety of microenvironments [94]. Endoglin (CD105) is a transmembrane glycoprotein that is mostly expressed in endothelial cells that are actively undergoing angiogenesis, such as tumor endothelial cells [96]. It is a component of the TGF-1 receptor complex, a pleiotropic cytokine involved in cellular proliferation, differentiation, and migration [97]. Endoglin inhibition increased TGF-1's ability to restrict growth, migration, and the ability of developed endothelial cells to form capillaries.

VEGFR2 is a tyrosine kinase endothelial receptor that is activated by VEGF A. The VEGF/VEGFR2 pathway activates various signaling networks, resulting in endothelial cell survival, mitogenesis, migration, differentiation, and vascular permeability [98].

It is essential in developing novel molecular imaging methods aimed at seeing tumor angiogenesis markers that are overexpressed in early-stage cancer for screening reasons. Knowledge of the temporal expression levels of tumor angiogenic markers could also be relevant for drug development and personalizing future treatment regimens in cancer patients.

Targeted contrast material–enhanced ultrasonography (US) is a potential noninvasive molecular imaging technique that permits in vivo assessment of tumor angiogenesis molecular markers [99-101]. Because the contrast chemicals used for this imaging method have a diameter of several micrometers, they remain inside the vascular compartment, allowing for the exclusive observation of angiogenesis-related molecular markers expressed on tumor vascular endothelial cells [102].

Discussion

By all accounts and based on verified results, it appears that understanding the activation of proangiogenic factors, estimating the pathway of angiogenesis, and studying the influence of antiangiogenic factors may aid in the development of an effective treatment for diseases with pathological angiogenic conditions, especially for several malignancies.

Angiogenesis is thus a potential therapeutic target. The potential use of several angiogenesis inhibitors is now being studied in clinical trials. A greater understanding of the biology of angiogenesis may lead to the identification of new therapeutic targets for a variety of disorders connected with this complex process.

Tumor angiogenesis is important in tumor growth and metastasis. Tumor angiogenesis is a complex process involving several components and several distinct or similar signal pathways. Despite fast development in the field, there are numerous unanswered questions about the molecular process of tumor angiogenesis. Once we fully comprehend the precise activities of these pro-and anti-angiogenic molecules in tumor angiogenesis, therapeutic use of those innovative study findings for tumor therapy will be achievable [10-105].

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