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Review Article

Antiangiogenic mechanisms and factors in breast cancer treatment

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Abstract

Breast cancer is known to metastasize in its latter stages of existence. The different angiogenic mechanisms and factors that allow for its progression are reviewed in this article. Understanding these mechanisms and factors will allow researchers to design drugs to inhibit angiogenic behaviors and control the rate of tumor growth.

Keywords: Angiogenesis, breast cancer, metastasis, therapy, tumor vasculature

INTRODUCTION

The human body has the ability to form new blood vessels from existing vessels to ensure proper vascularization during embryonic growth, reproductive cycles, and proper wound healing. Vascularization from preexisting blood vessels is termed angiogenesis. While angiogenesis is beneficial in most processes, it is also what maintains tumor growth and malignancy. Cancer has the ability to grow and metastasize if ample vascularization is successfully maintained; hence, hindering cancer growth via anti-angiogenic mechanisms has generated research interest. To properly understand the anti-angiogenic mechanisms, it is imperative that pro-angiogenic mechanisms and growth factors that induce these processes be studied in detail.

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Cancer cells need ample blood supply to enable metastatic processes including angiogenic factor induction and signaling, growth stimulating factor induction and signaling, enabling proteolytic enzymes, expressing cell adhesion proteins, and exerting resistance to immunogenic molecules.[1] To achieve the metastatic behavior, growth factors and other such molecules are released in order to induce nondifferentiated stromal cells to the site of tumor growth. These cells, also known as mesenchymal stem cells (MSCs), enable tumor growth by providing tumor cells with the necessary signals. MSCs, which are located in the bone marrow and can undergo osteogenesis; chondrogenesis; and adipogenesis if needed, are shown to increase breast cancer progression and metastasis by allowing cell motility via chemokine

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secretion.[2] Furthermore, MSCs have been shown to secrete vascular endothelial growth factor-A (VEGF-A) and interleukin-6 (IL), which are potent angiogenic factors in breast cancer growth.[3]

ANGIOGENIC MECHANISM

Understanding angiogenic mechanisms and studying the different factors which bring about healthy angiogenesis can allow researchers to inhibit angiogenic behaviors, which in turn can lead to a better awareness of how to induce tumor suppression. Through these studies, we can determine the role of angiogenesis and its impact on breast cancer tumor progression.

Distinguishing between regular angiogenesis and tumor-associated angiogenic processes is imperative for effectively treating breast cancer. In humans, regular angiogenesis can be defined as the integration of endothelial cell precursors that form capillary plexus and later become blood vessels. Some processes in which normal angiogenesis occurs include embryo nutrition, tissue repair, and physiological changes associated with growth. During these common processes, there is an intricate balance between pro- and anti-angiogenic signals that is rigorously maintained, in order for newly formed blood vessels to attain maturity and stability in a timely manner.[4] However, in tumor-associated angiogenesis, the balance between these angiogenic factors is lost, allowing blood vessels to develop uncontrollably. This negative shift leads to changes in normal vasculature characteristics including their physical properties.[4,5]

TUMOR VASCULATURE AND ANGIOGENESIS

Tumor vasculature is markedly distinct from normal vasculature in that blood vessels that supply tumor tissue are irregularly sized and arranged in a disorganized manner, where they share characteristics of arterioles, capillaries, and venules simultaneously. In normal tissue vessels, blood flow and density are controlled by the tissue's metabolic needs to avoid over-feeding or under-feeding its cells.[6,7] However, in tumor vasculature, sporadic blood flow is observed, leading to damaged capillary network systems.[7,8]

Tumors are composed of various cellular components that allow for effective angiogenic growth. First, functional vasculature contains adipose tissue that is surrounded by stromal cells that provide a proper framework for the developing tumor's vascular network. White adipose tissue (WAT) maintains vascular growth and has been shown to aid breast cancer development and progression in mouse models,[9] while brown adipose tissue (BAT) enables metabolic processes, such as efficient oxygen and nutrient transport that aids tumor growth.[10] WAT and BAT are both known to be in charge of producing angiogenic factors, with the most common ones in relation to breast cancer being VEGF A, B, and C; basic fibroblast growth factor (bFGF)/FGF-2; matrix metalloproteinases (MMPs); and IL-8.[10,11] The release of these factors is strictly dependent upon the pro-versus antiangiogenic balance at the adipose tissue pad that is in proximity to the tumor tissue.[10]

Another element responsible for tumor vasculature formation and angiogenesis is vascular endothelial cells, which are recruited by growth factors such as VEGF and bFGF/FGF-2 to propagate, migrate and form tube-like structures.[12,13] Endothelial precursor cells migrate from the bone marrow into the bloodstream, where they eventually settle into a niche and begin forming new blood vessels, with the help of VEGF, FGF, and platelet-derived growth factor.[7,14-16] It is these newly formed blood vessels that provide vascular networks for the burgeoning tumor to grow, eliminate waste from its rapidly dividing cells, and allow metastasis.[17]

The earliest stage of tumor angiogenesis occurs when VEGFs cause vasodilation of existing capillaries that enables diffused plasma proteins to lay down a matrix for endothelial cells to migrate to and loosen the smooth pericyte covering of the blood vessel. This process is aided by the involvement of the tyrosine kinase receptor 2 (TIE2) and one of its ligands, angiopoietin-2 (ANG-2).[18] The vascular membrane and matrix are then degraded in order for endothelial cells to gain entrance into the lumenal space and migrate toward the pro-angiogenic stimuli. In normal angiogenic endothelial migration, pericyte processes decrease cell proliferation and decrease VEGF dependence.[13] This behavior is unseen in tumor tissue angiogenesis, where the pericyte influence on endothelial proliferation is curtailed or sometimes nonexistent. As is the case of VEGF-A inhibition by blood vessels, other cytokines such as ANG-1 and placental growth factor (PlGF) are known to send growth signals to endothelial cells.[4,7,19,20] In addition, VEGF can interact with the tumor via different pathways such as PI3K/AKT and mitogen-activated protein kinase (MAPK),[21,22] as well as express an E-cadherin repressor that is involved in breast cancer cell invasiveness.[23]

ANGIOGENIC FACTORS AND THEIR ROLES IN BREAST CANCER PROGRESSION AND TREATMENT

Tumor cells establish angiogenesis by secreting various angiogenic factors. The most studied and understood of these factors are VEGF and IL-8. VEGF and IL-8 secretion are especially apparent in breast cancer angiogenesis,[19,22,24-28]

in addition to bFGF/FGF-2 and MMPs. Current research shows that tumor angiogenesis requires a combination of the aforementioned factors, if not all of them, in order for a tumor to efficiently undergo development and potential metastasis.[4,29,30]

Vascular endothelial growth factors

While VEGFs are most known for their role in endothelial cell proliferation and migration, their expression has been observed in macrophages; epidermal cells; thrombocytes; and tumor cells, with involvement in normal physiological processes such as development; osteogenesis; and wound healing, in addition to numerous pathologies.[31-34] Five mammalian VEGF ligands exist, VEGF-A/B/C/D and PlGF, which can interact with three different VEGF receptors (VEGFR), VEGFR-1/2/3.[32,35-37] Of the VEGF ligand-receptor interactions, the ones most involved in breast cancer development, progression, and metastasis are VEGF-A and VEGFR-1 or 2.[35-42]

In tumor angiogenesis, each VEGF family member plays some role, either directly or indirectly, to enhance pathological progression. As previously stated, the most expressed VEGF member, VEGF-A, stimulates angiogenesis most potently via its interaction with VEGFR-2,[32,33,39-41,43] even though it interacts with a higher affinity with VEGFR-1. VEGFR-1 can act as a decoy receptor that can control VEGF-A interaction with, and activation of, VEGFR-2, and ultimately impact angiogenesis and its involvement in tumor development.[32,33,37,43]

VEGF-B, which is highly expressed in the brain and skeletal system, as well as breast tumors, promotes angiogenesis indirectly by binding VEGFR-1 on endothelial cells in order to initiate plasminogen activation, and eventually, metastasis.[17,33-35,42,44-46] VEGF-C promotes angiogenesis and lymphangiogenesis via still unknown mechanisms through its binding with VEGFR-2 and VEGFR-3, respectively, while VEGF-D is known to ensure lymphatic vessel growth.[17,33-35,42] High overall VEGF expression levels are associated with breast cancer aggressiveness and metastasis, as well as poor treatment responsiveness.[36,47]

Finally, PlGF, which only binds and activates VEGFR-1, is primarily known for its role in embryogenesis; however, recent studies have demonstrated its involvement in cancer development via its pro-inflammatory, pro-angiogenic actions that aid metastasis.[35,48,49]

Interleukins

ILs are a class of cytokines secreted by cells in response to various stimuli, in order to initiate the immune response to a pathological condition. IL-8, a member of the IL class, is produced by a variety of cells, including endothelial and tumor cells, in order to activate its receptors, CXCR1 and 2, and potentiate signaling pathways that can relate to cell migration and mobilization and angiogenesis, which are important for breast cancer progression and metastasis.[22,26-28,50,51] Secretion of IL-8 is elicited in response to the presence of several chemokines and growth factors, including VEGF and MMPs, to facilitate the aforementioned physiological processes.[4,28] Studies have shown that tumors, including breast carcinomas, expressing high levels of IL-8 are found to be more aggressive and invasive, and less responsive to traditional treatment protocols, making it a target to future antiangiogenic therapies.[4,22,26,27,51,52]

Fibroblast growth factors

In addition to VEGF, FGFs are also known to be a family of potent angiogenic motivators with an association with breast cancer risk.[53] While FGF-1 is known as the acidic polypeptide, FGF-2 is the bFGF polypeptide and has been shown to aid in proliferation and differentiation of endothelial cells.[54,55]

The bFGF/FGF-2 protein is known to exist in five isoforms as a result of multiple polyadenylation sites and altered mRNA translation, where they are categorized into low or high molecular weight forms.[56-58] The 18 kDa bFGF/FGF-2, which is the most common FGF, interacts with all four high-affinity FGF-receptors (FGFRs), but specifically FGFR-1 and FGFR-2-IIIC, with the help of heparan sulfate proteoglycans that are located on the cell surface.[59-62] bFGF/FGF-2 activation is thought to occur following the degradation of heparan sulfate within the extracellular matrix (ECM), which leads to sprouting of new blood vessels.[63,64] Molecules in the extracellular environment, such as heparan sulfate proteoglycans; integrin receptors; ECM proteins; cytokines; and serum components, can alter FGF-2/FGFR-2 interactions, which can enhance tumor progression and metastasis through regulation of angiogenesis, although less so than the aforementioned growth factors.[55,59,61,62,65]

Matrix metalloproteinases

Finally, a class of proteolytic enzymes called MMPs, is involved in angiogenesis through their ability to remodel the ECM. Some of the initial steps of angiogenic blood vessel formation, which include destabilization of the established blood vessel wall and degradation of matrix proteins in order for mobilization and migration of endothelial cells, are performed by MMPs.[66-75] MMPs, which are divided into at least five categories based on the matrix substrates they destabilize-collagenases (MMP-1, MMP-8, and MMP-13), gelatinases (MMP-2 and MMP-9), stromelysins (MMP-3,

MMP-10, and MMP-11), matrilysins (MMP-7), and elastase (MMP-12) are initially secreted as inactive zymogens and then activated extracellularly by other proteolytic enzymes.[66-68,71,73,75] As a result, MMPs are currently being studied for their role in breast cancer invasion and metastasis.[67,71-73,76-78] MMPs are typically regulated by a group of natural inhibitors, known as tissue inhibitors of metalloproteinases, which are being investigated for their contribution to cancer development and as potential treatments.[4,67,73,75,79]

EXAMPLES OF ANGIOGENIC INHIBITORS AND THEIR MODES OF ACTION

Numerous antiangiogenic compounds exist in various phases of development to clinical practice, both endogenous and exogenous; however, this section will examine a select few of the most commonly studied inhibitors including interferons-α/β, endostatin, angiostatin, thrombospondin (TSP), and decorin.

Interferons-α/β

Interferons-α/β are types of class I interferons that regulate the immune system and control cell growth and differentiation, two important aspects of tumor formation. During the last two decades, research on interferons-α/β has shown that they have the ability to impair tumor angiogenesis via downregulation of mRNA expression of the growth factor bFGF/FGF-2 and reduced expression of the MMP-2 gene,[80,81] making their development as potential antiangiogenic therapies crucial.[82]

Endostatin

Endostatin is a naturally occurring fragment of collagen XVIII generated by tumor cell proteases that inhibits endothelial cell proliferation and migration.[83-86] Endostatin is thought to have several possible mechanisms of action in relation to the inhibition of tumor angiogenesis including prevention of tumor necrosis factor alpha (TNFα) activation of the JNK signaling pathway,[87] antagonism of the cell surface receptors a_v- and a_5-integrins,[86] and inhibition of cell cycle progression of endothelial cells.[85] The JNK signaling pathways, c-Jun NH2-terminal kinase, are activated by different types of cellular stresses and signals and utilizes TNFα to elicit cell death.[87]

As previously stated, endostatin inhibits TNF activation of JNK and pro-angiogenic genes dependent on it.[87] In reference to the cell cycle, endostatin causes G1 arrest by decreasing the phosphorylated state of retinoblastoma genes and cyclin D1 mRNA and protein expression.[88] While the protein itself has not shown any direct cytotoxicity in tumor cells, gene transfer has been hypothesized as a means of delivery in order to induce apoptosis and ultimately tumor regression/inhibition,[82,85] which has proven successful in a breast cancer study that exhibited a 90% reduction in tumor growth compared to the untreated control.[89]

Angiostatin

As with endostatin, angiostatin is a proteolytic fragment of a larger protein, specifically, plasminogen, that acts as a metastatic suppressor by blocking the formation of blood vessels and is thought to impair tumor progression.[82,85,90-92] One mechanism by which angiostatin, whose receptors include adenosine triphosphate (ATP) synthase and integrin $\alpha_v\beta_3$, is hypothesized to inhibit tumor growth is via the binding of ATP synthase at its catalytic subunit.[93] As a result, ATP synthesis is terminated, leading to inhibition of the cells' uncontrolled proliferation.[92,93]

In addition, prolonged angiostatin treatment has also been shown to inhibit the activation of the MAPK, extracellular-signal-regulated kinases-1 (ERK1) and ERK2, by FGF-2 or VEGF in human skin vascular cells.[94] The MAPK/ERK pathway functions in cellular proliferation, differentiation, and even survival following phosphorylation of specific threonine and tyrosine residues.[94] ERKs regulate growth factor-responsive targets in the cytosol and are also able to translocate to the nucleus, where they phosphorylate a number of transcription factors that regulate gene expression. The role of FGF-2, which is to stimulate phosphorylation of ERK-1 and 2, is blocked by angiostatin;[89,94] this leads to a loss of integrity of the cell cycle and eventually impairment of angiogenesis.

Finally, other potential mechanisms of action by which angiostatin inhibits angiogenesis are through suppression of VEGF activities and arrest of the cell cycle at the G2-to-M transition.[89] As with endostatin, angiostatin has been considered as an antiangiogenic gene therapy due to issues with delivery and treatment with its protein form.[82,85,95]

Thrombospondin

TSPs are a family of five matricellular glycoproteins involved in cell proliferation, migration, and survival through their interactions with numerous cell surface and ECM proteins, indicating their importance in angiogenesis. Significant research shows that TSPs, which are identified in breast cancer, can act as potent endogenous antiangiogenic factors that inhibit the aforementioned cellular processes within endothelial cells, leading to tumor suppression.[96-101]

The most studied of the TSPs is TSP-1, which binds $\alpha_v\beta_3$ integrins, heparin sulfate proteoglycans, transforming growth factor-β (TGF-β), and other ECM proteins and

proteases, and inversely regulates proliferation and migration of vascular smooth muscle and endothelial cells.[100-102] Through its various peptide binding sequences, TSP-1 acts as a tumor suppressor by inhibiting bFGF/FGF-2 and VEGF through binding heparin sulfate receptors on the cell surface and ECM or inhibiting MMP-9 activation, inhibiting angiogenesis via its interaction with the RGD sequence on $\alpha_v\beta_3$ integrins, inhibiting tumor growth through its binding and activation of TGF-β, and inducing apoptosis by inhibiting MMP-9 activation.[100,102-109] TSP-2, which is structurally similar to TSP-1, demonstrates similar antiangiogenic, antitumor capabilities making it another option for drug development.[110,111]

Decorin

Decorin is a member of a family of small leucine-rich proteoglycans involved in various cellular processes including matrix organization, formation/"decoration" of collagen fibrils, wound healing, and maintenance of cell proliferation through its interaction with other ECM proteins and growth factors.[112-122] Decorin, which is secreted by mesenchymal cells; connective tissue cells; and tumor stromal cells, inhibits tumor angiogenesis; progression; and metastasis through its interactions with such receptors and proteins as EGFRs; TGF-β; VEGF and VEGFR-2; and bFGF/FGF-2 making it a potential anticancer treatment.[116,117,119,121-156]

While one of decorin's mechanisms of angiogenic and growth inhibition may involve the potential impeding of epidermal growth factor receptors (EGFRs) interaction with EGF due to an overlap in binding sites,[145] it is known that its interaction with EGFR leads to MAPK activation, utilization of intracellular calcium, upregulation of the cell cycle cyclin-dependent kinase inhibitor, p21, and a drastic reduction in EGFR activity, in addition to internalization and lysosomal degradation of the receptor.[116,117,119,121,122,132,134,135,140-142,144,146,148,157] In the case of breast cancer, which exhibits high EGFR expression, specifically ErbB2 (human epidermal growth factor receptor 2), decorin inhibits the receptor's synthesis and activity, while reducing cell growth and migration, leading to a reduction in tumor size at the primary site, as well as the development and expansion of metastases within the lungs.[117,119,121,122,141,144,151,154]

TGF-β is a growth factor secreted by most cells, including healthy and cancerous breast tissue that is multifaceted in its involvement in all aspects of cell survival and death. Depending on the stage of breast cancer development and progression that the growth factor is present, it can act as either a pro- or anti-oncogenic protein. In the case of late stage, aggressive, metastatic breast cancers, TGF-β is highly oncogenic making it a frequent target for therapies. In the presence of decorin binding, TGF-β, and subsequently, its receptor's activity is impaired leading to tumor suppression.[119,121,122,125,127,128,130,137] Decorin is also known to inhibit tumor angiogenesis and growth through its negative interactions with VEGF and its receptor and bFGF/FGF-2 by downregulating VEGF and bFGF/FGF-2 expression and activities, and by binding VEGFR-2 to impair its interaction with, and ultimate activation by, VEGF.[118,121,122,136,149,155,156]

CLINICAL TRIALS FOR ANTIANGIOGENIC TREATMENTS IN BREAST CANCER

Numerous therapies to combat angiogenesis in breast cancer have passed from clinical trials to use with varying levels of success; however, they can all be divided into different categories based on what aspect of tumor angiogenesis they affect, including those that inhibit pro-angiogenic growth factors and/or their receptors (such as VEGF-A and VEGFR-1 and -2), ECM proteins (such as integrins), endothelial cell quantitative and spatial expansion/spreading, and proteases (such as MMPs).[17,24,158-160] A few examples of drugs that have undergone clinical investigation, and their mechanisms of action are described here.

Bevacizumab

Bevacizumab, also called Avastin, is a humanized monoclonal antibody that binds VEGF-A and impairs its activity and interactions with VEGFR-1 and -2, leading to a reduction in tumor growth.[33,47,158,159,161-165] As the first US Food and Drug Administration (FDA) approved antiangiogenic, it was utilized as a combination treatment with other chemotherapeutics for metastatic colon cancer,[166] with its single and combinatorial use expanded to nonsmall cell lung cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, advanced kidney cancer, glioma, leukemia, and breast cancer.[19,47,158-160,167-187] In a phase II study testing only bevacizumab in 75 patients with metastatic breast cancer patients that had received treatment in the past, only 9.3% responded effectively with four being progression-free beyond a year.[158,168] While treatment with bevacizumab alone or in combination with traditional chemotherapy was well-tolerated, it produced a range of side effects including bleeding and blood clots, abnormal excreted protein levels, and high blood pressure.[158,167] Since completion of the phase II Cobleigh study (2003), additional phase II and phase III trials utilizing bevacizumab in combination with capecitabine demonstrated improvements in response rates, but no noticeable changes in progression-free or overall survivals rates, while its use with taxanes; cyclophosphamide; doxorubicin; and gemcitabine resulted in extended

progression-free survival lengths.[154,160,187-195] While a majority of these studies were performed in later stage, metastatic breast cancer patients, other trials completed in individuals diagnosed with early breast cancer also exhibited increased response rates when compared to those receiving standard care protocols.[160,196,197] As November 2011, bevacizumab's FDA approval for use as a metastatic breast cancer therapy was removed due to lack of significant improvements in response and survival; however, it continues to be investigated in various breast cancer treatment trials and prescribed in clinical practice.[198]

Cilengitide

Cilengitide is classified as an antiangiogenic drug due to its ability to inhibit the cellular adhesion receptors $\alpha_v\beta_3/\alpha_v\beta_5$ integrins.[107,164,199,200] Cilengitide has shown effectiveness in preclinical studies through its induction of cell detachment and reduced proliferation in a panel of four breast cancer cell lines, as well as enhanced treatment effectiveness and cell death and inhibited bone metastasis that was furthered when combined with radiotherapy when utilized in breast cancer xenografts.[200-202] Cilengitide has been investigated in glioblastoma, nonsmall cell lung cancer, and prostate cancer with noted tumor reduction and negligible toxicity; however, overall survival was not significantly increased compared to currently-available treatments.[203-206] Currently, a phase I trial is underway to evaluate cilengitide as a combination therapy with paclitaxel in patients with advanced solid tumors, particularly those diagnosed with high-grade, aggressive breast cancers.[207]

Vitaxin

Vitaxin, also referred to as Abegrin, is a humanized monoclonal antibody that affects the vitronectin receptor, $\alpha_v\beta_3$ integrin, leading to impaired endothelial cell expansion and tumor growth.[158,208,209] Previous clinical studies have been performed with Vitaxin, but showed little results, leading to its modification to Abegrin.[209] In a small scale, phase II study investigating Abegrin's effects in various metastatic cancer patients that had received prior treatment, including one individual breast cancer, the drug was well tolerated but did not produce clinically relevant results, possibly due to its specificity for $\alpha_v\beta_3$.[208]

CONCLUSIONS AND FUTURE PROSPECTIVE

Despite the fact that angiogenesis is a naturally occurring process that is necessary for activities ranging from embryonic development to wound healing, it also possesses detrimental aspects that are involved in disease occurrence and progression. When the angiogenic balance is disturbed and various signaling pathways are exploited, uncontrolled cell growth occurs, which can result in the propagation of cancer. Through the use of natural inhibitors such as endostatin, angiostatin, TSP, and decorin, the likelihood of tumor progression and metastasis are reduced, though not eliminated. Although most antiangiogenics have proven poorly effective against breast cancer, their development and investigation in clinical trials have provided a basis for identifying drug targets that can impair tumor angiogenesis, and potentially tumor growth and migration. While more effective treatments to combat tumor angiogenesis appear to be further in the future, continued investigation is necessary to establish potential new therapies, as well as to determine the possibility to repurpose old drugs.

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Conflicts of interest

There are no conflicts of interest.

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