Angiogenesis in Cancer

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Introduction

It took two centuries to describe the role of angiogenesis inhibitors in tumor shrinkage by Judah Folkman, after the term angiogenesis was initially coined by John Hunter. Even later, the vascular endothelial growth factor (VEGF) was discovered by Napoleon Ferrara. This concept of angiogenesis has revolutionized the field of oncology in better understanding the mechanism of cancer progression, resulting in the development of numerous targeted therapies for cancer treatment. Hence, in 2000, Hanahan and Weinberg rightly enumerated the induction of angiogenesis as one of the hallmarks of cancer.

Definition

The terms vasculogenesis and angiogenesis, both meaning formation of new vessels, are used interchangeably, but they have a clear difference. Vasculogenesis is the process of the de novo blood vessel formation in early life (during embryogenesis), either from circulating or tissue-resident endothelial stem cells, while angiogenesis is the process of new blood vessel formation in later life (after birth) by the extension from a preexisting vessel (sprouting) or by division within the vessel (splitting).[1]

Types of Angiogenesis

Sprouting

This type of angiogenesis involves the release of angiogenic growth factors, which bind to corresponding receptors on the endothelial cell (EC). This binding leads to production of proteases, which degrades the basement membrane. Through chemotaxis, EC escapes and migrates to the tumor, incorporates, and proliferates in tumor stroma. This results in solid sprouts (pericytes and smooth muscle cells), followed by formation of lumen and branching of the new blood vessel.

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Splitting/Intussusceptive

This model of angiogenesis involves the extension of the capillary wall into the lumen and splits a single vessel into two. It has four phases.: First, two opposing capillary walls establish a contact zone. Second, the EC junctions are reorganized, and the two-layered vessel is perforated facilitating the entry of growth factors. In the third step, a core consisting of pericytes and smooth muscles is formed between the two new vessels at the contact zone. Finally, the core is separated and two new blood vessels are formed.

Role of Angiogenesis

The physiological angiogenesis is seen in wound healing, tissue regeneration, and in menstruation. Pathologically, angiogenesis plays an important role in tumorigenesis, diabetic retinopathy, and in chronic Inflammation.

Angiogenic Switch

Up to the volume of 2 mm^3, the tumor can derive oxygen and nutrients from surrounding vessels through diffusion and beyond this critical volume results in a hypoxic environment. This hypoxia stimulates the production of hypoxic inducible factor-1 alpha (HIF-1α). This HIF-1α is destroyed in normal cell with normoxemic conditions. However, in hypoxia, this protein is not destroyed and its level is upregulated leading to turning "ON" mode of angiogenic switch. Once angiogenesis is initiated, the grade of neovascularization of the tumor depends on the subtle balance between proangiogenic and antiangiogenic factors (►**Fig. 1**), which in turn is dependent on tumor biology. Examples of hypervascular tumors are renal cell carcinoma and thyroid cancer. The typical example of hypovascular tumors is pancreatic adenocarcinoma.

Steps of Angiogenesis in Cancer

- Angiogenic switch
- Secretion of chemokines
- EC activation

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- EC proliferation
- Directional migration
- Extracellular matrix (ECM) remodeling
- Tube formation
- Loop formation and organization into arteries and veins
- Vascular stabilization

Differences between Tumoral Blood Vessels and Normal Blood Vessels

Tumoral blood vessels are disorganized (tortuous and undefined) and unevenly distributed. These are excessively dilated, and are highly permeable (leaky) due to lack of basement membrane, pericytes intermittently, resulting in sluggish flow with leaking of blood into the tumoral tissues. This leads to increased interstitial pressure in the tumor resulting in decreased drug delivery to tissues.[2]

Pathways Modulating Angiogenesis

1. Direct-acting:
   i. VEGF pathway:
   Increases vascular permeability and stimulates EC migration and proliferation
   - VEGF receptors: 1,2,3
   - VEGF ligands: A, B, C
   - ECM proteins
   - Matrix metalloproteinases cause basement degradation
   - Integrins help in migration and organization into tubes
   - Angiopoietin and Tie 2
     - Angiopoietin 1 and Tie 2 recruit peri-ECs and pericytes
     - Angiopoietin 2 and Tie 2 stabilize the ECs

   ii. DLL4-notch pathway
   Promotes functional vessels downstream of VEGF both physiologically and pathologically
2. Indirect/secondary pathways:
   These pathways redirect cells to the site of angiogenesis that is mediated by transforming growth factor-α (TGF-α), TGF-β, hepatocyte growth factor, androgens, and estrogens.

Strategies for Antiangiogenic Therapies

- Drugs that stop formation of new blood vessels by sprouting (angiogenesis inhibitors).
- Drugs that attack the tumor's established blood supply (vascular disrupting drugs).
- Drugs attacking both cancer cells or immune cells and blood vessels (dual/double-barreled approach)

A. Approved antiangiogenic agents: Table 1 summarizes the various FDA approved anti- angiogenics till date.

B. Vascular disrupting agents: These drugs target the EC and its receptors are still investigational.

C. Combination therapies: Antiangiogenic therapies can be combined with radiation therapy, signal transduction inhibitors, oncolytic virus therapy, vascular disrupting agents, chemotherapy, or immune checkpoint inhibitors (ICI).

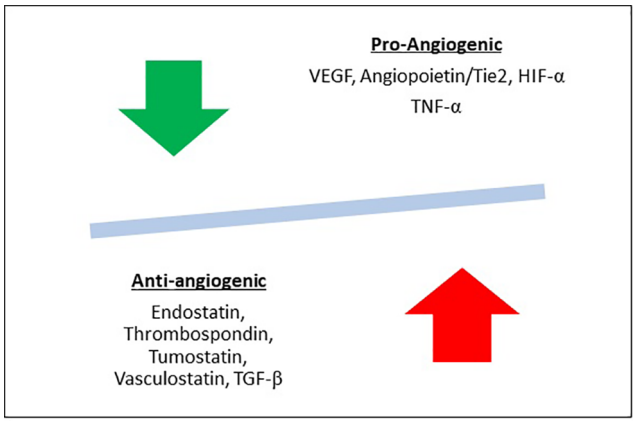

Fig. 1 The pro and anti-angiogenic factors in angiogenesis.

Table 1 Approved antiangiogenic agents

mAbs	Small molecule TKI—VEGF A, B, C, PDGFR	Drugs with secondary antiangiogenetic function
Bevacizumab – VEGF A	Sorafenib, sunitinib, imatinib, pazopanib, lenvatinib, regorafenib, cabozantinib, vandetanib, axitinib	Immunomodulatory drugs—thalidomide, lenalidomide mTOR inhibitors—Temsirolimus, everolimus EGFR TKI—gefitinib, erlotinib, afatinib EGFR mAbs—cetuximab, panitumumab COX2 inhibitors—Celecoxib HDAC inhibitors—Belinostat, Vorinostat
Ramucirumab—VEGFR 2		
Receptor fusion protein		
Ziv-Aflibercept-VEGF Trap—VEGF-A, VEGF-B, PlGF		

Abbreviations: PDGFR, Platelet derived growth factor receptor; COX, cyclo-oxygenase; EGFR TKI, epidermal growth factor receptor-tyrosine kinase inhibitors; HDAC, histone deacetylase; mAbs, monoclonal antibodies; mTOR, mammalian target of rapamycin; PlGF, placental growth factor; VEGF, vascular endothelial growth factor.

The Rationale for Chemotherapy and VEGF Combined Therapies

- More effective intratumoral delivery of chemotherapy drugs with normalized vasculature.
- Extended drug-free periods.
- Stem cells become more sensitive to chemotherapy after disruption of its microenvironment.
- Chemotherapy amplifies the antiangiogenic effect by direct action on ECs.

Clinical Implications

Few of the many indications for angiogenesis targeting therapies in combination with chemotherapy are enumerated in ►**Table 2**.

The Rationale for ICI-VEGF Combination Therapies

There are potential interactions of angiogenic pathways, in particular VEGF and tumor immune response. In the priming phase of the immune response, VEGF shall inhibit the dendritic cell maturation leading to reduced antigen presentation and also cause exhaustion of T cells by inhibiting their activation. In the effector phase, VEGF recruits myeloid-derived suppressor cells and regulatory T cells (Treg) and suppresses the activity of primed T cells in the tumor niche. VEGF also results in neoangiogenesis that can alter the quality and quantity of infiltrate of the tumor immune microenvironment adding to immune suppression. VEGF-induced immune suppression can be reversed by using VEGF TKIs and anti-VEGF antibodies which increases the efficacy of ICIs.[3]

Clinical Implications

In ►**Table 3**, some of the recently approved indications for ICI-VEGF combination therapies have been listed out.

Biomarkers for Antiangiogenic Therapies

There are no approved biomarkers to select patients for antiangiogenic therapies and some are under investigation.

- Circulating biomarkers—VEGF levels in serum, plasma, urine.
- Noninvasive imaging of blood vessels for a reduction in tumor microvessel density.
- Dynamic contrast-enhanced magnetic resonance imaging, computed tomography scan with flow parameters, high-frequency microultrasound, positron emission tomography-computed tomography.
- Elevated blood pressure (hypertension).
- Circulating endothelial progenitor cells.
- Tumor biopsy analysis for vessel density.
- Genetic VEGF single nucleotide polymorphisms.

Table 2 FDA-approved drugs for angiogenesis and their indications

	Drug	Indications
1.	Bevacizumab	Recurrent and/or metastatic GBM, mNSCLC, Stage III, IV and metastatic EOC, mCRC
2.	Ramucirumab	2nd line metastatic gastric/ GE junction adenocarcinomas, mCRC
3.	Panitumumab	KRAS wild mCRC
4.	Cetuximab	KRAS wild mCRC, mHNSCC
5.	Sorafenib	HCC,
6.	Sunitinib	RCC, GIST, Pancreatic NET
7.	Lenvatinib	mRCC, HCC
8.	Regorafenib	3rd line mCRC
9.	Pazopanib	RCC, metastatic soft tissue sarcomas
10.	Vandetanib, cabozantinib	Medullary thyroid cancer

Abbreviations: EOC, epithelial ovarian cancer; FDA, U.S. Food and Drug Administration; GBM, glioblastoma multiforme; GE, gastroesophageal; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal carcinoma; mHNSCC, metastatic head and neck squamous cell carcinoma; mNSCLC, metastatic nonsmall cell lung cancer; NET, neuroendocrine tumors; RCC, renal cell carcinoma.

Table 3 FDA-approved ICI-VEGF combination therapies and their indications

	Primary diagnosis	ICI-VEGF
1.	mNSCLC (adenocarcinoma)	Pembrolizumab + bevacizumab + chemotherapy (PD-L1 by TPS 1–49%)
1.	RCC	Pembrolizumab + axitinib, nivolumab + cabozantinib
2.	HCC	Atezolizumab + bevacizumab
3.	Endometrial carcinoma	Pembrolizumab + lenvatinib

Abbreviations: FDA, U.S. Food and Drug Administration; HCC, hepatocellular carcinoma; ICI-VEGF, immune checkpoint inhibitor vascular endothelial growth factor; mNSCLC, metastatic nonsmall cell lung cancer; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; TPS, tumor cell proportion score.

Side Effects of Antiangiogenic Therapies

Most common side effects of antiangiogenic therapies are bleeding (20–50%), gastrointestinal (GI) perforation (0.3–2.4%), arterial and venous thromboembolism (2.4%), and proteinuria (<1%). Angiogenesis, an important process for healing of surgical sites, is counteracted by the antiangiogenic therapies. Hence, anti-VEGF therapies are withheld 4 weeks prior to surgery and restarted 6 to 8 weeks postsurgery.

Contraindications of Antiangiogenic Agents

The most common U.S. Food and Drug Administration (FDA) labeled contraindications for antiangiogenic agents are hypersensitivity to that particular drug or its components, GI fistulas/perforation, and recent history of hemoptysis. Other contraindications specific to each drug include ocular or periocular infection, active intraocular inflammation (aflibercept), pregnancy (thalidomide and lenalidomide), severe hepatic impairment (Vorinostat), and history of asthma, urticarial, or allergic reaction to aspirin (celecoxib).

Mechanisms of Resistance to Antiangiogenic Drugs[4]

Intrinsic

Escape by different modes of vascularization

1. Vasculogenesis 2. Vascular Co-optation 3. Vascular mimicry

Acquired

1. Amplification of proangiogenic genes
2. Secretion of multiple proangiogenic factors
3. Recruiting proangiogenic bone marrow-derived dendritic cells

Conclusion

Despite being one of the hallmarks of cancer, targeting and treatment with single-agent antiangiogenic therapies gave disappointing results. This is probably due to the various resistance mechanisms as explained above. Combination therapies with chemotherapeutic drugs and ICIs have helped to overcome this hurdle. One has to be cautious about the bleeding and thrombotic complications of these drugs. Research is ongoing for newer ways of targeting angiogenesis with nanotechnology and use of bispecific allelic antibodies.

Conflict of Interest
None declared.

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