

Angiogenesis in Cancer; Pathogenesis and Drug Targets

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Adapted from Edition 3 of the Tocris Cancer Product Guide

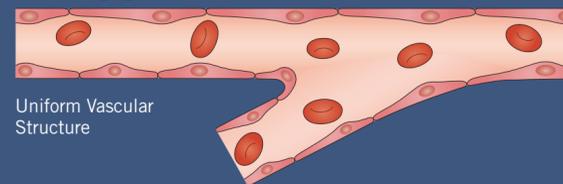
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Angiogenesis (also known as neovascularization) is the generation of new blood vessels from pre-existing vasculature. It is a hallmark of cancer and plays a key role in enabling tumor growth, progression and metastasis. This poster discusses differences between normal angiogenesis physiology, and tumor vascularization, and highlights therapeutic targets aimed at suppressing angiogenesis. Researchers are now favoring a combination of strategies, which target different stages of angiogenesis in order to prevent tumor growth and expansion.

Angiogenesis

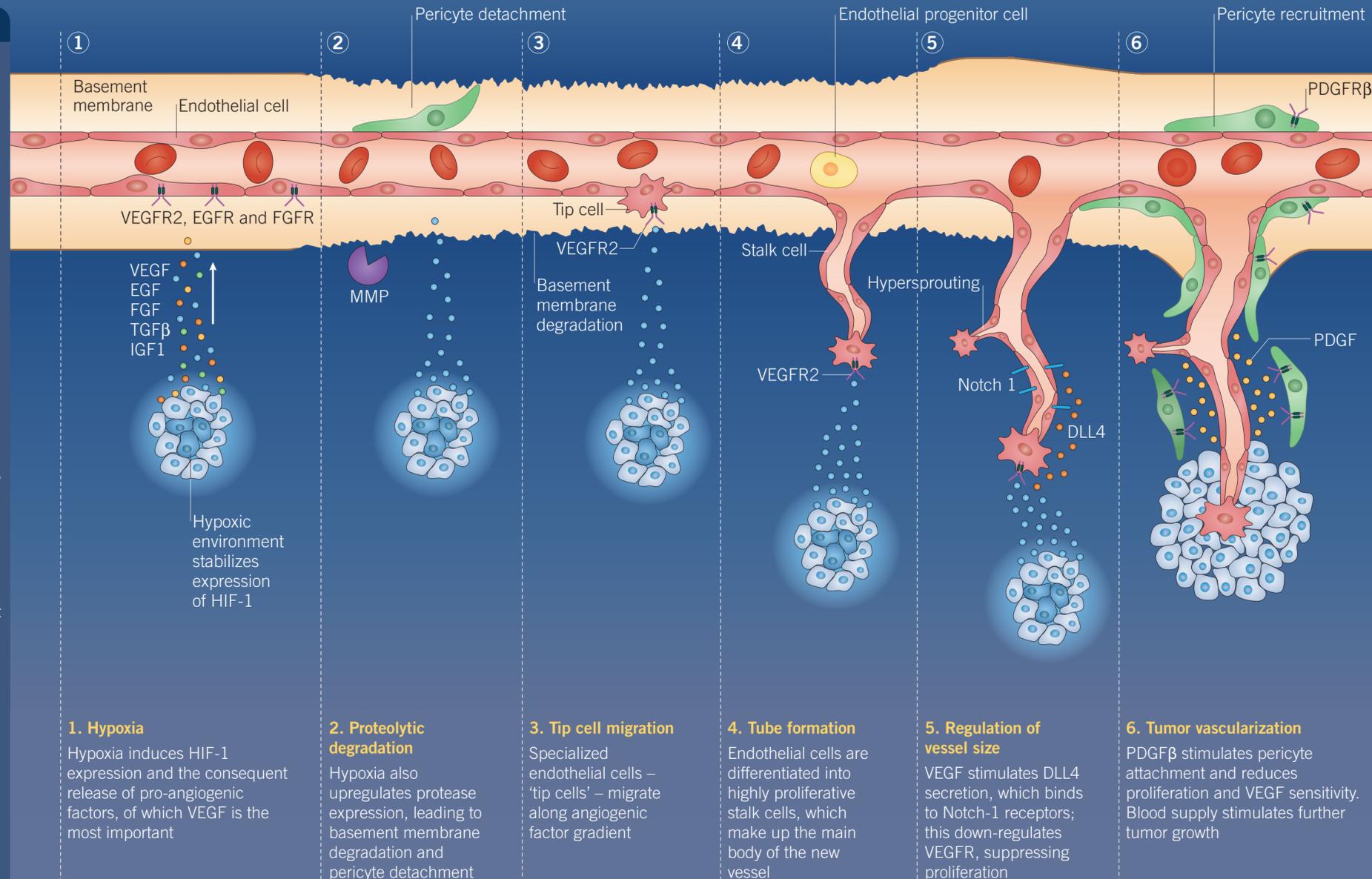
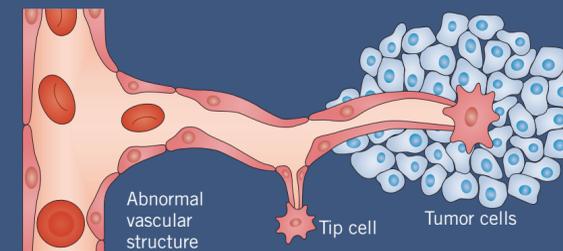
Angiogenesis is the generation of new blood vessels from pre-existing vasculature. It is a normal process in growth and development, which is required for the formation of arteries, veins, and capillaries in the embryo. Proliferation of new blood vessels also takes place in adults and is essential for the repair or regeneration of tissue during wound healing. Angiogenesis in normal tissues is a carefully regulated process, coordinated by pro- and antiangiogenic factors such as vascular endothelial growth factor receptor (VEGF) and endostatin respectively, to produce well-structured uniform vasculature.

Normal Angiogenesis



Angiogenesis is also a hallmark of cancer and plays a key role in enabling tumor growth, progression and metastasis. When a tumor develops, its size is limited by the availability of oxygen, glucose and other necessary nutrients from the existing vasculature. As a consequence of their genetic instability, tumors are heterogeneous in nature. Tumor angiogenesis can therefore differ significantly from physiological angiogenesis, producing poorly formed blood vessels with aberrant blood flow and differing permeability. In addition, factors such as a tumor's p53 status, can affect blood vessel formation because p53 regulates angiogenic cytokines.

Tumor Vascularization



1. Hypoxia

Hypoxia induces HIF-1 expression and the consequent release of pro-angiogenic factors, of which VEGF is the most important

2. Proteolytic degradation

Hypoxia also upregulates protease expression, leading to basement membrane degradation and pericyte detachment

3. Tip cell migration

Specialized endothelial cells – 'tip cells' – migrate along angiogenic factor gradient

4. Tube formation

Endothelial cells are differentiated into highly proliferative stalk cells, which make up the main body of the new vessel

5. Regulation of vessel size

VEGF stimulates DLL4 secretion, which binds to Notch-1 receptors; this down-regulates VEGFR, suppressing proliferation

6. Tumor vascularization

PDGFβ stimulates pericyte attachment and reduces VEGF sensitivity. Blood supply stimulates further tumor growth

Tumor Vascularization – Therapeutic Targets

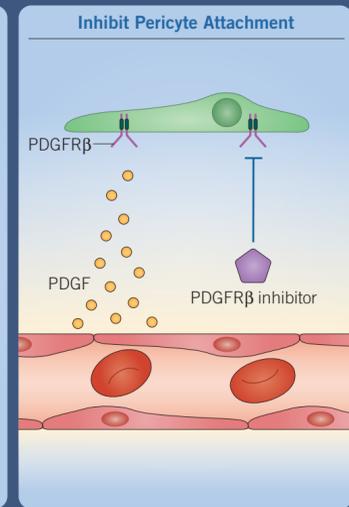
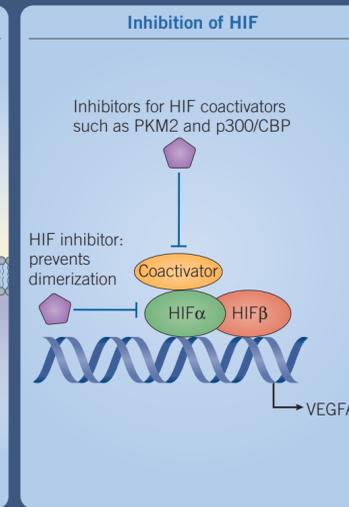
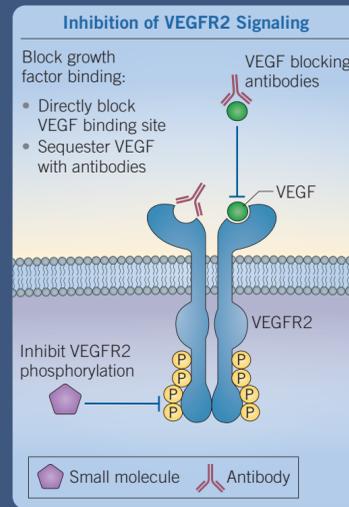
A primary trigger for the growth of new blood vessels in a tumor is hypoxia. Hypoxia inducible factor 1 (HIF-1) undergoes prolyl hydroxylation, which facilitates ubiquitination and its destruction. In a hypoxic environment the expression of HIF-1 is stabilized; HIF-1α associates with HIF-1β, initiating transcription by binding to the response element of HIF-responsive genes, as well as binding the cofactors p300/CBP and pyruvate kinase isoform M2 (PKM2). This leads to the secretion of proangiogenic factors that encourage new vessel formation.

Tumors secrete several proangiogenic factors that induce endothelial cell proliferation and facilitate vessel patterning. Their receptors are very important in antiangiogenic research; key targets include vascular endothelial growth factor receptor 2 (VEGFR2), epidermal growth factor receptor (EGFR) and fibroblast growth factor receptor (FGFR). The most important and commonly secreted proangiogenic factor is VEGF, which binds VEGFR2 and neuropilin, increasing vasodilation and vascular permeability.

Matrix metalloproteases (MMPs) are also secreted from tumor cells and from VEGF-stimulated endothelial cells. They help break down the extracellular matrix (ECM) and mobilize proangiogenic proteins from the stroma. Platelet-derived growth factor receptor β (PDGFRβ) activation stimulates the attachment of pericytes along the new vessel branch forming cell-to-cell and gap junctions, followed by basement membrane formation. Pericyte attachment reduces endothelial cell proliferation and their sensitivity to VEGF.

Finally, Notch signaling plays a key role in differentiating and shaping the new vascular branch. VEGF stimulates the tip cell to secrete Delta-like 4 (DLL4), which binds to Notch-1 receptors expressed on the stalk cells. This causes down-regulation of VEGFR, which suppresses endothelial cell proliferation, regulating the size of the vessel.

Each of these stages presents an opportunity for therapeutic interventions. Interruption of one or more of these can prevent vascularization of the tumor, cutting off vital nutrient supplies and oxygen, as well as preventing waste removal. Attenuating tumor vascularization can stunt the growth of the tumor or cause the tumor environment to become so toxic that the tumor cells die. Another strategy being looked at is the stabilization of angiogenesis in tumors, so that cytotoxic drugs can be efficiently delivered to the tumor cells.



Products available from Tocris

Antiangiogenics

- Obtustatin
- Combretastatin A4
- OGT 2115

EGFR

- AG 490
- AV 412
- Canertinib
- Iressa
- JNJ 28871063
- PF 6274484

FGFR

- FIIN 1
- SU 5402
- PD 173074

Focal Adhesion Kinases

- PF 573228
- PF 431396
- Y 11
- FAK Inhibitor 14

Hedgehog Signaling

- SAG
- GANT 61
- PF 5274857
- SANT-1
- Cyclopamine
- U 18666A

HIF

- ML 228
- DMOG
- TC-S 7009
- GN 44028
- IOX 2

Integrins

- Cilengitide
- α1 isoform
- Echistatin

Matrix Metalloproteases

- Batimastat
- GI 254023X
- GM 6001
- Marimastat
- WAY 170523

PDGFRβ

- SU 16f
- SU 6668

VEGFR

- Axitinib
- Sunitinib
- SU 5416

Wnt Signaling

- AZ 6102
- ICG 001
- CCT 031374
- IWP 2
- endo-IWR 1
- JW 67

Angiogenesis antibodies from our sister brands

R&D Systems

- hVEGF MAb (MAB293)
- hVEGF R2 MAb (FAB357P)
- hNeuropilin-1 PAb (AF3870)
- hPDGFRβ PAb (AF385)
- mDLL4 PAb (AF1389)

Novus Biologicals

- VEGF MAb (NB100-664)
- HIF-1α MAb (NB100-105)
- MMP-2 PAb (NB200-193)
- DNMT1 PAb (NB100-264)
- Actin Mab (NB100-74340)

References:
Greer et al (2012) *EMBO J*, 31 2448
Raza et al (2010) *Am J Hematol*, 85 593
Roca and Adams (2007) *Genes Dev*, 21 2511
Weis and Cheresh (2011) *Nat. Med.*, 17 1359

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