Technology Networks

What Is Angiogenesis?

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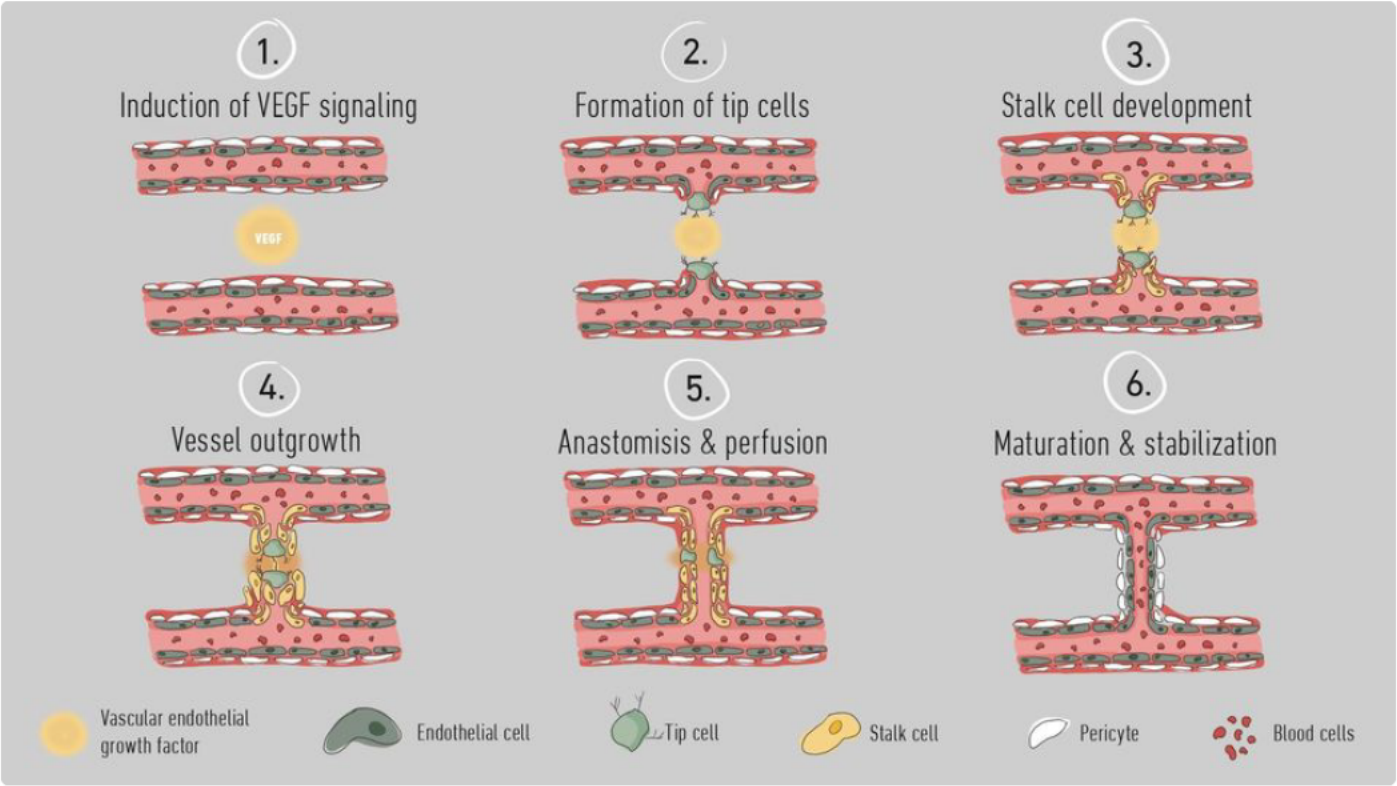

Angiogenesis is the formation of new blood vessels, an essential process that facilitates tissue growth and wound healing in living things. However, diseases like cancer can take advantage of angiogenesis and use it to grow and spread. In this article, we will describe the different types of angiogenesis, how it goes out of control in cancer and how we can use drugs to inhibit angiogenesis and reduce tumor growth.

Angiogenesis definition

Angiogenesis is defined as the process by which new blood vessels are formed

from existing ones. The term angiogenesis comes from the words “angio” meaning blood vessels and “genesis” meaning creation.

Angiogenesis begins during embryo development, when the growth of new blood vessels is essential for the development of new cells and tissues. The new veins, arteries and capillaries are needed to supply cells with oxygenated blood and nutrients and take away deoxygenated blood and waste products. In adult organisms, the endothelial cells that line the inside of blood vessels (the lumen) are largely dormant. However, specific signals can reactivate these cells and induce angiogenesis when their environment is low in oxygen (hypoxic), after injury or in placenta formation during pregnancy.

Angiogenesis was first described in 1794, with the observation that pronounced metabolic activity is dependent on the extent of the vascular system.[1] More recent research investigating how angiogenesis works in cancer began in 1971 with the hypothesis that the growth of cancerous tumors is dependent on angiogenesis.[2]

Regulation of angiogenesis

Angiogenesis is a tightly regulated process. Strict control is necessary to make sure that new vasculature is only formed when and where it is needed, and organisms have several “off” and “on” switches to facilitate this.

If these signals controlling angiogenesis are unbalanced, this can result in the abnormal formation of blood vessels, which can play a role in the pathogenesis of many diseases. Increased angiogenesis can lead to diseases such as cancer, arthritis, retinopathy and atherosclerosis.[3] On the other hand, impaired angiogenesis can lead to heart and limb ischemia and delayed wound healing.[4]

Therefore, it is important to maintain this balance between pro-angiogenic and

anti-angiogenic signals, which is known as the “angiogenic switch”. This steady equilibrium is maintained through the activity of cellular signaling pathways, particularly through the activation of growth factor receptors.

Pro-angiogenic factors include[5]:

- **VEGFR** – vascular endothelial growth factor receptor
- **EGFR** – endothelial growth factor receptor
- **PDGFR** – platelet-derived growth factor receptor
- **TIE2** – angiopoietin-1 receptor

Anti-angiogenic factors and endogenous angiogenesis inhibitors include[6]:

- Angiostatin
- Endostatin
- Thrombospondin

Types of angiogenesis

Angiogenesis is split into two main types: sprouting angiogenesis and intussusceptive angiogenesis. These occur both in adult organisms and *in utero*, taking place in nearly all organs and tissues.

Sprouting angiogenesis

First discovered almost 200 years ago, sprouting angiogenesis is the more well understood of the two types. During sprouting angiogenesis, new blood vessels sprout from pre-existing ones following a gradient of growth factor signals

produced by endothelial cells.[1,7] It is initiated and driven by the secretion of pro-angiogenic growth factors such as VEGF.

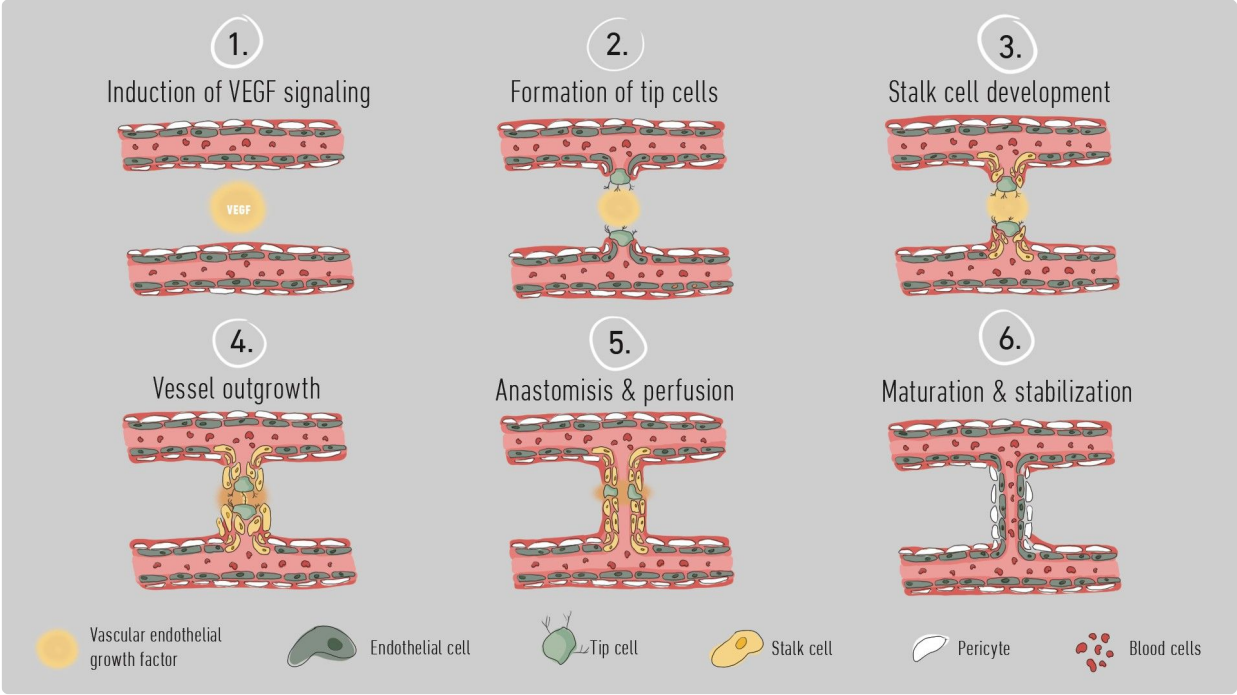

Figure 1: *The stages of sprouting angiogenesis.*

The main stages of sprouting angiogenesis are:

1. **Induction of VEGF signaling** – Cells near blood vessels produce VEGF, which forms a gradient of high to low intensity.
2. **Formation of tip cells** – The endothelial cell exposed to the strongest VEGF signals becomes a "tip" cell. Tip cells have thin cellular processes called filopodia, which secrete enzymes designed to degrade the extracellular matrix and guide the extension of the developing vessel across the VEGF signal gradient.
3. **Stalk cell development** – The tip cell stimulates NOTCH signaling in adjacent cells, transforming them into "stalk" cells as the tip cell follows the VEGF gradient.
4. **Vessel outgrowth** – Stalk cells proliferate and drive the outgrowth of the new

vessel.

5. **Anastomosis and perfusion** – As stalk cells proliferate, opposing tip cells are guided together, fusing the new vessels in a process called anastomosis. A continuous lumen is created that allows blood to flow between the pre-existing vessels.
6. **Maturation and stabilization** – Finally, recruitment of pericytes and deposition of extracellular matrix along the walls of the vessel result in maturation and stabilization.

Intussusceptive angiogenesis

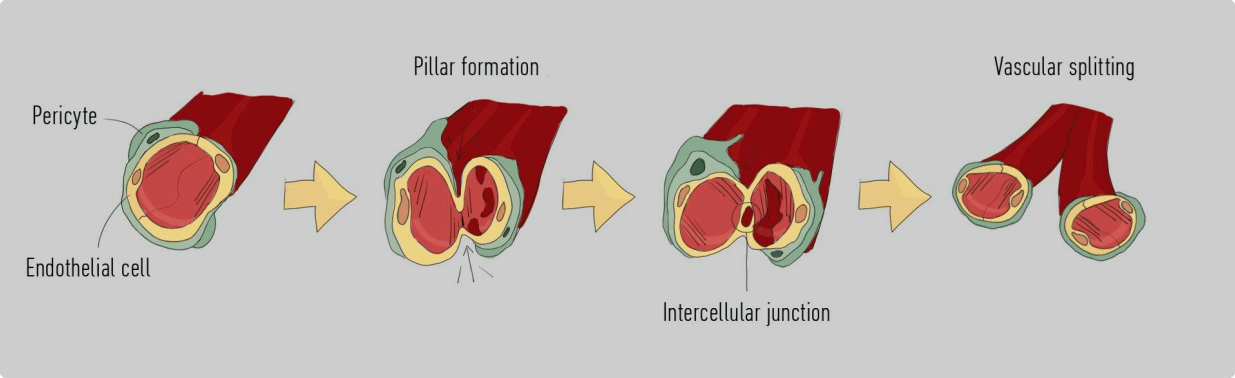

Figure 2: *The stages of intussusceptive (splitting) angiogenesis.*

Intussusceptive angiogenesis was first discovered in 1986 and is less well understood than sprouting angiogenesis.[7] Also known as "splitting" angiogenesis, pre-existing vessels are effectively split in two. Small hollow pillars form within the pre-existing vessel, eventually expanding to create two parallel capillaries. This is thought to be quicker and more efficient than sprouting angiogenesis, initially only requiring the reorganization of existing endothelial cells and not the growth or proliferation of new cells.[1]

Intussusceptive angiogenesis occurs throughout life, taking place in the eye,

intestine, kidney, ovary and uterus. It is also particularly important in embryo development; a situation where fast growth is needed without being too energetically demanding.

Angiogenesis in cancer

Cancer and angiogenesis were first linked in 1971 with the observation that malignant tumors have extensive vascular networks while benign tumors do not.[2]

Sustained angiogenesis is one of the fundamental hallmarks of cancer.[8] Tumor cells gain the ability to flip the "angiogenic switch", resulting in an overabundance of pro-angiogenic signals and a lack of endogenous anti-angiogenic signals. This promotes their growth and spread to other parts of the body in a process known as metastasis. During metastasis, blood vessels carry tumor cells to establish themselves in distant sites, typically in the liver, lungs and skeletal system.[9]

In this way, angiogenesis and cancer go hand-in-hand, as tumors cannot grow more than 2–3 mm^3 in diameter without support from the growth of additional blood vessels. To do this, tumors use both sprouting and intussusceptive angiogenesis to secure extra blood supply and provide themselves with oxygen and nutrients.[7]

Without an adequate blood supply, rapidly growing tumor cells suffer from a lack of oxygen and become hypoxic. Hypoxia is a key part of angiogenesis in tumors as it upregulates many pro-angiogenic signals, often through hypoxia-inducible factors (HIFs). HIFs are transcription factors that activate and upregulate the transcription of various genes in response to low oxygen availability. HIFs bind to areas of DNA within target genes known as hypoxia response elements (HREs). Once bound, HIFs activate the transcription of genes such as *VEGF*, thereby increasing angiogenesis.[10]

Angiogenesis inhibitors

Several angiogenesis inhibitors, also known as anti-angiogenics, have been developed and approved by regulatory authorities such as the U.S. Food and Drug Administration (FDA) to treat cancer. These prevent tumors from growing new blood vessels, cutting off the incredibly resource-hungry cancer cells from much-needed nutrients and oxygen. In this way, angiogenesis inhibitors "starve" tumors with the goal of preventing them from growing and metastasizing, or even helping to shrink them.

Anti-angiogenic drugs have been approved for several cancers such as kidney, colorectal and lung cancer. However, the success of angiogenesis inhibitors has been limited as they are often effective only for short periods before the cancer cells become resistant. Resistance is common and is often acquired through tumor cells activating alternative cellular pathways that induce blood vessel growth.[11]

Anti-angiogenic therapy is given either as a pill or through a vein (intravenously). These inhibitors can be used on their own (i.e., as monotherapy) or in combination with other treatments such as chemotherapy or radiotherapy. Using angiogenesis inhibitors as a combination therapy can help increase the efficacy of the drug(s) they are paired with and reduce the likelihood of developing drug resistance.[9]

Examples of angiogenesis inhibitors and their targets are summarized in the table below, along with examples of some of the cancer types they are approved to treat (this is not an exhaustive list).[11,12]

However, there are many possible side effects of anti-angiogenics.[12] This is because angiogenesis is still needed to create new blood vessels in non-cancerous,

Drug name	Target(s)	Approved cancer type(s)
Axitinib (Inlyta)	VEGFR, PDGFR	Kidney
Bevacizumab (Avastin)	VEGF-A	Cervical, colorectal, glioblastoma, kidney, liver, non-squamous small-cell lung cancer (NSCLC)
Cabozantinib (Cometriq, Cabometyx)	VEGFR	Kidney, liver, thyroid
Lenvatinib (Lenvima)	VEGFR1–3, PDGFR	Endometrial, kidney, liver, thyroid
Ramucirumab (Cyramza)	VEGFR2	Colorectal, liver, NSCLC, stomach
Regorafenib (Stivarga)	VEGFR1–3, TIE2	Colorectal, gastrointestinal, liver
Sorafenib (Nexavar)	VEGFR, PDGFR	Kidney, liver, thyroid
Sunitinib (Sutent)	VEGFR, PDGFR	GI, kidney, pancreatic neuroendocrine

healthy tissue.

Relatively common side effects include:

- High blood pressure (hypertension)
- Dry, itchy, rash-prone skin

- Diarrhea
- Fatigue
- Impaired wound healing

More serious side effects can also occur with anti-angiogenesis inhibitors, such as bleeding, blood clots and holes in the intestine (bowel perforations) – although these are very rare.

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