Technology Networks

What Is Angiogenesis?

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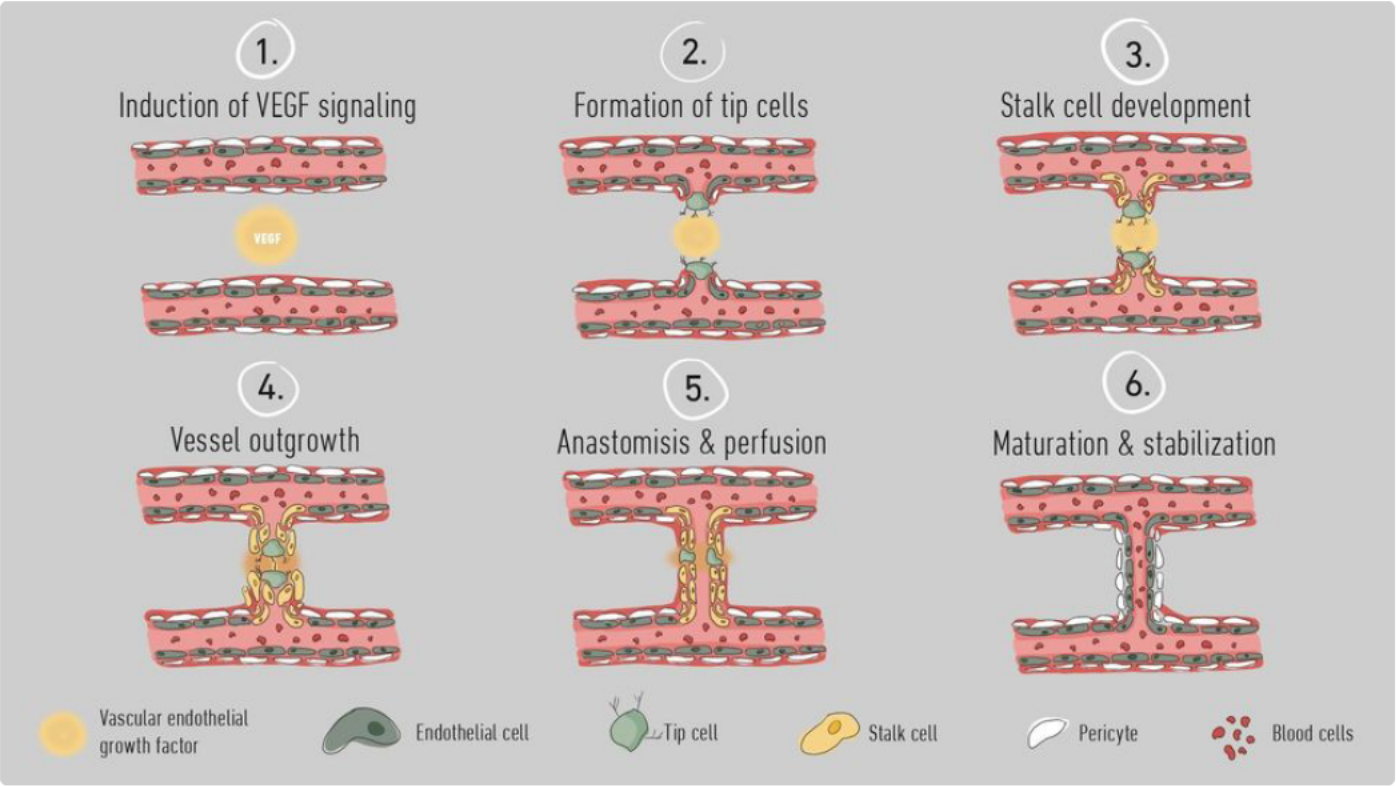

Angiogenesis is the formation of new blood vessels, an essential process that facilitates tissue growth and wound healing in living things. However, diseases like cancer can take advantage of angiogenesis and use it to grow and spread. In this article, we will describe the different types of angiogenesis,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

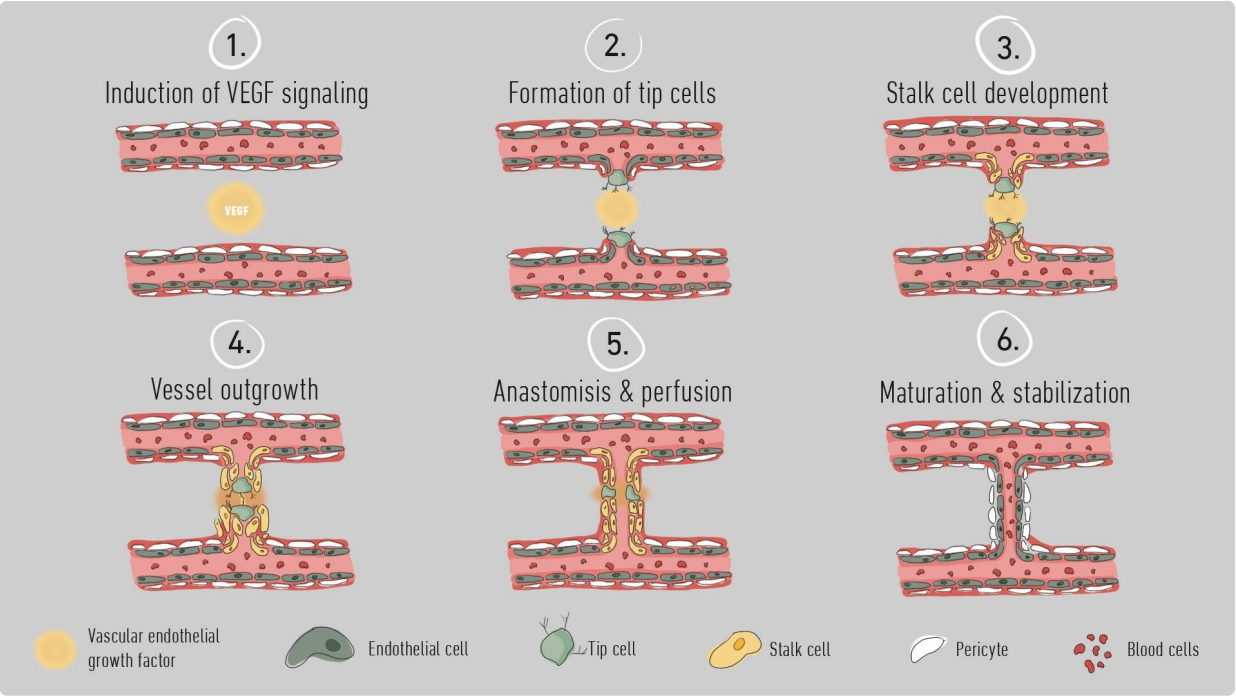

Figure 1: *The stages of sprouting angiogenesis.*

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

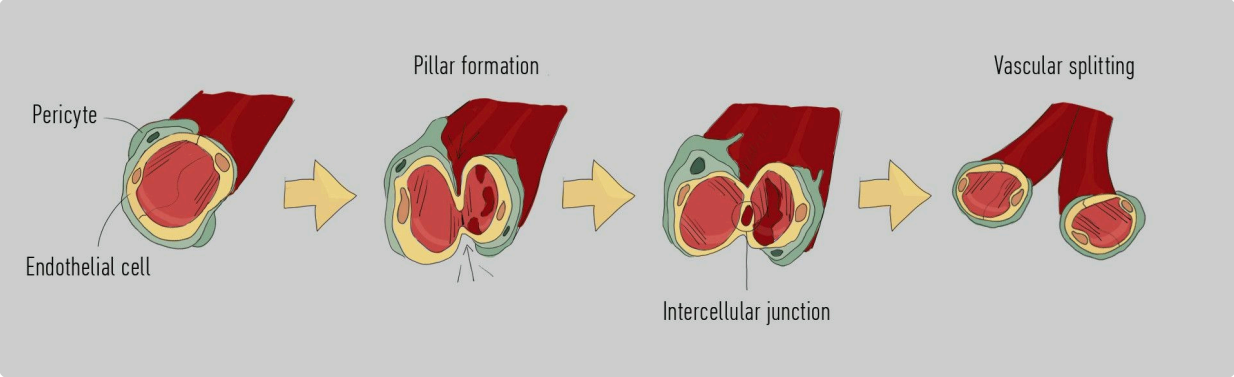

Figure 2: *The stages of intussusceptive (splitting) angiogenesis.*

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,

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