Perspective

CLINICAL INVESTIGATION

Intussusceptible Angiogenesis

Submitted: 03 December 2021; Accepted: 15 December 2021; Published online: 23 December 2021

Jennifer Stewart*

Editorial Office, Journal of Clinical Investigation, London

*Author for correspondence: clinicalinvest@escienceopen.com

Abstract

Angiogenesis is the physiological process through which new blood vessels develop from pre-existing vessels that were produced earlier in the vasculogenesis process. Angiogenesis is the process of the vasculature sprouting and splitting to continue its expansion. Although arguments are not always clear, vasculogenesis is the embryonic development of endothelial cells from mesoderm cell progenitors and neovascularization (especially in older texts). Vasculogenesis is responsible for the formation of the first vessels in the developing embryo, while angiogenesis is responsible for the majority, if not all, blood vessel growth during development and disease.

Angiogenesis is a normal and important process that occurs during growth, development, wound healing, and the production of granulation tissue. It is, nevertheless, a crucial phase in the progression of tumours from benign to malignant, which leads to the use of angiogenesis inhibitors in cancer treatment. Judah Folkman first hypothesised the importance of angiogenesis in tumour growth in 1971, describing tumours as "hot and bloody" demonstrating that, at least for many tumour forms, flush perfusion and even hyperemia are common.

Types

Angiogenesis of sprouts

Sprouting angiogenesis was the first type of angiogenesis discovered, and as a result, it is much better understood than intussusceptive angiogenesis. It happens in a series of well-defined stages. The initial signal is generated by tissue areas devoid of vasculature. The hypoxia observed in these areas causes the tissues to demand the presence of nutrients and oxygen in order to carry out metabolic activities. As a result, parenchymal cells produce Vascular Endothelial Growth Factor (VEGF-A), a proangiogenic growth factor. These biological signals activate receptors on endothelial cells that are already present in blood vessels.

Endothelial cells migrate in tandem as sprouts extend toward the source of the angiogenic stimulus, using adhesion molecules known as integrins. As cells migrate to the site of angiogenesis, these sprouts form loops and eventually become a full-fledged vessel lumen. Sprouting occurs at a rate of several millimetres per day, allowing new vessels to grow across vasculature gaps. It differs from splitting angiogenesis in that it creates entirely new vessels rather than splitting existing ones.

Angiogenesis intussusceptible

Intussusceptive angiogenesis, also known as splitting angiogenesis, is the process by which a new blood vessel is formed by splitting an existing blood vessel in two.

In neonatal rats, intussusception was first observed. The capillary wall extends into the lumen to split a single vessel in two in this type of vessel formation. Intussusceptive angiogenesis occurs in four stages. To begin, the two opposing capillary walls form a zone of contact. Second, the endothelial cell junctions are reorganised, and the vessel bilayer is perforated, allowing growth factors and cells to enter the lumen. Third, a core of pericytes and myofibroblasts forms between the two new vessels at the point of contact.

Stimulation by mechanical means

Mechanical stimulation of angiogenesis is poorly understood. There is a lot of debate about how shear stress acts on capillaries to cause angiogenesis, but current knowledge suggests that increased muscle contractions may increase angiogenesis. This could be due to an increase in nitric oxide production during exercise. Nitric oxide causes blood vessel vasodilation.

Stimulation by chemicals

Various angiogenic proteins, such as integrins and prostaglandins, as well as growth factors such as VEGF and FGF, chemically stimulate angiogenesis.

Medical applications

Angiogenesis as a potential therapeutic target. Angiogenesis may be a therapeutic target for diseases characterised by either poor vascularisation or abnormal vasculature, such as heart disease. The use of specific compounds that can inhibit or induce the formation of new blood vessels in the body may aid in the treatment of such diseases. The presence of blood vessels where none should be may affect a tissue's mechanical properties, increasing the likelihood of failure. The lack of blood vessels in a repairing or otherwise metabolically active tissue may impair repair or other essential functions.

Angiogenesis in tumours

A tumour cannot grow beyond a certain size without angiogenesis. Cancer cells have lost their ability to divide in a controlled manner. A malignant tumour is made up of a population of rapidly dividing and growing cancer cells that accumulate mutations over time. Tumors, on the other hand, require a dedicated blood supply to provide the oxygen and other essential nutrients they require to grow beyond a certain size (generally 1mm2-mm3).

Tumor blood vessel formation

Angiogenesis is the process by which blood vessels form as a result of the spontaneous division of tumour cells caused by a mutation. Tumor cells then release angiogenesis stimulators. These then travel to pre-existing blood vessels nearby and activate their endothelial cell receptors. This causes the vasculature to release proteolytic enzymes. These enzymes attack a specific point on the blood vessel, causing a pore to form. This is the site where the new blood vessel will form. Tumor cells require a blood supply because they cannot grow larger than 2 millimetres-3 millimetres in diameter without an established blood supply, which is equivalent to approximately 50 cells-100 cells.

Cardiovascular disease angiogenesis

Angiogenesis is a promising therapeutic target in the treatment of cardiovascular disease. It is a powerful, physiological process that underpins our bodies' natural response to a decrease in blood supply to vital organs, namely neoangiogenesis: the formation of new collateral vessels to compensate for the ischemic insult. A large number of preclinical studies with protein, gene and cell-based therapies have been conducted in animal models of cardiac ischemia as well as models of peripheral artery disease.

Age-related macular degeneration

VEGF overexpression increases blood vessel permeability while also stimulating angiogenesis. VEGF promotes capillary proliferation into the retina in wet macular degeneration. Because angiogenesis causes edoema, blood and other retinal fluids leak into the retina, causing vision loss. Anti-angiogenic drugs that target the VEGF pathways are now successfully used to treat this type of macular degeneration.