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Angiogenesis: An Alternate Approach To Cardiovascular Disease Treatment

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Abstract

As cardiovascular disease continues to be the number one killer of humans across the globe, a new approach in treatment and prevention needs to be found. Angiogenesis is a promising young field of study that can change the way we treat patients with cardiovascular complications.

Introduction

Cardiovascular Disease: 17.3 million deaths worldwide each year
Current Treatments: Medication, CABG surgery, Minimally invasive coronary reperfusion.
Angiogenesis: Is the natural process that our bodies use to create new blood vessels from preexisting ones. Angiogenesis usually occurs in the development process of life but can occur afterward as a response to blood vessel damage. It is also used by tumors to recruit new blood vessels to feed cancer cells with oxygen and nutrients, which allow them to grow. In relation to heart disease, angiogenesis is the body's response to blocked arteries by creating new blood vessels (called collaterals) to bypass the blockage and restore blood flow downstream to the affected artery. In order for angiogenesis to occur, biological signals known as angiogenic growth factors are sent to the receptors on the endothelial layers of the blood vessel that is requesting new blood flow. Once the basement membrane of the blood vessel has degraded enough, the new vessel escapes the old vessel and starts to grow towards the source of the original growth factor signal. [Figures 1,2]

Accelerating or enhancing the body's natural response to blood vessel injury and tissue damage is not a new concept. In the early 2000's scientists pioneered therapeutic angiogenesis by showing the effects Vascular endothelial growth factor had in re-perfusing blood flow in a rabbit hindlimb after blood flow was cut off, this research proved that a single growth factor could have positive effects to promote angiogenesis in patients suffering from heart disease.

Current Research Focuses on three approaches: Gene therapy's overall goal is to make the body's cells increase angiogenic production when they are triggered by re-writing the host's genetic makeup. Cell therapy involves the use of several stem and progenitor cells like bone marrow to build new vessels through stimulation of growth factors that are triggered by local paracrine release after ischemia. Protein therapy involves the introduction of growth factors themselves directly into the patient. This is achieved by local or general administration (pumps, IV, scaffolds, injection). In both forms of delivery, the protein is released for a certain amount of time and in certain doses. Though protein therapy is very effective, the argument against, is that proteins rapidly diffuse *in vivo*. So bolus injection doesn't work. Controlled release shows the most promise but is also the most challenging. The ideal agent should be potent, be able to target ishemic tissue, have sustained release, no side effects, adequate exposure, and should not need readministration.

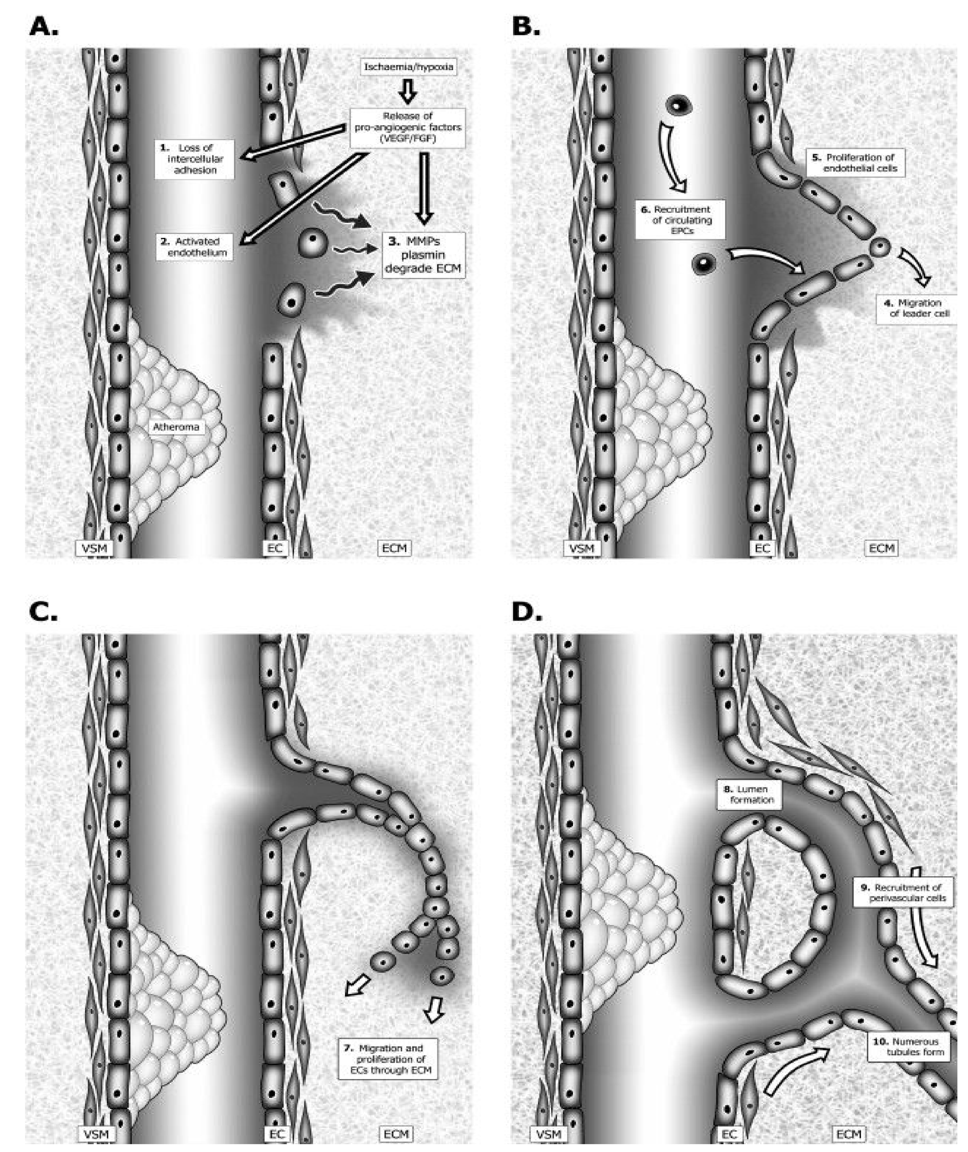

Figure 1. Schematic showing the various stages of angiogenesis. Ischemia/hypoxia, growth factor release, endothelial degradation (A). Proliferation of endothelial cells, cell recruitment (B). Cell migration through the extracellular matrix (C). Tube formation, lumen formation, vessel remodeling (D).

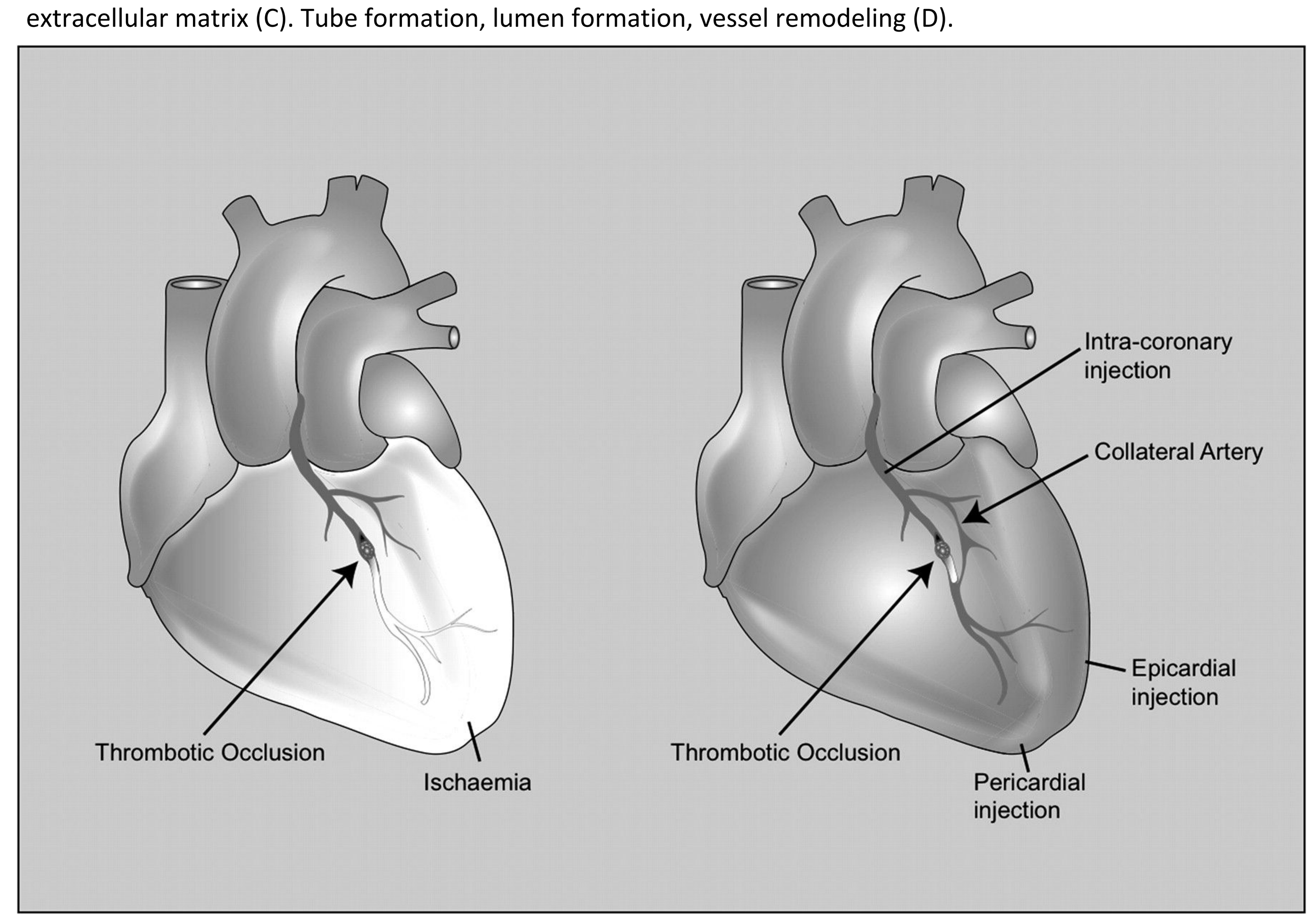

Figure 2. Angiogenesis naturally bypassing a coronary artery blockage using multiple current delivery methods of growth factors. Each method has varying degrees of success in unique situations.

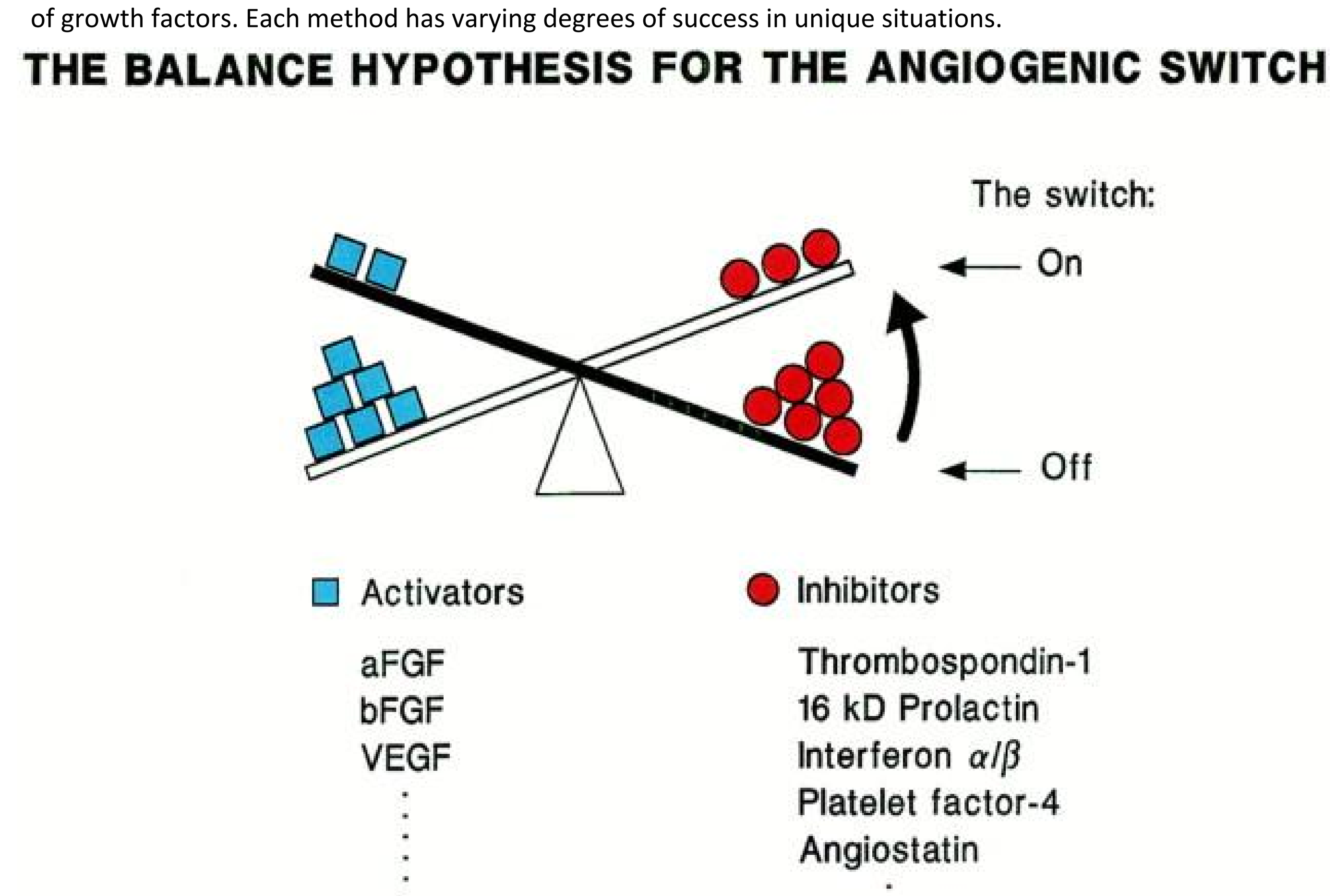

Figure 3. Visualization of the angiogenic switch. Important growth factors and inhibitors shown. For therapeutic angiogenesis to be successful the correct activators and suppression of inhibitors must be utilized.

Methods

The way angiogenesis is triggered in the body has many different steps and can be broken down into 3 categories: The mechanical trigger, the chemical trigger, and the molecular trigger. The process as a whole is more commonly known as the angiogenesis signaling cascade.
Because mechanical triggers are not well known and chemical triggers is the body's natural response to blockages during tissue hypoxia, the molecular trigger makes more sense for growth factor therapy. The centerpiece of angiogenesis research revolves around the growth factors that activate or inhibit blood vessel growth. To this date there are 19 known angiogenic growth factors and over 300 angiogenesis inhibitors. Fibroblast growth factor (FGF) is one of the most researched growth factor families, it is also one of the most effective. Another important stimulant is vascular endothelial growth factor (VEGF), which causes a large signaling cascade in endothelial cells to create new capillaries. On the other hand, angiogenic inhibitors are far more well known in large part to the research done using them as anti-cancer treatments in the 1970s. As a result of their obvious mechanism, the inhibitors are often overlooked in therapy. But inhibitors play a key role in the activation of blood vessel development. Because angiogenesis is such a tightly controlled balance of counteracting factors, checking the inhibitors and promoting the activators flicks a "switch" that allows new blood vessels to begin growing. This is better known as the balance hypothesis for the angiogenic switch. [Figure 3]

Hypothesis

Up until this point research has only focused on angiogenic activators and ineffective growth factor administration
Focusing on the angiogenic switch and the use of a bioresorbable stent coated with angiogenic growth factors *and* anti-inhibitors for prolonged local administration would solve the problems with dosage and controlled release that could push therapeutic angiogenesis over the edge as an extremely effective treatment for cardiovascular disease

Next Steps

•Development of a stent based delivery system focusing on protein therapy/ growth factor release and disabling growth factor inhibitors
•Continued research into finding the most effective growth factors
•Animal and human clinical trials using these new methods

Acknowledgements

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References

References can be found on page 16 of the origial paper: https://goo.gl/dBWLYk