ZHITTYA
REGENERATIVE MEDICINE INC.

The Future of Vascular Medicine: Angiogenesis

Clinical Evidence and Future Possibilities

I. Introduction

A. Blood Perfusion

Lack of blood perfusion to an organ or tissue is the single biggest cause of death in the world. To survive, all cells need a constant supply of blood to bring oxygen and nutrients to the cells and remove waste products and this is achieved through the body's circulatory system which is depicted in Figure 1 below. Heart attacks, strokes and the complication of diabetes all result from a decreased flow of blood into a tissue or organ. In the U.S., the American Heart Association reports that 1/3 of all deaths are from cardiovascular disease caused by a lack of blood perfusion to the heart or brain (2014 AHA statistics). In the U.S., 24 million Americans have diabetes, and

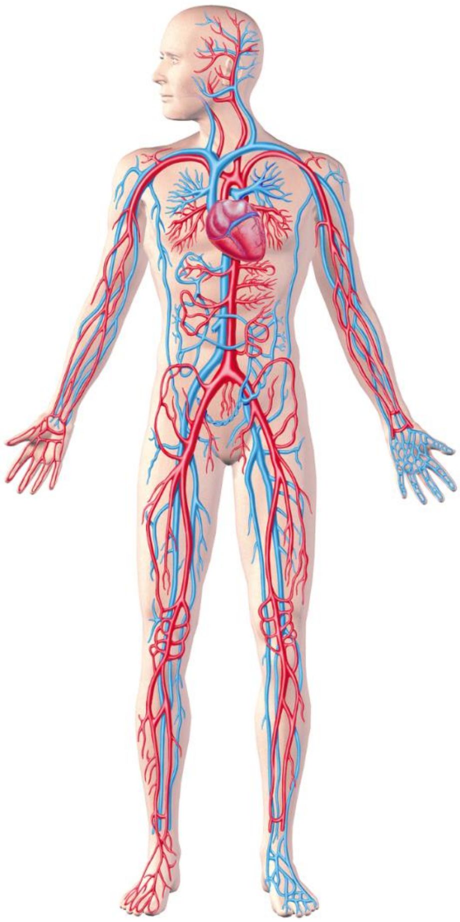
Figure 1: The Human Circulatory System

A significant percentage of these patients go on to develop vascular complications of their diabetes including foot ulcers, peripheral vascular disease and critical limb ischemia. In fact, according to the Angiogenesis Foundation in Cambridge, MA, over 70 human diseases have been linked to a lack of blood perfusion. A partial listing of these perfusion-related diseases is shown in Figure 2 below.

Figure 2: A partial listing of conditions which can lead to poor blood perfusion or are a result of a perfusion defect

Local/Tissue Perfusion Disorders

- Atherosclerosis/coronary artery disease
- Small vessel disease
- Woman's syndrome X (severe angina)
- Hyperlipidemia
- Hypertension
- Myocardial infarction
- Peripheral artery disease (PAD)
- Critical limb ischemia
- Berger's disease (form of PAD)
- Diabetic foot ulcers
- Venous ulcers
- Burns
- Bed sores
- Stroke
- Dementia
- Ischemic inner ear disease
- Degenerative disc disease and lower back pain
- Defective cartilage repair
- Renal failure
- Periodontal disease
- Necrotic hip syndrome
- Impaired bone fracture repair
- Hair loss
- Intestinal Ischemia
- Pancreatitis
- Inflammatory bowel disease
- Erectile dysfunction



Perfusion is a normal physiologic process that requires the heart to pump blood through healthy open blood vessels for distribution to organs and tissues throughout the body (as in Figure 1). Maintaining cardiovascular health is essential to optimal perfusion. The extent of tissue damage from impaired perfusion depends on the size and location of the blood vessel and whether the blood supply is reduced or completely interrupted. When the blood supply is available but decreased, tissue damage or ischemia results, as seen when blood flow is interrupted to the coronary arteries in coronary artery disease and myocardial ischemia occurs. Chest pain or angina is produced as a result of this ischemia and the function of myocardial cells is reduced, but the cells do not die. However, prolonged ischemia of heart tissue leads to necrosis and death of the myocardial cells which cannot regenerate.

B. Angiogenesis: A Solution to Impaired Perfusion

What is Angiogenesis?

New blood vessel growth or angiogenesis can solve this problem. Angiogenesis, the growth of new capillary blood vessels and arteriogenesis, the growth of small arterioles in the body, are important natural processes used for healing. The body induces angiogenesis in damaged tissues by releasing a barrage of growth factors that stimulate new vessel growth. Insufficient blood perfusion is now recognized as a “common denominator” underlying many deadly and debilitating conditions, including diabetic ulcers, cardiovascular disease, peripheral artery disease, stroke, and many others as shown in Figure 2. The list of diseases that have angiogenesis as an underlying mechanism grows longer every year.

What is Angiogenesis-Based Medicine?

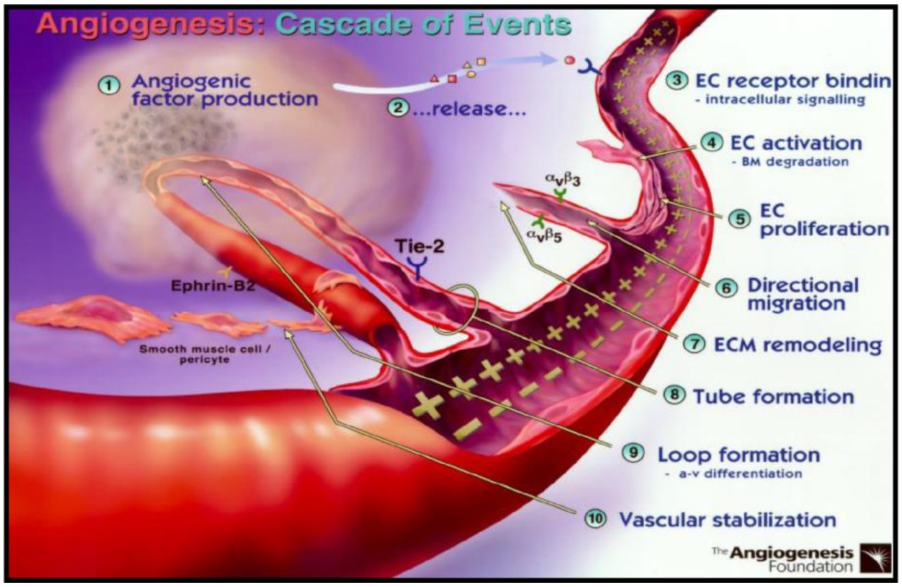
Angiogenesis-based medicine is the use of natural growth factors found in our bodies to stimulate the process of new vessel growth in under-perfused organs or tissues. By testing in well-controlled clinical trials experimental medical treatments that induce angiogenesis, physicians are attempting to prolong the lives of many patients who may be facing heart failure, amputation of a limb or other life-threatening complications that come about when a tissue is poorly perfused.

Therapeutic angiogenesis stimulates angiogenesis where it is required but is lacking. This technique is used to replenish the blood supply to chronic wounds to speed healing, and it prevents unnecessary amputations. New research suggests this approach can also be used to save limbs afflicted with poor circulation, and even oxygen-starved hearts. Therapeutic angiogenesis may even help to regenerate damaged or lost tissues in ways that were previously considered impossible, such as with nerves and brain tissue. It is a natural process; when we cut ourselves, angiogenic growth factors in our bodies are released which stimulate the growth of new blood vessels in the injured tissues. When a person is afflicted with coronary artery disease, growth factors can fashion a new “collateral” blood circulation network in the heart.

Figure 3 below gives a schematic view of how angiogenesis occurs in our body. A key concept in this process is the fact that new vessels branch off of pre-existing blood vessels as shown in Figure 3. Important cellular components in this process are the endothelial cells which line the interior of all blood vessels. These cells migrate into the adjacent tissues and form hollow tubes, which are the precursors of new capillaries. Fibroblasts also help direct and guide the formation of these new vessels. Finally, a coating of smooth muscle cells gives strength and elasticity to these newly formed blood vessels, and these vessels are now ready to perfuse the adjacent tissue.

Figure 3: Schematic Representation of Angiogenesis and New Blood Vessel Formation
Formation of a new vessel occurs as endothelial cells bud off of an existing blood vessel to form hollowtubes which are furthered modeled into capillaries.

C. Fibroblast growth factor 1 (FGF-1), a Potent Stimulator of Angiogenesis



Several growth factors have been shown to stimulate angiogenesis, including VegF (vascular endothelial cell growth factor) and EGF (epidermal growth factor), but one growth factor in particular, FGF-1, stands out due to its potency and its ability to stimulate the production of not only capillaries, but larger arterioles, which are critical in bringing more blood into the injured tissue. This growth factor was first isolated in the laboratory of Dr. Ralph Bradshaw in the 1980's[1]. Dr. Bradshaw is a noted biochemist who went on to isolate other growth factors as well, most notably nerve growth factor.

Dr. Ken Thomas, a post-doctoral fellow in Dr. Bradshaw's laboratory, continued working on the FGF-1 protein at Merck, where he was able to determine its primary structure for which Merck received composition of matter patents[2,3]. Dr. Thomas continued the FGF-1 R&D program for almost 20 years at Merck and was able to successfully advance this growth factor through successful Phase II clinical trials in diabetic wound healing studies.

FGF-1 is a natural protein contained within our bodies. It is released upon tissue injury and is the body's natural response to tissue repair[4]. Human FGF-1 is a 141 amino acid single chain protein devoid of any requisite post-translational modifications such as glycosylation. A schematic representation of the protein molecule is shown below in Figure 4.