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Short communication

In Vivo Angiogenesis: Therapeutic Potential and Challenges

Randall W Franz*

Vascular and Endovascular Surgery, Central Ohio Vascular Services, USA

Blood vessels supply oxygen, nutrients, hormones, and immune components throughout the human body to all the tissues and organs and carry the non-useful metabolite products from tissues to the excretory systems. Angiogenesis is a phenomenon where the endothelial cells of existing vasculature are stimulated by pro-angiogenic signals such as vascular endothelial growth factor (VEGF) resulting in the formation of new blood vessels. Angiogenesis is a complex and highly coordinated process that involves degradation of the basement membrane, endothelial cell migration, proliferation, fusion, vessel maturation, and remodeling. In response to proangiogenic stimuli, the vascular endothelial cells rapidly change from cellular quiescent to proliferative and migratory states. Vascular endothelial cells rely on aerobic glycolysis than on oxidative phosphorylation for ATP generation during angiogenesis. This glycolytic feature is critical for cell proliferation, migration, and response to the inducers. There are several signaling effectors such as Nitric oxide, epidermal growth factor, stromal cell-derived factor-1, Transforming Growth Factor and VEGF that participate in the modulation of angiogenesis. The equilibrium between the angiogenic stimulators and inhibitors directs the angiogenic fate in the specified tissue or organ. There are several regulators available for glucose metabolism, fatty acid oxidation, glutamine metabolism that can modulate the angiogenesis from vascular endothelial cells. However further studies on the flexibility and adaptability of angiogenic metabolism of vascular endothelial cells will facilitate new angiogenesis-based therapeutic strategies. In addition to these effectors, hypoxia is one of the biological conditions that trigger angiogenesis. Angiogenesis is of two types one is the sprouting angiogenesis where the VEGF stimulates tip cells of the original blood vessel to induce sprouting and the other one is intussusceptive angiogenesis wherein vascular splitting leads to expansion and remodeling of the microvascular network. Vascularization supports tissue innervations and reinstatement of tissue function and therefore angiogenesis is very critical for transplantations, tissue engineering, regenerative medication, growth, development, pregnancy, exercises, and wound healing [1-4].

Inadequate vascular supply or vascular disorders can lead to tissue ischemia, myocardial infarction, stroke, and impedance in wound healing. The ability to modulate angiogenesis will be of immense significance in facilitating better drug efficacy in the treatment of malignant tumors and also enables successful transplantation of in vitro regenerated tissue in case of damages or surgically treated tissues. However, the rate of therapeutic angiogenesis is very slow and often with inadequate vascularization because the angiogenesis depends on the balance between the pro-as well as anti-angiogenic factors and the cytokines. In situ production of pro-angiogenic factors leads to vessel regeneration however the process is dependent on the tissue requirements.

Cardiac tissues have restricted regeneration capability and the restoration of ischemic injury and recovery of the muscle function is very essential. Angiogenesis plays a critical role in the treatment of such cardiovascular disorders. Efforts were made to therapeutically stimulate angiogenesis by delivering growth factors, but these attempts yielded limited clinical success. Some of the main limitations for this approach of vascularization are lack of control on the precise growth factor delivery, a short phase of activity necessitating higher physiological concentrations, and high manufacturing costs. Recombinant expression of C-terminal fragment of Human Perlecan DV was found to promote angiogenesis by promoting endogenous growth factor signaling or co-delivered pro-angiogenic growth factor mediated induction. Restoration of the epicardial coronary artery leading to the recovery of the blood flow to the infarcted region decreases the extent of myocardial necrosis however, for myocardial restoration functional microvascular system of the ischemic heart is important. In this context, angiogenesis facilitates reperfusion in the ischemic myocardium following myocardial infarction and also aids in prolonged remodeling of the left ventricular that inhibits heart failure.

Endothelial progenitor cells and mesenchymal stem cells are considered appropriate for angiogenesis via the secretion of growth factors or differentiation into cells that are responsible for angiogenesis. It was shown that systematic injection of mesenchymal stem cells, migrates them to the infarcted region of the myocardium and they can differentiate into cardiac phenotype or may participate in angiogenesis in the infracted region. Similarly, multipotent stem cells' delivery show improved tissue perfusion and enhanced left ventricular function. However, there are certain limitations for effective multipotent stem cells therapy due to the risk of immune rejection. VGEF injection into the ischemic area induces angiogenesis and cardiac regeneration however due to the leaky nature and unstable properties of blood vessels it is generally

***Correspondence to:** Randall W Franz, Vascular and Endovascular Surgery, Central Ohio Vascular Services, USA, E-mail: Randall.Franz@ohiohealth.com

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used along with fibroblast growth factor and platelet-derived growth factor. Exosomes derived from cardiac progenitor cells can induce intracardiac angiogenesis and reduce fibrosis, improve cardiac function, and decrease cardiac apoptosis. Biomaterial scaffolds are used for improving the angiogenic effects but may pose different stability, degradation properties, and growth factor release timing. Therefore, there is a need to develop alternate strategies and prove their safety and efficacy. VGEF and bFGF are under clinical trials for stimulation of angiogenesis in ischemic areas. However, they have certain limitations such as short half time, rapid rate of diffusion, poor stability, uncontrolled angiogenesis rate. Metallothionein is regarded as a smart molecule as it could accelerate healing by induction of angiogenesis and inhibition of angiogenesis in malignant tumors. Melatonin has the potential to control angiogenesis at the molecular and cellular levels [5-8].

Some botanical active components were found to be associated with angiogenesis such as astragalin, kaempferol, myricetin, quercetin, and β-sitosterol sourced from Polygoni cuspidati Morus alba and Forsythiae fructus. Panax notoginseng saponins were also found to promote endothelial progenitor cell angiogenesis via the Wnt/β-catenin pathway. Overall, Calotropis procera plant extracts in combination with chitosan in the form of hydrogel exhibits significant healing properties that can be further utilized in wound healing applications. It was noticed that the Calotropis hydrogel showed the highest formation of granulation tissues and blood vessels compared with the control and other hydrogels.

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