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Cell-Based Treatment of Ischemic Heart Disease: Rationale for the Use of VEGF-Eluting Adult Progenitor Cells

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Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide, with coronary ischemic heart disease accounting for 80% of deaths from CVD [1-3]. While heart-healthy lifestyle changes remain essential to reducing one's lifetime risk of CVD, prevention and treatment options have otherwise relied on control of blood pressure and blood sugar and cholesterol levels. Interventional techniques have relied on percutaneous coronary intervention and coronary artery bypass grafting [2]. With the total treatment costs of cardiovascular disease rising and expected to reach $1.1 trillion in 2035 in the United States alone [4], heart failure is in need of new therapies to prevent, as well as reverse, cardiac arterial pathology and enhance cardiovascular regeneration. Herein is presented a concise review of the utility of vascular endothelial growth factor (VEGF) in angiogenesis and rationale for the use of VEGF-eluting stem cells in the treatment of ischemic disease.

Keywords: Adipose-derived stem cells, adult stem cells, VEGF, heart disease, progenitor cells.

VEGF, Cancer, and VEGF Blockade

The field of angiogenesis has become a target of focused research for both therapeutic angiogenesis as well as therapeutic anti-angiogenesis. As no metabolically active tissue is but a few hundred micrometers from a capillary, all tissues rely on the continual flow of oxygen and micro-nutrients to survive. The field of angiogenesis in the printed literature may be followed back to the Scottish anatomist and surgeon John Hunter. He was the first to provide scientific insights to the fields of angiogenesis and blood flow in his Treatise in 1794; his remarks generally addressed the importance of balance between vascularity and metabolism [5]. The modern era of basic and clinical research related to angiogenesis was anchored by Dr. Judah Folkman in his landmark paper discussing tumor angiogenesis in 1971 [6]. A direct correlation was then established between tumor vascular density and extent of tumor burden, stage, and prognosis [7]. However, it was not until the next decade that the essential protein needed for angiogenesis was discovered: VEGF. VEGF was discovered by Senger and Dvorak in 1983, though they termed it the "vascular permeability factor." [8] Later that same decade (1989), VEGF was independently identified by Ferrara and Henzel as it was isolated from the conditioned media of bovine pituitary cells [9]. Slightly 30 years past the release of Dr. Folkman's seminal paper, and 25 years past Senger and Dvorak's discovery of VEGF, in 2004 the Food & Drug Administration approved the first anti-angiogenic medication, bevacizumab (Avastin®; Genentech, San Francisco, CA), for human use in the treatment of cancer [10]. Bevacizumab is a monoclonal antibody which prevents VEGF binding, which then prevents growth and maintenance of tumor vessels. This medication has significantly added to our chemotherapeutic armamentarium for the treatment of several cancers.

Role of VEGF in angiogenesis

As VEGF is instrumental in promoting tumor progression, it is also critical in normal tissue and organ development. The maintenance and production of vessels rely on several growth factors and cytokines; VEGF is one of the most critical and well-studied angiogenic growth factors [11]. VEGF is involved in several angiogenic functions, to include endothelial cell migration, mitogenesis, vascular sprouting, and vascular tube formation [12,13]. Several isoforms of VEGF are endogenously active; VEGF factor A (VEGF-A) is the most active isoform and is essential for mammalian development and function [14,15]. As the family of VEGF comprise a family of both pro- and anti-angiogenic isoforms and related proteins [14,16-19] the delicate balance between these competing peptides presumably maintains vascular homeostasis in vivo while significant increases in anti-angiogenic VEGF-A isoforms, such as VEGF-A165b, reflect impaired vascularization [18].

VEGF protein therapy

Cytokine therapies, to include fibroblast growth factor, hepatocyte growth factor, stromal cell-derived factor-1α, and recombinant human VEGF, have shown promise in treating ischemic diseases [20]. Several phase I trials using intracoronary and intravenous infusions of VEGF in patients with the coronary disease showed favorable trends [21-23]. However, clinical trials of VEGF gene therapy as well as trials using high dose VEGF therapy, in patients with coronary artery disease or peripheral artery disease, have not demonstrated statistical clinical benefit [22-27]. In the placebo-controlled double-blinded phase II VIVA trial, VEGF failed to show sustainable improvements over placebo in anginal frequency and treadmill test time at four months [23]. Reasons for such failure may lay in the poor stability and cell permeability of exogenous VEGF. Administered peripherally, VEGF demonstrates a short in vivo half-life of about 30 minutes while hypotensive side effects also limit the utility of the infused recombinant protein to achieve angiogenesis [21,23].

Several manufactured VEGF protein delivery vehicles have been developed to improve both targeting damaged tissues and delivery of VEGF. Examples include scaffolds such as cross-linked heparin, hydrogels to nano- and micro-particles of PLGA and collagen, engineered polymers and microspheres [28-30]. Such vehicles may prolong the half-life of payload growth factors and related cytokines [31].

Cell-based therapies

Cell-based therapies have shown particular promise in several difficult-to-treat conditions and diseases, including neurological, autoimmune, and gastrointestinal targets [32-34]. Similarly, cell-based therapy is a promising and emerging new option for promoting angiogenesis and treating ischemic diseases [35-39]. Cell-based therapeutic approaches have involved several classes of putative stem cells, ranging from bone marrow-derived mononuclear cells, endothelial progenitor cells, mesenchymal stem cells (MSCs), and pluripotent stem

cells [40]. CD-34 positive bone marrow-derived stem cells, in particular, have been well characterized and have been used clinically to rebuild the hematopoietic system after chemotherapy; such utility in the treatment of ischemic heart disease is promising [41,42].

Mesenchymal stem cell-based therapies

MSCs exist in several tissues in an undifferentiated state with the ability to self-renew and differentiate along several mesodermal lineages [43-50]. Human MSCs derived from adipose, so-called adipose-derived stem/stromal cells (ASCs), are easily isolated from lipoaspirate and secrete a wide array of proangiogenic cytokines and differentiate into multilineage progenitor cells [16,47,51-53]. Since angiogenesis and organogenesis are normally coupled, it is possible that human adipose-derived progenitor cells (APCs) could modulate levels of vascular endothelial growth factor (VEGF) in a lineage-dependent manner. Animal studies have shown that ASCs have the potential to differentiate *in vivo* into endothelial cells and cardiomyocytes [54-56]. MSCs have also shown to be immune-evasive and, as such, may be both effective *in vivo* after autogeneicor allogeneic transplantation [57]. Additionally, culture-expanded MSCs have been shown to decrease inflammation and T-cell proliferative responses because of their reduced expression of surface histocompatibility antigens [58].

While the use and potential benefit of MSCs in cardiovascular disease have been widely published, such benefit seems unlikely solely from the differentiation of these cells to cardiomyocytes. MSC-derived cardiomyocytes have been shown to fail permanent engraftment and become nonviable within a few hours after administration [59,60]. However, APCs may elaborate greater quantities of paracrine and autocrine cytokines comparative to MSCs in their undifferentiated state [59-62].Therefore, modification of MSCs to APCs before delivery could promote expression of VEGF-A, favorably augmenting the capacity for cardiac repair.

VEGF-eluting adult progenitor cell therapies

MSCs differentiate down both mesodermal and endothelial lineages while participating in angiogenesis by secreting angiogenic paracrine factors, including VEGF, basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) [63-67]. Such the dichotomy is well revealed in an embryologic study of vessel formation. A delicate balance lies between differentiated mesodermal embryonic stem cells and endodermal paracrine signaling. Angioblasts, as derived from the splanchnic mesoderm, give rise to capillaries. The angioblasts assemble themselves into a primitive vascular plexus under the influence of VEGF [68]. VEGF-A binds to Fetal Liver Kinase-1 (FLK-1), which activates several intracellular transduction pathways for vessel formation [68]. It has been shown that in mice lacking FLK-1, the mice develop angioblasts but not vessels; as such, VEGF signaling is critical to the development of vessels [68]. High and low levels of VEGF also lead to differing second messenger expression, determining the development of arteries (high VEGF concentration) and veins (lower VEGF concentration) [68,69].

Proangiogenic signal transduction and feedback loops between developing and renewing stems cells and their cytokines continue beyond the embryonic period and into undifferentiated adult stem cells, [12]. ASCs have been shown to promote angiogenesis by producing VEGF, human growth factor (HGF), and tissue growth factor-β. VEGF-A has been shown to be a key regulator of perichondrial angiogenesis and osteoblast differentiation at the early stages of bone development [70, 71]. Additionally, autocrine, or intracellular, VEGF has been shown to play a key role in the differentiation of MSCs, not only by modulating cell surface receptors but by also linking to protein lamin A on the nuclear envelope [72].

Therapeutically, ASCs have been shown to improve blood flow in a mouse model of hindlimb ischemia by secreting growth factors, including VEGF and HGF [73]. Laboratory studies and limited clinical trials have shown ASC feasibility and safety [74] and have revealed potential mechanisms of action of stem cell therapy in ischemic diseases, such as stroke and ischemic cardiomyopathy [74-77]. However, even with efficacy in animal studies, functional human benefits after transplantation of stem cells remain equivocal in patients with stroke [75] and heart failure [59, 60]. Microvesicles and exosomes present a promising outlook for the treatment of ischemic diseases as well. The proangiogenic potential of ASC-released microvesicles has been shown and linked to associated micro-RNA-31 in the microvesicles [78].

By classification, stem cells undergo a finite period of multiplication as progenitor cells before completing differentiation into functional cell types [79]. Along the pathway to final differentiation, progenitor cells elicit and respond to cytokine signals that encourage cell migration and extracellular matrix invasion. Such responses have been shown in vitro for endo-

thelial progenitor cells [80]. Relatedly, research for therapeutic angiogenesis has largely focused on the use of progenitor endothelial stem cells [81,82].

Through *in vivo* cellular plasticity, progenitor cells, which have started down a differentiation developmental pathway, may be able to reverse the pathway back to its native state, or possibly to another differentiation lineage [83]. As such, depending on epigenetic cues, it may be possible for a differentiating osteoblastic progenitor cell to de-differentiate to a basal stem state, then down an endothelial lineage. Osteoblastic progenitor cells, as they are heavily involved in VEGF stimulated responses in embryonic and adult perichondrial angiogenesis and bone formation may be a logical VEGF vehicle for the treatment of ischemic disease. Their benefit may lie in the possible sustained paracrine elaboration of VEGF after engraftment, as well as possible dedifferentiation to cardiomyocyte lineage and/or endothelial lineage. Additionally, progenitor cell homing, whereby the cells are attracted to the chemoattractant gradient in response to ischemic tissue injury, occurs in all tissues for the replacement of cells [84-86]. Peripherally infused osteogenic progenitor cells may be able to home to the affected ischemic tissue for therapy. As such, the progenitor cell may hold several tools in its therapeutic toolbox, beyond our traditional understanding of multi-differentiation and cytokine elaboration.

Conclusions

VEGF remains a critical constituent for angiogenesis and organ development. Similarly, VEGF therapy alone has shown encouraging trends in the clinical treatment of ischemic disease. Modulating VEGF delivery with regenerative cell-based vehicles, such as with osteogenic progenitor cells, may improve clinical efficacy in the treatment of ischemic disease.

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