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VEGF-B: Friend or Foe to the Heart in Times of Nutrient Excess?

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Diabetes mellitus is among the strongest cardiovascular disease risk factors, increasing all cause cardiovascular mortality, particularly ischemic heart disease.(3, 18, 29) However, independent of ischemic episodes, diabetes mellitus results in a remodeling of the myocardium, leading to diabetic cardiomyopathy.(31) Similar to obesity, diabetic cardiomyopathy is often characterized by impaired diastolic function (with a preservation of systolic function).(4) Numerous mechanisms have been proposed to contribute significantly towards the etiology of diabetic cardiomyopathy, ranging from neurohumoral imbalances and extracellular remodeling, to perturbations in the intrinsic properties of cardiomyocytes, including alterations in contractile proteins, calcium homeostasis, signaling, and metabolism.(31) In the latter case, the heart during diabetes has been described as ‘starving in the midst of plenty’.(30) Such a statement was proposed largely following observations that the heart exhibits impaired oxidative metabolism (secondary to mitochondrial dysfunction) in the face of elevated circulating nutrients (glucose [i.e., hyperglycemia], fatty acids/lipids [i.e., dyslipidemia], ketone bodies [in the case of uncontrolled type 1 diabetes mellitus], and amino acids [particularly branched chain amino acids]) during diabetes.(5) It is important to note an increasing acknowledgement that nutrients are more than just fuels, acting also as signaling molecules capable of influencing a multitude of processes critical to cardiac function. Thus, the mismatch between nutrient availability and oxidation that occurs during diabetes leads in an accumulation of metabolic intermediates within the myocardium, which perturb transcription (e.g., fatty acid activation of PPARs), translation (e.g., nutrient activation of mTOR), protein posttranslational modifications (e.g., acetylation, O-GlcNAcylation), signaling species (e.g., phospholipid derivatives), and electrophysiology (e.g., acyl-carnitines influence on ion channels).(9, 25, 27, 32) When such a mismatch persists for chronic periods of time, cardiomyocytes are susceptible to both lipid and glucose induced cell death (termed lipo- and gluco- toxicity, respectively).(17, 21)

Nutrient-induced cardiomyocyte dysfunction and death likely plays a pivotal role in the development of diabetic cardiomyopathy.

Vascular endothelial growth factor (VEGF) is a secreted protein consisting of 5 primary family members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PGF).(12) VEGF binds to transmembrane spanning tyrosine kinase receptors, of which 4 main isoforms have been identified (VEGFR-1, VEGFR-2, VEGFR3, and neuropilin-1).(7) Additional complexity exists in this system, at the level of alternative splicing, stability and translation of VEGF family members, which has important functional consequences, as well as modulating heparin sulfate proteoglycan (HSPG) binding on the cell surface.(2) For example, VEGF-B_{167} and VEGF-B_{186} are splice variants of VEGF-B, of which only VEGF-B_{186} possesses the HSPG binding domain.(19) Classically, VEGF has been considered to play key roles in angiogenesis and neovascularization; often induced under hypoxic conditions, VEGF (VEGF-A) is classically thought to promote vessel formation, thereby promoting blood flow to the hypoxic region (e.g., following a myocardial infarction) and is a direct target of the hypoxia inducible factor-1alpha (HIF1α).(12) More recently, additional functions have been defined for VEGF, such as neurogenesis, wound healing, immunomodulation, and metabolism.(6, 10, 14, 28) This range of functions is in part due to isoform specific functions (both VEGF and VEGFR isoforms) in tissue and cell type specific manners. In the heart, all VEGF isoforms and receptors are present, with VEGFB and VEGFR2 most highly abundant under normal conditions (although VEGF-C and VEGF-D are induced during heart failure).(1, 24) VEGF-B is highly expressed in a number of metabolically active tissues, and consistent with its tissue distribution, has been shown to both modulate metabolic processes (e.g., fatty acid uptake and oxidation) and be regulated by the PGC-1alpha/ERRalpha axis.(10, 20) Nutrient levels have also been shown to

influence epigenetic changes, which ultimately regulate the expression of VEGF-B; different dietary fatty acids have been shown to affect the methylation status of the VEGF-B promoter, influencing both mRNA and protein expression of VEGF-B.(22) In addition, VEGF-B appears to exert a cardioprotective role, as evidenced by VEGF-B-induced preservation of cardiac function following a myocardial infarction.(16) Interestingly, VEGF-B levels decrease in both animal models of, and humans with, heart failure.(16) Collectively, these observations suggest that VEGF-B may play an important cardioprotective role, which is lost in the failing myocardium. However, whether alterations in VEGF-B signaling contribute towards either the development of diabetic cardiomyopathy, or decreased tolerance of the heart to ischemic events during diabetes, is currently unknown.

The study by Lal and colleagues investigated the relationship between VEGF-B signaling and cardiomyocyte survival, in the setting of hyperglycemia/diabetes. Following confirmation of heparin-releasable VEGF-B in isolated adult rat cardiomyocytes, the investigators revealed that elevated glucose levels (25mM) induced VEGF-B release from cardiomyocytes when co-cultured with endothelial cells. Similarly, culturing cardiomyocytes with condition media collected from endothelial cells challenged with high glucose resulted in VEGF-B release; this effect was likely secondary to high glucose induced heparinase secretion from endothelial cells. The investigators subsequently reported that VEGF-B activated the ERK/GSK3β signaling axis in both cardiomyocytes and endothelial cells, which was associated with attenuation of hydrogen peroxide induced caspase 3 and PARP activation (i.e., cell death pathway markers). Collectively, these observations revealed an important interaction between endothelial cells and cardiomyocytes, wherein endothelial cell glucose sensing results in protection of both cardiomyocytes and endothelial cells via autocrine and paracrine

(respectively) actions of VEGF-B (Figure 1A). Having established this novel mechanism of VEGF-B mediated protection following acute glucose challenge, the investigators next addressed the question as to whether this mechanism is altered/disrupted during diabetes (streptozotocin [STZ] induced uncontrolled type 1 diabetes mellitus). Profound alterations were observed, including decreased heparinase levels in hearts of STZ-diabetic rats, as well as decreased VEGF-B levels in isolated cardiomyocytes. Moreover, despite increased VEGFR1 expression in cardiomyocytes isolated from diabetic rats, these cells exhibited attenuated VEGF-B mediated ERK and GSK3β phosphorylation (i.e., VEGF-B resistance). This was associated with increased activation of caspase and PARP in hearts isolated from diabetic rats. These observations suggest decreased myocardial VEGF-B levels, in combination with VEGF-B resistance, may increase susceptibility of cardiomyocytes to dysfunction and/or death in response to the hostile diabetic milieu. This in turn could lead to contractile dysfunction (i.e., diabetic cardiomyopathy; Figure 1B).

These findings highlight a previously unknown communication between endothelial cells and cardiomyocytes revolving around VEGF-B, which potentially plays an important role in cell survival. Strengths of the study include the relatively thorough nature with which this relationship was assessed in a cell-based system. Furthermore, the studies extended beyond physiologic conditions, highlighting a disruption of this relationship during a chronic disease state (i.e., uncontrolled diabetes). Interestingly, the current study reported that treatment of STZ-diabetic rats with insulin normalizes both glycemia and cardiac VEGF-B levels within 2-hrs, suggesting that hyperglycemia acutely promotes release of VEGF-B from the heart. Consistent with release of VEGF-B from its HSPG anchor in response to hyperglycemia, and an apparent depletion of VEGF-B from the heart during diabetes (and obesity), previous studies have reported elevated

circulating VEGF-B levels during diabetes. Such observations raise the possibility that VEGF-B resistance observed in cardiomyocytes isolated from diabetic rats may be due to chronic stimulation (although elevation of circulating VEGF-B secondarily to systemic VEGF-B resistance cannot be ruled out). Clearly, the precise mechanisms leading to VEGF-B resistance requires further elucidation. Additional unanswered questions exist, including: 1) the contribution of endothelial-cardiomyocyte coupling in cardiomyocyte development, repair and survival (13, 23); 2) the role of other proteases (such as matrix metalloproteinases) that might contribute to release of VEGF-B and other growth factors that can act in an autocrine or paracrine function (8); 3) the mechanisms by which glucose induces heparinase-mediated VEGF-B release; 4) whether VEGF-B release acutely protects cardiomyocytes and/or endothelial cells from high glucose induced cell death (both apoptosis and/or necrosis); 5) whether VEGF-B resistance significantly contributes towards the etiology of diabetic cardiomyopathy (i.e., impact on contractile function of the heart); and 6) whether the cell-cell communication described has roles beyond cell survival. Here, we expand upon the latter possibility.

An interrelationship between endothelial cells and cardiomyocytes involving VEGF-B has been proposed previously. Studies from Hagberg et al have shown that VEGF-B promotes trans-endothelial transport of circulating fatty acids, for subsequent utilization by myocytes (both cardiac and skeletal).(10) Excess myocardial fatty acid uptake and utilization is known to attenuate glucose utilization is a number of ways, including substrate competition and modulation of insulin signaling.(5) An increase in fatty acid oxidation leads to a rise in mitochondrial acetyl-CoA levels, which subsequently inhibits pyruvate dehydrogenase (the gatekeeper of pyruvate entry into the TCA cycle); this in turn inhibits glucose oxidation, with subsequent attenuation of glycolysis (termed the Randle cycle, a phenomenon first described in the heart).(26) Moreover, an imbalance

between fatty acid uptake and oxidation leads to accumulation of fatty acid species that alter cardiac gene expression and signaling; the latter includes attenuation of insulin-mediated glucose uptake.(5) Consistent with these concepts, Hagberg et al reported that genetic depletion of VEGF-B prevents high fat diet induced suppression of cardiac glucose uptake (and also maintains whole body glucose homeostasis).(11) Conversely, cardiomyocyte specific overexpression of VEGF-B leads to ceramide accumulation and mitochondrial dysfunction.(15) Such observations lead to the intriguing possibility that an acute release of VEGF-B in response to glucose may signify the fed state, thus promoting the trans-endothelial movement of fatty acids (likely chylomicron-derived) across the endothelium. During diabetes, when both circulating glucose and fatty acids are chronically elevated, a depression of VEGF-B sensitivity may initially function as an adaptation, helping to prevent excessive accumulation of lipotoxic species in the myocardium. However, in light of the observations of Lal et al, this VEGF-B resistance may also result in impaired cardioprotection. Thus, aberrant VEGF-B signaling during diabetes may serve both adaptive and maladaptive roles.

In summary, Lal and colleagues have uncovered a novel interaction between endothelial cells and cardiomyocytes, whereby endothelium-derived heparinase mediates release of cardiomyocyte bound VEGF-B. Upon binding to its receptor (likely VEGFR1), VEGF-B promotes cell survival. Importantly, this mechanism appears to be severely attenuated in the setting of uncontrolled diabetes mellitus. Several fundamental questions remain unanswered with regards to the mechanisms by which VEGF-B resistance ensues during diabetes, as well as the functional consequences, the novel findings described by these studies may have identified an important mechanism contributing towards increased susceptibility of the heart to damage/dysfunction during diabetes.

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Disclosures

None.

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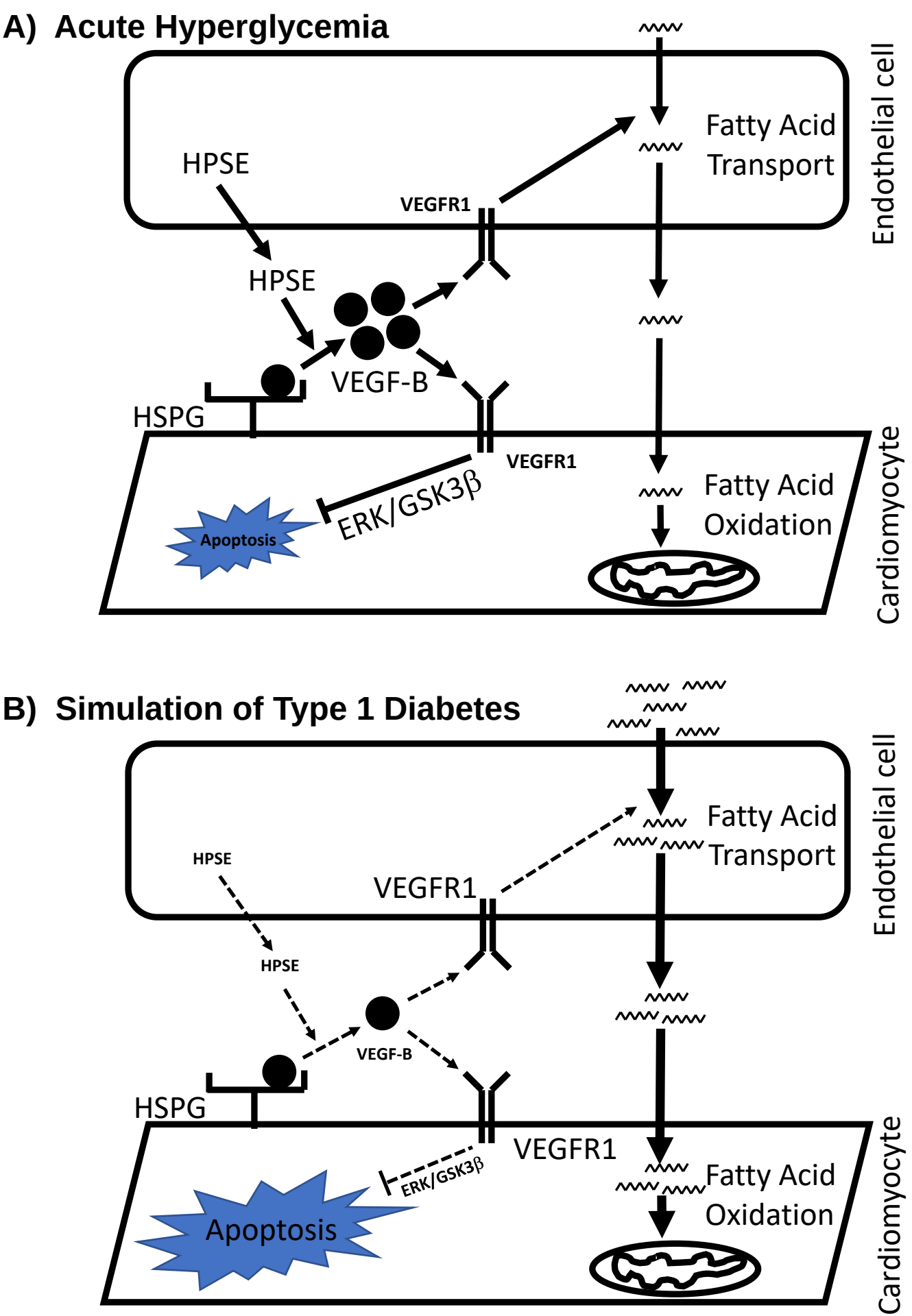
Figure Legends

Figure 1. Hypothetical model by which elevated glucose levels influence cardioprotection in a VEGF-B dependent manner. A) Acutely, heparanse (HPSE) is secreted from endothelial cells in response to elevated glucose levels (e.g., fed state), resulting in the release of VEGF-B from the heparan sulfate proteoglycan (HSPG); VEGF-B then binds to the VEGFR1 receptor on endothelial cells (increasing fatty acid uptake, and subsequent utilization by cardiomyocytes as a fuel) and on cardiomyocytes to attenuate apoptosis (via activation of the ERK/GSK3β signaling axis). B) Chronic hyperglycemia during simulated type 1 diabetes mellitus decreases HPSE secretion and local VEGF-B levels; despite a compensatory increase in VEGFR1 expression, VEGF-B resistance occurs during diabetes, which likely influences cardiomyocytes in both adaptive (e.g., attenuates fatty acid delivery in the face of hyperlipidemia) and maladaptive (e.g., attenuation of cardioprotection via the ERK/GSK3β signaling axis) manners.


A) Acute Hyperglycemia
Endothelial cell
Fatty Acid Transport
HPSE
VEGFR1
HPSE
VEGF-B
HSPG
VEGFR1
ERK/GSK3β
Apoptosis
Fatty Acid Oxidation
Cardiomyocyte
B) Simulation of Type 1 Diabetes
Endothelial cell
Fatty Acid Transport
HPSE
VEGFR1
HPSE
VEGF-B
HSPG
VEGFR1
ERK/GSK3β
Apoptosis
Fatty Acid Oxidation
Cardiomyocyte