Review

Endothelium as a gatekeeper of fatty acid transport

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The endothelium transcends all clinical disciplines and is crucial to the function of every organ system. A critical, but poorly understood, role of the endothelium is its ability to control the transport of energy supply according to organ needs. Fatty acids (FAs) in particular represent a key energy source that is utilized by a number of tissues, but utilization must be tightly regulated to avoid potentially deleterious consequences of excess accumulation, including insulin resistance. Recent studies have identified important endothelial signaling mechanisms, involving vascular endothelial growth factor-B, peroxisome proliferator-activated receptor-γ, and apelin, that mediate endothelial regulation of FA transport. In this review, we discuss the mechanisms by which these signaling pathways regulate this key endothelial function.

Endothelium as a key energy barrier

Our understanding of the endothelial layer has progressed significantly since its historical view as an inert layer of cells that serve as the inner lining of 'plumbing' for the circulatory system [1]. Now more than ever, the endothelium is implicated in regulation of physiologic and pathologic processes via its signals and cues to the encasing organs in the context of development and function. The heterogeneity of the endothelial layer is also remarkable, from differences that exist based on the location of the conduit vessels (arteries vs veins) to the functional heterogeneity in the context of specific organs, such as the heart, liver, and adipose tissue. Such diversity of the endothelium is key to the specialized roles of its function, including regulation of permeability, leukocyte trafficking, and hemostasis marking some important aspects of endothelial function.

The dense network of endothelial capillaries is especially important for function of multiple organ systems, and indispensable for regulating transport of fluids and nutrients from the circulation to the target tissues. Endothelial cells (ECs) outnumber the tissue-specific cells in many cases, with minimal intercapillary distances (as close as 15 μm) in organs such as the heart [2]. Such architecture provides optimal context for the diffusion and transport of nutrients and oxygen to the target tissues.

The vascular network needs to adapt readily to significant fluctuations in metabolic changes. Periods of fasting are associated with increased release of FAs from the white adipose tissue (WAT) into the circulation, to be utilized by highly metabolic tissues such as the heart and skeletal muscles. This release of FAs, as well as the endothelial-mediated uptake, needs to be closely regulated. The concept of endothelial-mediated FA transport has existed for many years, but has transitioned from a viewpoint of passive, diffusive transfer to a highly regulated, active process that involves multiple, complex signaling pathways [3]. This metabolic function of the endothelium, which probably has adapted evolutionarily to accommodate periods of fasting and regular diet, has been challenged by the emergence of obesity as a worldwide public health problem. Deleterious consequences of excess FA uptake in tissues including the skeletal muscle and the heart, and the resulting metabolic derangements such as impaired glucose uptake and insulin resistance [4,5], continue to rise exponentially.

Obesity, metabolic syndrome, and endothelial dysfunction

Global changes, including trade liberalization, economic growth, and urbanization, have promoted lifestyle changes that have resulted in a net positive energy balance, with greater sedentary lifestyles and transitions to increased consumption of animal products, refined grains, and sugar [6]. The worldwide obesity pandemic associated with these changes has brought to the forefront the need to understand better the endothelial mechanisms that can be targeted as novel therapeutic strategies to protect against the metabolic derangements in such a context. These changes in metabolic state, in turn, have been widely associated with endothelial dysfunction. Endothelial dysfunction refers to the abnormal behavior of ECs under conditions that are associated with metabolic disturbances, including diabetes and insulin resistance. Signaling perturbations including excess of proinflammatory cytokines, such as interleukin (IL)-6 [7,8] and tumor necrosis factor (TNF)-α [9] probably have a significant impact on promoting endothelial conversion from a quiescent phenotype toward an activated one.

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Additional consequences include disruption of nitric oxide (NO) synthesis and its homeostatic effects [10], and exacerbation of reactive oxygen species (ROS)-mediated effects [11]. These proinflammatory milieus probably place a significant burden on the endothelial signaling mechanisms that mediate the normal uptake of circulating FAs, leading to accumulation in non-adipose tissues such as the heart and skeletal muscles. Excess FAs in these organs are widely associated with impairment of glucose uptake and insulin signaling, leading to insulin resistance [4,5]. What regulates the endothelial function as a regulator of FA transport and uptake by the target tissues has remained poorly defined until recently; emerging evidence makes it evident that there is a clear orchestration of endothelial FA transport by a number of molecules, including vascular endothelial growth factor (VEGF)-B, peroxisome proliferator-activated receptor (PPAR)-γ, and apelin, that directly target the endothelium and determine its ability to maintain a balance of energy transfer and storage.

VEGF-B targeting of endothelial FA transport proteins

The VEGF family of growth factors has been studied extensively as key regulators of angiogenesis [12]. There are at least five members in this family, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). All members of the VEGF family bind to the VEGF receptors (VEGFRs), which are tyrosine kinase receptors expressed by ECs and some leukocytes [13]. Of these factors, VEGF-B has been found to be less potent than the other class members in promoting angiogenesis, but does promote coronary arterialization in rats [14]. Other studies have demonstrated both proangiogenic and antiangiogenic effects of VEGF-B in ocular angiogenesis and tumor angiogenesis, respectively [15,16]. A transgenic mouse line with cardiomyocyte-specific overexpression of VEGF-B was found to induce cardiac hypertrophy with preservation of cardiac contractility, but was also found to have mitochondrial lipotoxicity [17]. Based on the predominant expression of its receptors, namely VEGFR1 and neuropillin 1 (NRP1), being in the ECs, these observed changes in the myocardium are thought to be predominantly mediated via the endothelium.

Two recent studies shed further insights into the endothelial-based mechanisms by which VEGF-B regulates endothelial metabolic control (Figure 1). Hagberg *et al.* made the initial observation that VEGF-B expression was closely correlated to expression of nuclear-encoded mitochondrial genes, suggesting that VEGF-B may be important in metabolism [18]. Evaluation of *Vegfb*$^{-/-}$ mice led to the observation that lipid uptake in the heart, skeletal muscle, and brown adipose tissue (BAT) was significantly decreased, whereas excess lipid uptake was observed in WAT. This was associated with a likely compensatory increase in glucose utilization and insulin sensitivity, which was in part attributed to increased expression of *Glut4*, a glucose transporter in heart and skeletal muscles.

The endothelial-based metabolic effects of VEGF-B were linked to increased expression of FA transport proteins 3 and 4 (FATP3 and FATP4). FATPs (solute carrier family 27) are a family of integral transmembrane proteins that enhance cellular long-chain FA uptake [19–21]. The mechanism by which FATPs mediate long-chain FA uptake remains poorly defined, and may involve cooperation with other transmembrane proteins such as cluster of differentiation (CD)36 [22,23]. Of the FATPs evaluated in response to VEGF-B stimulation, only FATP3 and FATP4 were induced in ECs [18]. FATP3 and FATP4 were increased in mouse hearts that overexpress VEGF-B, and conversely were reduced in *Vegfb*$^{-/-}$ mouse hearts. VEGF-B effect on FATP3

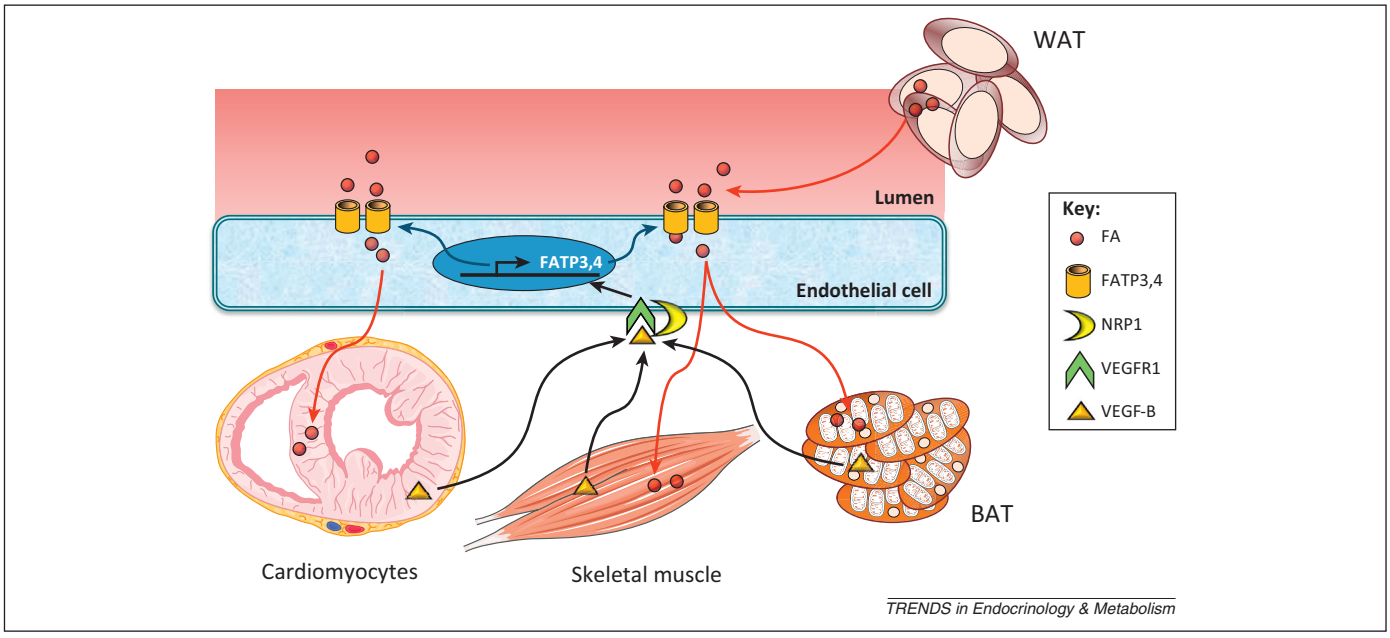

Figure 1. Mechanism of VEGF-B-mediated FA uptake. Vascular endothelial growth factor (VEGF)-B expressed in skeletal muscle, heart, and brown adipose tissue (BAT) binds to VEGF receptor-1 (VEGFR1) and neuropillin 1 (NRP1) on the endothelial cells to induce expression of fatty acid (FA) transport proteins 3 and 4 (FATP3/FATP4). Increased FA uptake in these tissues in diabetic mice results in insulin resistance and increased blood glucose. Abbreviation: WAT, white adipose tissue.