Vascular endothelial growth factor-B as a therapeutic target to prevent ectopic fat deposition

Insulin resistance, a key feature of type 2 diabetes, contributes to a variety of pathological conditions including dyslipidemia, hypertension, atherosclerosis, cognitive disorders and cancer. Obesity, defined as increased lipid deposition in adipose tissue, is one of the most common and important causative factors for insulin resistance. However, obesity is also often associated with lipid deposition in non-adipose tissues. Such ectopic accumulation of lipid, together with the entropic accumulation, is thought to be related to the pathogenesis of insulin resistance. Much evidence thus suggests that the extent of lipid deposition in skeletal muscle, a major target organ of insulin, is highly correlated with whole-body glucose disposal triggered by this hormone. Whereas a mechanistic link between ectopic lipid deposition and the pathogenesis of insulin resistance has remained to be definitively shown, prevention of lipid deposition in skeletal muscle might be expected to have beneficial effects on insulin sensitivity and glucose tolerance.

The family of vascular endothelial growth factors (VEGFs) comprises VEGF (or VEGF-A), VEGF-B, VEGF-C, VEGF-D and placental growth factor (PLGF). VEGF-A is a potent angiogenic factor, but it also regulates the permeability and contractility of arteries. PLGF, which is expressed predominantly in the placenta, heart and lung, is thought to regulate arteriogenesis, the formation of collateral arteries from pre-existing arterioles. VEGF-C and VEGF-D play important roles in the growth of lymphatic vessels. Although VEGF-B promotes angiogenesis under certain conditions, such as in response to inflammation or ischemia, the physiological functions of this secreted protein have remained ambiguous. VEGF-B is abundantly expressed in skeletal muscle, heart and brown adipose tissue, all of which are enriched in mitochondria and rely predominantly on fatty acids as an energy source, suggesting that VEGF-B might play a role in energy metabolism.

Hagberg et al.\textsuperscript{1} recently showed that VEGF-B acts at the vascular endothelium to stimulate transendothelial transport of circulating fatty acids into skeletal muscle and the heart. This effect was shown to result from the interaction of VEGF-B with VEGF receptor 1 (VEGFR1) and its coreceptor neuropilin 1 in the vascular endothelium, and consequent induction of the expression of fatty acid transport protein 3 (FATP3) and FATP4\textsuperscript{1,2}. Mice deficient in VEGF-B thus showed reduced levels of fatty acid uptake and lipid accumulation in skeletal muscle, as well as in the heart and brown adipose tissue, compared with wild-type animals. These findings suggested that inhibition of the function of VEGF-B attenuates ectopic lipid accumulation in skeletal muscle and might thus prevent the development of insulin resistance.

Hagberg et al.\textsuperscript{2} have now assessed more directly the therapeutic potential of targeting the VEGF-B pathway to control insulin resistance (Figure 1). They examined the effects of genetic ablation of VEGF-B in \textit{db/db} mice and in mice fed a high-fat diet, both of which are animal models characterized by obesity, ectopic lipid deposition in skeletal muscle and insulin-resistant diabetes. Ablation of VEGF-B in these models resulted in reduced levels of FATP3 expression and lipid deposition in skeletal muscle as well as in the heart, and these effects were associated with marked amelioration of hyperglycemia and hyper-insulinemia. Furthermore, the administration of neutralizing antibodies to VEGF-B in \textit{db/db} mice also reduced lipid deposition in skeletal muscle, as well as ameliorated insulin resistance and hyperglycemia. Hagberg et al.\textsuperscript{2} administered the antibodies to young, prediabetic \textit{db/db} mice, and this intervention was found to protect the animals from the development of overt diabetes. Glucose clamp analyses also showed that administration of the antibodies to rats with insulin resistance induced by a high-fat diet increased whole-body glucose disposal, and enhanced insulin-induced glucose uptake in skeletal muscle and the heart. Neither genetic ablation nor antibody-dependent neutralization of VEGF-B reduced body or adipose tissue mass, however. Rather, genetic ablation of VEGF-B actually increased body and adipose tissue mass both in \textit{db/db} mice and in mice fed a high-fat diet. The researchers thus concluded that the targeting of VEGF-B attenuated insulin resistance not through the amelioration of obesity, but through the prevention of ectopic fat deposition. They proposed that prevention of fatty acid transport into muscle and the heart results in a shunting of lipid into adipose tissue, leading to an increase in adipose tissue mass (Figure 1).

This study thus clearly showed that the targeting of VEGF-B efficiently ameliorated insulin resistance and glucose intolerance in rodent models. It is indeed likely that the reduction in ectopic lipid accumulation in skeletal muscle resulting from attenuation of fatty acid transport in the endothelium contributes to the beneficial effects of VEGF-B targeting. Given that pharmacological agents that prevent ectopic lipid deposition are not
The role of vascular endothelial growth factor-B (VEGF-B) in the regulation of fatty acid transport. (a) VEGF-B is abundantly expressed in skeletal muscle. The interaction of VEGF-B with its endothelial receptor, vascular endothelial growth factor receptor 1 (VEGFR1), increases fatty acid transport protein 3 (FATP3) expression and consequent uptake of circulating fatty acids into muscle. Upregulation of VEGF-B and FATP3 expression under conditions of overnutrition results in lipid accumulation in muscle, which in turn leads to whole-body insulin resistance. (b) Targeting of VEGF-B by genetic ablation or the administration of neutralizing antibodies attenuates lipid accumulation in muscle by downregulating endothelial transport of fatty acids mediated by FATP3, resulting in amelioration of insulin resistance. Ab, antibody.

The physiological functions of these proteins in this tissue remain largely unknown. A recent study showed that an increase in body mass in humans was negatively correlated with the expression level of VEGF-B and positively correlated with that of VEGF-A in white adipose tissue. Furthermore, suppression of VEGF-A expression in mice, which was associated with the upregulation of VEGF-B expression in white adipose tissue, conferred a lean phenotype and protected the animals from obesity induced by a high-fat diet. These findings collectively suggest that VEGF-B, together with VEGF-A, plays a role in the regulation of adipose tissue function. Does the targeting of VEGF-B affect inflammation of adipose tissue or modulate the expression of genes related to glucose and lipid metabolism? Does such treatment influence the expression of adiponectin? Answers to such questions would add much to our understanding of the underlying mechanism of this therapeutic approach. Furthermore, the vascular endothelium appears to control whole-body insulin sensitivity through a variety of mechanisms including the regulation of both vessel inflammation and the transport of insulin from the circulation into interstitial fluid. It will also be interesting to know whether the modulation of VEGF-B signaling affects such functions of the endothelium.

The findings of Hagberg et al. show that the targeting of VEGF-B is a potential new approach to the treatment of insulin resistance and type 2 diabetes. Furthermore, they provide a stimulus to further characterization of the pathogenesis of insulin resistance, as well as of the interactions between muscle and adipose tissue. Further investigation of the functions of VEGF-B should contribute to our understanding of insulin resistance and might provide a basis for the development of novel drugs for diabetes.

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REFERENCES

1. Hagberg CE, Falkevall A, Wang X, et al. Vascular endothelial growth factor B controls endothelial fatty acid uptake. Nature 2010; 464: 917–921.

2. Hagberg CE, Mehlem A, Falkevall A, et al. Targeting VEGF-B as a novel treatment for insulin resistance and type 2 diabetes. Nature 2012; 490: 426–430.

3. Tinahones FJ, Coín-Aragüez L, Mayas MD, et al. Obesity-associated insulin resistance is correlated to adipose tissue vascular endothelial growth factors and metalloproteinase levels. BMC Physiol 2012; 12: 4.

4. Lu X, Ji Y, Zhang L, et al. Resistance to obesity by repression of VEGF gene expression through induction of brown-like adipocyte differentiation. Endocrinology 2012; 153: 3123–3132.

5. Kubota T, Kubota N, Kumagai H, et al. Impaired insulin signaling in endothelial cells reduces insulin-induced glucose uptake by skeletal muscle. Cell Metab 2011; 13: 294–307.