Microvascular Management of Systemic Insulin Sensitivity

Katya B. Rubinow, Karin E. Bornfeldt

Microvascular disease is a well-recognized complication of long-standing diabetes mellitus and is preceded by impaired vasoreactivity, a consequence largely of decreased endothelial cell (EC) generation of NO. This loss of normal vasodilation is evident particularly in EC responses to insulin and may arise early in states of obesity and insulin resistance.1–3 In addition, ECs serve as purveyors of other paracrine signals, with targets beyond vascular cells. Thus, a broader scope of endothelial function is being recognized, with increased attention now focused on the dynamic interactions between the microvasculature and surrounding tissues. Indeed, recent findings suggest that ECs might be critical metabolic mediators, obscuring a clear boundary between vascular biology and metabolism. Accordingly, dysregulated EC function may prove to be not only a sequela of diabetes mellitus but also a contributing factor to the pathogenesis and progression of metabolic disease.

The role of ECs in regulating systemic insulin sensitivity has received relatively little attention to date because animals with EC-targeted deletion of proteins are required to observe such a role, and generation of such animals is time-consuming. However, mouse models expressing Cre recombinase under control of EC-selective promoters/enhancers, combined with mouse models with floxed target genes, are now becoming more routinely used for metabolic studies. The most commonly used promoter is the Tie2 promoter, which encodes endothelial-specific receptor tyrosine kinase,4 but other promoters are used as well. The Tie2 promoter is active in ECs but also in hematopoietic cells and female germ cells. Such mouse models have begun to reveal a metabolic role for ECs. Thus, when fed a high-fat diet, mice with EC-selective deficiency of peroxisome proliferator–activated receptor-γ, a target of the thiazolidinediones class of insulin-sensitizing drugs, develop less insulin resistance than controls.5 This effect was attributed to reduced expression of proteins involved in fatty acid handling in ECs, such as CD36 (Figure), resulting in protection from triacylglycerol accumulation in skeletal muscle.5

In other studies, the insulin receptor or signaling molecules downstream of the insulin receptor have been deleted or mutated in ECs. Mice that lack functional insulin receptors or the downstream insulin receptor substrate 1 or FoxO in ECs show normal systemic insulin sensitivity,6,7 whereas mice that lack insulin receptor substrate 2 in ECs demonstrate reduced insulin action in skeletal muscle through a mechanism believed to be attributable to reduced transport of insulin to the interstitial space and reduced capillary blood flow (Figure).8 Thus, distinct arms of insulin receptor signaling in ECs may have different effects on systemic insulin sensitivity.

The findings of Messmer-Blust et al10 published in this issue of Circulation Research, further support a role for ECs in managing systemic insulin sensitivity. The described studies demonstrate that the transcription factor related transcriptional enhancer factor-1 (RTEF-1, encoded by the mouse gene Tead4; TEA domain family member 4) promotes insulin sensitivity by its expression in ECs.10 RTEF-1 is generally considered enriched in muscle, because it binds to M-CAT elements found in the promoters of muscle-specific genes.11 Its activity in ECs is stimulated by hypoxia and results in increased expression of mitogenic and angiogenic signals, including vascular endothelial growth factor and the fibroblast growth factor receptor-1, as well as NO generation.12,13 In addition, Messmer-Blust et al10 now report that RTEF-1 directly regulates the expression of insulin-like growth factor binding protein 1 (IGFBP-1) in ECs and, furthermore, seems to do so by binding to an insulin response element on the IGFBP-1 promoter. Whereas insulin signaling confers a repressive transcriptional effect, RTEF-1 binding augments IGFBP-1 expression. When RTEF-1 was knocked down in ECs, mice exhibited decreased circulating levels of IGFBP-1 and increased insulin resistance during high-fat feeding. Conversely, RTEF-1 overexpression resulted in enhanced IGFBP-1 levels and attenuated the insulin resistance induced by a high-fat diet.10 In clinical cross-sectional studies, IGFBP-1 concentrations correlate inversely with cardiovascular risk factors and extant cardiovascular disease, as well as with insulin resistance and the presence of metabolic syndrome.14 Supporting a direct role for IGFBP-1, overexpression of IGFBP-1 in mice confers improved insulin sensitivity, lower blood pressure, and protection from atherosclerosis.15 The majority of circulating IGFBP-1 derives from hepatic production,16 but IGFBP-1 is also produced by ECs. These novel findings lend additional weight to a broader view of EC function, placing ECs at the interface of vascular and metabolic physiology (Figure).

Is IGFBP-1 the mediator of the effects of endothelial RTEF-1 on systemic insulin resistance? This interpretation is favored by Messmer-Blust et al10 based on their findings and evidence from the literature that IGFBP-1 regulates insulin sensitivity. However, although changes in insulin sensitivity were associated with altered IGFBP-1 levels after
RTEF-1 manipulation, a causal relationship is yet to be established in this model. RTEF-1 in ECs modulates several different genes, including angiogenic and vasodilatory factors. It is thus possible that RTEF-1 in ECs causes expression of additional secreted mediators of insulin sensitivity or that the effect of RTEF-1 is a result of increased capillary blood flow in insulin target tissues.17 Accordingly, the EC-targeted insulin receptor substrate 2–deficient mouse has an insulin resistance phenotype similar to that of the EC-targeted RTEF-1–deficient mouse, an effect attributed to reduced transport of insulin into the skeletal muscle interstitial space resulting from reduced capillary blood flow.8 Furthermore, a similar phenotype is seen in the endothelial NO synthase–deficient mouse.18 The exact mechanism(s) of action of endothelial RTEF-1 in regulating systemic insulin sensitivity is an interesting area of future research. Furthermore, if the effects of RTEF-1 are mediated by secretion of IGFBP-1 from ECs, what is the mechanism of action of this IGFBP-1? It is possible that IGFBP-1 sequesters insulin-like growth factor-1 (IGF-1) and thereby inhibits its activity.16 Indeed, infusion of IGFBP-1 confers mild hyperglycemia and abrogates the hypoglycemic effect of systemic IGF-1 delivery.19 Furthermore, IGFBP-1 can associate with α2-macroglobulin, which inhibits its interaction with IGF-1. IGFBP-1 also can mediate IGF-1–independent effects by signaling through integrin receptors, best described for α5β1-integrin. IGFBP-1 signaling through this integrin can promote phosphatidylinositol 3-kinase/Akt signaling, a downstream target of the insulin receptor; thus, loss of IGFBP-1 action could promote insulin resistance through IGF-1–independent mechanisms.16 Consequently, EC-derived IGFBP-1 could exert potentially discrepant paracrine effects contingent on the surrounding cell types, the local concentrations of IGF-1 and IGFBP-1, and the relative expression of αβ-integrins and insulin/IGF-1 receptors. Other interesting questions remain, principal among which is whether diminished RTEF-1 activity characterizes the endothelial dysfunction that evolves in states of insulin resistance and diabetes mellitus. The tissue-specific distribution of RTEF-1, for example in hematopoietic cells, also requires further investigation.

In aggregate, the findings of Messner-Blust et al10 underscore the pivotal role of EC function within the tissue microenvironment in establishing systemic insulin sensitivity. Their data present powerful evidence that the microvascularity may play a critical role in the progression of insulin resistance and related complications.

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**Disclosures**

None.

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