Microvascular Management of Systemic Insulin Sensitivity

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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. 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, 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 thiazolidinedione class of insulin-sensitizing drugs, develop less insulin resistance than controls. 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.

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, 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). Thus, distinct arms of insulin receptor signaling in ECs may have different effects on systemic insulin sensitivity.

The findings of Messmer-Blust et al, 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. RTEF-1 is generally considered enriched in muscle, because it binds to M-CAT elements found in the promoters of muscle-specific genes. 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. In addition, Messmer-Blust et al 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. In clinical cross-sectional studies, IGFBP-1 concentrations correlate inversely with cardiovascular risk factors and extend cardiovascular disease, as well as with insulin resistance and the presence of metabolic syndrome. Supporting a direct role for IGFBP-1, overexpression of IGFBP-1 in mice confers improved insulin sensitivity, lower blood pressure, and protection from atherosclerosis. The majority of circulating IGFBP-1 derives from hepatic production, 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 al 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...
Increased capillary blood flow

RTEF-1 might also affect targets other than IGFBP-1 to increase systemic insulin sensitivity, possibly by increasing capillary blood flow. FGF-R indicates fibroblast growth factor receptor-1; VEGF, vascular endothelial growth factor.

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Disclosures

None.

References


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