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Secreted MG53 From Striated Muscle Impairs Systemic Insulin Sensitivity

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Diabetes mellitus is 1 of the most prevalent health challenges worldwide, affecting >422 million people. In the United States alone, >30 million people were diagnosed with diabetes mellitus in 2015, and this number is predicted to double by 2030.[1] More than 1 of every 3 adults in the United States has prediabetes, indicated by elevated blood glucose levels but below those of full-blown diabetes mellitus. Prediabetic patients are generally insulin-resistant, meaning that their muscle, fat, and liver cells are resistant to glucose uptake from the blood. Despite decades of research, we still do not fully understand the underlying causes of insulin resistance and prediabetes.

Skeletal muscle is the major site of glucose uptake in humans.[2] Maintaining the integrity of the insulin signaling pathway is essential for normal insulin-mediated glucose uptake in muscle. Skeletal muscle participates in systemic metabolism not only by taking up glucose, but also by sending messengers, such as secreted myokines, to communicate with other tissues. Like skeletal muscle, the heart also secretes myokines, called cardiokines.[3] Secretome analysis of exercised muscle in humans and rodents previously led to the discovery of a number of myokines that were shown to have beneficial effects on body metabolism.[4] Indeed, many of the identified myokines have been shown to be involved in various processes of exercise adaptation, muscle growth, and regulation of whole-body glucose/lipid metabolism. The existence of myokines and cardiokines has enhanced our understanding of how muscles communicate with other tissues such as adipose tissue, liver, bone, and brain to regulate whole-body metabolism. The list of new myokines is continuously increasing, and some are promising targets for the treatment of metabolic disorders, although their physiological actions remain largely unexplored.

Skeletal muscle insulin resistance is recognized as the primary defect in patients with type 2 diabetes mellitus (T2D).[5] However, the etiologic factors causing muscle insulin resistance

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remain unclear. It is also unknown whether diabetic muscle communicates with other tissues to promote systemic metabolic disorders. It is plausible that myokines or cardiokines secreted by diseased muscle might contribute to the systemic diabetic state. Similar to exercise-induced myokines that elicit a beneficial effect, myokines secreted by diabetic muscle may drive the pathogenesis of the disease, thereby impairing systemic metabolism. Understanding both the beneficial and deleterious functions of myokines in regulating systemic metabolism may help identify druggable targets for future treatment of insulin resistance and T2D.

In this issue of *Circulation*, Wu et al[6] report the discovery of a novel myokine, mitsugumin 53 (MG53), which impairs whole-body insulin sensitivity, further supporting the complex role of muscle as an endocrine tissue in regulating systemic metabolism. MG53 is expressed predominantly in cardiac and skeletal muscle. Unexpectedly, it was first identified as a muscle-specific E3 ubiquitin ligase involved in the repair of membrane damage.[7] Subsequently, Song et al[8] reported that intracellular MG53 targets the insulin receptor (IR) and IR substrate 1, for ubiquitination and degradation, thereby controlling insulin signaling in skeletal muscle. In the present study, Wu et al show for the first time that MG53 is secreted from perfused striated muscle and that the levels of circulating MG53 are elevated by glucose or insulin stimulation. The authors confirm that the secretion of MG53 is regulated by Ca^{2+} and the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors) binding protein–dependent secretory pathway. By measuring circulating MG53 levels and metabolic parameters in diabetic rodents and humans, the authors found that circulating MG53 levels directly correlated with hyperglycemia and hyperinsulinemia. These findings indicate that circulating MG53 may serve as a biomarker for insulin resistance and T2D.

To elevate levels of circulating MG53 in the body, transgenic mice that overexpress MG53 in the heart (MG53 h-TG) were developed. As early as 1 week of age, the MG53 h-TG mice showed a 1.5-fold elevation in circulating MG53 along with increased levels of blood glucose and insulin, without a significant change in body weight. By 4 months of age, MG53 h-TG mice exhibited moderate glucose and insulin intolerance. It is striking that, by 7 months of age, MG53 h-TG mice on a normal diet showed severe obesity and the onset of metabolic syndrome. More notably, intravenous administration of MG53 protein in 8- to 10-week-old wild-type mice impaired whole-body insulin sensitivity, which supports the hypothesis that circulating MG53 acts as a disease-causing factor, directly attenuating the insulin response systemically. It is interesting to note that the ablation of blood MG53 by antibody neutralization decreased blood glucose and promoted insulin sensitivity in diabetic mice. However, this improvement is not sufficiently robust to serve as a treatment for T2D. In diabetic patients and mice, it was reported that the expression of MG53 was increased in muscle tissue.[8,9] Therefore, both intracellular and secreted MG53 are increased in the diabetic state. It can be speculated that the low efficacy of MG53 monoclonal antibodies may indicate that targeting only circulating MG53 is not sufficient to restore the insulin sensitivity produced by both intracellular and secreted MG53. Thus, targeting both circulating MG53 and intracellular MG53 would likely be necessary for an effective strategy for treatment of T2D.

Mechanistically, the authors identified the extracellular domain (ECD) of the IR as a binding site for circulating MG53. It is important to note that the affinity of MG53 binding to the IR ECD is high (K_D=8.0 nmol/L). Plus, the concentration of serum MG53 in diabetic rats measured by ELISA is ≈3 to 8 nmol/L. These data indicate that circulating MG53 directly binds to the IR ECD at nanomolar concentrations in the diabetic state. The authors specifically showed that the C-terminal domain of MG53 is important, but the RING (Really Interesting New Gene) domain, which is the E3 ubiquitin ligase catalytic domain of MG53, is dispensable for the interaction between MG53 and IR ECD. These data indicate that, in contrast to intracellular MG53, the actions of extracellular MG53 on the IR are independent of its E3 ubiquitin ligase enzyme activity. It is surprising that, although the affinity of MG53 binding to the IR ECD is higher than that of insulin (K_D=28.0 nmol/L), the extracellular MG53 binding to the IR does not interrupt the binding of insulin. The authors commented that circulating MG53 may act as an allosteric, but not a competitive, blocker of IR. The binding of MG53 to the IR might impair the phosphorylation and activation of IR downstream of insulin binding, but this was not addressed. The underlying mechanism whereby extracellular MG53 blocks insulin signaling needs further investigation.

This study revealed the unexpected secretion of MG53 from diabetic muscle, providing a new avenue for exploration of the role of MG53 in regulating whole-body metabolism. However, it raises additional questions to be answered. For example, the mechanism whereby high glucose and insulin induce the secretion of MG53 remains unclear. Of note, MG53 protein is much larger than other previously reported myokines. Whether the secreted MG53 is located inside exosomes released by striated muscle is undetermined. A comprehensive screen of binding sites of secreted MG53 will be needed to further understand how extracellular MG53 systemically inhibits insulin sensitivity. Whether the secretion of MG53 correlates with muscular contractions or exercise activity in vivo also remains to be defined.

There are numerous studies showing muscle and heart as endocrine tissues that control systemic metabolism.[10–14] The study by Wu et al[6] provides evidence for the notion that myokines produced from diseased striated muscle could be pathological factors increasing systemic insulin resistance. This study provides proof-of-principle that the depletion of serum MG53 might potentially improve insulin sensitivity. Deciphering the mechanism of how MG53 impairs insulin signaling both intra- and extracellularly may provide new insights into the causes and treatment of insulin resistance and T2D.

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