Glucose homeostasis is maintained by a balance between glucose uptake by the skeletal muscle, heart and adipose tissue, and gluconeogenesis by the liver, kidney and gut. When excessive insulin or insulin secretagogues are used to treat diabetes, lipogenesis is promoted in the liver and other tissues. It might cause unwanted pathological conditions, such as severe insulin resistance and non-alcoholic fatty liver disease. Jiang et al. recently identified Isthmin-1 (ISM1) as a unique adipokine that promotes glucose uptake by adipocytes and muscle cells, suppresses lipogenesis, and promotes protein synthesis in hepatocytes in an insulin-independent manner. ISM1 activates phosphoinositide 3-kinase–protein kinase B (AKT) signaling through an unknown receptor (Figure 1).

Aiming to identify adipocyte-derived proteins with hormonal properties, Jiang et al. used an integrative approach utilizing a ribonucleic acid sequencing (RNA-seq) database, a multiplexed proteomic secretome and a phosphokinase array. They first screened for genes predicted to encode secretory proteins using a ribonucleic acid sequencing dataset from mature adipocytes isolated from murine inguinal white adipose tissue, epididymal white adipose tissue and brown adipose tissue. Furthermore, the results were compared with those of proteomic analysis of the supernatants of cultured adipocytes.

Among the candidates, ISM1 was identified as a factor that could promote glucose uptake into adipocytes and myocytes within a few minutes to a few hours. They not only observed ISM1’s ability to increase glucose uptake into adipocytes in the absence of insulin, but also found that there was an additive effect when ISM1 was added together with insulin, suggesting that ISM1 exerts its effect through a mechanism distinct from that of insulin. They used a phosphokinase array to identify the intracellular signaling pathway of ISM1. They found that ISM1 strongly phosphorylated AKT within several minutes to tens of minutes. AKT phosphorylation and stimulation of glucose uptake by ISM1 were completely suppressed by phosphoinositide 3-kinase inhibitors, suggesting that ISM1 shares a common intracellular signaling pathway with insulin. Although ISM1’s action was unaffected by the insulin-like growth factor 1 receptor/insulin receptor inhibitor, it was completely suppressed by an inhibitor targeting multiple receptor tyrosine kinases. These results show that ISM1’s action is mediated by an unknown receptor tyrosine kinase distinct from the insulin-like growth factor 1 and insulin receptors (Figure 1).

In the hepatocyte cell line alpha mouse liver 12, forced expression of ISM1 markedly repressed sterol regulatory element-binding protein-1c expression. In addition, ISM1 counteracted the insulin-mediated increase in the expression of sterol regulatory element-binding protein-1c and its target genes, such as *Fas*, *Acc* and *Scd1*, in a dose-dependent manner. In contrast, ISM1 increased the phosphorylation of SgK233/SgK236, the key regulator of protein synthesis; furthermore, they showed an increase in protein synthesis by measuring the incorporation of H3-leucine into proteins (Figure 1).

The authors intravenously administered recombinant ISM1 to mice (10 mg/kg), and observed the activation of AKT signaling in inguinal white adipose tissue, brown adipose tissue, skeletal muscle and...
the liver. To investigate the long-term effects, 16-week-old diet-induced obese mice were treated daily with ISM1 (5 mg/kg), metformin (100 mg/kg) or both for 21 days. They observed that glucose tolerance and insulin sensitivity were significantly improved in the treatment groups compared with the control group, and were the highest in the combined treatment group. To test whether ISM1 is effective in non-alcoholic fatty liver disease, they treated a non-alcoholic fatty liver disease model with ISM1 for 14 days and found that a 5 mg/kg dose of ISM1 was effective in reducing lipid accumulation in the liver, and the effect was comparable to that of a daily treatment with the farnesoid X receptor agonist GW4064 (30 mg/kg) for 14 days. They further examined transgenic mice overexpressing ISM1, and showed that the mice were more glucose-tolerant and insulin-sensitive under a high-fat diet, and exhibited more attenuated fatty liver than the wild-type mice.

Collectively, ISM1 is an adipokine that has a potent glucose-lowering effect by stimulating a common intracellular signaling pathway with insulin through a distinct receptor and has an inhibitory effect on lipogenesis in the liver, whereas insulin has the opposite effect. Therefore, ISM1 is expected to have clinical benefits in the treatment of diabetes.

However, many questions need to be answered. First, it is essential to identify the ISM1 receptor. Second, regulation of ISM1 levels under physiological and pathological conditions should be determined. Third, it is important to know whether there is a condition in which resistance to ISM1 develops just as resistance to insulin develops in obese individuals. Finally, it is intriguing to know whether the unique ability of ISM1 to stimulate protein synthesis and suppress lipogenesis in the liver is also observed in the muscle. If yes, ISM1 might be ideal for treating patients with sarcopenia, a pathological condition that is becoming a major problem in the aging society2.

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DISCLOSURE

The authors declare no conflict of interest.

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