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Exercise training decreased lipid accumulation in murine skeletal muscle through Sestrin2-mediated SHIP2-JNK signaling pathway

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Objective Obesity is becoming increasingly prevalent and is an important contributor to the worldwide burden of diseases. It is widely accepted that exercise training is beneficial for the prevention and treatment of obesity. However, the underlying mechanism by which exercise training improving skeletal muscle lipid metabolism is still not fully described.

Sestrins (Sestrin1-3) are highly conserved stress-inducible protein. Concomitant ablation of *Sestrin2* and *Sestrin3* has been reported to provoke hepatic mTORC1/S6K1 activation and insulin resistance even without nutritional overload and obesity, implicating that Sestrin2 and Sestrin3 have an important homeostatic function in the control of mammalian glucose and lipid metabolism. Our previous results demonstrated that physical exercise increased Sestrin2 expression in murine skeletal muscle, while the role of Sestrin2 in regulating lipid metabolism remains unknown.

SH2 domain containing inositol 5-phosphatase (SHIP2) acts as a negative regulator of the insulin signaling both in vitro and in vivo. An increased expression of SHIP2 inhibits the insulin-induced Akt activation, glucose uptake, and glycogen synthesis in 3T3-L1 adipocytes, L6 myotubes and tissues of animal models. Alterations of SHIP2 expression and/or enzymatic function appear to have a profound impact on the development of insulin resistance. However, the regulatory function of SHIP2 in lipid metabolism after exercise remains unclear. It has been reported that SHIP2 modulated lipid metabolism through regulating the activity of c-Jun N-terminal kinase (JNK) and Sterol regulatory element-binding protein-1 (SREBP-1).

JNK is a subclass of mitogen-activated protein kinase (MAPK) signaling pathway in mammalian cells and plays a crucial role in metabolic changes and inflammation associated with a high-fat diet.

Inhibition of JNK reduces lipid deposition and proteins level of fatty acid de novo synthesis in liver cells. It has been reported that Sestrin2 regulated the phosphorylation of JNK, however the underlying mechanism remains unclear. SREBP-1 is important in regulating cholesterol biosynthesis and uptake and fatty acid biosynthesis, and SREBP-1 expression produces two different isoforms, SREBP-1a and SREBP-1c. SREBP-1c is responsible for regulating the genes required for de novo lipogenesis and its expression is regulated by insulin. SREBP-1a regulates genes related to lipid and cholesterol production and its activity is regulated by sterol levels in the cell.

Altogether, the purpose of this study was to explore the effect and underlying mechanism of Sestrin2 on lipid accumulation after exercise training.

Methods Male wild type and *SESN2*^{-/-} mice were divided into normal chow (NC) and high-fat diet (HFD) groups to create insulin resistance mice model. After 8 weeks the IR model group was then divided into HFD sedentary control and HFD exercise groups (HE). Mice in HE group underwent 6-week treadmill exercise to reveal the effect of exercise training on lipid metabolism in insulin resistance model induced by HFD. We explored the mechanism through which Sestrin2 regulated lipid metabolism in vitro by supplying palmitate, overexpressing or inhibiting SESNs, SHIP2 and JNK in myotubes.

Results We found that 6-week exercise training decreased body weight, BMI and fat mass in wild type and *SESN2*^{-/-} mice after high-fat diet (HFD) feeding. And exercise training decreased the level of plasma glucose, serum insulin, triglycerides and free fatty acids in wild type but not in *Sestrin2*^{-/-}

$-/-$ mice. Lipid droplet in skeletal muscle was also decreased in wild type but did not in Sestrin2 $-/-$ mice. Moreover, exercise training increased the proteins expression involved in fatty acid oxidation and decreased the proteins which related to fatty acid de novo synthesis. The results of oil red staining and the change of proteins related to fatty acid de novo synthesis and beta oxidation in myotubes treated with palmitate, Ad-SESN2 and siRNA-Sestrin2 were consisted with the results in vivo, which suggested that Sestrin2 was a key regulator in lipid metabolism. Exercise training increased Sestrin2 expression and reversed up-regulation of SHIP2 and pJNK induced by HFD in wild type mice but not in Sestrin2 $-/-$ mice. In parallel, overexpression of Sestrin2 decreased the level of SHIP2 and pJNK induced by palmitate while Sestrin2 knock down by siRNA-Sestrin2 treatment did not change the expression of SHIP2 and pJNK, which suggested that Sestrin2 modulated SHIP2 and JNK in the state of abnormal lipid metabolism. Inhibition of SHIP2 reduced the activity of JNK, increased lipid accumulation and the proteins of fatty acid synthesis after palmitate treatment and over expression of Sestrin2, which suggest that Sestrin2 modulated lipid metabolism through SHIP2/JNK pathway.

Conclusions Sestrin2 plays an important role in improving lipid metabolism after exercise training, and Sestrin2 regulates lipid metabolism by SHIP2-JNK pathway in skeletal muscle.