



The potential role of MG53 in exercise-mediated modulation of diabetic cardiomyopathy in db/db mice

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Objective Diabetic cardiomyopathy is a major complication of Type 2 diabetes. Recent studies have shown that as an E3 ligase targeting insulin receptor (IR) and insulin receptor substrate 1 (IRS1), MG53 could result in insulin resistance and metabolic disorders. However, it is still to be investigated whether MG53 plays a role in the pathogenesis of diabetic cardiomyopathy, as well as whether the effect of exercise intervention on diabetic cardiomyopathy is mediated by MG53.

Methods 20 db/db mice and 20 m/m mice were randomly assigned to Groups DC (db/db control, N=10), DE (db/db exercise, N=10), MC (m/m control, N=10) and ME (m/m exercise, N=10). The mice of Groups ME and DE were trained to run on the treadmill for 12 weeks in total. For Week 1, the mice ran for 20min at 7-13m/min, four times a week. Since the second week, the mice were trained to run at 13.3m/min, 6d/wk, and the running duration was increased from 30-45min/d for Week 2 to 1h/d since the third week. At the end of the intervention period, IPGTT and IPITT were performed to determine the effect of exercise training. The mice were then euthanized and the heart was removed. Real-time PCR and Western blotting were performed to determine the expression levels of mRNA and proteins.

Results According to the result of IPGTT and IPITT, glucose concentration was significantly higher in DC compared to MC, and exercise intervention significantly decreased the glucose level of diabetic mice. Heart weight to tibia length ratio was not significantly different between MC and DC, but was higher in DE than in DC. As expected, the mRNA expression of MG53 was significantly higher in the diabetic mice, and was significantly decreased by exercise training. However, the protein level of MG53 was not significantly different between MC and DC, even though exercise intervention caused lower MG53 protein level in DE. The protein level of p-IR- β (Tyr1146) was significantly higher in DC than MC. Exercise intervention significantly decreased the protein level of p-IRS1 (Ser1101) in both the lean and diabetic mice. Diabetes caused a significant decrease in p-AKT (Ser473), while exercise training increased the protein level of p-AKT (Ser473) of the diabetic mice. The mRNA expressions of Ppargc1a, Cpt1b, Acadm, Acadvl, Acacb and Acaa2 were significantly increased in DC compared to MC, suggesting that fat metabolism was enhanced in the hearts of diabetic mice. To the contrary, the enhanced fat metabolism was compromised by exercise intervention, as revealed by the mRNA expression level of Cpt1b, Acadm, Acacb and Acaa2. Besides, the mRNA expression of Pdk1 and Pdk2 were significantly increased in db/db mice, suggesting that glucose metabolism was reduced by diabetes. PPAR- α is an important regulator of fat metabolism. The protein level of PPAR- α was significantly increased in DC compared to MC, and was decreased in DE compared to DC. Besides, the mRNA expression of key components of PPAR- α pathway, including Cd36, Ppargc1b and Fabp3 were all significantly increased in db/db mice, while exercise intervention significantly decreased the mRNA expression of Cd36 and Ppargc1b.

Conclusions MG53 is involved in the pathogenesis of diabetic cardiomyopathy of db/db mice by inhibiting insulin signaling, downregulating glucose metabolism and promoting fat metabolism. The state of insulin resistance and alteration of substrate utilization brought by diabetes could be improved by 12 week treadmill training, partly through the regulation of PPAR- α pathway.