



## Exercise Biochemistry Review

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Proceedings of IBEC 2018, Beijing, China, October 23-25  
PO-063

### Exercise alleviates insulin resistance by regulating MG53 and IR/IRS/AKT/mTOR signaling in db/db mice skeletal muscle

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**Objective** In the current study, we aim to investigate whether 12-week treadmill exercise alleviates insulin resistance and muscle atrophy, and to explore whether MG53 along with IR/IRS/AKT/mTOR cascade play a role in the physiopathological changes of db/db mice.

**Methods** 20 db/db mice and 20 age-matched non-diabetic m/m mice were assigned to 4 groups as MC (m/m control) group, ME (m/m exercise) group, DC (db/db control) group and DE (db/db exercise) group. After an intervention of treadmill exercise of moderate intensity for 12 weeks, glucose and insulin tolerance tests, insulin resistance index (HOMA-IR, homeostasis model assessment of insulin resistance) and lipid metabolic profile were determined using blood samples. Skeletal muscles were utilized for determination of cross-sectional area (CSA), protein level detection of MG53 and insulin signaling pathway.

**Results** Compared with MC mice, the AUC (areas under curve) of IPGTT (intraperitoneal glucose tolerance test) and IPITT (intraperitoneal insulin tolerance test) as well as HOMA-IR were significantly increased, and lipid parameters (serum triglyceride and total cholesterol) increased significantly in DC group. The upregulation of MG53 protein in different skeletal muscles (quadriceps, gastrocnemius and soleus muscle) could be observed in DC mice. Phosphorylated proteins of IR- $\beta$  ( $\beta$  subunit of insulin receptor), IRS1, AKT (protein kinase B), mTOR (mammalian target of rapamycin), p70S6k and S6 ribosomal protein after acute insulin stimulation were downregulated with significance, whereas no significant difference was found in total protein levels of IR- $\beta$  and AKT except IRS1 in DC group. The results of AUC of IPGTT and IPITT, HOMA-IR and serum lipid parameters in DE group were significantly decreased compared with DC group. 12-week moderate exercise was sufficient to downregulate the expression of MG53 in skeletal muscles of diabetic db/db mice. In addition, treadmill exercise-induced improvement of insulin signal transduction and insulin-dependent protein synthesis may partially account for the heavier muscle mass and larger muscle size.

**Conclusions** In summary, insulin resistance and muscle atrophy of diabetic db/db mice could be effectively attenuated by 12-week moderate treadmill exercise by regulating MG53, MG53-mediated ubiquitin-dependent degradation of IRS1 and insulin signaling transduction.