DOI 10.18699/SBB-2022-483

Role of HSP70 proteins in regulation of mitochondrial protein content in skeletal muscle

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Key words: skeletal muscle, proteome, transcriptome

Motivation and Aim: At a normal level of physical activity, skeletal muscles intensively oxidize carbohydrates and fats, playing a key role in the regulation of carbohydrate and fat metabolism, and insulin sensitivity in the organism. A decrease in the content of mitochondria in skeletal muscles and their oxidative capacity is one of the factors in the development of metabolic disorders. Increased physical activity effectively stimulates mitochondrial biogenesis in muscles, thereby positively regulating carbohydrate and fat metabolism. We aimed to study the specificity of the regulation of mitochondrial biogenesis in skeletal induced by regular physical exercise and the role of HSP70 family proteins in the regulation of the content of mitochondrial proteins.
Methods and Algorithms: In a study with volunteers, the effects of 2-month physical training on the content of proteins (shotgun quantitative [with isobaric labeling] proteomic) in skeletal muscle (*m. vastus lateralis*) and their mRNA expression (RNA sequencing) were studied. In an experiment on *D. melanogaster* line *Hsp70-*(*Df(3R)Hsp70A, Df(3R)Hsp70B*), we studied the effects of knockout of 6 genes (out of 9) of the HSP70 heat shock protein family on the performance (climbing speed) of flies and the content of mitochondrial proteins in the skeletal muscles of their limbs.
Results: In human skeletal muscle, regular physical training increased the content of ~250 proteins (out of 800 detected), including ~100 mitochondrial proteins. Interestingly, a training-induced increase in the content of some proteins (mainly mitochondrial) was not accompanied by an increase in their mRNA level. An analysis of the available databases showed that these proteins (especially mitochondrial proteins) and their mRNAs are highly abundant proteins and mRNAs with superior stability. Additionally, training causes an increase in the content of 20 chaperones (including those from the HSP70 family), proteins that play an important role in the regulation of proteostasis. Knockout of the *Hsp70* genes in *D. melanogaster* caused a decrease in the content of individual mitochondrial proteins in skeletal muscle and the vertical running speed of flies compare to the control line.
Conclusion: In skeletal muscle, the increase in the content of mitochondrial proteins induced by increased physical activity is not regulated by the increase in the corresponding mRNAs and, apparently, depends on the rate of mitochondrial protein synthesis and their degradation/stability. The latter, in part, may be associated with the functions of heat shock proteins of the HSP70 family.
Acknowledgements: The study was supported by the Russian Science Foundation (grant 21-15-00405).