Exercise Biochemistry Review

Proceedings of IBEC 2018, Beijing, China, October 23-25
PO-175

Interruption of mitochondrial homeostasis inhibits Irisin biosynthesis in C2C12 Myoblast

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Objective Irisin is a PGC-1α dependent myokines suggested to provide the basis for the crosstalk between skeletal muscle and other organs. PGC-1α induces the expression of a membrane protein fibronectin type III domain-containing protein 5 (FNDC5), and exercise triggers the cleavage of FNDC5 to secrete irisin into the bloodstream. It was found that low level of Irisin in circulation was accompanied with impaired skeletal muscle mitochondrial homeostasis during aging. However, the relationship between mitochondrial homeostasis and Irisin induction is merely correlative. This study established mitochondrial homeostasis interrupt model in order to explore whether mitochondrial homeostasis involved in regulation of Irisin synthesis.
Methods C2C12 myoblasts were treated with OPA1 siRNA for 48 hours. Mitochondrial energy metabolism was measured with seahorse XF24 Extracelluar Flux Analyzer. Mitochondrial reticulum morphology was monitored with confocal laser scanning microscopy. Protein expressiont of Mfn1, Mfn2, OPA1, Drp1, FNDC5, PGC-1α, SirT1and GCN5 were measured with Western blot. Content of Irisin in culture medium was determined with Elisa.
Results Compared with control, in OPA1 siRNA myoblast, the expression of Mfn2(-35%, $P<0.01$), Drp1(-45%, $P<0.01$), Irisin(-10%, $P<0.05$), FNDC5(-33%, $P<0.01$), PGC-1α(-48%, $P<0.01$), SirT1(-40%, $P<0.01$), GCN5(-22%, $P<0.05$) proteins and the levels of cell membrane potential(-92%, $P<0.01$) and the basic OCR(-20%, $P<0.01$), ATP potential(-20%, $P<0.05$), max respiration capacity of mitochondrial(-29%, $P<0.05$) were decreased significantly. The expression of Mfn1(+39%, $P<0.01$) was increased significantly.
Conclusions Interruption of mitochondrial homeostasis inhibits Irisin biosynthesis. This may be related to mitochondrial ATP loss and imbalance energy-sensitive signaling SirT1/GCN5, which in turn suppress PGC-1α and its downstream Irisin.
Supported by NSFC (No. 31771320, 81370454, 31110103919).