Endoplasmic reticulum stress reduces PGC-1α in skeletal muscle through ATF4 and the mTOR-CRTC2 axis

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Video Byte

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Abstract

Insulin resistance and its progression to type 2 diabetes mellitus is an important public health concern. Both endoplasmic reticulum (ER) stress and reduced levels of the regulatory protein PGC-1α have been implicated in insulin resistance, but little is known about any interactions between them in this context. A recent study used cultured human skeletal muscle cells and mouse experiments to examine these potential interactions. In both cultured cells and mice, induced ER stress led to a decrease in PGC-1α and an increase in expression of ATF4, a transcription factor. To see if ATF4 was influencing PGC-1α expression, researchers increased ATF4 expression without ER stress, which also decreased PGC-1α expression, and reducing ATF4 before inducing ER stress blocked the drop in PGC-1α. ER stress activated mTOR, a major regulatory protein, and reduced levels of CRTC2, which is a transcription co-activator that increases PGC-1α transcription. Inhibiting mTOR activity or blocking one of its downstream targets prevented the ER stress-induced reduction in CRTC2 and PGC-1α expression. These results demonstrate that PGC-1α transcription is regulated by ATF3 and the mTOR-CRTC2 axis in ER stressed skeletal muscle. and point to these pathways as potential therapeutic targets for insulin resistance.