

Exercise regulates TFEB expression to influence body metabolism

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Abstract: Skeletal muscle is the largest organ in the body. It is also the regulator of glucose homeostasis and is responsible for 80% of postprandial glucose uptake from the circulation. Skeletal muscle is crucial to metabolism, both for its role in glucose uptake and for its importance in exercise and metabolic disease. In this article, we outline the importance of skeletal muscle in metabolism, describe its role in glucose uptake and the diseases associated with dysmetabolism of skeletal muscle. We focus on the role of skeletal muscle in peripheral insulin resistance and the potential of skeletal muscle-targeted therapies in combating insulin resistance and diabetes, as well as other metabolic diseases such as ageing and obesity. In particular, we outline the molecular mechanisms underlying the beneficial effects of exercise on metabolic diseases, including a focus on the TFEB nucleus, which is an important regulator of glucose transport to skeletal muscle. In this article, we give an overview to summarise and discuss the important role of TFEB in metabolic and adaptive responses during exercise.

Keywords: Exercise; Skeletal muscle; Autophagy; TFEB.

1. Introduction

With the changes in modern lifestyle, high fat diet has become a way of life for many people. And with that comes, obesity is becoming a global epidemic, increasing the health burden of associated complications of insulin resistance and diseases such as diabetes mellitus. Skeletal muscle represents 40% of total body mass and is essential for motor function and whole-body metabolic control. The autophagy-lysosome system is a proteolytic pathway that is responsible for the breakdown of long-lived, aggregated proteins and organelles. The transcription factor EB (TFEB) plays an important role in the control of cell and organismal homeostasis. TFEB responds to cellular nutrient levels and regulates lysosomal biogenesis and autophagy. In other words, TFEB improves metabolic syndrome via autophagy-dependent regulation of lipid and glucose metabolism in the adipose tissue and liver. Under nutrient-rich conditions, TFEB resides in the cytoplasm and translocates to the nucleus in response to starvation and lysosomal stress. Therefore, it is necessary to clarify the mechanism of TFEB regulation of glucose metabolism and lysosomal biogenesis under exercise conditions.

2. TFEB improves metabolic via autophagy-dependent regulation of lipid and glucose metabolism

TFEB belongs to the MiT family of helix-loop-helix leucine zipper transcriptional factors, together with TFE3, MITF and TFEC. Active TFEB is unphosphorylated and localizes to the nucleus where it induces transcription of lysosome and autophagy genes which contain the CLEAR (Coordinated Lysosomal Expression and Regulation) motif in their promoters. Metabolic signals tightly control the activity of TFEB. Sub-cellular localization of TFEB is controlled by their phosphorylation status on particular serine residues. Energy-sufficient condition inactivates TFEB through mTORC1-mediated phosphorylation although energy-deficient state promotes TFEB transcriptional activity. A

variety of stimuli are able to induce TFEB cytoplasm-to-nucleus translocation. In the liver, fasting activates TFEB, which promotes lipophagy and lipid catabolism via induced expression of the transcription co-activator Pgc1a and nuclear receptor Ppara. They also previously reported that liver-specific loss of TFEB exacerbates diet-induced obesity, while, TFEB overexpression effectively reduces glycogen accumulation in skeletal muscle of PD model mice. Moreover, acid- α -glucosidase enzyme activity was partially restored and glycogen accumulation improved to some extent by TFEB overexpression. Mechanistically, loss of oxidative capacity serves to up-regulate TFEB levels and subsequently autophagic and lysosomal proteins. It also has been shown that in both denervation-induced muscle atrophy and aging muscle mitochondrial functional impairments are correlated with a greater abundance of autophagy and lysosome proteins, which is in part driven by greater TFEB protein. It has been proved that twelve weeks of aerobic exercise enhanced lysosomes and alleviated abnormal autophagy by activating the AdipoR1/AMPK/TFEB signaling pathway in the brains of AD mice, thereby alleviating A β deposition and its associated AD-like abnormalities. Someone also demonstrated that TFEB activates Akt (AKT serine/threonine kinase) signaling and glucose uptake via upregulation of IRS1 and IRS2 in endothelial cells. In addition, one group confirmed that the IKK-I κ B α -p65 signaling axis is indeed regulated by TFEB. Someone proposes that elevated Ang II serum concentrations, as occur in patients with congestive heart failure, could activate the PKD1/HDAC5/TFEB/MuRF1 pathway to induce skeletal muscle wasting. TFEB acts as a central coordinator of insulin sensitivity, glucose homeostasis, lipid oxidation, and mitochondrial function in the adaptive metabolic response.

3. Exercise promotes TFEB nuclear expression to improve metabolism

Calcineurin-regulated transcription factor TFEB which promotes mitochondrial biogenesis and other metabolic adaptations. Meanwhile, they revealed TFEB activation in

normal muscle was not sufficient to enhance autophagy and TFEB and/or TFE3 deletion did not impair autophagy or cause muscle loss in single gene KO studies [23, 24], but recent evidence shows autophagy inhibition in muscle if both genes are deleted. In murine models of lysosomal storage disease, activation of TFEB was able to increase autophagic flux in muscle [15,16,25] but in other studies, TFEB activation did not restore lysosomal homeostasis or autophagy in the presence of defective autophagic lysosome reformation (ALR). This result is consistent with an interpretation that the ALR membrane-recycling pathway plays a distinct and essential role in maintaining lysosomes during autophagy in skeletal muscle that cannot be compensated for by TFEB-dependent lysosomal biogenesis. Apart from that, vesicles arranged along the plasma membrane are double-labeled with the lysosomal marker LAMP1 and the autophagosomal marker LC3, indicating that TFEB induces the exocytosis of autolysosomes. Furthermore, the effects of TFEB are almost abrogated in autophagy-deficient Pompe mice, suggesting a previously unrecognized role of autophagy in TFEB-mediated cellular clearance. Acute exercise inductions in the transcriptional activation of TFEB, as well as its enhanced nuclear localization. However, one study also pointed that although aging led to an overall decrease in TFEB transcription, exercise was able to up-regulate it to the level observed in young muscle. In other words, aging blunts aspects of autophago-somal turnover and lysosome biosynthesis with acute exercise, it enhances TFEB transcription, which, if repeated over time, may serve to re-establish lysosome function and homeostasis. Studies have found that exercise restored HFD/HF-induced autophagy flux deficiency, evidenced by increased LC3-II concomitant with p62 reduction and restoration of lysosome function-related proteins such as TFEB. Study also presented evidence that performing two exercise sessions separated by a short recovery period increases the nuclear abundance of TFEB. Besides, acute exercise inductions in the transcriptional activation of TFEB, as well as its enhanced nuclear localization. Exercise was able to activate TFEB promoter activity regard-less of age, which can promote lysosome biogenesis. Chronic contractile activity (CCA) in muscle cells induced mitochondrial biogenesis and coordinately enhanced the expression of TFEB. In contrast, someone detected no significant change in the nuclear translocation of TFEB, a regulator of lysosomal biogenesis, CCA increased total TFEB protein, as well as LAMP1, in skeletal muscle. Thus, they pointed out that chronic muscle activity reduces mitophagy in parallel with improved mitochondrial function, and this is supported by enhanced lysosomal degradation capacity. FoxO1 interacted with transcription factor EB (Tfeb), a key regulator of autophagosome and lysosome, and mediated the expression of UCP1, UCP2 and UCP3 differentially via autophagy in adipocytes. UCP1 was down-regulated but UCP2 and UCP3 were upregulated during adipocyte differentiation, which was associated with increased Tfeb and autophagy activity. Chromatin immunoprecipitation assay demonstrated that FoxO1 interacted with Tfeb by directly binding to its promoter, and silencing FoxO1 led to drastic decrease in Tfeb transcript and protein levels. Chronic contractile activity reduced the exaggerated expression of TFEB evident in aged muscle, which may be promoting the age-induced increase in lysosomal markers. Furthermore, study shows that AMPK promotes dephosphorylation and nuclear localization of TFEB independently of mammalian

target of rapamycin activity and the AMPK-TFEB-FLCN axis is conserved across species. A correlation was observed between the levels of the autophagy-lysosome master regulator transcription factor EB (TFEB) and PGC-1 α in muscle, supporting their coordinated regulation. Glycogen synthase kinase (GSK)-3 β inactivation causes dephosphorylation and nuclear translocation of TFEB resulting in TFEB-dependent induction of Pgc-1 α expression in skeletal muscle. Additionally, research shows that running exercise activates lysosomal function in the brain through AMPK-SIRT1-TFEB pathway and long-term exercise is superior to short-term exercise in promoting autophagy-lysosomal level. Combined, these studies suggest that TFEB is an important regulator in skeletal muscle, is responsive to muscle contraction, and that the lysosomal pool is plastic and can adapt to chronic exercise/contraction.

4. Conclusions and perspectives

TFEB improves metabolic via autophagy-dependent regulation of lipid and glucose metabolism and maintains cellular homeostasis by participating in the regulation of transcriptional levels of autophagy/lysosome-related genes. TFEB holds promise as a new target for intervention in metabolic diseases.

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