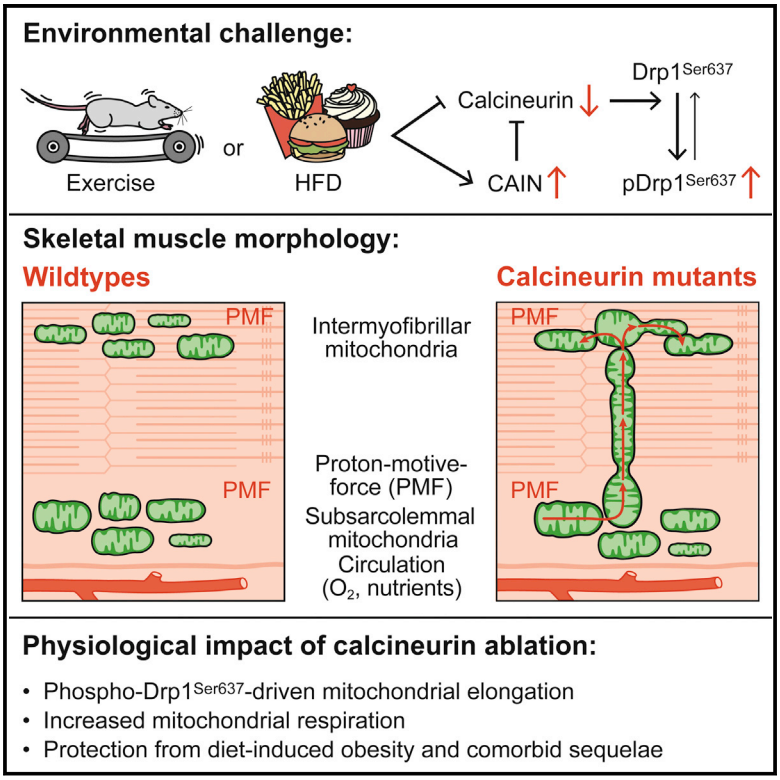
Article

Cell Metabolism

Calcineurin Links Mitochondrial Elongation with Energy Metabolism

Graphical Abstract



Highlights

- Fly mutants for calcineurin (Ppp3) display low body weight and high respiration
- Global and skeletal muscle-specific Ppp3 KO mice are protected from obesity
- Ppp3 ablation enhances Drp1^{S637}-hyperphosphorylation and mitochondrial respiration
- Ppp3 KO mice display elongated mitochondria but attenuated exercise capacity

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In Brief

Pfluger et al. reveal an evolutionary conserved role for the phosphatase calcineurin in the adaptive regulation of body weight and energy homeostasis in flies and mice. Calcineurin ablation from skeletal muscle enhances Drp1^{Ser637}-hyperphosphorylation, increases mitochondrial elongation and respiration, and protects from diet-induced obesity while attenuating exercise capacity.

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SUMMARY

Canonical *protein phosphatase 3*/calcineurin signaling is central to numerous physiological processes. Here we provide evidence that calcineurin plays a pivotal role in controlling systemic energy and body weight homeostasis. Knockdown of calcineurin in *Drosophila melanogaster* led to a decrease in body weight and energy stores, and increased energy expenditure. In mice, global deficiency of catalytic subunit *Ppp3cb*, and tissue-specific ablation of regulatory subunit *Ppp3r1* from skeletal muscle, but not adipose tissue or liver, led to protection from high-fat-diet-induced obesity and comorbid sequelæ. Ser637 hyperphosphorylation of dynamin-related protein 1 (Drp1) in skeletal muscle of calcineurin-deficient mice was associated with mitochondrial elongation into power-cable-shaped filaments and increased mitochondrial respiration, but also with attenuated exercise performance. Our data suggest that calcineurin acts as highly conserved pivot for the adaptive metabolic responses to environmental changes such as high-fat, high-sugar diets or exercise.

INTRODUCTION

The homeostatic control of energy metabolism includes multiple organs and pathways that sense and transduce environmental stimuli into adaptive responses. Mitochondria play an integral role in this rapid adaptation to varying nutrient substrates and bioenergetic demand by forming interwebbed mitochondrial networks, which are reshaped dynamically by fusion and fission events (Liesa and Shirihai, 2013). Mitochondrial fusion, governed by enzymes such as mitofusin 1/2 and optic atrophy factor 1 (OPA1), mitigates cellular stress by distributing damaged mitochondrial content over a wider compartment. Fragmentation of mitochondria by fission, mainly catalyzed by the enzyme dynamin-related protein 1 (Drp1), helps to dispose damaged mitochondria via mitophagy (Liesa et al., 2009). While the complete lack of fusion or fission was linked to severe neurodegenerative diseases such as Parkinson's disease or Alzheimer's disease (Reddy et al., 2011), shifts in balance between fusion and fission are an important adaptive process required to retain mitochondrial flexibility and health upon changes to our environment (Dietrich et al., 2010; Schneeberger et al., 2013).

To date, little is known about the exact molecular mechanisms that control mitochondrial dynamics elicited by environmental stimuli. Calcineurin (Protein Phosphatase 3, *Ppp3*), a ubiquitously expressed calcium-sensitive serine-threonine phosphatase comprised of a 61 kD calmodulin-binding catalytical subunit A (gene name, *Ppp3c*) and 19 kD Ca^{2+}-binding regulatory subunit B (gene name, *Ppp3r*) (Klee et al., 1979), is known to dephosphorylate and thereby inhibit Drp1 activity (Cereghetti et al., 2008; Cribbs and Strack, 2007). Three genes are encoding the catalytic subunit A: *Ppp3ca* (isoform α), *Ppp3cb* (isoform β), or *Ppp3cc* (isoform γ), with *Ppp3ca* and *Ppp3c* displaying partially overlapping expression patterns and functions (Rusnak and Mertz, 2000). For the regulatory subunit B, two genes have been described (*Ppp3r1* and *Ppp3r2*), but *Ppp3r2* expression