Cell Metabolism
Previews

Autophagy Works Out

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Autophagy is generally considered to be a cytoprotective response to stress, whether in the form of nutrient deprivation or the presence of dysfunctional organelles. He et al. now show in *Nature* that exercise-induced autophagy is needed for some of the beneficial effects of exercise on metabolism (He et al., 2012).

Macroautophagy (hereafter autophagy) is a conserved homeostatic process that occurs in all eukaryotes. The morphological hallmark of autophagy is the formation of a double-membrane cytosolic vesicle, the autophagosome, which sequesters cytoplasm and delivers it to the lysosome where it is degraded and recycled. Although typically considered to be degradative, autophagy also functions in homeostatic and even biosynthetic processes. Autophagy is involved in various aspects of development and cellular function, and autophagic dysfunction is associated with a wide range of diseases including certain types of neurodegeneration and cancer (Gonzalez et al., 2011; Sridhar et al., 2012). Changes in autophagy have also been observed in mouse models of obesity and insulin resistance; however, the underlying mechanisms remain obscure (Yang et al., 2010). Recently, it was shown that physical exercise, which modulates glucose homeostasis, also stimulates skeletal muscle autophagy (Grumati et al., 2011), and the accompanying removal of dysfunctional mitochondria is critical for muscle homeostasis (Grumati et al., 2010). Now, a recent study published in *Nature* extends these findings and demonstrates that autophagy induction is needed for various beneficial effects of exercise (He et al., 2012).

BECN1, the ortholog of the yeast autophagy-related protein Atg6, is a critical component required for a lipid kinase complex involved in autophagy induction. BCL2 is an antiapoptotic and autophagy-regulating protein; when bound to BECN1, BCL2 prevents the former from participating in autophagy. Autophagy occurs constitutively at a basal level, but is substantially induced by various stressors. In order to specifically examine the role of stress-induced autophagy in exercise, He et al. developed a transgenic mouse model in which a phosphorylation-defective version of BCL2 remains constitutively bound to BECN1, therefore preventing autophagy induction in response to stress in skeletal and cardiac muscle, liver, pancreas, and adipose tissue. They show that these mutant mice display decreased exercise capacity and endurance, which is not accounted for by differences in baseline properties of the muscle tissue. Rather, the BCL2 mutant mice have elevated levels of plasma glucose and insulin compared to normal mice following exercise, suggesting disrupted glucose homeostasis and possibly insulin resistance.

Alterations in lipid and glucose homeostasis are associated with obesity and insulin resistance, which can be improved by exercise training. He et al. show that excessive weight gain on a high-fat diet is reversed by subsequent exercise in both mutant and wild-type mice. Furthermore, exercise increases glucose uptake in wild-type mice, which reduces the demand for insulin, and lowers serum cholesterol and triglyceride levels. In contrast, glucose uptake is unaffected by exercise in BCL2 mutant mice, who continue to display impaired glucose tolerance and insulin resistance even after exercise. In addition, exercise is not able to lower serum lipids as effectively in the mutant mice, highlighting the importance of autophagy for the beneficial effects of exercise on glucose and lipid homeostasis. Interestingly, mutant mice fed a high-fat diet but not exercised are largely indistinguishable from wild-type mice regarding these metabolic parameters, suggesting that basal autophagy does not contribute substantially to resting lipid or glucose homeostasis.

To investigate how a defect in autophagy translates into this type of metabolic disorder, the authors focus on AMP-activated protein kinase (AMPK), a central regulator of energy homeostasis. When activated by depletion of ATP (and an increase in AMP), as would occur during exercise, AMPK inhibits enzymes that catalyze anabolic processes such as lipid synthesis, while stimulating fatty acid oxidation to provide energy (Figure 1). In addition, activation of AMPK or the AMPK family member NUAK2/SNARK mediates increased glucose uptake into muscle after exercise, via the translocation of the glucose transporter SLC2A4/GLUT4 (Koh et al., 2010). AMPK is also a positive regulator of autophagy via its inhibition of the MTORC1 pathway. The study from the Levine lab indicates that exercise-dependent AMPK activation is compromised in BCL2 mutant mice compared to wild-type controls, suggesting a feed-forward loop in which autophagy regulates its own activation via AMPK (He et al., 2012). AMPK induces autophagy not only by inhibiting MTORC1, but also by activating a key component of the autophagy machinery, the ULK1 kinase. There is clearly a potential for ULK1 to phosphorylate AMPK as well; however, current data suggest that this type of modification inhibits AMPK to limit the extent of autophagy (Löffler et al., 2011).

Questions persist regarding the mechanisms underlying autophagy-mediated benefits of exercise and whether the primary impact of exercise is to modulate AMPK or autophagy. Whereas previous studies have suggested that contraction-stimulated AMPK is the result of changes in calcium concentrations in cells, leading to regulation of CaM kinase kinase and perhaps other kinases (Steinberg and Kemp, 2009), the current data indicate that autophagy might have a previously unexpected role in regulating the AMPK

pathway. He et al. demonstrate that AICAR activation of AMPK is not affected in the mutant mice, suggesting that the enzyme complex is fully capable of activity and thus pointing toward autophagy-induced regulation of upstream events (He et al., 2012). Although there were no detectable changes in muscle morphology or mitochondrial function, it will be interesting to determine whether autophagy leads to changes in AMP levels in cells. Furthermore, it will be important to ascertain whether any of the upstream kinases in the pathway such as CAMKK, STK11/LKB1, or FYN are altered or whether changes in cAMP or calcium signaling occur. Likewise, it is also unclear whether the effects of exercise on autophagy in muscle are cell or tissue autonomous, and it remains possible that the exercise-induced release of myokines such as IL-6 or others (Pedersen and Febbraio, 2008) might play an important role.

The study by He et al. reveals that autophagy plays an important and previously unrecognized role in muscle metabolism. Autophagy is necessary for the benefits derived from exercise, though whether activation of autophagy is sufficient to mimic these effects remains unknown. Nonetheless, modulation of autophagy represents an attractive target for therapeutic intervention in diabetes and obesity.

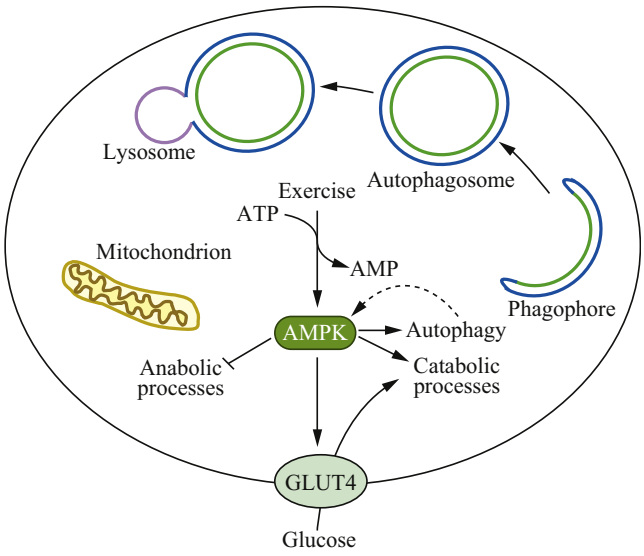

Figure 1. Exercise-Induced Autophagy Is Connected with AMPK, a Central Regulator of Energy Homeostasis

Autophagy involves the formation of an initial sequestering compartment, the phagophore, which expands into a double-membrane autophagosome. Cytoplasm sequestered within the autophagosome is broken down after fusion with a lysosome, and the resulting macromolecules are used for energy or macromolecular synthesis. Various types of stress induce autophagy, including the depletion of ATP (increase of AMP), which activates AMPK, a positive regulator of autophagy. AMPK also facilitates the plasma membrane translocation of the SLC2A4/GLUT4 transporter, thus enhancing the uptake of glucose. He et al. show that defective autophagy in muscle results in decreased exercise capacity and endurance, possibly due to the absence of a feedforward regulatory mechanism that limits the activation of AMPK (He et al., 2012).

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