Autophagy Mediates the Metabolic Benefits of Endurance Training

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Exercise-Induced BCL2-Regulated Autophagy Is Required for Muscle Glucose Homeostasis


In a recent issue of Nature, He et al demonstrate that autophagy is required for optimal physical endurance as well as for the beneficial effects on glucose and lipid metabolism. These data not only shed new insights into the mechanisms whereby exercise is healthy, but also indirectly strengthen the notion that autophagy exerts lifespan-extending effects.

Macroautophagy (hereafter referred to as autophagy) is a finely regulated catabolic pathway for the degradation of intracellular constituents including portions of the cytoplasm, organelles, and protein aggregates. In virtually all cells, baseline levels of autophagy ensure the removal of potentially dangerous structures such as permeabilized mitochondria, thus contributing to the maintenance of intracellular homeostasis. Moreover, several (though probably not all) cell types upregulate autophagy in response to a wide array of adverse conditions, encompassing nutrient shortage, hypoxia, xenobiotics, and invasion by intracellular pathogens. Thus, in the majority of settings, autophagy constitutes a cytoprotective response by which cells preserve or attempt to reestablish homeostasis. However, autophagy can also contribute to the execution of cell death, in particular in developmental scenarios or during the response of some types of cancer cells to specific chemotherapeutics. Defects in the autophagic machinery have been associated with multiple distinct human diseases, including neurodegenerative disorders, altered responses to infection, cardiovascular conditions, and cancer. In addition, autophagy has been suggested to be a key regulator of healthy aging, for at least 3 reasons. First, genetic or pharmacological inhibition of autophagy triggers degenerative changes that resemble those associated with aging.

Second, both normal and pathological aging are linked to a reduced autophagic potential. Third, inhibition of autophagy compromises the longevity-promoting effects of several distinct maneuvers that extend lifespan in model organisms, including inhibition of the insulin-like growth factor pathway, caloric restriction, rapamycin (an inhibitor of the central regulator of autophagy mammalian target of rapamycin [mTOR]), resveratrol (a polyphenol found in grapes and red wine), and spermidine (a polyamine contained in soy beans, tea leaf, and mushrooms). In a recent issue of Nature, the group of Beth Levine demonstrates that physical exercise constitutes a bona fide inducer of autophagy in several tissues, that exercise-induced autophagy is controlled by the interaction between Bcl-2 and the essential modulator of autophagy Beclin-1, and that autophagy is required for the beneficial effects of acute and chronic exercise on glucose and lipid metabolism. The findings by He and colleagues provide important mechanistic insights into the beneficial effects of physical exercise on human health. In addition, these results allude to the fact that...
a regular workout, by activating autophagy, may not only underlie a healthy aging, but also de facto extend lifespan.

He and colleagues observed that mice subjected to a physical workout (treadmill exercise) activate autophagy in skeletal and cardiac muscles as well as in multiple tissues involved in energy homeostasis, including liver, pancreatic β islets, and adipose tissue. Importantly, exercise-induced autophagy was found to require the dissociation of Beclin-1 from inhibitory interactions with Bcl-2. To characterize in detail their observations, He et al generated transgenic knock-in mice bearing a variant of Bcl-2 that cannot be phosphorylated in response to adverse conditions (Bcl-2AAA), due to the substitution of 3 critical residues in its nonstructured loop (T69, S70, and S84). Homozygous Bcl2AAA/AAA mice were born at Mendelian ratios and were fertile; had normal size, weight, and organ histology; expressed Bcl-2 to similar extents than their wild-type (WT) counterparts; and were characterized by normal baseline levels of autophagy. However, in Bcl2AAA/AAA mice subjected to starvation or physical exercise, Bcl-2 was not phosphorylated and the Bcl-2/Beclin-1 complex remained associated, de facto preventing the upregulation of autophagy in several tissues. This defect in stimulus-induced autophagy was not associated with increased cell death but was accompanied by a consistent reduction in physical endurance that could not be attributed to differences in baseline cardiac and skeletal properties (including muscle strength and types of fibers, cardiac size and function, mitochondrial number and activity, and glycogen content).

To understand the mechanisms whereby defects in stimulus-induced autophagy negatively affect physical endurance, He and colleagues focused their studies on the insulin-glucose axis. Normally, physical exercise results in increased insulin sensitivity as well as in enhanced glucose uptake by skeletal muscle cells, owing to the redistribution of the glucose transporter Glut4 at their plasma membrane. These physiological modifications were not observed in exercised Bcl2AAA/AAA mice, which cleared plasma glucose and insulin more slowly than their WT counterparts and failed to manifest the redistribution of Glut4 to the plasma membrane of skeletal muscle cells. This latter defect was paralleled by an impaired activation of the AMP-activated protein kinase (AMPK), which is known to regulate the intracellular localization of Glut4 as well as to impinge on the regulation of autophagy at multiple levels. Importantly, limited physical endurance, impaired redistribution of Glut4, scarce glucose uptake by skeletal muscle cells and reduced activation of AMPK were detected in other transgenic models of deficient stimulus-induced autophagy, including mice haploinsufficient for Beclin 1 (Beclin1+/+) and mice expressing low levels of the autophagic protein Atg16L1. Altogether, these observations suggest that autophagy is (at least partially) required for the activation of AMPK in response to physical exercise (Figure A).

Finally, He and colleagues analyzed the impact of the Bcl2AAA/AAA genotype on whole body energy metabolism, using a high-fat diet (HFD) model of obesity and glucose intolerance, alone or in combination with physical exercise. In response to HFD, Bcl2AAA/AAA mice gained slightly more body weight than age-matched WT mice, yet were as sensitive at their WT counterparts to exercise-induced weight loss. However, in comparison with their WT littermates, Bcl2AAA/AAA mice exhibited altered exercise-induced protection against HFD-triggered glucose tolerance, a phenotype that could not be attributed to deficient insulin production. At odds with their WT counterparts, Bcl2AAA/AAA mice subjected to a HFD were unable to restore normal circulating levels of leptin (an appetite-inhibiting adipokine) and adiponectin (an anti-diabetic adipokine) in response to physical exercise. Moreover, HFD-fed WT (but not Bcl2AAA/AAA) mice responded to exercise with a reduction in the plasma levels of triglycerides and cholesterol and were more metabolically active than their Bcl2AAA/AAA counterparts, as determined by oxygen consumption, CO2 production, and heat generation during resting periods. These observations, which could not be explained with baseline differences in food intake, spontaneous physical activity, or general mitochondrial functions, suggest that exercise-induced autophagy may be critical for ameliorating metabolic defects associated with diet-induced obesity.

Multiple epidemiological studies indicate that a regular workout reduces the risk of chronic diseases and extends life expectancy in humans. Moreover, it has recently been shown that endurance exercise rescues the progeroid phenotype in a murine model of accelerated aging. The findings by He et al demonstrate that physical exercise exerts beneficial effects on glucose and lipid metabolism in autophagy-proficient (but not autophagy-deficient) mice, closely resembling previous reports on the salutary effects of other inducers of autophagy. For instance, loss-of-function mutations in essential Atg genes have been shown to prevent the gain of longevity triggered by the genetic inhibition of insulin-like growth factor signaling in Caenorhabditis elegans. The longevity phenotype resulting from a genetic model of dietary restriction (eat-2[ad1133] allele) in C. elegans is abolished when the worm orthologs of Beclin 1 and ATG7 are knocked-down by RNA interference. Resveratrol and spermidine increase the lifespan of Saccharomyces cerevisiae, C. elegans, and Drosophila melanogaster, provided that the autophagic machinery is functional. Finally, rapamycin, which potently stimulates autophagy by inhibiting the kinase activity of mTOR, exerts lifespan-extending effects in multiple model organisms including mice. Whereas formal evidence causally linking rapamycin-triggered longevity extension to autophagy in mammals is missing, unambiguous proofs in support of this hypothesis exist for lower model organisms, encompassing yeast, worms, and flies.

Altogether, these observations raise one central question: does physical exercise extend lifespan (at least in part) by activating autophagy? He et al convincingly demonstrated that the beneficial effects of exercise on glucose and lipid metabolism are mediated by autophagy and provided consistent correlative evidence in support of this hypothesis. However, they did not formally address it. Irrespective of this unresolved issue, autophagy constitutes a crucial antiaging (and anticancer) process. The molecular circuitries underpinning such beneficial effects of autophagy have not yet been precisely elucidated, although they presumably relate to...
reduced levels of potentially dangerous intracellular species, including prooxidants and protein aggregates. Thus, maneuvers that activate autophagy in several tissues, including caloric restriction, exercise, as well as the consumption of natural products that contain proautophagic compounds such as resveratrol and spermidine, may contribute to healthy aging by facilitating the maintenance of intracellular homeostasis (Figure B). In this scenario, the question is: where does the acceptable equilibrium between pleasure (ie, healthy food and drinks) and sacrifice (ie, caloric restriction and physical exercise) stand?

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None.

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