

Role of autophagy in bone and muscle biology

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Abstract

Autophagy in eukaryotic cells is a constitutive process and functions as a homeostatic mechanism; it is up-

regulated in response to specific stress stimuli such as starvation, hypoxia and as oxidative stress. In addition to playing a crucial role in adaptive responses to different stimuli, autophagy is also required for intracellular quality control. This second aspect is important to prevent the activation of pathological processes. Autophagy also plays a central role in cellular development and differentiation because it is involved in the regulation of energetic balance. This final aspect is critical for maintaining proper bone and muscle function as well as to prevent any pathological changes. Therefore, identifying new molecular targets involved in autophagy is critical to assure a good quality of life.

Key words: Autophagy; Bone; Muscle

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Core tip: Autophagy is a major catabolic process in eukaryotic cells in which damaged macromolecules and organelles are degraded and recycled. Several studies have demonstrated its crucial role in bone and muscle cell homeostasis. Deficiency or dysfunction in autophagy can result in pathological conditions such as osteoporosis and sarcopenia, which are associated with ageing. It is important to understand the role of the macromolecules involved in autophagy to devise how to counteract its decline and to hinder irreversible cell damage.

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AUTOPHAGIC MACHINERY

Autophagy is a key process in cellular homeostasis and is involved in removing and recycling misfolded proteins, damaged organelles or dysfunctional cell components. Autophagy may be distinguished into

the following three categories: (1) macroautophagy; (2) microautophagy; and (3) chaperone-mediated autophagy^[1,2]. Macroautophagy is the most prevalent form of autophagy among different cell types^[3,4]. It starts with the formation of a phagophore, which is a membrane protrusion that expands to engulf the cellular cargo, generating an autophagosome. This latter structure matures *via* fusion with lysosomes. TOR kinase is a major player in autophagy and acts as a signalling node downstream of growth factor receptor signalling, hypoxia, changes in ATP levels and insulin signalling. It is activated downstream of Akt kinase, PI3-kinase and growth factor receptors and acts to inhibit autophagy by modulating the Ulk1 (Atg1) complex. In response to autophagy cascade activation, the class III PI3K complex produces PI(3)P and induces other Atg proteins, including Atg12-Atg5-Atg16, as well as the LC3 (Atg8)-phosphatidylethanolamine complex. LC3 is the commonly used term for microtubule-associated protein 1 light chain 3. After translation, proLC3 is proteolytically cleaved by Atg4 protease, which generates LC3-I. Upon induction of autophagy, LC3-I is conjugated to the highly lipophilic phosphatidylethanolamine (PE) moiety by the Atg7, Atg3 and Atg12-Atg5-Atg16L complex to generate LC3-II. Finally, PE promotes the integration of LC3-II into lipid membranes to promote autophagosome formation.

Mice lacking Atg7, which is a specific liver gene for autophagosome formation, developed severe hepatomegaly as a consequence of intracellular accumulation of aggregates and non-functional organelles^[5]. Furthermore, knockout mice bearing a neural-specific deletion of either Atg7 or Atg5, both of which are required for autophagosome formation, developed ataxic gait, abnormal motor coordination and systemic tremor^[3,4]. In addition to recycling amino acids after protein degradation, autophagy may also contribute to energy production through the generation of free fatty acids^[6].

Recent studies have shown that autophagy might play different roles depending on the cellular context, leading to either apoptosis or survival by modulating key genes^[7].

In addition, perturbations of the autophagy machinery have been linked to different disorders such as ischaemic cardiomyopathy and neurodegenerative diseases^[8,9].

AUTOPHAGY IN BONE BIOLOGY

Osteoblasts, the bone-forming cells, secrete the skeletal matrix (osteoid) and have a principal role in bone mineralization. During differentiation, the osteoblast assumes the characteristics of an osteocyte, which orchestrates bone remodelling. At present, 2 families of transcription factors involved in the autophagy process, the forkhead box O (FOXO) and cAMP responsive element binding protein (CREB) families, are known to regulate osteoblasts. FOXO activation promotes autophagy by binding to the promoter regions of target genes, and studies have shown that deletion of *FOXO* genes causes oxidative stress and apoptosis. Conversely, overexpression of FOXO3

reduces bone impairment associated with ageing^[10]. The involvement of *FOXO* genes in the regulation of bone homeostasis may conceivably be due, at least in part, to the induction of autophagy. ATF4 (a member of the CREB family) is required to support osteoblast function and maturation as well as to reduce cellular stress due to amino acid starvation because it increases amino acid trafficking into cells. Reduced ATF4 activity has been associated with skeletal impairments such as Coffin-Lowry syndrome and neurofibromatosis type I^[11]. Another autophagy protein involved in osteoblast biology is the autophagy receptor NBR1 (a neighbour of *BRCA1* gene 1), which interacts with the MAP1LC3 protein family through its LC3-interacting region^[12]. Autophagy is also involved in osteoclastogenesis. The autophagy proteins Atg5, Atg7, Atg4B and MAP1LC3 are required for osteoclast differentiation; these cells are responsible for bone resorption. Among others, Atg5 and Atg7 promote bone remodelling by inducing bone resorption *via* directing lysosomes through the plasma membrane into the extracellular space^[13].

AUTOPHAGY IN MUSCLE

Autophagy plays a crucial role in muscle cells under both healthy and adverse conditions. The highly structured organization of skeletal muscle cells and their function may cause damage to proteins and organelles; mitochondria are particularly susceptible because of the increased generation of reactive oxygen species compared to other tissues. Muscle cells therefore require efficient housekeeping mechanisms that can quickly eliminate unfolded and toxic proteins as well as dysfunctional organelles. Under physiological conditions, basal levels of autophagy guarantee muscle cell homeostasis, whereas upregulation of the autophagic machinery contributes to cell survival under various stress conditions, including calorie restriction (CR), atrophy, and sarcopenia, by maintaining the required amino acid supply and metabolite levels^[14].

AUTOPHAGY AND PHYSICAL EXERCISE

A chaperone-assisted selective autophagy process (CASA) has been characterized as a tension-induced autophagy pathway essential for the adaptation of mechanically strained tissues such as skeletal muscle, heart, lung and kidney. In striated skeletal muscle, the CASA machinery is located at the Z-disk; this is of critical importance because the complex mediates the degradation of large cytoskeleton components (*e.g.*, FLNC, filamin C) damaged during contraction. Recent studies demonstrated that strenuous resistance exercise caused a significant increase in CASA activity in muscles of healthy men who trained moderately^[15]. Impairment of CASA in animal models, however, leads to muscle weakness^[16].

AUTOPHAGY AND MUSCLE DISORDERS

The hallmark of autophagy, autophagosomes, are found

in most myopathies and dystrophies. In many acquired and genetic muscle diseases, however, misregulation rather than upregulation of autophagic and protein degradation machineries appear to be the cause of muscle degeneration^[17].

AUTOPHAGY AND AGEING

Sarcopenia, which is ageing-related skeletal muscle loss, is a common debilitating condition affecting 5%-13% of the elderly population over 60. Imbalance between protein synthesis and protein degradation; the accumulation of denatured, misfolded or aggregated molecules; mitochondrial dysfunction; and excessive apoptosis caused by complex intrinsic and extrinsic factors can result in sarcopenia. Growing molecular evidence supports the idea that dysregulated autophagy may contribute to sarcopenia. Strategies (*e.g.*, CR and life-long exercise) aiming to induce an appropriate autophagic process in muscle cells may reduce age-associated muscle wasting^[18]. Autophagy is therefore a potential target for sarcopenia; bioactive molecules known to modulate autophagy can play a beneficial role at the cellular level in the ageing process^[19].

CONCLUSION

It is not surprising that bone and muscle structures and functions are tightly regulated by endogenous and environmental factors. Autophagy plays a relevant role in physiological and pathological conditions: A well-balanced performance of the autophagic machinery is essential for both bone and muscle homeostasis. Thus, in-depth knowledge of autophagy may provide new molecular targets for maintaining bone and muscle formation and metabolism to assure a good quality of life.

REFERENCES

- Klionsky DJ**, Emr SD. Autophagy as a regulated pathway of cellular degradation. *Science* 2000; **290**: 1717-1721 [PMID: 11099404 DOI: 10.1126/science.290.5497.1717]
- Komatsu M**, Ichimura Y. Selective autophagy regulates various cellular functions. *Genes Cells* 2010; **15**: 923-933 [PMID: 20670274 DOI: 10.1111/j.1365-2443.2010.01433.x]
- Komatsu M**, Waguri S, Chiba T, Murata S, Iwata J, Tanida I, Ueno T, Koike M, Uchiyama Y, Kominami E, Tanaka K. Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature* 2006; **441**: 880-884 [PMID: 16625205 DOI: 10.1038/nature04723]
- Hara T**, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H, Mizushima N. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. *Nature* 2006; **441**: 885-889 [PMID: 16625204 DOI: 10.1038/nature04724]
- Komatsu M**, Waguri S, Ueno T, Iwata J, Murata S, Tanida I, Ezaki J, Mizushima N, Ohsumi Y, Uchiyama Y, Kominami E, Tanaka K, Chiba T. Impairment of starvation-induced and constitutive autophagy in Atg7-deficient mice. *J Cell Biol* 2005; **169**: 425-434 [PMID: 15866887 DOI: 10.1083/jcb.200412022]
- Christian P**, Sacco J, Adeli K. Autophagy: Emerging roles in lipid homeostasis and metabolic control. *Biochim Biophys Acta* 2013; **1831**: 819-824 [PMID: 23274236 DOI: 10.1016/j.bbailp.2012.12.009]
- Yu L**, Lenardo MJ, Baehrecke EH. Autophagy and caspases: a new cell death program. *Cell Cycle* 2004; **3**: 1124-1126 [PMID: 15326383 DOI: 10.4161/cc.3.9.1097]
- Nixon RA**. Autophagy in neurodegenerative disease: friend, foe or turncoat? *Trends Neurosci* 2006; **29**: 528-535 [PMID: 16859759 DOI: 10.1016/j.tins.2006.07.003]
- Wu J**, Niu J, Li X, Li Y, Wang X, Lin J, Zhang F. Hypoxia induces autophagy of bone marrow-derived mesenchymal stem cells via activation of ERK1/2. *Cell Physiol Biochem* 2014; **33**: 1467-1474 [PMID: 24854431 DOI: 10.1159/000358711]
- Almeida M**. Unraveling the role of FoxOs in bone--insights from mouse models. *Bone* 2011; **49**: 319-327 [PMID: 21664311 DOI: 10.1016/j.bone.2011.05.023]
- Yang X**, Karsenty G. ATF4, the osteoblast accumulation of which is determined post-translationally, can induce osteoblast-specific gene expression in non-osteoblastic cells. *J Biol Chem* 2004; **279**: 47109-47114 [PMID: 15377660 DOI: 10.1074/jbc.M410010200]
- Waters S**, Marchbank K, Solomon E, Whitehouse CA. Autophagy receptors Nbr1 and p62 coregulate skeletal remodeling. *Autophagy* 2010; **6**: 981-983 [PMID: 20814249 DOI: 10.4161/auto.6.7.13155]
- DeSelm CJ**, Miller BC, Zou W, Beatty WL, van Meel E, Takahata Y, Klumperman J, Tooze SA, Teitelbaum SL, Virgin HW. Autophagy proteins regulate the secretory component of osteoclastic bone resorption. *Dev Cell* 2011; **21**: 966-974 [PMID: 22055344 DOI: 10.1016/j.devcel.2011.08.016]
- Sandri M**. Autophagy in skeletal muscle. *FEBS Lett* 2010; **584**: 1411-1416 [PMID: 20132819 DOI: 10.1016/j.febslet.2010.01.056]
- Ulbricht A**, Gehlert S, Leciejewski B, Schiffer T, Bloch W, Höhfeld J. Induction and adaptation of chaperone-assisted selective autophagy CASA in response to resistance exercise in human skeletal muscle. *Autophagy* 2015; **11**: 538-546 [PMID: 25714469 DOI: 10.1080/15548627.2015.1017186]
- Arndt V**, Dick N, Tawo R, Dreiseidler M, Wenzel D, Hesse M, Fürst DO, Saftig P, Saint R, Fleischmann BK, Hoch M, Höhfeld J. Chaperone-assisted selective autophagy is essential for muscle maintenance. *Curr Biol* 2010; **20**: 143-148 [PMID: 20060297 DOI: 10.1016/j.cub.2009.11.022]
- Sandri M**, Coletto L, Grumati P, Bonaldo P. Misregulation of autophagy and protein degradation systems in myopathies and muscular dystrophies. *J Cell Sci* 2013; **126**: 5325-5333 [PMID: 24293330 DOI: 10.1242/jcs.114041]
- Wohlgemuth SE**, Seo AY, Marzetti E, Lees HA, Leeuwenburgh C. Skeletal muscle autophagy and apoptosis during aging: effects of calorie restriction and life-long exercise. *Exp Gerontol* 2010; **45**: 138-148 [PMID: 19903516 DOI: 10.1016/j.exger.2009.11.002]
- Fan J**, Kou X, Jia S, Yang X, Yang Y, Chen N. Autophagy as a Potential Target for Sarcopenia. *J Cell Physiol* 2016; **231**: 1450-1459 [PMID: 26580995 DOI: 10.1002/jcp.25260]

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