Macroautophagy (simply referred to as autophagy), which literally means self-eating, constitutes one of two major intracellular proteolytic systems in eukaryotic cells along with the ubiquitin-proteasome. In the initial step of autophagy, portions of the cytoplasm, including soluble proteins and organelles, are engulfed within a double membrane vesicle called autophagosome. Then, the autophagosome fuses with the lysosomes to degrade the sequestered materials by various lysosomal hydrolytic enzymes, followed by generation of amino acids that are recycled for macromolecular synthesis and energy production 1,2.

Mammalian autophagy plays important physiological roles in human health and diseases by means of two different ways. One is to degrade proteins in the cell through continuous operation at a low rate, the process known as "basal or constitutive autophagy." This process plays pivotal roles in maintaining cellular homeostasis through the turnover of long-lived proteins, disposal of excess or damaged organelles, and clearance of aggregate-prone proteins 3-5. The other is known as “adaptive autophagy”, the degradation of large quantity of cell constituents at a high rate in response to environmental stresses, such as nutrient starvation, hypoxia, oxidative stress, pathogen infection, radiation, or anticancer drug treatment for adaptation and survival. Indeed, this type of autophagy is rapidly induced as a cytoprotective response under stress conditions 6,7.

Recent genetic studies by our group using tissue-specific autophagy-deficient mice have highlighted the importance of constitutive autophagy in non-dividing cells, such as hepatocytes and neurons, in which loss of autophagy results in severe liver injury 3 and neurodegeneration 4,5, respectively. Unexpected findings in these studies are that loss of autophagy causes cytoplasmic accumulation of ubiquitin-positive proteinaceous inclusions, together with hepaticytic and neuronal death without expression of proteins with disease-associated mutations 6,5. These results imply that inclusion bodies formed as a result of autophagy impairment are deeply associated with the pathogenic mechanism of human diseases.

Aging is a universal phenomenon characterized by progressive deterioration of cells and organs due to accumulation of macromolecular and organ-

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Abstract

Macroautophagy, which literally means self-eating, constitutes one of two major intracellular proteolytic systems in eukaryotic cells along with the ubiquitin-proteasome. Our previous studies imply that inclusion bodies formed as a result of autophagy impairment are deeply associated with the pathogenic mechanism of human diseases. Recent studies have suggested that autophagy is also related to longevity and sarcopenia. It seems important to develop exercise/sports practical program for maintaining muscles in elder people from the aspect of regulation of autophagy. Efforts for this goal may eventually give a hint how to live longer and healthy.
elle damage⁷. Growing evidence indicates that autophagic activity declines with age, and that accumulation of damaged macromolecules and organelles play a role in age-related symptoms. In addition, experimental conditions that extend life span in various species are consistent with activation of autophagy. These conditions include dietary restriction and negative modulation of the insulin-signaling and TOR pathways. Also, genetic evidence for the significance of autophagy in the aging process has been provided in lower eukaryotes and plants⁷. In C. elegans, for instance, autophagy is required for the extension of lifespan by a loss-of-function mutation in the insulin-like signaling pathway. Recently, it has been demonstrated that rapamycin (an mTOR inhibitor) treatment initiated late in life extends lifespan in mice⁸, although whether or not activation of autophagy is a requirement in this process is yet to be elucidated in mammals. We must await further study whether autophagy contributes actively in aging process.

Sarcopenia, the loss of skeletal muscle mass and function, is a common feature of aging and brings a severe impact on individual health and quality of life. Several cellular mechanisms are involved in the pathogenesis of this syndrome, including mitochondrial dysfunction, altered apoptosis and autophagic activity. It has been shown recently that autophagy-deficient muscles are characterized as muscle atrophy, weakness and features of myofiber degeneration⁹. Controversially, many studies also strongly suggest that excessive autophagy significantly contributes to muscle loss, namely sarcopenia. At present, which of these two possibilities, inhibition of autophagic activity or stimulation of autophagy-lysosomal system, is more beneficial for preventing sarcopenia remains to be answered.

Anyway, it seems important to develop exercise/sports practical exercise program for maintaining muscles in elder people from the aspect of regulation of autophagy. Efforts for this goal may eventually give a hint how to live longer and healthy.

References