Autophagy; The Cellular Guardian Against Diseases and Aging

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Autophagy is an evolutionarily conserved membrane trafficking from the cytoplasm to lysosomes. Most of our understanding of the process has come after identification of yeast autophagy related genes in 1993 by Yoshinori Ohsumi. This breakthrough brought a dramatic expansion of the field and Ohsumi received the Nobel Prize in Physiology or Medicine in 2016. I started to expand his achievement in yeast to mammalian by joining his lab in 1996 and have been studying mechanisms and physiological relevance of mammalian autophagy. Now we know that autophagy maintains cellular homeostasis thorough turnover of cellular constituents and elimination of harmful materials including pathogens, protein aggregates and damaged organelles, thereby suppressing many diseases and sustaining immune and nervous system. We identified for the first time a mammalian autophagosome-binding protein and the protein LC3 has been mostly used as a golden marker in autophagy studies until now. This single paper has been cited in over 7,000 papers, which is the most cited paper in the field.

During last two decades, genetic studies using model organisms lead to the discovery of different longevity pathways. Interestingly, these lifespan-extending intervention activates autophagy, and the activated autophagy is required for these animals to live long. On the other hands, autophagic activity is known to decline with age. We found that the amount of a negative regulator of autophagy, Rubicon, which we identified previously increased in various tissues of aged animals thereby causing age-dependent suppression of autophagy. We demonstrated that KD/KO of Rubicon extends lifespan and ameliorates several age-associated phenotypes including Parkinson's disease, kidney fibrosis, and osteoporosis. We further showed that Rubicon also increases during cellular senescence; up-regulation of autophagy by Rubicon KD suppresses cellular senescence. The results suggest that autophagy could be a target to develop a strategy for health span extension.