INSIGHTS INTO MEMBRANE DYNAMICS OF AUTOPHAGY AND ITS IMPLICATIONS IN DISEASES

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Autophagy is an evolutionarily conserved membrane trafficking from the cytoplasm to lysosomes. Although the term “autophagy” (self-eating in Greek), was officially used for the first time in 1963, most of our understanding of the process has come after identification of yeast autophagy-related (ATG) genes in 1993 by Yoshinori Ohsumi. This break through brought a dramatic expansion of the field and Ohsumi received the Nobel Prize in Physiology or Medicine in 2016. In autophagy, the unique double membrane-bound autophagosomes transiently emerge in the cytoplasm, sequester portion of the cytosol and organelles, and eventually fuse with lysosomes to degrade the contents. In addition to the basic role in nutrient supply under starvation conditions, the process unexpectedly functions in development, longevity, immunity, and suppression of various diseases including infectious diseases, inflammatory diseases, tumorigenesis, neurodegeneration, type II-diabetes, etc.

I started to study mammalian autophagy in Ohsumi’s lab in 1996 and have been devoting my effort to understand its mechanisms and physiological relevance for the last 20 years. We could visualize autophagosome in living cells for the first time by identifying an 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 4,000 papers. Recently, we have provided new insights into biogenesis of autophagosome, which have been topic of longstanding debate. We showed that autophagosome forms at the ER-mitochondria contact site. We also found that autophagy selectively eliminates invading pathogenic bacteria, opening a new field on host-pathogen interaction. Then, we unraveled that autophagy recognizes damage of endosomal membrane including bacteria rather than bacteria itself. We also found a new role of autophagy; selective elimination of damaged lysosomes. This “lysophagy” suppresses development of nephropathy in hyperuricemic

mice. I also discuss about our recent finding that high fat diet increases the amount of a negative regulator of autophagy, Rubicon, which we identified. Knockout of the gene dramatically improved non-alcoholic fatty liver disease (NAFLD) in mice fed high fat diet.