A Novel Autophagy-Related Gene Regulates Autophagy Through Endolysosomal Pathway

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Autophagy is a “self-eating” cellular pathway. It is a core molecular mechanism for cellular and organismal homeostasis and is also a pro-longevity mechanism. Autophagy dysfunction links the pathogenesis of human disorders including cancer as well as neurodegenerative, metabolic, infectious, and cardiovascular disorders. In this study, I found the key autophagy-related gene 12 (ATG12) messenger RNA (mRNA) encodes two in-frame ATG12 proteins, named ATG12-140 (140 amino acids in length) and ATG12-187(187 amino acids in length). The ATG12-140 has been well studied, which is indispensable for autophagosome biogenesis. In comparison, ATG12-187 protein is translated less from the same ATG12 mRNA. The unique 47 amino acids at the N-terminus of the ATG12-187 protein determines its novel function for autophagy regulation: via its N-terminal 47aa domain, the ATG12-187 protein trafficks from trans Golgi network to early endosome and late endosome membrane, where it is invaginated into the intraluminal vesicles through ubiquitination of the ATG12-187 protein. Eventually, ATG12-187 is degraded in the lysosome. Significantly, the core ATG proteins that are required for autophagosome biogenesis including ATG3 and ATG5 are also simultaneously degraded in lysosome with the ATG12-187 protein. Thus, ATG12-187 tunes the autophagy pathway via regulating core ATG protein levels for autophagosome biogenesis. This is the first ATG protein found so far that is able to regulate autophagy through lysosome pathway.

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