http://www.tandfonline.com/doi/abs/10.4161/auto.6.7.13065

Autophagy. 2010 Oct;6(7):961-3.

Autophagy, proteases and the sense of balance.

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Autophagy, proteases and the sense of balance

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The knowledge of the molecular mechanisms underlying autophagy has considerably improved after the isolation and characterization of autophagy-defective mutants in the yeast *Saccharomyces cerevisiae*. Two ubiquitin-like conjugation systems are required for yeast autophagy. One of them requires the participation of Atg8 synthesized as a precursor protein, which is cleaved after a Gly residue by a cysteine proteinase called Atg4. The new Gly-terminal residue from Atg8 is activated by Atg7 (an E1-like enzyme) then transferred to Atg3 (an E2-like enzyme) and finally conjugated with membrane-bound phosphatidylethanolamine (PE) through an amide bond. The complex Atg8-PE is also deconjugated by the protease Atg4, facilitating the release of Atg8 from membranes. This modification system, which is essential for the membrane rearrangement dynamics that accompany the initiation cells by a single orthologue. It has been suggested that the multiplication of Atg4 orthologues may reflect a regulatory heterogeneity of functionally redundant proteins or, alternatively, derive from the acquisition of new functions that are not related to autophagy. Our first approach to elucidate this question was based on the generation of *autophagin-3/Atg4C*-deficient mice, which, however, presented a minor phenotype. With the generation of *autophagin-1/Atg4B*-deficient mice, recently reported, we have progressed in our attempt to identify the in vivo physiological and pathological roles of autophagins.

Previous studies on *Atg4B*, based on protein overexpression, RNA interference or cell-free approaches, have yielded interesting results regarding its substrate specificity and activity. However, the definition of the actual physiological role for