

大学院特別講義

池田 史代 博士 (IMBA・グループリーダー/九州大学・生医研・教授)

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The ubiquitin enzymes IAPs in the regulation of autophagy

Fumiyo Ikeda^{1, 2, 3}

1 Institute of Molecular Biotechnology of Austrian academy of sciences (IMBA), Vienna, Austria

2 Vienna BioCenter (VBC), Vienna, Austria

3 Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan

※ 口の難病セミナーを兼ねます
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Lysosome and proteasome are key organelles for the cellular waste disposal system where ubiquitin plays a critical role. Regulatory mechanisms by which ubiquitin regulates proteasome-dependent protein degradation is well understood, and involvement of ubiquitin in the autophagy-lysosome-dependent pathway is known. However, to date, only handful ubiquitin enzymes that regulate the autophagy-lysosome pathway have been identified, thereby mechanisms how ubiquitin regulates autophagy-dependent substrate degradation remain largely unclear.

To identify such ubiquitin enzymes and to understand the regulatory mechanisms behind, we first performed a screen using an originally generated shRNA library targeting known ubiquitin enzymes and fibroblasts expressing a pH-dependent autophagy sensor, mCherry-eGFP-LC3B. By screening, we identified new positive autophagy regulators, the IAP (inhibitor of apoptosis protein) family members, BRUCE and XIAP, which are well known anti-apoptosis factors. In both BRUCE- and XIAP-deficient MEFs, starvation-dependent autophagy flux is suppressed examined by flow cytometry using the autophagy sensor. In BRUCE knockout MEFs, starvation-induced lipidation of ATG8, autophagosomes formation, the endocytosis pathway and lysosomal functions are normal, however, fusion of autophagosomes and lysosomes is severely defective. This fusion step is also suppressed in XIAP-knockout MEFs. BRUCE interacts with autophagosomal proteins important for autophagosome-lysosome fusion, Syntaxin 17 and SNAP29, further suggesting its role in autophagosome-lysosome fusion.

In conclusion, we identified a novel role of two IAP family members in the regulation of autophagosome-lysosome fusion. I will further discuss about the mechanistic aspect of autophagy regulated by IAPs including unpublished data.

問い合わせ先：生化学教室 (x 2887)