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Research Interests

Autophagy, Phase Separation, Structural Biology, In Vitro Reconstitution

Education

2001 | Ph. D., Graduate School of Pharmaceutical Sciences, The University of Tokyo

Professional Career

2001 - 2005 | Postdoctoral Fellow, Hokkaido University
2005 - 2007 | Research Associate, Hokkaido University
2007 - 2011 | Lecturer with Tenure, Hokkaido University
2011 - 2017 | Chief Researcher, Institute of Microbial Chemistry
2017 - present | Laboratory Head, Institute of Microbial Chemistry

Scientific Activities

2002 - present | Structural biology of autophagy
2016 - present | In vitro reconstitution of autophagy and phase separation

Honors

2012 | Young Investigator Award, The Japanese Biochemical Society

Publications

1. Y. Fujioka, J. M. Alam, D. Noshiro, K. Mouri, T. Ando, Y. Okada, A. I. May, R. L. Knorr, K. Suzuki, Y. Ohsumi, N. N. Noda, “Phase separation organizes the site of autophagosome formation”, Nature, 578 (2020) 301-305.

2. A. Yamasaki, J. M. Alam, D. Noshiro, E. Hirata, Y. Fujioka, K. Suzuki, Y. Ohsumi, N. N. Noda, “Liquidity is a critical determinant for selective autophagy of protein condensates”, Mol. Cell, 77 (2020), 1163-1175.

3. T. Osawa, T. Kotani, T. Kawaoka, E. Hirata, K. Suzuki, H. Nakatogawa, Y. Ohsumi, N. N. Noda, “Atg2 mediates direct lipid transfer between membranes for autophagosome formation”, Nat. Struct. Mol. Biol., 26 (2019), 281-288.

Autophagy regulation by liquid-liquid phase separation

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Autophagy is an intracellular degradation system that involves de novo generation of autophagosomes, which sequester cytoplasmic materials and deliver them to the lysosome/vacuole for degradation. When autophagy is induced by starvation, autophagy-related (Atg) proteins gather to form the pre-autophagosomal structure (PAS), which functions as a place for generating bulk autophagosomes that randomly sequester cytoplasmic materials. On the other hand, there exist selective types of autophagy termed “selective autophagy”, during which autophagosome generation proceeds on the specific large cargo that includes membrane-bound and membraneless organelles. Recently, we noticed that the PAS is a liquid droplet of Atg proteins that is formed by liquid-liquid phase separation (LLPS) [1]. LLPS of the PAS is strictly regulated by the phosphorylation state of Atg13, an intrinsically disordered protein. Upon starvation, Atg13 is dephosphorylated, which links Atg17 dimers to each other to form a large assemblage [2]. In vitro mixing of Atg13 with Atg17 resulted in the formation of liquid droplets, and point mutations in Atg13 or Atg17 that impaired the droplet formation in vitro also impaired the PAS formation in vivo, suggesting that the PAS is formed by the LLPS of the Atg13-Atg17 complex. High-speed atomic force microscopy observation of the Atg13-Atg17 droplets revealed randomly arranged, mobile Atg17 molecules inside the droplets, supporting the liquid-like feature of the droplets [1]. Aminopeptidase I (Ape1) is known to be a specific cargo for selective autophagy. We noticed that Ape1 undergoes LLPS to form Ape1 droplets both in vitro and in vivo [3]. Mutations that impair LLPS or solidify the Ape1 droplets impaired the selective autophagy of Ape1, suggesting that the liquid-like feature of Ape1 droplets is important for selective autophagy. In vitro reconstitution experiments revealed that liquid-like Ape1 droplets formed by LLPS, but not Ape1 aggregates that lost the liquidity by a mutation, were selectively sequestered by a membrane coated with Atg proteins. These data suggest that LLPS can be a general mechanism for regulating both bulk and selective autophagy.

References

[1] Y. Fujioka, J. M. Alam, D. Noshiro, K. Mouri, T. Ando, Y. Okada, A. I. May, R. L. Knorr, K. Suzuki, Y. Ohsumi, N. N. Noda, “Phase separation organizes the site of autophagosome formation”, Nature, 578 (2020) 301-305.

[2] H. Yamamoto, Y. Fujioka, S. W. Suzuki, D. Noshiro, H. Suzuki, C. Kondo-Kakuta, Y. Kimura, H. Hirano, T. Ando, N. N. Noda, Y. Ohsumi, “The intrinsically disordered protein Atg13 mediates supramolecular assembly of autophagy initiation complexes”, Dev. Cell, 38 (2016) 86-99.

[3] A. Yamasaki, J. M. Alam, D. Noshiro, E. Hirata, Y. Fujioka, K. Suzuki, Y. Ohsumi, N. N. Noda, “Liquidity is a critical determinant for selective autophagy of protein condensates”, Mol. Cell, 77 (2020), 1163-1175.