Department of Biochemistry Mini-Symposium
Time: March 14th, Thu, 2024
Place: Tokyo Medical and Dental University, M&D Tower 11th floor, Graduate School Lecture Room 3

Chaperone-mediated autophagy: Regulatory mechanism of intracellular protein homeostasis

Part 1

Chaperone-mediated autophagy as a therapeutic and preventive target for neurodegenerative diseases

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In neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, inclusion bodies, which are thought to be abnormal accumulations of proteins, are frequently observed within nerve cells. Thus, decreased activity of the proteolytic system is assumed to be related to the onset of neurodegenerative diseases. Autophagy-lysosomal protein degradation is one of the major degradation systems for intracellular proteins, and the pathways that transport substrates to lysosomes can be divided into macroautophagy (so-called autophagy), microautophagy, and chaperone-mediated autophagy (CMA). In CMA, substrate proteins recognized by the molecular chaperone Hsc70 are taken up into lysosomes and degraded depending on the lysosomal membrane protein LAMP2A.Unlike macroautophagy and microautophagy, CMA is a pathway that exists only in mammalian cells and is thought to be particularly involved in higher-order regulation. Since it was reported in 2004 that CMA is involved in the degradation of α-synuclein that accumulates in Parkinson's disease, many reports have been made suggesting that CMA activity is reduced in the onset of Parkinson's disease.

Among neurodegenerative diseases, I have focused on spinocerebellar ataxia (SCA) and analyzed its relationship with CMA. SCA is classified into SCA1-49 depending on the causative genes, but the functions of the causative genes are diverse, and the common pathogenic mechanism remains unknown. We developed a CMA activity marker and established an experimental system to easily evaluate CMA activity in primary cultured cerebellar neurons using fluorescence observation.Using this method, we revealed that various SCA-causing proteins commonly induce a decrease in CMA activity. Furthermore, we found that reducing CMA activity by suppressing LAMP2A expression selectively in cerebellar neurons causes an SCA-like phenotype. These results strongly suggest that reduced CMA activity is involved in the common pathogenesis of SCA. The involvement of reduced CMA activity in other neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease has also been reported, and CMA is attracting attention as a therapeutic and preventive target for neurodegenerative diseases.

Part 2

Elucidation of molecular mechanism of chaperone-mediated autophagy using genetic code expansion technologies

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I would like to talk about how I came across chaperone-mediated autophagy (CMA) through various circumstances (since this is part of a graduate school lecture, we will mainly talk about the molecular mechanism of CMA). I was originally interested in the structure of proteins on membranes, and in the first half of my research career I obtained results showing that the lymphocyte surface antigen CD38 forms a tetramer on cell membranes. In order to investigate the structure of CD38 multimers on membranes, I found that it is effective to site-specifically introduce photoreactive cross-linking sites using expanded genetic coding technology. “Expanded genetic coding technology” was researched in the laboratory where I received my degree, but I only realized its significance more than ten years later. Based on our experience with CD38, we next decided to analyze lysosomal-associated membrane protein 1/2 (LAMP1/LAMP2), a protein present in the lysosomal membrane. Both LAMP1 and LAMP2 are single-pass transmembrane proteins, and the majority of the proteins reside in the lumen of lysosomes, with only a short portion of 11 amino acid residues at the C-terminus protruding into the cytoplasm. Both have similar structures, but while LAMP1-deficient mice are almost normal, half of LAMP2-deficient mice become lethal by 40 days after birth. Our first result suggested that the mode of multimer formation may be different between LAMP1 and LAMP2. Thus, we conducted research to elucidate the structural basis of multimerization by applying expanded genetic coding technology to LAMP2. LAMP2 has three variants LAMP2A/2B/2C with different C-terminal structures, and LAMP2A is an essential factor for CMA (a pathway in which intracellular proteins recognized by the chaperone protein Hsc70 are taken into lysosomes and degraded). Although there have been many reports on the functional role of CMA and its relationship to pathological conditions, I was surprised to find that much of the molecular mechanism of CMA remains unknown. To date, we have been using expanded genetic coding technology to analyze the interactions between LAMP2A multimers, Hsc70, and proteins degraded by CMA on the lysosomal membrane and in the lysosomal lumen. We hope that this will help clarify the molecular mechanism of CMA.