DATE: Day 19 Month 4 Year 2019

SUMMARY of
2018 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		**Structure of N-degron recognition domain of autophagy receptor**
Applicant	**Name**	**Hyun Kyu Song**
	Affiliation	**Korea University**
	Present Title	**Crystal structure of ZZ-domain of p62 autophagy receptor in complex with N-degron peptide**
Research Collaborator (Host PI)		**Atsushi Nakagawa**

Summary

Protein homeostasis regulated by autophagy as well as the ubiquitin-proteasome pathway is critical in all eukaryotic life cycles. The autophagy adaptor p62/SQSTM1/Sequestosome-1 plays a key role in selective autophagy, and interestingly also recognizes N-end rule substrates, suggesting involvement of the N-end rule pathway, a well-known ubiquitin-proteasome system. Furthermore, p62 also acts as a hub in various cellular signaling pathways, and has been extensively studied. However, the function of the central ZZ-domain of p62 has only recently been identified, and was shown to bind to both type-1 and -2 N-degrons. Furthermore, p62 is degraded together with R-BiP N-degron substrates (N-terminal arginine modified ER-chaperone). Despite its central importance in many cellular processes, no structural information concerning the ZZ-domain of p62 has been reported.

We determined the complex structure of the ZZ-domain of p62 in complex with type-1 N-degron Arg-peptide at 1.45 Å resolution and the specificity displayed towards N-degron substrates can now be clearly explained. The negatively charged patch of p62 is formed by three β-strands, one α-helix, and two zinc atoms. The zinc-coordinating residues are strictly conserved and are located in zig-zag order for the first zinc atom (Zn1) coordinated by four cysteine residues and the second zinc atom (Zn2) coordinated by two cysteine and two histidine residues. As expected, the binding site of the ZZ-domain comprises a negatively charged patch for recognition of the positively charged N-terminal NH_3^+ group of R-BiP. The side chains of Asp129 and Asp149 in the ZZ-domain form hydrogen bonds with the α-amino group of R-BiP. Two side chain carboxylates from Asp129 and Asp149 tightly hold the NH_3^+ group of the N-degron simultaneously. Details concerning the precise manner by which p62 is regulated during the autophagic process is a long sought-after goal in the field of selective autophagy, and the current structural and biochemical analysis deepens our understanding of the functional repertoire of the N-end rule pathway.

***Deadline: May 17, 2019**
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