

Structural insight into degradation mechanism of N-end rule substrates by p62/SQSTM1
selective autophagy adaptor
DO HOON KWON
Leehyeon Kim
Hyun Kyu Song

Korea University

p62/SQSTM1 is the key autophagy adaptor protein and the hub of multi-cellular signaling. It was recently reported that autophagy and N-end rule pathways are linked via p62. However, the exact recognition mode of degrading substrates and regulation of p62 in the autophagic pathway remain unknown. Here, we present the complex structures between the ZZ-domain of p62 and various type-1 and -2 N-degrons. The binding mode employed in the interaction of the ZZ-domain with N-degrons differs from that employed by classic N-recognins. It was also determined that oligomerization via the PB1 domain can control binding affinity to the R-BiP substrate. Unexpectedly, we found that self-oligomerization and disassembly of p62 are pH-dependent. These findings broaden our understanding of the functional repertoire of the N-end rule pathway and provide an insight into the regulation of p62 during the autophagic pathway.

Keywords: aggregation; autophagy; BiP/GRP78; degradation; N-end rule;p62/SQSTM1; PB1 domain; structure; ubiquitin; ZZ-domain