ABSTRACT for Mizutani Foundation Research Grant

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Grant Title: Role of Cnx in delivery of ATZ from the ER to endolysosomes for clearance

About 30% of the eukaryotic cells proteome is folded and assembled in the endoplasmic reticulum (ER). Folding-defective and terminally misfolded polypeptides must be efficiently cleared from the ER lumen. Failure to do so, leads to the intraluminal accumulation of aberrant gene products that compromises maintenance of cellular proteostasis (i.e., the capacity to produce the proteome in appropriate quality and quantity). Paradoxically, the ER lumen does not contain degradative devices. Most misfolded polypeptides generated in the ER are therefore extracted from futile folding cycles, are delivered at translocation sites embedded in the ER membrane and are eventually retro-translocated into the cytosol for clearance by the ubiquitin-proteasome-system. Protein aggregation disfavors proteasomal degradation and activates poorly characterized catabolic pathways where misfolded proteins generated in the ER lumen are delivered to lysosomal compartments for clearance in catabolic pathways defined ER-to-lysosome-associated protein degradation (ERLAD). We recently found that calnexin, a lectin chaperone of the ER, is required for delivery of proteasome-resistant ATZ polymers from the ER lumen to RAB7-/LAMP1-positive endolysosomes for clearance. Strikingly, calreticulin and ERp57, the calnexin teammates in glycoprotein folding and quality control in the ER, are dispensable for this catabolic pathway.
The support of the Mizutani Foundation was instrumental to establish that a specific N-glycan of ATZ is required for segregation of ATZ polymers within ER subdomains that are shed from the bulk ER and eventually fuse with endolysosomes thereby ensuring clearance of their toxic content