Ubiquitin/proteasome-mediated protein degradation and quality control of misfolded proteins in the endoplasmic reticulum

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Ubiquitin is a 76-amino acid protein that is covalently linked to target proteins, and the proteasome recognizes and degrades proteins that are tagged with ubiquitin chains. The proteasome consists of a cylindrical 20S catalytic particle, capped by PA700 or PA28 regulatory unit. The ubiquitin/proteasome system plays an important role in the degradation of short-lived and regulatory proteins in a variety of cellular processes, including cell cycle progression, modulation of cell surface receptors and ion channels, and quality control of misfolded proteins in the endoplasmic reticulum (ER). Thus, misfolded proteins currently are postulated to be degraded by ubiquitin/proteasome pathways after association with ER chaperones and retrotranslocation from the ER to the cytosol.

We have shown that misfolded secretory proteins such as gamma-carboxylation-deficient protein C (cd-PC), a vitamin K-dependent coagulation protein, and genetic variants of thyroglobulin, antithrombin and factor XII were degraded by the proteasome system. Our studies also showed that specific mannose trimming catalyzed by ER mannosidase I was critical for the ER-associated degradation of these glycoproteins. Notably, the undegraded protein fraction remained microsome-associated. To clarify the retrotranslocation in ER-associated degradation of cd-PC, we constructed and expressed chimeras with GFP which was NH_2-terminally fused to a fragment of protein C. Interestingly, LC-GFP, which is a chimera of the light chain of protein C and GFP, time-dependently formed intranuclear inclusions in the presence of a proteasome inhibitor. After removal of the proteasome inhibitor, these inclusions disappeared with chase, suggesting that inhibition of the proteasome activity correlates with the formation of the intranuclear inclusions. Taken together, the data suggest that specific mannose trimming enhances the efficiency of retrotranslocation of misfolded glycoproteins from the ER lumen to the cytosol, and subsequently they form intranuclear inclusions under the inhibition of the proteasome activity that might be related with the cellular basis of several neurodegenerative diseases.

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