

Abstract

The endoplasmic reticulum (ER) is essential for the folding and post-translational modification of secreted proteins. A dysfunctional ER as a result of environmental conditions, aging or structural mutations may cause a multitude of diseases. The regulation of translation, transcription and degradation by the ER-associated protein degradation (ERAD) system prevents the accumulation of damaged proteins in the ER-lumen.

Point mutations in the serine protease inhibitor Neuroserpin result in degradation-resistant protein aggregates in the ER-lumen, which are associated with the neurodegenerative disease familial encephalopathy with neuroserpin inclusion bodies (FENIB). The *Caenorhabditis elegans* homolog SRP-2 possesses a high degree of similarity to the human Neuroserpin. In this thesis it was shown that also pathogen point mutations (H302R) in SRP-2 result in clustering and stabilisation. Analysis of the aggregation behaviour of SRP-2^{H302R} revealed that the unfolded protein response (UPR), the heat-shock response and glycosylation regulate the polymerisation of SRP-2^{H302R}.

The degradation of damaged proteins occurs primarily by ERAD. The ERAD-system was extensively studied in the yeast *Saccharomyces cerevisiae*, however little is known about the physiological relevance in a multicellular organism. In order to characterize the ERAD-System, mutated Pro Cathepsin L (CPL-1*) was established as a model-substrate for misfolded ER-proteins in *C. elegans*. Using immunoprecipitation, mass spectrometry and genetic screens the E3-ligase SEL-11, the protein disulfid isomerase PDI-1/2 and the EDEM1 homolog C47E12.3 were validated as ERAD-proteins and the so far uncharacterized ERAD-components F48E8.4, Y105E8A.2, F48B9.8 and C03H12.1 were identified.

Surprisingly, mutations in components of the systemic RNAi response RDE-1, DRH-1 and RRF-1 result also in a specific stabilisation of the ERAD-substrate CPL-1*. The characterisation of the underlying mechanism shows that RDE-1 and DRH-1 regulate the stabilisation of CPL-1* in a parallel pathway to the ERAD-system. However, they do not regulate the degradation of the model-substrate, they rather control the mRNA-level of CPL-1*. Furthermore it was shown that RDE-1 and DRH-1 also regulate the mRNA-level of the sodium-proton-transporter NHX-2 in response to ER-stress. In conclusion, this thesis identified a novel regulation mechanism of secreted and membrane bound proteins in the presence of ER-stress. These findings may contribute to the molecular understanding of pathogen mechanisms in the context of viral infections as well as aging related diseases in the long run.