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Title: Substrate specificity of the endoplasmic reticulum chaperone proteins EDEM1 and EDEM2, and their role in the intracellular transport of ricin

Abstract:

The endoplasmic reticulum (ER) is a highly versatile protein factory that is equipped with chaperones and enzymes essential for protein folding. ER quality control guided by these chaperones is one of the central issues determining the proper functioning of all human cells. This system ensures that properly folded proteins are exported from the ER whereas unfolded proteins are retrotranslocated to the cytosol and degraded by the 26S proteasome in a multistep process called ER-associated-degradation (ERAD). ER degradation-enhancing α-mannosidase-like proteins (EDEM) recognize ERAD substrates and direct them to the ER translocons. Interestingly, ER-cytosol retrotranslocation machinery can be used not only by ERAD substrates but also by some toxins that utilize this transport step in their intoxication cycle. Ricin is a natural, extremely potent protein toxin isolated from the seeds of the castor oil plant *Ricinus communis*. It is a heterodimeric glycoprotein composed of an RNA-specific *N*-glycosidase A-chain (RTA) connected by a disulfide bond to the cell binding lectin B-chain (RTB). RTA is recognized by EDEM1 and EDEM2 that facilitate its transport to the cytosol, however, the role of both EDEM chaperone proteins in this process seems to be different. Results of our experiments performed with ricin A-chain and with a model misfolded protein BACE457 indicate that the structure of the protein substrate as well as the hydrophobic regions of proteins are important in their recognition by EDEM1 and EDEM2. This seminar describes the differences in substrate specificity of EDEM proteins, summarizes the role of EDEM1 and EDEM2 in ricin intracellular transport and discusses possibilities for the practical use of this knowledge in the future.