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A proteomic approach to identify yeast proteins responding to accumulation of misfolded proteins inside the cells

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In growing number of diseases it has been shown that aggregation of specific proteins has an important role in pathogenesis of the disorder. This has been demonstrated in structural details with the liver cirrhosis of α_1-antitrypsin deficiency, and it is now believed that similar protein aggregation underlies many neurodegenerative disorders such as autosomal dominant Parkinson disease, prion diseases, Alzheimer disease, and Huntington disease. α_1-Antitrypsin, a member of serine protease inhibitor (serpin) family, functions as an inhibitor of neutrophil elastase. Genetic variants of α_1-antitrypsin, such as the Z (Glu342→Lys) and S_{iiyama}(Ser53→Phe), undergo polymerization, which leads to retention of the molecules within endoplasmic reticulum (ER) of the hepatocytes and subsequent decrease in the plasma concentration of active α_1-antitrypsin. To identify proteins that responded to accumulation of misfolded proteins in ER, we expressed the z and S_{iiyama} type variants of α_1-antitrypsin in yeast. Protein expression profile was analyzed by using 2D-gel electrophoresis and 55 candidate spots were identified by peptide mass fingerprinting using MALDI-TOF MS and database search. Some of these are classified in such functional catalogs as intracellular transport, protein destination, and cell rescue. Results will be discussed.