Proteasomal dysfunction and endoplasmic reticulum stress enhance trafficking of prion protein aggregates through the secretory pathway and increase accumulation of pathologic prion protein.

Abstract:

A conformational change of the cellular prion protein (PrP(c)) underlies formation of PrP(Sc), which is closely associated with pathogenesis and transmission of prion diseases. The precise conformational prerequisites and the cellular environment necessary for this post-translational process remain to be completely elucidated. At steady state, glycosylated PrP(c) is found primarily at the cell surface, whereas a minor fraction of the population is disposed of by the ER-associated degradation-proteasome pathway. However, chronic ER stress conditions and proteasomal dysfunctions lead to accumulation of aggregation-prone PrP molecules in the cytosol and to neurodegeneration. In this study, we challenged different cell lines by inducing ER stress or inhibiting proteasomal activity and analyzed the subsequent repercussion on PrP metabolism, focusing on PrP in the secretory pathway. Both events led to enhanced detection of PrP aggregates and a significant increase of PrP(Sc) in persistently prion-infected cells, which could be reversed by overexpression of proteins of the cellular quality control. Remarkably, upon proteasomal impairment, an increased fraction of misfolded, fully glycosylated PrP molecules traveled through the secretory pathway and reached the plasma membrane.
These findings suggest a novel pathway that possibly provides additional substrate and template necessary for prion formation when protein clearance by the proteasome is impaired.