Aggregate formation and cell death in polyglutamine diseases

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Polyglutamine diseases, including Huntington's disease (HD) and spinocerebellar ataxia 3 (SCA3), form a group of neurodegenerative diseases that are caused by an expanded CAG repeat in a transcribed gene. All these diseases are characterized by progressive neuronal dysfunctioning starting around mid-life and resulting in severe neurodegeneration. Pathological hallmarks include atrophy of affected areas and the formation of dystrophic neurites and neuronal intranuclear inclusions.
In Alzheimer's disease it was found that a mutant form of ubiquitin accumulates in the hallmarks of the disease. This ubiquitinB^{+1} (UBB^{+1}) is formed by a dinucleotide deletion during transcription leading to a +1 reading frame in the mRNA and subsequent translation to a protein with an aberrant C-terminus. In vitro studies with UBB^{+1} have shown that although it is degraded by the proteasome it also inhibits proteasomal degradation and leads to cell death in neuroblastoma cells.
Neuronal intranuclear inclusions in HD and SCA3 comprise of expanded polyglutamine proteins, ubiquitin and several cellular chaperones. We found accumulation of UBB^{+1} in these inclusions as well, indicating impairment of the proteasome in these neurons. Presence of UBB^{+1} could result in inefficient degradation of expanded polyglutamines and might contribute to neurodegeneration.
A cellular model, using plasmids containing polyglutamine stretches of different length together with UBB^{+1} constructs, shows that UBB^{+1} is incorporated in the aggregates in vitro as well. Furthermore, we found that UBB^{+1} not only increased aggregate formation of expanded polyglutamines in cell lines, but also had a synergistic effect on apoptotic cell death due to expanded polyglutamine proteins. These findings implicate UBB^{+1} as an aggravating factor in polyglutamine-induced neurodegeneration, and clearly identify an important role for the ubiquitin proteasome system in polyglutamine diseases.
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