Heat shock proteins in neurodegenerative diseases:
pathogenic roles and therapeutic implications.

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Abstract

Neurodegenerative diseases including amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and polyglutamine (polyQ) diseases are thought to be caused by protein misfolding. Heat shock proteins (HSPs), which function mainly as molecular chaperones, play an important role in the folding and quality control of proteins. The histopathological hallmark of neurodegenerative diseases is accumulation and/or inclusions of the disease-causing proteins in residual neurons in targeted regions of the nervous system. The inclusions combine with many components of molecular chaperone pathways and ubiquitin-proteasome, raising the possibility that misfolding and altered degradation of mutant proteins may be involved in the pathogenesis of neurodegenerative diseases. Overexpression of HSPs has been reported to reduce the number and size of inclusions and accumulation of disease-causing proteins, and ameliorate the phenotypes in neuronal cell and mouse models. Hsp90 inhibitors also exert therapeutic effects through selective proteasome degradation of its client proteins. Elucidation of its pathophysiology using animal models has led to the development of disease-modifying drugs, i.e., Hsp90 inhibitor and HSP inducer, which inhibit the pathogenic process of neuronal degeneration. These findings may provide the basis for development of an HSP-related therapy for neurodegenerative diseases.