Mol Cell Biochem
DOI 10.1007/s11010-013-1844-y

Association of heat-shock proteins in various neurodegenerative disorders: is it a master key to open the therapeutic door?

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Received: 31 March 2013 / Accepted: 26 September 2013

Abstract A number of acute and chronic neurodegenerative disorders are caused due to misfolding and aggregation of many intra- and extracellular proteins. Protein misfolding and aggregation processes in cells are strongly regulated by cellular molecular chaperones known as heat-shock proteins (Hsps) that include Hsp60, Hsp70, Hsp40, and Hsp90. Recent studies have shown the evidences that Hsps are colocalized in protein aggregates in Alzheimer's disease (AD), Parkinson's disease (PD), Polyglutamine disease (PGD), Prion disease, and other neurodegenerative disorders. This fact indicates that Hsps might have attempted to prevent aggregate formation in cells and thus to suppress disease conditions. Experimental findings have already established in many cases that selective overexpression of Hsps like Hsp70 and Hsp40 prevented the disease progression in various animal models and cellular models. However, recently, various Hsp modulators like geldanamycin, 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin, and celastrol have shown to up-regulate the expression level of Hsp70 and Hsp40, which in turn triggers the solubilization of diseased protein aggregates. Hsps are, therefore, if appropriately selected, an attractive choice for therapeutic targeting in various kinds of neurodegeneration and hence are expected to have strong potential as therapeutic agents in suppressing or curing AD, PD, PGD, and other devastative neurodegenerative disorders. In the present review, we report the experimental findings that describe the implication of Hsps in the development of neurodegeneration and explore the possibility of how Hsps can be used directly or as a target by other agents to prevent various neurodegeneration through preventing aggregation process and thus reducing the toxicity of the oligomers based on the previous reports.

Keywords Heat-shock proteins · Misfolding and aggregation · Neurodegeneration · Alzheimer's disease · Parkinson disease · Polyglutamine disease · Prion disease · Hsp90 inhibitors

Introduction

Neurodegenerative disorders are chronic and progressive, and are characterized by selective and symmetric loss of neurons in motor, sensory, or cognitive systems. Many neurodegenerative disorders are also known as "protein-misfolding disorders" or "proteinopathies" and are characterized by the accumulation of intracellular or extracellular protein aggregates. In almost all neurodegeneration condition, an error in folding occurs because of an undesirable mutation in the gene either of the disease-causing protein or, in a few cases, some less-known reason. The harmful effect of the misfolded protein is due to the deleterious "gain of function" as seen in many neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Polyglutamine disease (PGD) (poly Q), Hungtinton disease (HD), and Prion disease in which protein misfolding results in the formation of harmful amyloid [1, 2]. Protein aggregates are sometimes converted to a fibrillar structure containing a large number of intermolecular hydrogen bonds, which are highly insoluble and sometimes protease-resistant. They are commonly termed as amyloids and their accumulation occasionally results in a plaque-like structure [3]. The more

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Published online: 05 October 2013