HSP27 and cell death in spinocerebellar ataxia type 3

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Abstract
Spinocerebellar ataxia type 3 (SCA3) is an autosomal dominant spinocerebellar degeneration characterized by a wide range of clinical manifestations. In this review, we discuss the role(s) that heat shock protein 27 (HSP27) may play in the cell death process of spinocerebellar ataxia type 3.

Key words: Spinocerebellar ataxia type 3, ataxin-3, heat shock protein 27, cell death

Introduction
Spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease (MJD), one of dominantly inherited neurological diseases (1), is related to a common pathological mechanism with a polyglutamine expansion within the relevant disease protein. Polyglutamine-related diseases are dominantly inherited, typically late-onset, and fatal neurodegenerative disorders. Patients usually develop a slowly progressive movement disorder and die within 10 to 20 years after onset. These diseases affect various central nervous system (CNS) structures, but all eventually lead to brainstem dysfunction. Although the chief sites of neuropathology vary from one triplet disease to another, the function of most of the proteins remains unknown. Clinically, SCA 3 is characterized by a progressive ataxia in combination with various noncerebellar symptoms, including oculomotor abnormalities, spasticity, basal ganglia symptoms, peripheral neuropathy and cognitive disturbances (2,3). All affected SCA3 patients exhibit expanded trinucleotide repeat motifs (CAGs) with 55 to 84 repeats whereas normal individuals exhibit 13 to 51 repeats (4). The protein, ataxin-3, is widely expressed in neurons and outside the CNS and mutations ultimately lead to a selective neuronal loss in restricted brain regions (5). The nature of the toxic insult of a polyQ mutation and its biological consequences for the disease are unclear. Several studies have demonstrated that protein fragments containing an expanded polyglutamine possess an increased vulnerability to apoptotic death. However, the mechanisms underlying the slow cell death processes are largely unknown. It is possible that the polyQ expansion interferes with basic cellular process such as transcription, protein degradation and survival/death signaling (6). Genetic and molecular studies have suggested that polyQ causes altered gene expression, abnormal protein interactions, alteration of proteolysis, and activation of caspases and protein unfolding (7–11). However, the causal relation between these cellular events and the pathogenesis has not been elucidated.

Heat shock proteins and polyglutamine diseases
The mechanism that leads the polyglutamine-expanded proteins to aggregate is largely unknown.

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There is a possibility that the expanded polyglutamine tract may destabilize the protein to misfold and aggregate. Therefore, protein chaperones, also known as heat shock proteins (HSPs) which help restore proteins to their native conformation after they have been misfolded due to heat, ischemia, chemotoxicity or other cellular stressors (16), have drawn researchers’ attention in recent years (6,17,18). HSPs or stress proteins participate in protein synthesis, protein folding, transport and translocalization processes. Stress situations trigger a heat shock response leading to their induction. The up-regulation of stress proteins is an important step in prevention of protein aggregation and misfolding after stress, and also is essential during development and differentiation (19). Because of the late onset of polyglutamine diseases, aging may be associated with a decrease in the ability of mutant cells to cope with intracellular or environmental challenges. This may be partly due to the attenuation of a primordial stress response, the so-called heat shock (HS) response, which induces the expression of HSPs, composed of chaperones and proteases. The attenuation of the HS response during aging may be responsible for the accumulation of damaged proteins as well as abnormal regulation of cell death. Since 1998, a lot of publications have reported the effects of overexpression of chaperones in cellular models of polyglutamine aggregation and toxicity. HSP70 and HSP40 can function in an ATP-dependent process to catalyze the refolding of denatured or partially denatured modules into enzymatically active forms (20). Both HSPs have been identified as potent modulators of polyQ aggregation and/or cell death (21–29). Indeed, in SCA3 brain, HSP40 and HSP70 were found to localize to nuclear inclusions (NIs) (30,31). In addition, it was demonstrated that over-expressed chaperones in cells also reduce the size of the aggregates and even suppress polyglutamine toxicity (30,32). The most compelling data that supports a critical role for chaperones in protein misfolding diseases come from in vivo studies in fruit fly (33,34). In these studies, a *Drosophila melanogaster* model of SCA3 was used to characterize the effects of overexpression of human HSP70, which completely suppressed the external eye defects mediated by the expression of expanded polyQ in these flies. In addition, expression of the expanded polyQ protein in a fly line bearing a dominant-negative *Drosophila* HSP70 augmented the severity and kinetics of neurodegeneration, therefore, it was suggested that under normal conditions the endogenous fly HSP70 may partially mitigate the toxic effects of the expanded polyQ protein (33). Recently, offsprings of a cross between a mouse model of SCA1 and mice overexpressing the inducible form of HSP70 performed significantly better on tests of motor coordination than their SCA1 littersmates and had fewer neuronal derangements (27). It is worth noting that NIs, as a hallmark of neurodegeneration, were mostly found at the late stage of disease or in postmortem patients’ brain tissue. Although overexpression of HSP70 or HSP40 may enhance the solubility of polyQ proteins concomitant with protection against neurodegeneration, it does not have any effect on the morphology of polyQ aggregates as judged by light microscopy (35). Chaperones are one of the best examples of multifunctional proteins, and their protection against neurodegeneration may result from one or more of their activities in cells. Chaperones might play a role in other important protective events: they might divert the cells from the apoptotic program known to be triggered directly by misfolded proteins. Other evidence showed that the chief benefit of chaperones in polyglutamine disease might derive from their apoptosis-countering activities, which are largely independent of aggregation (28).

### Heat shock protein 27 and cell death

It is likely that other chaperones, such as the low-molecular-weight chaperones of the crystalline family and those involved in the unfolded stress response induced by misfolded proteins in the lumen of the endoplasmic reticulum, might also be involved in polyglutamine diseases. Different HSPs have been shown to directly inhibit several types of cell death pathways induced by a variety of toxic insults in neuronal cells (36–39). HSP27 is a powerful ATP-independent chaperone *in vitro*, that inhibits aggregation and promotes the refolding of denatured proteins (40). HSP27 is expressed in various cell types and tissues, at specific stages of differentiation and development (19), and the failure to obtain knock-out mice suggests that this protein is essential for development. The expression of HSP27 was shown to enhance the survival of mammalian cells exposed to a number of cytotoxic agents, including heat shock, oxidative stress, staurosporine, ligation of the Fas/Apo-1/CD95 death receptor, chemotherapeutic agents, and cytokines (41–45). Paradoxically, such stimuli often induce HSP27 overexpression, providing an example of how pro-apoptotic stimuli can elicit protective responses when delivered below a threshold level. HSP27 was reported to protect cells against oxidative stress and have anti-apoptotic properties in neuronal survival (46–48), which may be partly due to a decrease in reactive oxygen species (ROS) and an increase in glutathione (GSH) (46,49). Cells contain a number of antioxidant defenses to minimize fluctuations in ROS, but ROS generation often exceeds the cell’s antioxidant capacity, resulting in a condition termed oxidative stress. Host survival depends upon the ability of cells and tissues to