CHAPTER 1

CHAPERONES AND POLYGLUTAMINE EXPANSION DISORDERS

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Abstract: Polyglutamine expansion disorders are caused by the misfolding of proteins with abnormally long polyglutamine regions. This misfolding produces toxicity and leads to the dysfunction and ultimately to the demise of neurons in affected individuals. The molecular basis for polyglutamine toxicity is unclear and the number and complexity of documented cellular pathways involved in polyglutamine expansion disorders is daunting. However, the use of effective experimental model systems is rapidly advancing our understanding of polyglutamine misfolding and the cellular factors that govern the related toxicity. Molecular chaperones, the central regulators of cellular protein quality control, improve polyglutamine misfolding and hence ameliorate polyglutamine toxicity. Additionally, polyglutamine expansion proteins overwhelm molecular chaperones and thereby reduce their capacity to execute protein quality control. Hence, dysfunctional cellular protein quality control presents a very basic and fundamental problem of protein misfolding and therefore of polyglutamine toxicity. Thus, the elucidation of the interplay between polyglutamine expansion proteins and molecular chaperones contributes profoundly to our understanding of polyglutamine expansion disorders and offers great promise for developing effective therapeutic strategies in the treatment of these devastating maladies.

Keywords: Neurodegeneration; protein misfolding; protein aggregation; stress response; heat shock proteins; neuroprotection

INTRODUCTION

Nine different neurodegenerative diseases are caused by expansions of polyglutamine regions in different proteins: Huntington’s disease (HD); the Spinocerebellar Ataxias 1, 2, 3, 6, 7, and 17 (SCA1, 2, 3, 6, 7 and 17); Spinal and Bulbar Muscular Atrophy (SBMA, also known as Kennedy’s disease); and Dentatorubralpallidoluysian Atrophy (DRPLA) (Cummings and Zoghbi, 2000; Zoghbi and Orr, 2000). In each of

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these disorders, polyglutamine expansions arise from genetic mutations that generate the expansion of repeated CAG codons (encoding the amino acid glutamine) in the genes encoding the disease-proteins. Except for their polyglutamine regions, the nine disease-proteins differ profoundly in amino acid composition, subcellular localization and function. Consequently, the nine polyglutamine expansion disorders present distinct pathologies and affect different neurons in different regions of the brain (Zoghbi and Orr, 2000; La Spada and Taylor, 2003; Cowan and Raymond, 2006). For example, in HD medial spiny neurons of the striatum are primarily, and most severely, damaged by the polyglutamine expanded protein huntingtin (Graveland et al., 1985; DiFiglia et al., 1997; Cowan and Raymond, 2006) whereas Purkinje cells of the cerebellum and brain stem neurons are most affected by a polyglutamine expanded ataxin-1 protein in SCA1 (Gilman et al., 1996).

In spite of these differences, all nine polyglutamine disorders share important basic features (Ordway et al., 1999; Zoghbi and Orr, 2000; Gatchel and Zoghbi, 2005). All of them are late onset diseases, i.e. they usually manifest in midlife, or even at advanced age, and they are progressive, possessing symptoms that increasingly worsen throughout the course of the disease. Most polyglutamine expansion disorders share a threshold of about 40 glutamines in the disease-proteins: individuals who express disease-proteins with polyglutamine expansions beneath this threshold do not develop the disease, while individuals harboring a polyglutamine expansion above this threshold will eventually develop the disease. Strikingly, in each of the nine polyglutamine expansion disorders, the longer the polyglutamine expansion is, the earlier is the disease onset and the more severe the disease-phenotype. Finally, for each disorders, inclusions formed by the polyglutamine expanded proteins are found in specific types of neurons (Ross et al., 1999). These shared features imply that – at least at a very fundamental level – all polyglutamine expansion disorders are based upon a common pathological mechanism.

Polyglutamine expansion disorders can be regarded as protein conformational, or better, protein misfolding diseases. This term indicates that the conversion of a protein from its functional, benign conformation into an aberrant (misfolded), toxic conformation constitutes the molecular basis for the diseases. While the conversion from a benign into a toxic protein is triggered by discrete genetic mutations resulting in polyglutamine expansions, several other common protein misfolding diseases of the nervous system, such as sporadic cases of Alzheimer’s disease and Parkinson’s disease, are not caused by single mutations. In these diseases, the conversion of disease-proteins from benign into toxic conformations is mostly triggered by stochastic protein misfolding events that are elicited by stressful environmental conditions and aging (Soto, 2001; Forman et al., 2004; Selkoe, 2004).

From a cell biological perspective, the conversion of a disease-protein from a benign into a toxic conformation in protein misfolding diseases can be attributed to the failure of cellular protein quality control (Sherman and Goldberg, 2001; Welch, 2004). Cellular protein quality control consists of two major branches. One branch facilitates the production and preservation of accurately folded and