CHAPTER 4

HEAT SHOCK PROTEINS AS THERAPEUTIC TARGETS IN AMYOTROPHIC LATERAL SCLEROSIS

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Abstract: Amyotrophic lateral Sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the loss of motoneurons in the motor cortex, brainstem and spinal cord, resulting in paralysis and death within 1–5 years of diagnosis. Although the precise etiology of ALS remains elusive, approximately 20% of cases are known to be familial and of these approximately 10%–20% are due to mutations in the ubiquitously expressed human Cu/Zn superoxide dismutase (SOD1) gene. Transgenic mice that over-express the mutant human SOD1 (mSOD1) protein exhibit a phenotype and pathology that resemble that observed in ALS patients. ALS is widely regarded as a motoneuron-specific disorder but increasing evidence indicates that non-neuronal cells also play a significant role in disease pathogenesis. Some characteristics of the disease observed in mice and patient tissue, such as the presence of insoluble protein aggregates containing heat shock proteins (Hsps) as well as the apoptotic degeneration of motoneurons, suggest that manipulation of the heat shock response (HSR) may be a successful strategy for the treatment of ALS. In this chapter evidence for the involvement of the various Hsp families in disease pathology and their therapeutic potential is reviewed based on the molecular characteristics of the Hsp sub-families

Keywords: Motoneuron degeneration; motor neuron disease; protein aggregation; apoptosis; co-chaperones; HSF-1

INTRODUCTION

Motor neuron diseases (MND) are a group of progressive disorders involving the nerve cells responsible for innervating voluntary skeletal muscles. There are four main types of MND: (i) Amyotrophic Lateral Sclerosis (ALS); (ii) Progressive Muscular Atrophy; (iii) Progressive Bulbar Palsy and (iv) Primary Lateral Sclerosis, although there can be a great deal of clinical and pathological overlap between

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ALS was first described in 1869 by the French neurologist, Jean-Martin Charcot (Charcot and Joffroy, 1869). It is a fatal, adult onset neurodegenerative disease that affects the upper and lower motoneurons in the brain and spinal cord. The disease is characterized by weakness and paralysis of voluntary skeletal muscles due to the progressive loss of motoneurons, ultimately leading to respiratory failure and death, usually within 2–5 years of diagnosis. The incidence of ALS is approximately 2 per 100,000 of the population, with prevalence at any point in time of 6 per 100,000. The vast majority of ALS cases are sporadic, with around 10% of cases which are familial (inherited). Approximately 120,000 new cases of ALS are diagnosed worldwide each year, and although it can strike at any age it is more commonly found in the 40–70 year age group. Despite intensive research, particularly during the past 10 years, there remains no effective treatment for this devastating disease.

It is possible that the development of an effective disease-modifying therapy for ALS has been hindered by our relatively poor understanding of the pathogenesis of ALS. A major breakthrough came in 1993, with the discovery that approximately 10%–20% of the familial forms of ALS (FALS) were due to a mutation in the Cu/Zn Superoxide Dismutase 1 (SOD1) gene (Rosen et al., 1993) and to date, more than 100 mutations in the SOD1 gene have been discovered that are linked to ALS. Shortly following the discovery of mutant SOD1(mSOD1)-linked ALS, a transgenic mouse over-expressing the same mutant form of the human SOD1 protein was developed and this has become an indispensable tool for research not only investigating the pathogenesis of ALS but also as an animal model for preclinical testing of potential therapeutic agents (Gurney et al., 1994).

MECHANISMS UNDERLYING ALS PATHOLOGY

It is now clear that ALS is a multi-factorial disease in which a number of pathological mechanisms contribute to the selective and progressive degeneration of motoneurons. The sporadic and familial forms of ALS show both phenotypical and pathological similarities and so an understanding of the mechanisms involved in the death of motoneurons in SOD1 mice, which model the familial form, are likely to also be of relevance to the majority of sporadic cases of ALS (see Shaw and Eggett, 2000; Bruijn et al., 2004; Shaw, 2005; Boillee et al., 2006). Motoneurons have some specific functional and morphological characteristics that may actually contribute to their selective vulnerability in ALS. For example, as a consequence of their high metabolic load, motoneurons are particularly susceptible to excitotoxic insults and oxidative damage (Shaw, 2005), so that even healthy motoneurons are more susceptible to activation of AMPA receptors than other neuronal populations (Carriedo et al., 1996). Motoneurons also have particularly high energy demands (Briese et al., 2005) which makes them susceptible to mitochondrial dysfunction. Indeed, altered mitochondrial morphology, increased mitochondrial Ca\(^{2+}\) levels, mitochondrial deposits of mutant SOD1 protein and reduced complex IV activity