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Mini Review

Heat shock protein 27 in neuronal survival and neurite outgrowth

Danielle E. Read, Adrienne M. Gorman *

Cell Death and Survival Group, Department of Biochemistry, School of Natural Sciences, National University of Ireland, Galway, Ireland
National Centre for Biomedical Engineering Science, National University of Ireland, Galway, Ireland

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ABSTRACT

The small heat shock protein 27 (Hsp27) is well documented to promote neuronal survival in neurodegenerative diseases and following nerve injury. It can directly inhibit apoptotic pathways, and as a chaperone it can ameliorate the toxic effects of misfolded proteins. More recently, Hsp27 has been implicated to also play a role in neurite outgrowth. Thus, Hsp27 is situated at the intersection of neuronal survival and differentiation and, as such, it has dual potential as a key therapeutic target for neuroregeneration.

Introduction

The small heat shock protein of size 27 kDa (Hsp27) is a member of the heat shock protein family, which are highly conserved molecular chaperones. Hsp27 is transiently induced in response to cellular stress, facilitating protein folding, oligomeric assembly, transport or controlled switching between conformations [1]. In addition to its chaperone activity, Hsp27 can inhibit apoptotic pathways (reviewed in [2,3]), reduce oxidative stress [4] and modulate cytoskeletal elements [3]. Hsp27 contains a moderately conserved α-crystallin domain located at the C-terminal, enabling the formation of stable dimers that aggregate to tetramers and unstable oligomers of 16–32 subunits in length (for a review of Hsp27 structure see [5]). The dissociation of Hsp27 oligomers into dimers and tetramers occurs as a result of its phosphorylation by mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2), a downstream target of p38 MAPK signalling [5]. Some of the functional properties of Hsp27 vary with the phosphorylation status and level of self-association of the protein [6]. This mini-review will discuss current data illustrating the role of Hsp27 in promoting neuronal survival and regeneration in neuronal disorders and injury models. Furthermore, the recent findings regarding a specific role for Hsp27 in neurite outgrowth will be highlighted.

Hsp27 promotes neuronal survival in neurodegenerative disorders and following injury

Common neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), are often characterised by oxidative stress, abnormalities of the cytoskeleton and accumulations of insoluble, aggregated proteins in the form of either amyloid or intracellular inclusion bodies, resulting in selective neuronal death [7]. Neurons are vulnerable to the damaging effects of misfolded and aggregated proteins because of their postmitotic nature, which means harmful species cannot be diluted through cell division and thus accumulate during ageing [7]. Elevated Hsp27 levels are often found in individuals with neurodegenerative disorders. For example, Hsp27 is expressed in PD [8], ALS [9] and the protein and mRNA levels of Hsp27 are substantially elevated in the brains of patients with the rare Alexander disease [10]. It is probable that increased Hsp27 expression is part of a protective response mounted by neurons, acting as a chaperone to enhance the protein folding capacity of the neuron and thus promoting its survival [7,11]. In support of this, Hsp27 can decrease the level of hyperphosphorylated Tau (an AD-related protein) and rescue Tau-mediated cell death [12]. In PD models, Hsp27 promotes neuronal survival [13,14] and, in combination with Hsp104, can rescue striatal dysfunction and cell death in a Huntington's disease (HD) rat model and primary neuronal cultures [15]. Furthermore, neuroprotection due to Hsp27 overexpression has been observed in a mouse model of ALS, where the mice exhibited delayed motor strength decline, a significant improvement in the number of functional motor units and elevated spinal motor neuron survival during the early phase of disease [16]. Conversely, reduction in Hsp27 expression during disease progression is often linked with the onset of neuronal cell death. For example, in ALS mice expressing mutant SOD1 (G93A), Hsp27 protein expression decreases in motor neurons prior to the onset of motor neuron death [17], and in a model of Machado–Joseph disease (MJD)/spinocerebellar ataxia type 3 (SCA3) a low level of Hsp27 expression in the early stage of the disease

* Corresponding author. Fax: +353 91 495504.
E-mail address: adrienne.gorman@nuigalway.ie (A.M. Gorman).

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mitigates the ability of neuronal cells to cope with mutant ataxin-3-induced cytotoxicity, increasing cell death during disease progression [18]. Furthermore, mutations in Hsp27 cause axonal Charcot–Marie-Tooth (CMT) disease and distal hereditary motor neuropathies, conditions that exhibit age-dependent selective degeneration of motor neurons [19]. The mutant Hsp27 increases degeneration, loss of motor neuron viability and affects neurofilament assembly in CMT models, which can be reversed by wild-type Hsp27 overexpression [19,20].

Hsp27 has also been shown to be neuroprotective against acute nerve injury. Following nerve transection *in vivo* in the rat, neonatal motor neurons are rescued from cell death by Hsp27 overexpression and furthermore, the induction and phosphorylation of Hsp27 in adult axotomised neurons is protective against nerve injury-induced death [21–23]. In addition, Hsp27 is present in dorsal root ganglion (DRG) neurons following peripheral axotomy and accumulates in the dorsal horn and columns of the spinal cord, where it continues to be expressed for several months [24]. Hsp27 also presents considerable potential for long-term improvement in motor neuron disorders and nerve injury. Vagus nerve lesions, induced by crush or cut, result in a time-dependent Hsp27 up-regulation within distinct subpopulations of injured vagal and sensory neurons, often still present 90 days post-injury [25]. Additionally, Hsp27 exerts a long-term (5–6 months) neuroprotective effect following neonatal nerve crush in Hsp27-mice and moreover, the surviving motor neurons were able to regenerate, thus improving muscle functions such as contractile speed [26].

Hsp27 and neurite outgrowth

During development, the balance between cell death and differentiation is vital for optimal formation of the complex neuronal network. Hsp27 is associated with promoting cell survival and as such may be involved in regulating the decision of whether cells undergo apoptosis or differentiate during development. In addition to the wealth of evidence regarding the neuroprotective pro-survival effect of Hsp27, there is evidence to suggest Hsp27 is also a key protein in the process of neurite outgrowth. The transient expression of Hsp27, without a concomitant increase in other inducible Hsps, occurs during neurite development [27,28]. Hsp27 is also expressed in both transient and sustained patterns during brain development (reviewed in [29]). Overexpression of Hsp27 positively influences neurite outgrowth in DRG neurons, enhancing both length and branching, whilst Hsp27 knockdown reduced neurite complexity and length [30]. In addition, inhibition of Hsp27 phosphorylation generates an atypical growth pattern in adult DRG neurons [31], which may be linked to the ability of Hsp27 to regulate cytoskeletal stability. Hsp27 silencing also suppresses both pituitary adenylate cyclase-activating polypeptide 38 (PACAP38)- and Rin-mediated neurite outgrowth in PC6 cells (a subline of PC12), further supporting a role for Hsp27 in neurite outgrowth [32]. However, these conclusions are not supported by other cell lines. For example, recent findings from our group suggest that although Hsp27 is upregulated during nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells, it is not required, as neither overexpression of Hsp27, silencing, nor inhibition of phosphorylation affected neurite outgrowth [28]. These data are in agreement with another study in which Hsp27 expression was not detected during neuronal differentiation or neurite outgrowth in embryonic carcinoma P19 neurons, and antisense Hsp27 expression had no effect on these processes [33]. Furthermore, Hsp27 overexpression only slightly and transiently affected differentiation of rat olfactory neuroblasts, although overexpression inhibited cell death, suggesting that Hsp27 acts principally in a pro-survival capacity rather than as mediator of neuronal differentiation *per se* in these cells [27].

Thus, the relative importance of Hsp27 in neurite outgrowth appears to vary with cell type, possibly due to differing basal levels. Although Hsp27 can potently regulate the dynamics of various cytoskeletal elements, in particular actin microfilaments and tubulin [3], some cells may also possess adequate alternate mechanisms for cytoskeletal rearrangement in the absence of Hsp27. Alternatively, Hsp27 may predominantly provide a non-essential supportive role for other proteins during neurite outgrowth (in keeping with its chaperone function) as opposed to a more direct function in cytoskeletal remodelling. For instance, a physical relationship between Hsp27 and Akt has emerged, which in particular may be important for sustained Akt activity during neurite outgrowth in which it has a key role [34]. Hsp27 overexpression maintains Akt phosphorylation [35] and furthermore, an immuno-precipitable complex forms between Hsp27 and Akt in spinal motor neurons following nerve injury, indicating that these two proteins physically interact in neuronal cells [36]. Interestingly, following sciatic nerve axotomy in murine spinal motor neurons, the signalling pathways and expression of Hsp27 and Akt were elevated in the distal area of regenerating nerves, and these proteins formed a complex [37]. These data suggest a role for Hsp27 and Akt in motor neuron regeneration and support the idea of a close relationship between these proteins during neuronal differentiation.

Concluding remarks

The neuroprotective role of Hsp27 has been well-established and in recent years Hsp27 has also been implicated to positively influence neurite outgrowth. More data is now required, particularly from primary neuronal cells and *in vivo* models, in order to fully determine the significance of Hsp27 in neurite outgrowth. The inconsistency shown between different studies exploring the role of Hsp27 in neurite outgrowth could suggest that Hsp27 by itself is not always sufficient to affect neurite outgrowth. The complex milieu of cellular interactions, varying levels of Hsp27 and differences in the predominance of signalling pathways between cell types, may influence the effect of this protein on neurite outgrowth. In this regard, it would be interesting to determine whether enhanced neurite outgrowth occurs in primary neurons when co-expressing Hsp27 and Akt compared to either alone, for example. In conclusion, Hsp27 has significant therapeutic potential for neuronal regeneration, on account of its ability to both promote neuronal survival and positively influence neurite outgrowth.

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