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HSP27: Mechanisms of Cellular Protection Against Neuronal Injury

R. Anne Stetler^{1,2,3}, Armando P. Signore¹, Yanqin Gao², Guodong Cao^{1,2,3}, and Jun Chen^{1,2,3}

¹Department of Neurology and Center of Cerebrovascular Disease, Research University of Pittsburgh, Pittsburgh, PA 15261

²State Key Laboratory of Medical Neurobiology, Fudan University School of Medicine, Shanghai, China

³Geriatric Research, Educational and Clinical Center Veterans, Affairs Pittsburgh Health Care System, Pittsburgh, PA 15261

Abstract

The heat shock protein (HSP) family has long been associated with a generalized cellular stress response, particularly in terms of recognizing and chaperoning misfolded proteins. While HSPs in general appear to be protective, HSP27 has recently emerged as a particularly potent neuroprotectant in a number of diverse neurological disorders, ranging from ALS to stroke. Although its robust protective effect on a number of insults has been recognized, the mechanisms and regulation of HSP27's protective actions are still undergoing intense investigation. On the basis of recent studies, HSP27 appears to have a dynamic and diverse range of function in cellular survival. This review provides a forum to compare and contrast recent literature exploring the protective mechanism and regulation of HSP27, focusing on neurological disorders in particular, as they represent a range from protein aggregate-associated diseases to acute stress.

Keywords

HSP27; heat shock proteins; chaperones; ischemia; aggregates; injury

Introduction

The heat shock family of proteins consists of a group of heat-responsive cell stress proteins best characterized by their chaperone functions, especially following thermal stress. While heat shock proteins (HSPs) have been a regular focus of attention over the past four decades, recent experimental work has begun to emphasize the importance of novel HSPs, including HSP27, in protection against many cellular stressors. Despite the increased evidence for HSP27 involvement in suppression of cell death signaling, the mechanisms remain unclear, and may involve several points of action. Small HSPs (sHSPs), such as HSP27, appear distinct from other subgroups of HSPs in their activation and regulation. Transcriptional control, such as heat shock factor (HSF)-responsive transcriptional activation, is the primary hallmark of HSP induction following heat shock stress. In addition, HSP27 also undergoes several post-translational modifications, resulting in control of diverse functions. Site-specific

phosphorylation and differential oligomerization states have been observed following various stressors, and are associated with specific activity and survival roles of HSP27. The cellular signaling pathways of HSP27 regulating these modifications appear to involve archetypal phosphorylation cascades, such as MAPKAP and PRAK, and are observable within minutes following stress. The rapidity of post-translational modifications implicates HSP27 in the early response to stress, well before transcriptional activation.

In order to understand the implications of neuronal stress on HSP27 function, we will first discuss the various levels of molecular regulation that have recently been explored, with the premise that any of these mechanisms could be implemented in the pathogenesis of neurological disease. Current investigations into HSP27 as a protective molecule against neuronal injury will then be examined.

HSP27: Molecular characteristics and functional regulation

The heat shock family of proteins is highly conserved across species, identified primarily on the basis of their fast, typically protective response to cellular stressors. HSPs are rapidly induced at the transcriptional level following stress, but also undergo several post-translational modifications that alter their functional roles for use as immediate response elements. HSPs are divided into multiple subfamilies based on molecular weight, domain conservation and function. Small HSPs (sHSP), including HSP27, are widely expressed across species, and range in size from 15-42 kDa in the monomeric form. Although now classified as members of the HSP family, sHSPs were initially overlooked due to the wide variability in their N-terminal region. As typified by human HSP27, sHSPs have multiple domains and post-translational regulatory sites that are just now beginning to be investigated in relevance to stress response. We will first discuss the molecular regulation of sHSPs, using HSP27 as the prototypical HSP, and then explore the post-translational modifications that impact HSP27 cellular function.

HSP27 gene structure and transcriptional regulation

The HSP27 gene encompasses a 2.2-kb transcript that contains three exons encoding a 205-amino acid protein. General HSP family transcriptional activation has been best described as under the control of HSF transcriptional activators, which bind to consensus sequences within the promoter regions of HSP family genes. These consensus sequences are categorized as heat shock elements (HSE) and are highly conserved throughout species. The HSP27 gene contains two functional HSE binding sites (Fig. 1). The first of these occurs approximately -200 bp upstream of the first exon [1], whereas the second occurs within the first intron [2]. Recently, an atypical cAMP response element (CRE) was located at -678 bp upstream of the HSP27 exon 1 [3]. This atypical CRE sequence was recognized by both ATF3 and ATF5, where binding of these transcription factors induced transactivation of the HSP27 gene and was associated with cell survival against stress [3,4]. Several studies suggest that the specific trans-activation of HSP27 is stimulus dependent. During mitosis, HSF2 binds to the HSE of HSP27, whereas HSF1 appears to bind more robustly during hemin treatment [2,5]. Additionally, several HIF-1 binding sites were found to be necessary for endogenous upregulation of HSP27 in retinal neurons subjected to sublethal ischemic stress [6]. The transcriptional regulation of HSP27 appears to be under the control of multiple factors among various cell types and cellular states.

Differential expression of HSP27

A wide disparity in expression and induction of HSP27 has been observed amongst different cell types and stages. Thus, it is likely that transcriptional activation and subsequential protein expression of the HSP27 gene is dependent on multiple environmental trans-activating elements. This concept was illustrated in a study by Neininger et al., where the murine HSP25 (HSP25 is the murine HSP27) promoter derived from endogenously HSP25 expressing cells

was silent when overexpressed in cells which normally do not express HSP25 [7]. Consistently, the HSP27 promoter derived from cells devoid of HSP25 was transactivated when expressed in cells constitutively expressing HSP27 [7]. These results suggest that the constitutive expression of HSP27 is cell type dependent. In several cell types, HSP27 protein expression occurs just prior to differentiation, and has thus been postulated to be a predifferentiation marker [8]. Increased HSP27 protein expression is also highly correlated with tumorigenic phenotypes, and has been suggested to inhibit spontaneous apoptotic pathways. In postmitotic cell types, such as neurons, the expression level of HSP27 is relatively low, although certain cell subtypes, such as motor neurons, do express the protein constitutively in the post-mitotic state [9]. Given the variability among cell types in constitutive HSP27 expression, it is reasonable to consider levels of expression – either endogenous or induced – in the potential cellular stress response [10].

HSP27 protein structure and structural domains

The N-terminal domain of sHSPs is low in sequence homology across species, with the exception of a highly conserved hydrophobic motif (WDPF) (Fig. 2) [11,12]. This motif stabilizes the formation of the constitutive oligomeric state of HSP27 [13,14]. The functional significance of the multimeric versus monomeric HSP27 complex will be discussed below. With the exception of the WDPF motif, the sequence and length of the N-terminal region vary widely across species, and this region does not appear to contain highly ordered secondary domain structures [11]. However, the N-terminal possesses many of the regulatory post-translational modification sites discussed below.

While the amino acid sequence homology between species is low in the N-terminal region, the secondary structure of the C-terminal is highly conserved among the sHSPs, including the α -crystallins (Fig. 2) [1,15]. This region is a highly structured β -pleated sheet with several contact points allowing oligomer formation and stabilization [16]. Although the C-terminal end appears to associate and form oligomers [17], high molecular weight multimeric structures still require the presence of the N-terminal sequence. In addition to the well-structured β -pleated sheet domain, the C-terminal of sHSPs also contains a short, flexible extension that protrudes out of the domain [18,19]. The extension sequence is poorly conserved across sHSP family members, but most sHSPs, including HSP25 (the mouse homologue of HSP27), share similarity in this region, which has no defined secondary structural arrangement but is highly polar [19]. The inclusion of this flexible extension appears to increase HSP stability at higher temperatures, with the hydrophobic residues seemingly important for chaperone activity of an sHSP molecule with its substrate [20,21]. However, the extension itself does not appear to physically interact with the targeted substrate [20].

Post-translational modifications and the regulation of HSP27 function

Molecular regulation of the “classical” HSP chaperone function requires a series of molecular events in which an accessory HSP, such as HSP40, recognizes and binds the target protein, then promotes the hydrolysis of a different ATP-dependent HSP such as HSP70 (reviewed in [22]). However, the mechanism whereby HSP27 binds target proteins differs substantially from this classical chaperone model. Unlike HSP70, HSP27 does not contain an ATP binding site, and appears to function independently of ATP (Fig. 2). The regulation of HSP27 protein binding occurs at the level of phosphorylation and oligomerization. In addition to the functional domains evident in HSP27 species, the protein is highly enriched in serine residues. In human HSP27, three of these residues (amino acid positions 15, 78, and 82) appear to be critical for oligomerization regulation and hence for biological function [23].

Under native conditions, HSP27 typically exists as a high molecular weight multimeric structure and appears competent to form heterocomplexes with α -crystallins (Fig. 1). Upon

activation by signaling cascades, HSP27 is phosphorylated on multiple serine residues, resulting in reorganization of the complex into lower molecular weight structures [12,24]. The specific signaling cascade responsible for HSP27 phosphorylation remains unclear, and most likely is cell type specific. For example, in several cell lines PKC-beta/ERK1/2 and PKC-beta/p38 MAPK regulate HSP27 phosphorylation [25], but in pancreatic cancer lines PKD signaling is also involved [26]. The regulation of HSP27 phosphorylation has not been investigated in neurons or glia. Regardless of the cell-specific conditions leading to HSP27 phosphorylation, the final pathway leading to phosphorylation-dependent activation is the dissociation of HSP27 from high molecular weight multimers to lower ones. In addition, the expression and phosphorylation of HSPs themselves also provide feedback that influences HSF binding activity [27].

Negative regulation of HSP27 phosphorylation can occur either by the inhibition of upstream signaling pathways or via activation of phosphatases, leading to dephosphorylation and re-formation of the high molecular weight multimeric structures. In purified systems, PP2A, PP1 and PP2B were all capable of dephosphorylating HSP27 but with decreasing efficacy, respectively [28]. Consistently, the phosphatase PP2A appears to most efficiently decrease HSP27 phosphorylation and inhibit its function in cellular settings [29-31]. Due to the tissue- and developmentally-specific nature of HSP27 regulation, however, the exact mechanism of dephosphorylation is likely to be highly dependent on the cell type and model system studied.

Cellular stress and HSP27 cellular protective functions

In addition to multiple levels of regulation during basal cellular activity, HSP27 may mediate cell survival directly, including functions beyond the recognition and chaperoning of damaged or misfolded proteins. In several neuronal disease model systems including ischemia and neurodegeneration, HSP27 affects cell death signaling cascades, although the precise mechanistic controls are not well understood. Since HSP27 can bind to and affect protein function, one mechanism may be the interference with and inhibition of pro-death enzymes. Direct interaction between HSP27 and members of the apoptotic machinery leads to suppression of caspase activity, one of the major protease cell death effectors [32-35]. Despite the known targeting of caspase activation by HSP27, several other model systems have demonstrated robust protection by HSP27 in the absence of interaction with the apoptotic machinery [36]. Furthermore, high expression of HSP27 inhibits cytochrome c release and translocation of pro-death molecules to the mitochondria, indicating that the protective effects of HSP27 may target upstream of mitochondrial dysfunction and apoptosome formation in different cellular contexts [36,37]. Thus, in HSP27-mediated cellular survival, HSP27 has many cellular and molecular targets in addition to its traditional role as a chaperone. We will further discuss both the chaperone function and cell death signaling cascade interactions.

Chaperone function of HSP27

Heat shock proteins were originally described by their ability to bind proteins and aid in protein refolding following stress. While the mechanisms of protein binding have become increasingly clear, the physiological consequences of chaperone binding appear to differ significantly among various HSP family members. When dealing with rapidly induced proteins, HSP binding can lead to the rapid degradation of extensively misfolded or damaged protein products by targeting them for proteasomal degradation [38,39] or acting in the process of protein refolding [40]. Like most HSP members, the sHSPs are also capable of binding misfolded proteins. However, unlike the larger family members, the ability of sHSPs to refold proteins to their native conformation remains debatable. Despite its inability to refold denatured proteins, HSP27 colocalizes with stress granules and protein aggregates [41,42]. Currently, the binding of sHSPs is thought to lead to enhanced proteasomal degradation [43], decreased aggregation of misfolded proteins [44-47], or, as more recently demonstrated, inhibition of cell

death signaling (described below). Small HSPs bind to heat-denatured actin, leading to increased soluble complexes and thus preventing the formation of insoluble actin aggregates [47-49]. The ability of HSP27 to promote cell survival by limiting the levels of misfolded proteins may significantly contribute to regulating cell death.

The chaperone function of HSP27 occurs only when it forms large, unphosphorylated oligomers (Fig. 1) [24]. While the exact mechanisms remain unclear, several reports describe enhanced cellular protection associated with overexpression of non-phosphorylatable mutants of HSP27. Following thermal stress and in *in vitro* assays, non-phosphorylated HSP27 is capable of binding to eIF4G, leading to inhibition of cap-dependent protein translation [50]. In addition, transgenic overexpression of a non-phosphorylatable HSP27 was protective against cardiac ischemic/reperfusion injury [51], while phosphorylation of HSP27 following myocardial ischemia was associated with its translocation to the myofilament [52]. The induction of HSP27 phosphorylation and myofilament translocation were also observed in humans following cardioplegia and cardiopulmonary bypass [53], confirming animal models. While the consequences of myofilament translocation following ischemia are not well understood, the current hypothesis is that non-phosphorylated HSP27 could stabilize cytoskeletal components, such as actin, via its chaperone function [51].

HSP27 and suppression of cell death signaling

Recent evidence suggests that the phosphorylated form of HSP27 is a potent anti-apoptotic molecule that may directly interfere with cell death signaling pathways (Fig. 1) [54,55]. A number of studies have shown that overexpression of HSP27 reduces apoptotic cell death triggered by various stimuli, including hyperthermia, oxidative stress, staurosporine-induced apoptosis, ligation of the Fas/CD95 death receptor, and cytotoxic drugs [56-59]. Recently, HSP27 has been shown to inhibit apoptosis via the direct inhibition of caspase activation [34,60,61]. To this end, several studies suggest that HSP27 diminishes the activation of pro-caspase-9 by inhibiting interaction with cytochrome *c*, thus preventing the proper formation of the apoptosome complex [34,60,61]. Furthermore, HSP27 can inhibit caspase-3 activity by interacting with the pro-caspase-3 molecule [34,62]. These observations form a scenario in which HSP27 inhibits apoptosis by targeting the pathways downstream of the mitochondrial release of cytochrome *c*. However, this theory has been challenged by other studies showing little or no direct interaction between HSP27 and cytochrome *c* or caspase-3 [36,62]. Furthermore, recent experiments have suggested that HSP27 may instead inhibit apoptosis signals upstream of mitochondria. A number of these studies have shown that HSP27 overexpression results in reduced cytochrome *c* or Smac release from mitochondria in response to various stimuli [36,37,61,63]. The underlying mechanism for the inhibition of cytochrome *c* release by HSP27 is unknown. One possibility is that HSP27 may inhibit the intracellular redistribution of Bid, a pro-apoptotic member of the Bcl-2 family which, upon moving to mitochondria, induces cytochrome *c* release by stabilizing F-actin microfilaments [36]. However, this upstream pathway is unlikely to be the only one regulated by HSP27, as HSP27 was also found to inhibit cytochrome *c* release in conditions where F-actin is not altered during apoptosis [36]. More recent studies have demonstrated that HSP27 indirectly suppresses stress-induced Bax oligomerization and translocation to the mitochondria [37].

Other studies have proposed upstream pathways mediating HSP27 anti-apoptotic activity related to suppression of mitochondrial cell death signaling, including the demonstrated ability of HSP27 to activate the protective kinase Akt/PKB [64] or to inactivate the pro-death JNK pathway [65]. For example, in neutrophils, PC12, COS-7 and L929 cells, Akt physically binds HSP27, leading to the pro-survival activation of Akt [3,64,66-68]. Further investigation in neutrophils demonstrated that HSP27 promotes Akt activation by allowing interaction between the upstream activator MK2 and Akt [69]. Formation of the Akt-MK2 complex led to

phosphorylation of HSP27 on Ser-82, resulting in the dissociation of Akt and HSP27 [69,70]. During initiation of mitochondria-mediated cell death pathways, activation of Akt by HSP27 indirectly led to the suppression of Bax mitochondrial translocation and cell death in stressed renal epithelial cells via PI3K-dependent pathways [37]. While these data and others provide strong support for HSP27 mediating cellular neuroprotection via Akt activation, these studies used primarily tumorigenic cell lines, which have altered cell death pathways, or leukocytes, which are committed to the apoptotic cascade. In postmitotic cells such as neurons, the protective role Akt may play against neurological insults remains unclear, and the physical association of HSP27 with Akt has not been investigated in neuronal tissue. Further studies on potential interaction of HSP27 with upstream signaling cascades will likely yield exciting insight into the regulation of neuroprotection.

HSP27 in neuronal death

The expression of HSP27 in a neuronal context has been observed, both as constitutive expression and as induced expression in response to cellular stressors. HSP27 is differentially expressed in certain subclasses of neurons, where high constitutive expression is primarily limited to ganglia in the spinal cord and brain stem [71,72], and basal expression occurs in a distinct subclass of cerebellar Purkinje cells [73]. However, experimental evidence has formed a solid basis for the efficacy of HSP27 in decreasing neuronal injury in a variety of neuronal disease models (Table 1). Of particular interest is the observation that HSP27 can protect neuronal cells against certain apoptosis-inducing stimuli such as serum or nerve growth factor (NGF) withdrawal [74,75], whereas HSP70 and HSP90 do not [76,77]. While the mechanisms remain unclear and are primarily inferred from observations in non-neuronal systems, HSP27 may play a dynamic role in neuroprotection.

HSP27 and acute neurological injury

Although the constitutive expression of HSP27 in the brain is low, HSP27 expression can be induced in the central nervous system by several stressors, including hyperthermia [78], ischemia [79-82] and seizures [83]. With immunohistochemistry, expression of HSP27 appeared to be most robust in glial cells, and only in limited populations of neurons. Despite the questionable ability of neurons to normally induce HSP27 in response to stress, forced overexpression of HSP27 has been found to significantly augment neuronal survival in a number of contexts. Kalwy et al. reported that HSP27 delivered into the brain via a HSV vector could protect hippocampal neurons against kainate-induced apoptotic cell death [84]. A similar effect by HSP27 against kainate-induced neuronal apoptosis in the hippocampus was also observed in transgenic mice overexpressing the human HSP27 gene [85]. Increased endogenous expression of HSP27 was localized primarily in glial cells following cerebral ischemia [79,80,82,86]. Virally infused HSP27, but not HSP70, as well as transgenic overexpression of HSP27 significantly reduced ischemic lesion size following transient focal ischemia, a clinically relevant model of human stroke [87,88]. Systemic protein transduction with HSP27 effectively decreased hippocampal CA1 loss in a gerbil model of global ischemia [89].

A novel anti-apoptotic role for HSP27-induced neuroprotection following cerebral ischemia was described recently [88]. While reports in several toxicity contexts pinpointed HSP27's protective functions primarily downstream of mitochondrial cell death targeting, in particular inhibition of caspase activation [33,35], overexpression of HSP27 appeared to protect neurons upstream of mitochondrial signaling. HSP27 has been identified as a "scaffold" protein, capable of leading to the activation of prosurvival signaling molecules such as MK2 and Akt [33,35]. However, following neuronal ischemic conditions, HSP27 was also discovered to bind activated ASK1, a pro-death upstream signaling molecule, and inhibit its activity, leading to the suppression of JNK signaling and cell death [88]. Taken together, these observations

suggest that enhanced expression of HSP27 in brain may confer protection against acute neuronal cell death, and is attributable at least in part to HSP27's anti-apoptotic activity.

HSP27 and spinal nerve cell death

Although endogenous expression of HSP27 is limited in the brain, it exists constitutively in the spinal cord, including in dorsal root ganglion (DRG) neurons [71,72,90,91]. Dorsal root ganglion neurite growth and survival rely on and are enhanced by HSP27 expression [91-93]. Following peripheral nerve transection or heat shock, DRG neurons significantly upregulate HSP27 expression [74,90,91]. Ablation of HSP27 via siRNA knockdown resulted in heightened sensitivity to nerve injury in adult DRG cells [54] and failure of heat shock to induce protection against nerve growth factor (NGF) withdrawal [91]. Overexpression of HSP27 in DRG cultures or viral delivery *in vivo* decreased DRG cell death following NGF withdrawal [74], and afforded long-term protection of motor neurons following neonatal nerve crush [94]. Furthermore, *in vivo* delivery of phosphorylation-competent HSP27 provided protection to neonatal motor neurons, whereas a non-phosphorylatable mutant did not [54].

The mechanisms behind HSP27 neuroprotection of DRG neurons are unclear, but may be related to HSP27 interaction with the cytoskeleton. As mentioned earlier, HSP27 is capable of binding to and stabilizing actin [49]. When examined at the cellular level, HSP27 localized to the lamellipodia, filopodia and growth cones in branching and mature neurites in cultured DRG neurons, all regions with high amounts of actin filaments [92]. In support of the importance of HSP27 and actin interaction, inhibition of p38 MAPK blocked the phosphorylation of HSP27 in DRG neurons and disrupted neurite growth [92]. While these studies focus primarily on the function of HSP27 in cytoskeletal remodeling, the survival mechanisms of HSP27 may also include interaction with cell death signaling pathways. Further mechanistic studies should yield insights into the role HSP27 plays in neurite formation and protection against axonal injury.

A rare mutation linked to amyotrophic lateral sclerosis (ALS) was found in the HSE of HSP27 [95]. Further investigation has determined that this particular mutation leads to both decreased transcriptional activation of the HSP27 promoter and stress response. Transgenic overexpression of HSP27 significantly delayed motor decline and increased the survival of motor neurons in a mouse model of ALS (SOD1(G93A)), but did not provide long-term protection [96,97]. Interestingly, in HSP27/SOD1(G93A) double transgenic mice, HSP27 protein was downregulated during the later stages of the disease, indicating that the mutant SOD1 interfered with HSP27 translation or protein stabilization. Further experiments using protein transduction in later disease stages of ALS models may help to address these issues. Despite these *in vivo* studies, other reports using mutant SOD1-expressing neuroblastoma cultures did not find a role for HSP27, although heat shock was protective in the model [98]. While the data linking HSP27 expression and ALS are correlative in nature, HSP27 appears to be important in the development and survival of DRG neurons, and its absence may contribute to the selective loss of motor neuronal populations.

HSP27 and aggregate-associated neurodegenerative diseases

In multiple non-neuronal systems, HSP27 was found to decrease protein aggregate formation. The binding of sHSPs to heat-denatured actin decreased formation of insoluble aggregates [47-49]. The relevance of HSPs and denatured protein binding in neurological disorders has been under considerable debate. The implications of HSP27 interactions with actin are currently being investigated in terms of cytoskeletal remodeling during synaptogenesis and dendritic remodeling as well as in aggregate disease models, such as Huntington's disease (HD). Despite the biochemical evidence for increased actin solubilization and decreased aggregate formation following thermal stress in the presence of HSP27, no conclusive studies have defined the role HSP27 plays in aggregate-associated neurodegeneration. Endogenous

upregulation of HSP27 in chronic HD models, such as the R2/6 transgenic mouse, failed to occur [99,100], and transgenic overexpression of HSP27 in the same model did not decrease aggregate formation or disease progression [100]. Conversely, others have observed that viral co-expression of HSP27 with mutant huntingtin decreased cell death in both *in vitro* and *in vivo* HD models with no effect on total aggregate formation [101,102], suggesting that variation in model systems or transgene delivery may affect the neuroprotection afforded by HSP27 in aggregate diseases. Overexpression of phospho-mimetic HSP27 lost protective effects against poly(Q) overexpression [102], suggesting that the protection against cell death is independent of the traditional chaperone function described above. In the same *in vitro* model, deletion of the cytochrome c binding site was still effective at inhibiting cell death [102]. These data are consistent with a possible role for HSP27 cellular protection upstream of mitochondrial cell death signaling. Overexpression of HSP27 both *in vitro* and *in vivo* was able to protect cells and shift aggregate formation from large nuclear inclusions to smaller non-nuclear inclusions [101], indicating that HSP27 may increase aggregate solubilization and sequestration in poly (Q) repeat diseases.

In support of a differential role for small HSPs among aggregate-associated neurodegenerative diseases, endogenous HSP27 upregulation was observed in a transgenic Parkinson's disease model (α -synuclein A53T) [99], in viral overexpression of α -synuclein [103] and in human dementia with Lewy bodies [104], and elevated levels of HSP27 conferred protection against apoptosis induced by α -synuclein expression [54,104,105]. In Alzheimer's disease (AD) models, HSP27 bound to A β 1-40, and decreased aggregation and cytotoxicity in cerebrovascular cultures [106]. Small HSP proteins also decreased A β aggregation and toxicity in SH-SY5Y cells [107]. Increased expression of HSP27 was observed in AD brain [108], in both senile plaques and associated astrocytes [109]. A positive correlation was found in human neurofibrillary tangle pathology between soluble tau and chaperones, including HSP27 [110]. Linking HSP27 and neuronal aggregates may occur via functional bridging between HSP27 and ubiquitin moieties, which may result in the stabilization and diminished toxicity of protein aggregates [111]. Many of these studies are correlative and relatively lacking in functional analysis; thus, the role of sHSPs in chronic neurodegenerative diseases associated with aggregates remains largely unknown.

Therapeutic approaches

Several recent papers indicate that targeting HSP27 may be a useful therapeutic in the treatment of cellular insults. In terms of non-neuronal cells, recent clinical trials in China have emerged supporting the use of bicyclol in the treatment of hepatitis B and C [112]. Bicyclol has been best characterized to induce expression of HSP27 and HSP70 in hepatic cells, and may thus promote survival of hepatocytes via anti-apoptotic functions against viral hepatitis infections [113]. In support of a cell survival role, higher HSP27 expression has also been associated with poorer prognosis in several specific cancers as well as with chemoresistance in breast cancer and leukemia [114]. However, the use of HSP27 as a diagnostic and prognostic marker for cancer progression is primarily correlative, and has not yet been conclusively determined to underlie mechanistic or causal events.

Transgenic overexpression or viral or protein transduction delivery HSP27 provided robust neuroprotection against myocardial ischemic/reperfusion injury [51], focal and global cerebral ischemia [87-89], kainic acid toxicity [84], sensory and motor injury-induced death [54], NGF-withdrawal or ischemic stress in DRG neurons [75] and several protein aggregate models [101]. However, increased expression of HSP27 has also been correlated with several human gliomas [115,116], and may contribute to tumor progression in the presence of oncogenic factors [117]. HSP27 may also confer chemoresistance via suppression of apoptotic pathways [118]. Interestingly, transgenic HSP27 mouse have not been reported to have increased

spontaneous tumor formations (unpublished observations). While targeting HSP27 as a neuroprotective therapeutic may incur the risk of increased susceptibility to tumour formation or unresponsiveness to chemotherapy, treatment against acute neurological injury using shortterm therapies would hopefully circumvent or reduce these risks. The specificity of protection may lie in both the pathogenesis and the cell-specific population. Thus, pinpointing the mechanism and regulation of HSP27 may provide a molecular basis for pharmacological agents based on the transient survival mechanisms of HSP27.

Concluding remarks

Despite the historical focus on the “classical” HSP family members, HSP27 and related small HSP members have recently emerged as highly versatile and effective protective proteins under a variety of stressors. The regulation of HSP27 function is distinct from classical members of the HSP family. Both oligomerization and phosphorylation play critical roles in determining functional roles, in addition to transcriptional and potential translational controls that have not yet been fully explored. While little evidence suggests that neurons themselves are capable of inducing high amounts of HSP27 protein following cellular stress (with the exception of DRGs), substantial literature indicates that forced overexpression of HSP27 protein improves physiological outcomes against a variety of neurological insults. Much work is currently in progress to further elucidate the mechanism of neuroprotection, as well as the endogenous cellular regulation of this versatile molecule.

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List of Abbreviations

HSP	heat shock protein
sHSP	small heat shock protein
HSF	heat shock factor
MAPKAP	mitogen-activated protein kinase-activated protein
PRAK	p38 regulated/activated kinase, HSE: heat shock element
PKC	protein kinase C
ERK	extracellular regulated kinase
MAPK	mitogen-activated protein kinase
PP2A, PP1, PP2B	protein phosphatase 2A, 1 and 2B
PKB	protein kinase B
JNK	c-jun N-terminal kinase
MK2	MAPKAP kinase 2
DRG	dorsal root ganglion
siRNA	short interference ribonucleic acid

NGF	nerve growth factor
SOD1	superoxide dismutase-1
ALS	amyotrophic lateral sclerosis
HD	Huntington's disease
AD	Alzheimer's disease
Aβ	amyloid beta

Figure 1. Dynamic regulation of HSP27 cellular functions

HSP27 expression can be rapidly induced by a variety of factors, including stress, mitosis, or environmental changes, via several transactivation domains. Once transcribed, the nonphosphorylated HSP27 protein product forms large oligomeric structures associated with chaperone activity. Upon different stimuli, the N-terminal region may be phosphorylated, leading to the disruption of the high molecular weight structure into lower molecular weight structures. HSP27 has been associated with interference in cell death signaling, including binding caspase-3, cytochrome c, or upstream signaling kinases.

Figure 2. Functional domains of small heat shock proteins

HSP27 is comprised of a well-structured C-terminal domain containing β -pleated sheets functional in protein-protein interactions. The structure of the C-terminal domain is conserved among small heat shock family members. The N-terminal domain contains several serines susceptible to phosphorylation, allowing for the reconfiguration of oligomeric structure and function. The domains of the small heat shock proteins differ substantially from those of other members of the heat shock protein superfamily. For example, HSP70 contains an ATPase domain, whereas the small heat shock proteins do not require ATPase activity for function.

Table 1

Effects of HSP27 alterations in neurological injuries

Cell Type	Injury/Model	HSP27 modulation	Effect	Mechanism	Refs
Brain	Cerebral ischemia (focal)	Overexpression (viral, transgenic)	Protective	Inhibition of ASK1	[87,88]
Brain/hippocampal	Kainate-induced seizures	Overexpression (viral, transgenic)	Protective	Unknown	[84,85]
Primary dopaminergic cells	Cerebral ischemia (global)	Peptide-transduction	Protective	Unknown	[89]
Brain, nonneuronal cells	α -synuclein	Overexpression	Protective	Unknown	[104,105]
	HD, polyglutamine toxicity	Overexpression (viral)	Decreased cell death, no effect on number of aggregates	Possibly not chaperone, but upstream of mitochondrial	[101,102]
Brain	HD (R2/6)	Overexpression (transgenic)	No effect	---	[101]
Neuronal cells (SHSY5Y)	AD (A β toxicity)	Overexpression	Decreased toxicity and aggregates	Bridge with ubiquitin?	[111]
Spinal	ALS (SOD1(G93A))	Overexpression (transgenic)	Delayed motor effects, increased motoneuron survival, but not longterm	Unknown	[97]
Spinal	Nerve crush	Overexpression (transgenic)	Decreased cell death, regeneration, function	Unknown	[94]
	Neurite growth/survival	Endogenous, enhanced	Protective	Unknown	[91-93]
	Neonatal nerve crush	Overexpression (viral)	Protective	Actin stabilization?	[92,94]
Dorsal root ganglion	NGF withdrawal	Overexpression (viral, heat shock)	Protective	Unknown	[67,74,91]