

Heat Shock Response Modulators as Therapeutic Tools for Diseases of Protein Conformation*

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The disruption of protein folding quality control results in the accumulation of non-native protein species that can form oligomers, aggregates, and inclusions indicative of neurodegenerative disease. Likewise for over 100 other human diseases of protein conformation, a common feature may be the formation of off-pathway folding intermediates that are unstable, self-associate, and with time lead to a chronic imbalance in protein homeostasis with deleterious consequences on cellular function. This has led to a hypothesis that enhancement of components of the cellular quality control machinery, specifically the levels and activities of molecular chaperones, suppress aggregation and toxicity phenotypes to allow cellular function to be restored. This review addresses the regulation of molecular chaperones and components of protein homeostasis by heat shock transcription factor 1 (HSF1), the master stress-inducible regulator, and our current understanding of pharmacologically active small molecule regulators of the heat shock response as a therapeutic strategy for protein conformational diseases.

Heat Shock Proteins: Functions in Normal and Disease States

The heat shock response (HSR)² is an ordered genetic response to diverse environmental and physiological stressors that results in the immediate induction of genes encoding molecular chaperones, proteases, and other proteins essential for protection and recovery from cellular damage associated with the expression of misfolded proteins (Fig. 1). The list of “stressors” that activate transcription of these heat shock genes is large and includes various acute and chronic conditions such as elevated temperatures, heavy metals, small molecule chemical toxicants, infection, and oxidative stress. Mutations and environmental influences including inflammation, ischemia, tissue wounding and repair, cancer, and neurodegenerative diseases are also associated with the aberrant expression of heat shock proteins.

The heat shock gene superfamily is organized by molecular size and functional class, including the Hsp100, Hsp90, Hsp70, Hsp60, Hsp40 (J-domain proteins), and small heat shock protein (sHsp) families. Many of these proteins function as molecular chaperones to guide conformational states critical in the synthesis, folding, translocation, assembly, and degradation of proteins (1, 2). As chaperones are also central components in many signal transduction pathways (3), the proper regulation of chaperone expression is critical to the health of the cell.

Cytoprotection—Heat shock proteins function at the cellular level to protect cells against a wide array of acute and chronic stress conditions. Subacute activation of the HSR results in stress tolerance and cytoprotection against

otherwise lethal exposures to stress-induced molecular damage. This protective and adaptive response, also known as induced thermotolerance, ensures that the cell responds rapidly to repeated sub-acute challenges by diverse conditions of cell stress (4). The ability of heat shock proteins to protect against cell damage extends to pathophysiology and severe trauma such as ischemic insults to the heart and brain (5, 6). The induction of the HSR, therefore, may have broad therapeutic benefits in the treatment of various types of tissue trauma and disease.

Neurodegenerative Disorders—An increasing number of neurodegenerative disorders are associated with the expression of misfolded proteins and the appearance of non-native structures described as oligomers, protein aggregates, fibrils, or plaques. These include inherited disorders caused by CAG/polyglutamine expansion as occurs in Huntington disease, Kennedy disease, spinocerebellar ataxias, and other related neurodegenerative diseases including Parkinson disease, amyotrophic lateral sclerosis (ALS), and Alzheimer disease (7). The HSR and heat shock proteins have been implicated in many of these neurodegenerative diseases based on the association of chaperones with intracellular aggregates. For example, live cell imaging experiments show that Hsp70 associates transiently with huntingtin aggregates, with association-dissociation properties identical to chaperone interactions with unfolded polypeptides (8). This suggests that these chaperone interactions may reflect the efforts of Hsp70 to direct the unfolding and dissociation of substrates from the aggregate. Moreover, overexpression of the Hsp70 chaperone network suppresses aggregate formation and/or cellular toxicity. Collectively, these observations have led to the hypothesis that the elevated levels of heat shock proteins reduce or dampen aggregate formation and cellular degeneration (9, 10).

Neurodegenerative diseases often occur later in life when heat shock genes seem to be induced poorly (11, 12). The heat shock response has recently been implicated in the regulation of longevity in *Caenorhabditis elegans* in a pathway that overlaps with the insulin signaling pathway (13, 14). Reduction of heat shock transcription factor HSF1 levels cause a decreased life span in *C. elegans*, similar to life span effects observed in mutants of Daf-16, a FOXO transcription factor in the insulin signaling pathway. Daf-16 and HSF1 share a subset of downstream target genes, including sHsps. RNA interference experiments show that a decrease in sHsps and other Hsps leads to a decrease in longevity (13, 14). Therefore, in addition to the prevention of diseases of aging, increased levels of heat shock proteins may lead to increases in life span.

Signal Transduction and Cancer—Hsp90 and Hsp70 interact with and regulate many transcription factors, signaling molecules and kinases, including NF- κ B, p53, v-Src, Raf1, Akt, and steroid hormone receptors (3). Tumor cells typically express higher levels of heat shock proteins compared with non-transformed cells, leading to the suggestion that the aberrant expression of chaperones is associated with the tumorigenic state (15). Depletion of Hsp90 function by the inhibitory compound geldanamycin, or of Hsp70 levels by antisense RNAs in transformed cells, leads to cell growth arrest or cell death (16, 17). This has led to an intriguing proposition that tumor cells are dependent on elevated levels of Hsps, perhaps as a generalized mechanism to suppress cumulative mutations that would otherwise result in the expression of deleterious proteins. The chronic up-regulation of heat shock proteins could also promote cancer by the anti-apoptotic functions demonstrated for all chaperones. Hsp70, Hsp40, Hsp27, and Hsp90 act at multiple points in apoptosis, including inhibition of c-Jun NH₂-terminal kinase (JNK) activation, prevention of cytochrome *c* release, regulation of the apoptosome, prevention of lysosomal membrane permeabilization, and prevention of caspase activation (18). Therefore, compounds that down-regulate the HSR and chaperone levels, when given in combination with chemotherapy, may prove beneficial for cancer treatment.

Regulation of the Heat Shock Response and HSF1

The heat shock response is regulated at the transcriptional level by the activities of a family of heat shock transcription factors (HSF) (19). Of the three human HSF genes, *HSF1*, *-2*, and *-4*, HSF1 is the best characterized and essential for the heat shock response. The DNA binding and transcriptional activities of HSF1 are stress-inducibly regulated by a multistep activation pathway. HSF1 exists normally in a negatively regulated state as an inert monomer in either the cytoplasmic or nuclear compartments. Upon exposure to a variety of stresses, HSF1 is derepressed, trimerizes, and accumulates in the nucleus. HSF1 trimers bind with high affinity to the heat shock elements (HSEs) consisting of multiple contiguous inverted repeats of the pentamer sequence nGAAn located in the promoter regions of target genes. The HSF1-regulated

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² The abbreviations used are: HSR, heat shock response; HSF1, heat shock transcription factor 1; Hsp, heat shock protein; sHsp, small heat shock protein; ALS, amyotrophic lateral sclerosis; HSE, heat shock element; NSAID, non-steroidal anti-inflammatory drug; DCIC, 3,4-dichloroisocoumarin; TPCK, *N*- α -tosyl-L-phenylalanine chloromethyl ketone; TLCK, *N*- α -tosyl-L-lysine chloromethyl ketone; MG132, carbobenzoxy-L-leucyl-L-leucyl-leucinal; 17-AAG, 17-N-allylamino-17-demethoxygeldanamycin.

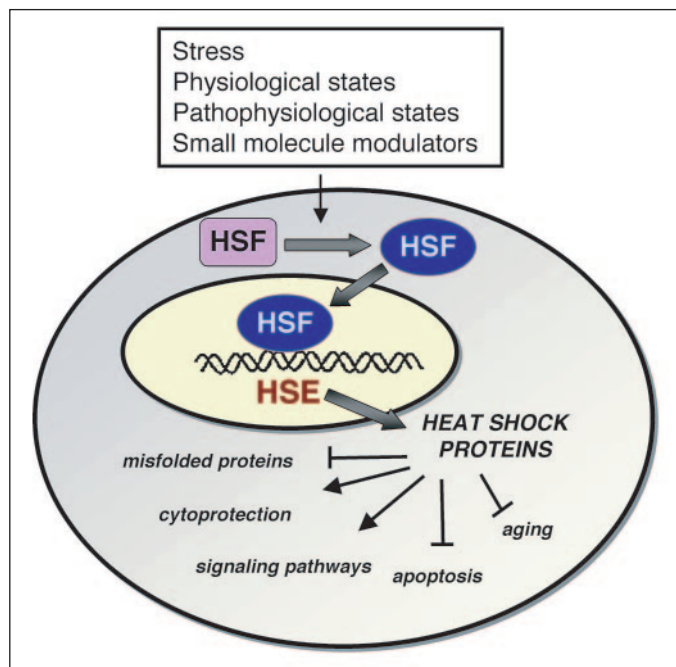


FIGURE 1. **The cell stress response.** Diverse stressors that activate the heat shock response are indicated. Upon activation, the heat shock transcription factor HSF rapidly induces expression of heat shock proteins, which have roles in preventing protein misfolding, inducing cytoprotection, promoting signaling pathways necessary for cell growth, protecting cells from apoptosis, and inhibiting aging.

genes encoding Hsp70, Hsp90, and sHsps are also transcribed constitutively due to multiple basal factors or binding of low levels of HSF1.

Although the overwhelming data in the literature support the proximal stress signal for the HSR as the appearance of misfolded proteins and an imbalance of protein homeostasis, other recent observations point to an involvement of additional signaling pathways. Alterations in intracellular redox status caused by changes in temperature or other stresses have been suggested to be involved in the activation of mammalian HSF1 (20). Additionally, recent work has indicated a role for stress-specific pathways in HSF1 activation (21, 22). Studies in *Saccharomyces cerevisiae* show that two distinct activators of HSF could work through different mechanisms: while HSF-dependent CUP1 expression during glucose starvation requires the Snf1 kinase, HSF-dependent CUP1 activation by heat shock is Snf1-independent (21). A study comparing heat shock and sodium arsenite induction of histone modifications on the murine Hsp70 promoter also shows differential kinase requirements. Sodium arsenite, but not heat shock, induces the phosphorylation of histone H3 in a p38 kinase-dependent manner that is required for Hsp70 transcription (22). Therefore, while many inducers of the HSR may function through a protein unfolding mechanism, these observations suggest that other inducers may work through distinct mechanisms.

HSF1 is post-translationally modified by phosphorylation and sumoylation to achieve further dynamic range (23). Sites of constitutive HSF1 phosphorylation (Ser³⁰³, Ser³⁰⁷, and Ser³⁰⁸) appear to be important for the negative regulation of HSF1, whereas sites of inducible phosphorylation (Ser²³⁰, Ser³²⁶, and Ser⁴¹⁹) promote HSF1 activity (24–26). The balance of kinase and phosphatase activities acting on HSF1 is of fundamental importance to regulation of the heat shock response, as suggested by mathematical modeling (27). While HSF1 is sumoylated on lysine 298 in a manner that requires phosphorylation on serines 303 and 307 (28, 29), the role of this modification on HSF1 activity is still unclear.

HSF1 activity in human cells is further regulated by an intranuclear equilibrium between HSEs in the promoters of HSF1-responsive genes and on chromosome 9 where the majority of HSF1 accumulates at a chromosomal site rich in satellite III repetitive sequences (30). These repetitive sequences are comprised of thousands of copies of redundant, degenerate HSEs that are actively transcribed, although the function of these transcripts and their association with the heat shock response is unknown (31).

HSF1 is negatively regulated by feedback control through interaction with Hsp70 and Hsp90 (32). In cells expressing high levels of these chaperones, the inducible expression of heat shock genes is attenuated. Thus, the HSR involves

TABLE ONE		
Compounds that modulate HSF1 activity		
Compound	Effective concentration	Selected Refs.
Activators		
Protein synthesis inhibitors:		
Puromycin	36 μM	33, 34
Azetidone	5 mM	33
Proteasome inhibitors:		
MG132	10 μM	35
Lactacystin	10–20 μM	35
Serine protease inhibitors:		
DCIC	5 μM	36
TPCK	50 μM	36
TLCK	75 μM	36
Hsp90 inhibitors:		
Radicicol	1–10 μM	40, 43
Geldanamycin	0.1–1 μM	39, 40, 42, 43
17-AAG	0.1–1 μM	40
Inflammatory mediators:		
Cyclopentenone prostaglandins	12 μM	46, 47
Arachidonate	20 μM	44
Phospholipase A ₂	2 μM	45
Triterpenoids:		
Celastrol	1–10 μM	49
Co-inducers		
NSAIDs:		
Sodium salicylate	20 mM	50
Indomethacin	1 mM	51
Hydroxylamine derivatives:		
Bimoclolmol	1–10 μM	53, 55
Arimoclolmol	10 mg/kg	54
Inhibitors		
Flavonoids:		
Quercetin	100 μM	56
Benzylidene lactam compound:		
KNK437	100 μM	57

a multistep pathway with both positive and negative regulators, each of which could be small molecule targets.

Small Molecule Regulators of the Heat Shock Response

Interest in the HSR and chaperones as potential targets for therapeutics has spurred investigations on small molecule regulators of HSF1. Therapeutically active small molecules that regulate HSF1 or modulate chaperone activities could benefit diseases that have in common alterations in protein conformation that cause an imbalance in protein homeostasis. The classes of small molecules that modulate the HSR are represented by a diverse set of chemically unrelated compounds consistent with the various environmental and physiological signaling pathways that induce the HSR (TABLE ONE).

Activators—Among the initially identified chemical inducers of the HSR are the protein synthesis inhibitor puromycin and amino acid analogue azetidone (33, 34). As this class of compounds results in the expression of prematurely terminated nascent chains or amino acid analogue-containing misfolded proteins, the appearance of misfolded proteins was subsequently proposed as a signal for induction of the HSR. Additional support for protein misfolding as the stress signal came from complementary observations that inhibitors of protein degradation, including the proteasome inhibitors MG132 and lactacystin and the serine protease inhibitors DCIC, TPCK, and TLCK, all induce HSF1 DNA binding, hyperphosphorylation, and the expression of heat shock proteins (35, 36). Presumably HSR activation prevents the accumulation of these degradation-targeted misfolded substrates to minimize their accumulation as oligomers and aggregates.

Another class of activators of the HSR is the fungal antibiotic radicicol and the benzoquinone ansamycin geldanamycin that are inhibitors of Hsp90. Radi-

cicol and geldanamycin were initially identified in screens for anti-cancer drugs and subsequently developed for their potential as cancer therapies (37). 17-AAG, a related analogue of geldanamycin, has completed multi-institution phase I clinical trials and phase II trials are underway (38). Although radicicol and geldanamycin are structurally distinct, both compounds bind to the ATP binding domain of Hsp90 and inhibit the ATPase. Down-regulation of Hsp90 by this class of compounds derepresses HSF1 activity leading to induction of the HSR and the expression of molecular chaperones (39, 40). These results complement observations from genetic studies in *S. cerevisiae* on the role of Hsp90 as a negative regulator of the HSR (41). Hsp90 inhibitors are likely to have a multitude of cellular effects, including altering protein homeostasis and interfering with autoregulation of HSF1 activity. Radicicol and geldanamycin inhibit the formation of huntingtin aggregates in both a mammalian cell culture model and in a mouse brain slice culture assay, perhaps due to elevated chaperone expression (42, 43).

Many molecules that regulate inflammation can activate the HSR by induction of HSF1, providing a potential link between the HSR and inflammation. The inflammatory response is induced by a signaling cascade involving arachidonic acid release and metabolism. Phospholipase A₂, which stimulates arachidonic acid release, and arachidonate itself both activate the HSR (44, 45). The cyclopentenone prostaglandins PGA₁, PGA₂, and PGJ₂, which are produced downstream of arachidonic acid release, also lead to activation of HSF1 (46, 47). This class of prostaglandin contains highly reactive unsaturated carbonyl moieties that readily adduct thiol groups in proteins. Therefore, the mechanism of HSR activation by this class of molecules may also be through alterations in protein homeostasis.

The triterpenoid celastrol and certain structural analogues represent a new class of heat shock inducers that were identified from a consortium screen for compounds that may be beneficial in treating Huntington disease and ALS (48). Celastrol, a natural product derived from the *Celastraceae* family of plants, potently activates the HSR in mammalian cells (48, 49). Unlike other compounds that activate the HSR with delayed kinetics of induction, celastrol induces HSF1 rapidly with kinetics similar to those observed for heat shock, leading to the complete expression of chaperone genes. The rapid kinetics and an EC₅₀ in the micromolar range may make celastrol or celastrol derivatives a promising candidate for further development as a therapeutic (49).

Co-inducers—Non-steroidal anti-inflammatory drugs (NSAIDs) are an example of a class of compounds that can co-induce the HSR. These compounds partially activate components of the HSR and often work in conjunction with a secondary stress signal for full induction of Hsp70 expression. This class of co-inducers is best represented by the NSAID sodium salicylate that induces HSF1 DNA binding by converting HSF1 from the monomeric to the trimeric state but does not induce HSF1 hyperphosphorylation and heat shock gene transcription (50). Sodium salicylate, however, reduces the temperature required for the HSR into the range attained by febrile conditions. In contrast, other NSAIDs such as indomethacin induce both HSF1 DNA binding and hyperphosphorylation of HSF1 (50, 51). Long term use of NSAIDs for arthritis and other inflammatory diseases is associated with better neurodegenerative disease outcome (52), suggesting a link between the continual up-regulation of the HSR and decreased neurodegenerative disease pathogenesis.

Other compounds suggested to co-induce the HSR are the hydroxylamine derivatives bimoclolol and arimoclolol. Both compounds appear to decrease the temperature threshold for induction of Hsp70, and a potential mechanism is associated with changes in fluidity of the cell membrane (53–55). Bimoclolol acts as a therapeutic for ischemia and wound healing (53), while arimoclolol delays ALS progression in a mouse model (54).

Inhibitors—Only a few compounds have HSR-inhibitory activities. The flavonoid quercetin and the benzylidene lactam compound KNK437 inhibit the HSR, although the targets and mechanisms of action have not been characterized (56, 57). Quercetin dampens multiple aspects of the HSR including reduced HSF1 DNA binding, HSF1 hyperphosphorylation, and Hsp70 expression (56). As inhibition of the levels of chaperones could have a beneficial consequence for cancer therapy, further investigation into HSR inhibitors is warranted.

Prospectus

The HSR offers great potential as a therapeutic target given the diverse array of human disease pathologies associated with trauma, stress, and the expression of damaged and misfolded proteins. While a number of small molecule regulators of the HSR have already been identified, only celastrol resulted from a high throughput screen. The identification of new small molecule regulators of the HSR together with mechanistic studies on many of the existing compounds will also prove invaluable as tools to dissect further the multistep

pathway of the HSR. With the discovery of the molecular targets of these compounds, it should be possible to generate specific activators or inhibitors with increased potency and selectivity. Given the pleiotropic functions of HSF and the Hsps, a major challenge will be developing activators and inhibitors of the HSR that alter the expression of specific chaperones and heat shock-regulated genes with some degree of tissue specificity.

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REFERENCES

- Hartl, F. U. (1996) *Nature* **381**, 571–579
- Bukau, B., and Horwich, A. L. (1998) *Cell* **92**, 351–366
- Pratt, W. B., and Toft, D. O. (2003) *Exp. Biol. Med. (Maywood)* **228**, 111–133
- Landry, J., Bernier, D., Chretien, P., Nicole, L. M., Tanguay, R. M., and Marceau, N. (1982) *Cancer Res.* **42**, 2457–2461
- Christians, E. S., Yan, L. J., and Benjamin, I. J. (2002) *Crit. Care Med.* **30**, S43–S50
- Mestrlil, R. (2005) *Methods* **35**, 165–169
- Kakizuka, A. (1998) *Trends Genet.* **14**, 396–402
- Kim, S., Nollen, E. A., Kitagawa, K., Bindokas, V. P., and Morimoto, R. I. (2002) *Nat. Cell Biol.* **4**, 826–831
- Warrick, J. M., Chan, H. Y., Gray-Board, G. L., Chai, Y., Paulson, H. L., and Bonini, N. M. (1999) *Nat. Genet.* **23**, 425–428
- Krobitch, S., and Lindquist, S. (2000) *Proc. Natl. Acad. Sci. U. S. A.* **97**, 1589–1594
- Soti, C., and Csermely, P. (2003) *Exp. Gerontol.* **38**, 1037–1040
- Shamovsky, I., and Gershon, D. (2004) *Mech. Ageing Dev.* **125**, 767–775
- Hsu, A. L., Murphy, C. T., and Kenyon, C. (2003) *Science* **300**, 1142–1145
- Morley, J. F., and Morimoto, R. I. (2004) *Mol. Biol. Cell* **15**, 657–664
- Jaattela, M. (1999) *Exp. Cell Res.* **248**, 30–43
- Nylandsted, J., Rohde, M., Brand, K., Bastholm, L., Elling, F., and Jaattela, M. (2000) *Proc. Natl. Acad. Sci. U. S. A.* **97**, 7871–7876
- Whitesell, L., Mimnaugh, E. G., De Costa, B., Myers, C. E., and Neckers, L. M. (1994) *Proc. Natl. Acad. Sci. U. S. A.* **91**, 8324–8328
- Mosser, D. D., and Morimoto, R. I. (2004) *Oncogene* **23**, 2907–2918
- Pirkkala, L., Nykanen, P., and Sistonen, L. (2001) *FASEB J.* **15**, 1118–1131
- Ahn, S. G., and Thiele, D. J. (2003) *Genes Dev.* **17**, 516–528
- Hahn, J. S., and Thiele, D. J. (2004) *J. Biol. Chem.* **279**, 5169–5176
- Thomson, S., Hollis, A., Hazzalin, C. A., and Mahadevan, L. C. (2004) *Mol. Cell* **15**, 585–594
- Holmberg, C. I., Tran, S. E., Eriksson, J. E., and Sistonen, L. (2002) *Trends Biochem. Sci.* **27**, 619–627
- Holmberg, C. I., Hietakangas, V., Mikhailov, A., Rantanen, J. O., Kallio, M., Meinander, A., Hellman, J., Morrice, N., MacKintosh, C., Morimoto, R. I., Eriksson, J. E., and Sistonen, L. (2001) *EMBO J.* **20**, 3800–3810
- Kim, S. A., Yoon, J. H., Lee, S. H., and Ahn, S. G. (2005) *J. Biol. Chem.* **280**, 12653–12657
- Guettouche, T., Boellmann, F., Lane, W. S., and Voellmy, R. (2005) *BMC Biochem.* **6**, 4
- Rieger, T. R., Morimoto, R. I., and Hatzimanikatis, V. (2005) *Biophys. J.* **88**, 1646–1658
- Hong, Y., Rogers, R., Matunis, M. J., Mayhew, C. N., Goodson, M. L., Park-Sarge, O. K., and Sarge, K. D. (2001) *J. Biol. Chem.* **276**, 40263–40267
- Hietakangas, V., Ahlskog, J. K., Jakobsson, A. M., Helleusuo, M., Sahlberg, N. M., Holmberg, C. I., Mikhailov, A., Palvimo, J. J., Pirkkala, L., and Sistonen, L. (2003) *Mol. Cell Biol.* **23**, 2953–2968
- Jolly, C., Morimoto, R., Robert-Nicoud, M., and Vourc'h, C. (1997) *J. Cell Sci.* **110**, 2935–2941
- Jolly, C., Metz, A., Govin, J., Vigneron, M., Turner, B. M., Khochin, S., and Vourc'h, C. (2004) *J. Cell Biol.* **164**, 25–33
- Morimoto, R. I. (1998) *Genes Dev.* **12**, 3788–3796
- Hightower, L. E. (1980) *J. Cell. Physiol.* **102**, 407–427
- Lee, Y. J., and Dewey, W. C. (1987) *J. Cell. Physiol.* **132**, 1–11
- Holmberg, C. I., Illman, S. A., Kallio, M., Mikhailov, A., and Sistonen, L. (2000) *Cell Stress Chaperones* **5**, 219–228
- Rossi, A., Elia, G., and Santoro, M. G. (1998) *J. Biol. Chem.* **273**, 16446–16452
- Whitesell, L., Bagatell, R., and Falsey, R. (2003) *Curr. Cancer Drug Targets* **3**, 349–358
- Bagatell, R., and Whitesell, L. (2004) *Mol. Cancer Ther.* **3**, 1021–1030
- Kim, H. R., Kang, H. S., and Kim, H. D. (1999) *JUBMB Life* **48**, 429–433
- Bagatell, R., Paine-Murrieta, G. D., Taylor, C. W., Pulcini, E. J., Akinaga, S., Benjamin, I. J., and Whitesell, L. (2000) *Clin. Cancer Res.* **6**, 3312–3318
- Duina, A. A., Kalton, H. M., and Gaber, R. F. (1998) *J. Biol. Chem.* **273**, 18974–18978
- Sittler, A., Lurz, R., Lueder, G., Priller, J., Lehrach, H., Hayer-Hartl, M. K., Hartl, F. U., and Wanker, E. E. (2001) *Hum. Mol. Genet.* **10**, 1307–1315
- Hay, D. G., Sathasivam, K., Tobaben, S., Stahl, B., Marber, M., Mestrlil, R., Mahal, A., Smith, D. L., Woodman, B., and Bates, G. P. (2004) *Hum. Mol. Genet.* **13**, 1389–1405
- Jurivich, D. A., Sistonen, L., Sarge, K. D., and Morimoto, R. I. (1994) *Proc. Natl. Acad. Sci. U. S. A.* **91**, 2280–2284
- Jurivich, D. A., Pangas, S., Qiu, L., and Welk, J. F. (1996) *J. Immunol.* **157**, 1669–1677
- Ohno, K., Fukushima, M., Fujiwara, M., and Narumiya, S. (1988) *J. Biol. Chem.* **263**, 19764–19770
- Amici, C., Sistonen, L., Santoro, M. G., and Morimoto, R. I. (1992) *Proc. Natl. Acad.*

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- Sci. U. S. A.* **89**, 6227–6231
48. Abbott, A. (2002) *Nature* **417**, 109
49. Westerheide, S. D., Bosman, J. D., Mbadugha, B. N., Kawahara, T. L., Matsumoto, G., Kim, S., Gu, W., Devlin, J. P., Silverman, R. B., and Morimoto, R. I. (2004) *J. Biol. Chem.* **279**, 56053–56060
50. Jurivich, D. A., Sistonen, L., Kroes, R. A., and Morimoto, R. I. (1992) *Science* **255**, 1243–1245
51. Lee, B. S., Chen, J., Angelidis, C., Jurivich, D. A., and Morimoto, R. I. (1995) *Proc. Natl. Acad. Sci. U. S. A.* **92**, 7207–7211
52. in t' Veld, B. A., Ruitenbergh, A., Hofman, A., Launer, L. J., van Duijn, C. M., Stijnen, T., Breteler, M. M., and Stricker, B. H. (2001) *N. Engl. J. Med.* **345**, 1515–1521
53. Vigh, L., Literati, P. N., Horvath, I., Torok, Z., Balogh, G., Glatz, A., Kovacs, E., Boros, I., Ferdinandy, P., Farkas, B., Jaszalts, L., Jednakovits, A., Koranyi, L., and Maresca, B. (1997) *Nat. Med.* **3**, 1150–1154
54. Kieran, D., Kalmar, B., Dick, J. R., Riddoch-Contreras, J., Burnstock, G., and Green-smith, L. (2004) *Nat. Med.* **10**, 402–405
55. Hargitai, J., Lewis, H., Boros, I., Racz, T., Fiser, A., Kurucz, I., Benjamin, I., Vigh, L., Penzes, Z., Csermely, P., and Latchman, D. S. (2003) *Biochem. Biophys. Res. Commun.* **307**, 689–695
56. Nagai, N., Nakai, A., and Nagata, K. (1995) *Biochem. Biophys. Res. Commun.* **208**, 1099–1105
57. Yokota, S., Kitahara, M., and Nagata, K. (2000) *Cancer Res.* **60**, 2942–2948