Role of heat shock proteins in aging

A&S300-002 Jim Lund

Stress resistance genes

- Antioxidant proteins.
  - SOD, catalase, GSH, thioreductin
- Heat shock proteins.
  - HSPs, HSP16s, HSP70s
- Innate and acquired immunity genes.
  - Antibacterial, antifungal

Heat shock proteins

- Initially discovered in Drosophila as proteins induced in response to culturing flies at high temperatures.
  (Ashburner and Bonner, 1978)
- Now known to be ubiquitous.
  - Bacteria, vertebrates, plants.

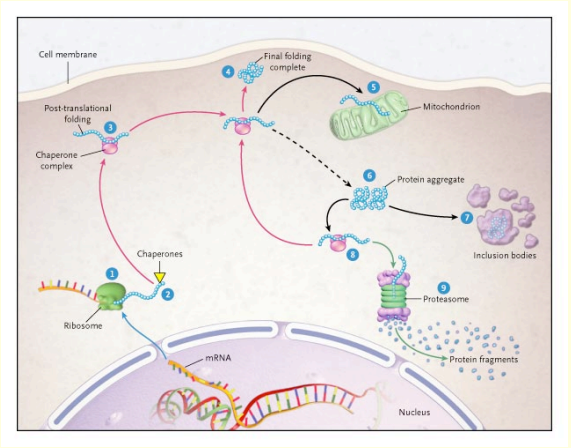
Heat shock proteins

- Induced in response to many stressors.
  - Heat shock
  - Heavy metals
  - Oxidative stress
- Also called HSPs, cellular stress proteins and molecular chaperones.

Heat shock protein function

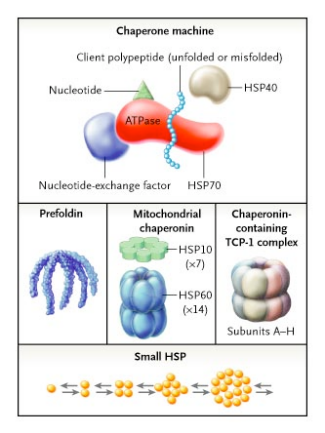
- Chaperones: help newly synthesized proteins fold.
- Protect proteins from cellular stresses that can cause unfolding and aggregation.
- Target proteins to degradation, prevent and clean up protein aggregates.

Cellular roles of HSPs



Macario el al., 2005

HSP complexes

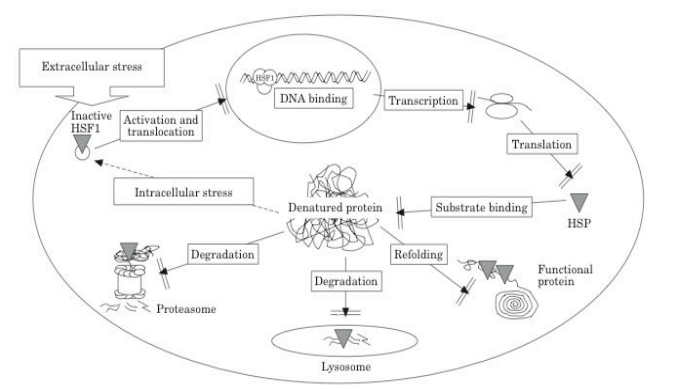


Macario el al., 2005

Heat shock protein function

- Present normally in cells.
- Stress increases levels of unfolded proteins, makes aggregates more likely to form.
- Stress increases levels of HSPs.
  - Both transcriptional and post-transcriptional mechanisms.
  - Total levels of protein synthesis in the cell inhibited by stress.

HSP response to stress



Verbeke et al., 2001

Heat shock induction declines with age

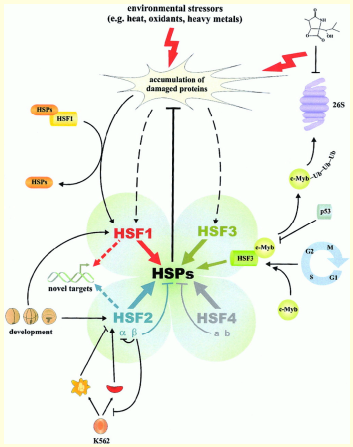
- Cells in young animals rapidly alter levels of HSPs.
- Older animals lose the ability to induce HSPs and other stress response proteins.
  - Observed in yeast, worms, flies, and mouse and human cell lines.

Transcriptional control of HSPs

- **Heat shock factors (HSF)**
  - **Major transcription factors responsible for stress-induced HSP expression**
- HSF1 and HSF4 (*hsf-1* in *C. elegans)*
  - Responsible for stress-induced HSP expression.
- HSF2 responsible for developmental regulation of heat shock proteins.
- HSF3, avian specific.

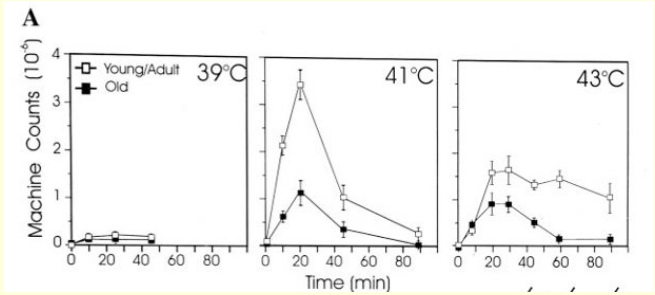
HSF1 is the best studied HSF.

HSF functions



Pirkkala et al., 2001

Induction of HSP70 in hepatocytes



Heydari, et al., 2000

Age-related changes in HSF1

- In rat hepatocytes, the regulation of HSF70 by HSF1 was studied.
- HSF1 induces HSP70 in cells from young rats, but HSP70 is only weakly induced in cells from old rats.
- HSF1 loses ability to bind the HSP70 promoter in old cells.
  - HSF1 undergoes post-transcription modification that alters promoter binding.

HSP overexpression can extend lifespan

- Hsp22 (a mitochondrial HSP) overexpression can extend lifespan in *Drosophila.*
  - Ubiquitous or targeted expression in motorneurons: 30% lifespan extension.

  (Kurapati et al., 2000)
- Drosophila lines selected for longevity.
  - Hsp22 2X - 10X higher expression relative to control outbred lines.
  - Hsp23 also significantly overexpressed.

  (Kurapati et al., 2004)

Mitochondrial HSPs

Overexpression of HSPs in mitochondria.

- Decreases production of free radicals.
- Increases mitochondrial efficiency.

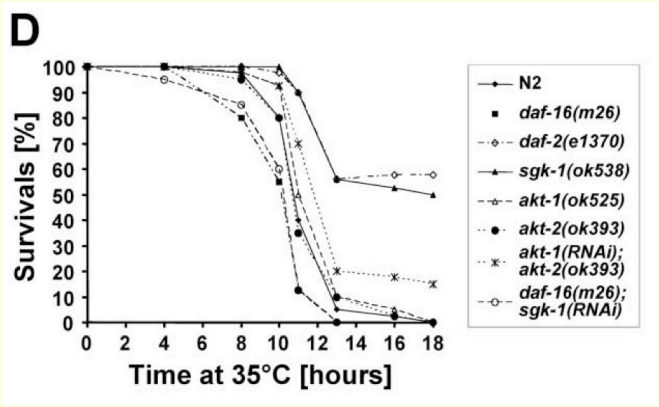
May be a mechanism by which HSP overexpression leads to longevity.

HSP overexpression can extend lifespan

- HSP16 in the worm is not expressed in young worms, but expressed in old (16+ days old) worms.
- Overexpression of HSP16 extends lifespan.
- Depends on DAF-16.
- Thermotolerance also increased.

Walker and Lithgow 2003

Thermotolerance is increased in *C. elegans* Daf mutants

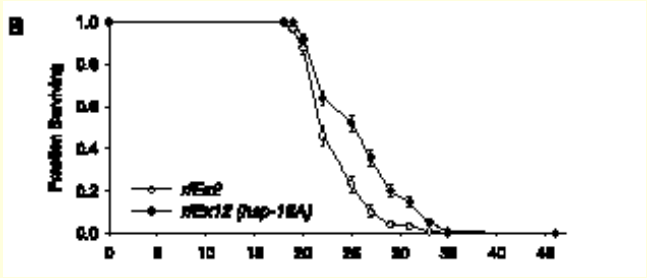


DAF-16 and HSPs

- HSP70 and HSP90 expression is also dependent on DAF-16 (Forkhead family transcription factor) expression.

Munox et al., 2003

HSP16 transgenics: +15% lifespan



HSF-1 expression affects lifespan

- *C. elegans hsf-1* knockout has reduced lifespan.
- *hsp-1* overexpression extends lifespan.
- Recall *daf-2* has a long lifespan. *hsf-1* is required for *daf-2* long lifespan.

Hsu et al., 2003

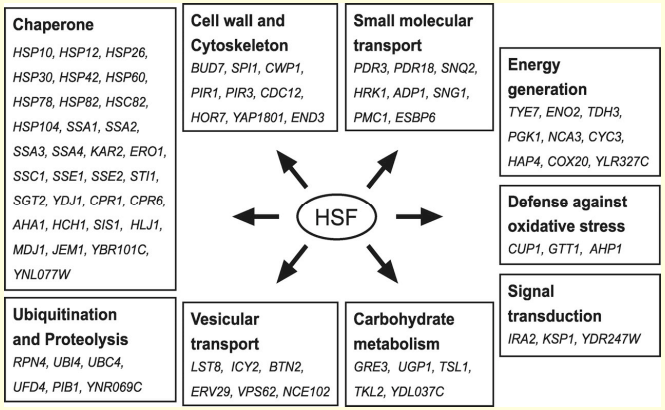
HSP and protein aggregation

- Protein aggregate formation is involved in the development of neurogenerative disease.
  - β-amyloid, tau,and polyglutamine protein aggregate formation is slowed by HSPs
  - Overexpression of HSPs delayed aggregate formation.
- *hsf-1* overexpression in *C. elegans* delays formation of polyglutamine protein aggregates (Hsu et al., 2003).

HSF transcription response

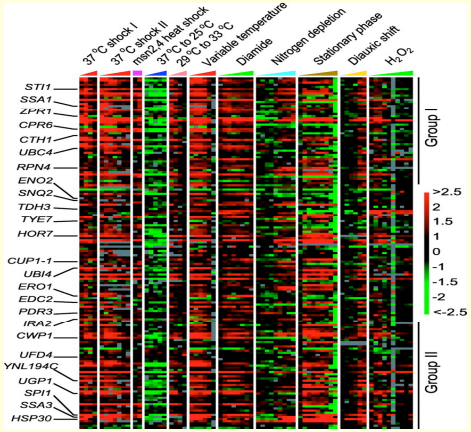
- Chromatin immunoprecipitation (ChIP) combined with DNA microarrays was used to identify direct trascriptional targets of HSF in yeast.
- 3% of yeast genes identified as targets:
  - Protein folding and degradation
  - Energy generation
  - Protein trafficking
  - Maintenance of cell integrity
  - Small molecule transport
  - Cell signaling
  - Transcription

HSF activated genes



Hahn et al., 2004

HSF activated genes are stress induced



Hahn et al., 2004