# Chaperone and Metalochaperones

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## chaperones

- **Molecular chaperones** are proteins that assist the non-covalent folding or unfolding and the assembly or disassembly of other **macromolecular** structures.

- The first protein to be called a chaperone assists the assembly of **nucleosomes** from folded histone and DNA
- One major function of chaperones is to **prevent** both newly synthesized polypeptide chains and assembled subunits from **aggregating** into **non-functional** structures

- **many chaperones**, (but not all), are also **heat shock proteins**
- **heat shock proteins**: expressed in response to elevated temperatures or other cellular stresses
- Some chaperone work as **foldases**: they support the folding of proteins
- The **crowded environment** of the cystol can accelerate the folding process.
  - crowding can **reduce yield** of correctly folded protein by increasing protein aggregation.
- Crowding may also increase the **effectiveness** of the chaperone proteins which could counteract this reduction in folding efficiency

- Chaperones are found in the **endoplasmic reticulum** (ER), since PROTEIN synthesis often occurs in this area.
- In the **ER** there are three types of chaperones
  - **General chaperones**: GRP78/Bip, GRP94, GRP190.
  - **Lectin chaperones**: calnexin and calretculin
  - **Non-classical**: HSP47and ERp29
- **Folding chaperones**:
  - Protein disulfide isomerase (PDI)
  - *Peptidyl prolyl cis-trans-isomerase* (PPI)

- There are many different families of chaperones; each family acts to aid protein folding in a different way.
- In bacteria like *E. coli*, many of these proteins are highly expressed under conditions of high stress, for example, when the bacterium is placed in high temperatures.
  - For this reason, the term "heat shock protein" has historically been used to name these chaperones.
  - The prefix "Hsp" designates that the protein is a heat shock protein

- Hsps have been classified into six major families according to their molecular size:
  - Hsp100, Hsp90, Hsp70, Hsp60, Hsp40, and small heat shock proteins (15 – 30kDa)
  - Hsp90 functions in both the cytosolic and nuclear compartments
  - Hsp70 family exhibit complex patterns of **growth-regulated** and **stress-induced** gene expression

## Metalloproteins

- All cells must acquire large numbers of transition **metal ions** for use as essential **cofactors**
- Cells control their metallome, in part, via specific **metalloregulatory proteins**, which sense changes in metal availability and **turn on** or **off** specific genes.
- these proteins **sense** changes in zinc concentration in the femtomolar range or copper in the zeptomolar range, and then adjust the transcription of metal homeostasis genes in a manner that keeps **free metal ion** concentrations in the cytosol at vanishing low levels
- Cells also **control metal availability** through a family of proteins, which facilitate trafficking of metals within the cell, namely **metallochaperone proteins**

## Heat Shock Proteins

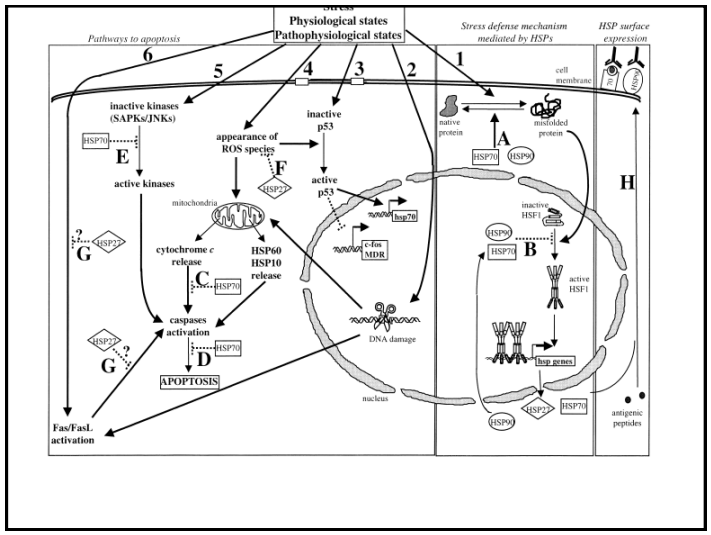
- HSPs assist in the **recovery from stress** either by
  - **repairing** damaged proteins (protein refolding) or
  - by **degrading** them, thus restoring protein homeostasis and promoting cell survival.
- The events of cell stress and cell death are linked
- heat shock response is **universal** and highly **conserved** and is an essential **defense** mechanism for protection of cells from a wide range of harmful conditions
- **misfolded proteins** may be **deleterious** by virtue of their altered biologic activities

- Cells or tissues from a wide range of **tumors** have been shown to express a typical levels of one or more Hsps thus could be used as **biomarkers**.
  - Hsp expression in breast or gastric cancer is associated with **poor prognosis** and resistance to chemotherapy or radiation therapy
- During the course of **viral infection**, the expression of heat shock genes is induced by activation of the **cellular stress response**
  - Adenovirus infection induces **Hsp70** and **Hsp90α**

## Stress Responses and Apoptosis: Cross-talk and Checkpoints

- Exposure of cells to **stress** activates a **survival response** via the induction of **Hsps**
- if the exposure to a specific **stress is intensified**, cell death will nevertheless occur, either by **necrosis** or **apoptosis**
- An increasing number of reports now reveal that the pathways leading to **apoptosis** and the **stress response** are linked
- Heat shock and other stressful conditions that induce the heat shock response can also lead to apoptosis or necrosis

- However, the heat shock response can also protect against stress-induced cell death via a cell-protective process known as **thermotolerance** or **cytoprotection**
- Both **Hsp27** and **Hsp70** have been shown to protect cells against the induction of cell death
- Since survival and death correspond to opposite cellular events, there should be multiple checkpoints and points of regulatory **cross-talk** to ensure that cells sustaining reparable molecular damage survive and that cells damaged beyond repair undergo cell death
- There is increasing evidence that **Hsps** may function at multiple points in the **apoptotic signaling pathway**


Stress
Physiological states
Pathophysiological states
Pathways to apoptosis
Stress defense mechanism mediated by HSPs
HSP surface expression
6
5
4
3
2
1
cell membrane
inactive kinases (SAPKs/JNKs)
HSP70
E
active kinases
appearance of ROS species
F
HSP27
inactive p53
active p53
hsp70
c-fos
MDR
native protein
misfolded protein
A
HSP70
HSP90
H
mitochondria
cytochrome c release
HSP60
HSP10
release
C
HSP70
G
HSP27
caspases activation
D
HSP70
APOPTOSIS
DNA damage
nucleus
inactive HSF1
HSP90
HSP70
B
active HSF1
hsp genes
HSP27
HSP70
HSP90
antigenic peptides
Fas/FasL activation