Chaperones and other ER proteins facilitate folding and assembly of proteins.

ER proteins that facilitate folding & assembly of proteins. Chaperones and other proteins facilitate folding and assembly of proteins.

BiP: a chaperone that prevents nascent chain from misfolding or forming aggregates.

PDI: stabilizes proteins with disulfide bonds.

Calnexin & calreticulin: lectins that bind a single glucose attached onto unfolded or misfolded polypeptide chains and prevent their aggregation. (p677)

Peptidyl-prolyl isomerase: facilitates folding by accelerating rotation about peptidyl-prolyl bonds.

In all cases, multimeric constituting in ER.
Unfolded protein vs. ER quality control

A glucose transferase can recognize an unfolded protein and add one terminal glucose to it.

Carbohydrate binding protein

Functions of The ER

- Chaperones: BiP
- Glycosylation
- GPI-linkages
- Disulfide bond formation
- Proper Folding - Quality Control
- Multisubunit (multimeric) assembly
- Specific proteolytic cleavages
- Secretory vesicles

The unfolded-protein response: increased expression of protein-folding catalysts.

1. In ER Unfolded protein ↑ binding to Bip
2. Ire1 (left) no bind to Bip → dimerization → activate endonuclease activity
3. Endonuclease → spliced immature Hac1 mRNA → Hac1 mRNA
4. Hac1 mRNA → transcription factor → enter nucleus → protein folding catalysts (ER chaperone gene transcript) Hac1 → a transcription factor promoting the transcription of ER chaperone genes low expression in the absence of UPR high expression when the UPR is induced expression level determined by the splicing of its mRNA in the cytosol

What if unfolded proteins start to accumulate within a cell?

unfolding in the cytosol:
leading to an increase of cytosolic chaperones (also called heat shock response)

unfolding in the ER:
leading to an increase of ER chaperones (also called unfolding protein response, UPR)

Translocated proteins can be exported to the cytosol.

There they are:
- ubiquitinated
- degraded by the proteasome
- a process known as ER-associated degradation.
Unassembled or misfolded proteins in the ER are often transported to the cytosol for degradation

**Proteasome:** an ATP-dependent protease complex composed of three parts: two side caps and one central core, each containing multiple subunits. It is found in the cytosol and the nucleus, and functions to degrade misfolded proteins.

Terminally misfolded proteins in the ER are returned to the cytosol for degradation. They are transported through the translocon back into the cytosol and degraded by ubiquitin-mediated proteolytic pathway.

Degradation of misfolded or unassembled proteins.

They are transported through the translocon back into cytosol and degraded by ubiquitin-mediated proteolytic pathway.

Unassembled or misfolded proteins are blocked from moving to the Golgi complex.

ERAD: ER-associated degradation

Misfolded protein for ubiquitin-dependent proteasome degrade.

Unassembled or misfolded proteins are blocked from moving to the Golgi complex.

ERAD: ER-associated degradation

Misfolded proteins remain bound to ER chaperones (e.g., BiP, calnexin) aberrant proteins are finally targeted for degradation and extruded back to cytoplasmic compartment through translocon.

N-glycanase in cytosol removes N-linked carbohydrate moieties.

Proteins are ubiquitinated in cytosol and degraded via proteasome complex.

- ubiquitin-conjugating enzymes are localized on cytoplasmic face of ER
- Ub-conjugating enzymes interact with integral membrane Ub ligases
- polyubiquitinated proteins are degraded in proteasomes
Emphysema 广泛性肺泡肺气肿

Misfolding protein in ER
The $\alpha_1$-antitrypsin mutation (release from hepatocytes, macrophage)
trypsin $\rightarrow$ degrade $\rightarrow$ elastin (ECM) $\rightarrow$ support down
Anti-trypsin inhibited trypsin

ECM: extracellular matrix

Pathway of protein breakdown in mammalian cells
Cytosolic protein
Abnormal protein
Short-lived protein
ER-associated protein
Long-lived protein

Endocytosed proteins
Membrane protein
Lysosomal pathway
Extracellular protein

Degradation of protein
1. Lyosome: primarily toward extracellular protein and aged or
defective organelles of the cells.
2. Proteasomes: Ubiquitin dependent; for intracellular unfolding, aged
protein.
   1. control native cytosolic protein
   2. misfolded in the course of their synthesis in the ER

Major modifications of proteins in the ER lumen

Enzyme-linked covalent modifications:
glycosylation: addition of saccharides
  N-linked (to Asn)
  O-linked (to Ser or Thr, occurring at the Golgi),
  (mediated by a group of glycosyltransferases)
disulfide bridge: R-SH + R-SH $\rightarrow$ R-S-S-R
  (an oxidation process between two Cys residues)
  (mediated by PDI, protein disulfide isomerase)
GPI anchor: addition of glycosylphosphatidylinositol to the C-terminus
  of specific cleaved proteins
  (mediated by GPI-transamidase)
proteolytic cleavages

Enzyme-linked non-covalent modification:
rotation of peptidyl-prolyl bond: rotation about the peptidyl-prolyl bond
  (mediated by peptidyl-prolyl isomerase)

Glycosylation, disulfide bridge formation and the rotation of peptidyl-prolyl bond occur
co-translationally and thus can affect the folding, assembly of a protein or protein complex
(folding vs. assembly)
Sorting of proteins to mitochondria and chloroplast

All organelles have a lipid bilayer.
Mitochondrial or chloroplast DNA and ribosome → synthesized protein → correct subcompartment
The mechanisms of Sorting of protein to mitochondria and chloroplast are similar to bacteria

The post-translational uptake of precursor proteins into mitochondria can be assayed in cell free system

Export to mitochondria, not co-translational translocation
Need energy and chaperone

Fig 13-22 The post-translational uptake of precursor proteins into mitochondria can be assayed in a cell-free system

Mitochondrial protein import requires outer membrane receptor and translocons in both membranes

1. Unfolded protein binding chaperones,
2. Precursor protein bind to an import receptor, which contact with inner membrane
3. Transferred into import pore
4. Translocation protein
5. To adjacent channel in the inner membrane
6. Translocated protein binding to matrix chaperones, remove targeting sequence by matrix protease, and release chaperones
7. Folding to mature protein

Mitochondrial import requires receptors and translocons
Two proteins = translocons of the outer membrane
Two proteins = translocons of the inner membrane
Amphiphatic N-terminal signal sequence direct proteins to the mitochondrial matrix:

Matrix-targeting sequences:
1. Located N-terminus
2. 20-50 amino acids in length
3. Rich in hydrophobic amino acids, positively charged amino acids (Arg, Lys), and hydroxylated ones (Ser, Thr)
4. Lack negatively charged acidic residues (Asp, Glu)
5. Alpha-helical conformation (one-hydrophobic, opposite side – charged amino acids: amphipathic)
6. Amphipathicity of matrix-targeting sequences is critical to their function

Tom 20/22 (import receptor) and Tom 40 (general import pore)
Tim 23/17 proteins
Contact sites – close proximity
Tim 44 (translocation channel)/ Hsc70 (a matrix chaperone)
The interaction - ATP hydrolysis by matrix Hsc70 chaperonin - facilitate folding (yeast Hsc60 defect – fail to fold)

Molecular chaperons: which bind and stabilize unfolded or partly folded proteins, thereby preventing these proteins from aggregating and being degraded
Chaperonins: which directly facilitate the folding of proteins

Studies with chimeric proteins demonstrate important features of mitochondrial import: only unfolded protein can entry

No function sequence
Matrix targeting sequence
DHFR
Cytochrome oxidase
Outer membrane
Intermembrane space
Mitochondrial matrix
Mitochondrial matrix
Spacious sequence

in the presence of chaperone prevent DHFR folding

Must unfold protein can enter mitochondrial matrix

Experiments with chimeric proteins show that a matrix-targeting sequence alone directs proteins to the mitochondrial matrix and that only unfolded proteins are translocated across both membranes
Precursor protein must be **unfolded** in order to traverse the import pores in the mitochondrial membranes.

MTX – binds tightly to the active site of DHFR and greatly stabilizes its folded conformation.

**Spacer sequence:** >50 amino acids long

- **Translocation intermediate is formed:** <35 residues
- Intermediate translocated proteins span both membranes in unfolded state
- **Chemically cross-linking exp.**
- **1000 general import pore (yeast mitochondria)**

Can not entry

Matrix-targeting sequence alone directs proteins to mitochondrial matrix.

Only unfolded proteins are translocated across both membranes.

- Import to mitochondria must be:
  1. After translation
  2. Before folding

- Bound to the translocation intermediate at a contact site

Three energy inputs are needed to import proteins into mitochondria:

1. **Cytosolic** Hsc70-ATP hydrolysis - unfolding function
2. **Matrix** Hsc70-ATP hydrolysis – molecular motor to pull the protein into the matrix (cf. chaperone BiP and Sec63 complex – in post-translational translocation into the ER lumen)
3. **H+ electrochemical gradient (proton-motive force)** across the inner membrane (inhibitor or uncouple of oxidative phosphorylation such as cyanide or dinitrophenol, dissipates this proton motive force - proteins bind to receptor, but not be imported)

One hypothesis: positive charges in the amphipathic matrix-targeting sequences – electrophoresed or pulled into the matrix by inside-negative membrane electrical potential

Translocation into chloroplast occurs via a similar strategy to the one used by mitochondria:

- Both occur post-translationally
- Both use two translocation complexes, one at each membrane
- Both require energy
- Both remove the signal sequence after transfer

However chloroplasts have a H+ gradient across the thylakoid membrane and use GTP hydrolysis to drive transfer
Multiple signals and pathways target proteins to submitochondrial compartments

Target:
1. Inner-membrane
2. Intermembrane space
3. Outer-membrane: unknown mechanism
4. Matrix

<table>
<thead>
<tr>
<th>Imported protein</th>
<th>Location of imported protein</th>
<th>Location of targeting sequences in preprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol dehydrogenase (ADH)</td>
<td>Inner membrane (path A)</td>
<td>Cleavage by matrix protease</td>
</tr>
</tbody>
</table>
| ATP synthase 

β-subunit B | Intermembrane space | Cleavage by matrix protease |

Two pathway for transporting proteins from the cytosol to the mitochondrial intermembrane space (intermembrane-space proteins)

1. Two targeting sequences
2. First N-terminal matrix targeting sequence removed
3. Second sequence = hydrophobic stop-transfer anchor sequence → stay in membrane
4. Protease cleaves; protein folds

Oxa1 also participates in the inner-membrane insertion of certain proteins encoded by mitochondrial DNA synthesized in matrix by mitochondrial ribosomes.

Mitochondrial import requires receptors and translocons

Tom proteins = translocon of the outer membrane
Tim proteins = translocon of the inner membrane
Two pathway for transporting proteins from the cytosol to the mitochondrial intermembrane space

Intermembrane space targeting sequence
Direct delivery to the inner membrane space

Unclear mechanisms
Need energy
Mitochondrial porin (P70) N-terminal sequence is important
P70 is hydrophobic, for stop-transfer, prevents transfer of the protein into matrix and anchors protein

Protein target to chloroplast
Targeting of chloroplast stromal proteins is similar to import of mitochondrial matrix protein
Proteins are targeted to thylakoids by mechanisms related to translocation across the bacterial inner membrane.
Protein Synthesis in cytosol → transport → thylakoid → photosynthesis

SRP: signal-recognition particle
Have four types of transport protein to chloroplast: closely related to bacteria.
Type I: SRP dependent
Type II: related Sec A
Type III: related mitochondrial Oxa 1
Type IV: for metal-containing protein, ΔpH pathway

Tom proteins = translocon of the outer chloroplast
Chloroplast encoded protein transport into thylakoid membrane

Four routes across the thylakoid membrane:

能耗要求：
- ATP电化学梯度
- H⁺电化学梯度
- 无

Type II

Peroxisome activity:

Peroxisomes are single membrane organelles. Peroxisomes house a variety of lipid oxidation reactions, these often utilize H₂O₂ hydrogen peroxide and/or O₂ (e.g. catalase & urate oxidase)

Examples:
- β-oxidation & breakdown of fatty acids
- Detoxification of H₂O₂ (catalase)
  
  \[ 2 \text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2 \]
- Synthesis of certain phospholipids (e.g. plasmalogen)
- Cholesterol breakdown to bile acids
Sorting of peroxisomal proteins via PTS

Peroxisomes are bounded by single membrane.
No DNA and ribosomes, all protein encoded by nuclear gene.
Has catalase for H2O2 into H2O, are most abundant in liver cell about 1-2%.

Transport protein into peroxisomes by cytosolic receptor Pex5 targets protein with an SKL sequence at the C-terminus into the peroxisomal matrix.

PTS1: Ser-Lys-Leu (SKL) at C-terminal,
- not cleaved after internalization (very different)
- translocate folded protein.

Similar to SRP and SRP receptor transport pathway.

Folded proteins can be translocated across the membrane.
Need ATP.

PTS1 directed import of peroxisomal matrix.

Synthesis and targeting of peroxisomal proteins

Encoded by nuclear DNA
Synthesized on free ribosomes

Proteins are folded in the cytosol then transported into peroxisome.

Peroxisomal targeting sequence (PTS1)
- Ser-Lys-Leu (SKL)

PTS1-tagged protein binds to soluble receptor in the cytosol.
Brought to the peroxisomal surface.
Moved through translocation channel (not clear).
- Soluble receptor dissociates.
- Needs ATP for translocation.
- PTS1 is not cleaved.

A short signal sequence directs the import of proteins into peroxisomes.

Peroxisome maturation

Pex19 like receptor for membrane targeting.
Pex3 and Pex16 are membrane protein for transport.

Division need Pex 11.

New peroxisomes are derived by growth and splitting of existing peroxisomes.

Fig 16-34 Model of peroxisomal biogenesis and division.
Zellweger syndrome

Characterized by a variety of neurological, visual, and liver abnormalities leading to death during early infancy.

Transport of proteins into peroxisomal matrix is impaired;

Genetic analyses of different Zellweger patients & of yeasts carrying similar mutations identify >20 genes required for peroxisomal biogenesis.

Zellweger syndrome is caused by the mistakes of protein import into the peroxisomes.

Accumulation of long chain fatty acids in plasma and tissues.

Causing severe impairment of many organs and death.

Peroxisomal disorders affecting either peroxisomal biogenesis or transport into peroxisomes affect fatty acid and lipid metabolism.

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Transport into and out of the nucleus

Nuclear Cargo

**Imported**
- Polymerases
- Histones
- Transcription factors
- Ribosomal proteins

**Exported**
- tRNAs
- mRNPs
- Ribosomal subunits
- Transcription factors

$10^6$ ribos => 560,000 ribo proteins imported/min
14,000 ribo subs exported/min
3-4K pores/cell => 150 ribo proteins/min/pore
Also 100 histones/min/pore etc.

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### Table 15-3 Some Typical Signal Sequences

<table>
<thead>
<tr>
<th>FUNCTION OF SIGNAL</th>
<th>EXAMPLE OF SIGNAL SEQUENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Import into ER</td>
<td>$^4$H$_2$N-Met-Ser-Val-Leu-Leu-Val-Ile-Prp-Leu-Prp-Tyr-Glu-Ala-Glu-Glu-Leu-Thr-Lys-Cys-Glu-Val-Phe-Gln-Lys-Asp-Glu-Leu-COO$^-$</td>
</tr>
<tr>
<td>Retention in lumen of ER</td>
<td>-</td>
</tr>
<tr>
<td>Import into mitochondria</td>
<td>$^4$H$_2$N-Met-Leu-Val-Arg-Gln-Arg-Val-Phe-Lys-Pro-Ala-Thr-Arg-Thr-Leu-Cys-Ser-Arg-Tyr-Leu-Leu</td>
</tr>
<tr>
<td>Import into nucleus</td>
<td>$^4$Pro-Pro-Lys-Lys-Lys-Arg-Lys-Val</td>
</tr>
<tr>
<td>Import into peroxisomes</td>
<td>Ser-Lys-Leu</td>
</tr>
</tbody>
</table>

Positively charged amino acids are shown in red, and negatively charged amino acids in blue. An extended block of hydrophobic amino acids is enclosed in a yellow box. "$^4$H$_2$N" indicates the N-terminus of a protein. COO$^-$ indicates the C-terminus. The ER retention signal is commonly referred to by its single-letter amino acid abbreviation, KDEL.

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P324

Overview of RNA processing and post-translational gene control

In nucleus: DNA → pre-mRNA → binding hnRNP → splicing → mRNA → export to cytosol via nuclear envelop → translation

From immature to mature mRNA are associated with heterogeneous ribonucleoprotein particles (hnRNP); mRNA + hnRNP → also called heterogeneous nuclear RNA (hnRNA)

Mature mRNA + associated specific hnRNP → messenger ribonuclear protein complex; mRNP
1) Splicing  
2) Splicing  
3) RNA surveillance (看守) mechanism  
4) Translation [poly(A)-binding protein  
5) Degradation (de-adenylation and de-capping)  
6) Cytoplasmic adenylation  
7) miRNAs  
8) tRNA, rRNA processing  
9) Degradation by nuclear exosome
Nuclear pore complex control import and export from the nucleus

**Nuclear pore complex (NPC)**

Has FG (phenylalanine glycine) amino acids repeat (hydrophobic)

Also called FG-nucleoporins

It form a barrier restricting the diffusion of larger molecules; across it must involved of soluble transporter protein interact with FG repeats of FG-nucleoporins

Model of transporter passage through and NPC

Nuclear pore complexes perforate the nuclear envelope

Can help cargo across NPC

Can help cargo across NPC

Composed by more than 30 different proteins called nucleoporins.
**Nuclear pore complex (NPC)**

Elaborate structure of approx. 30 proteins forming protein lined aqueous channel approx 9nm diameter; the protein also called nucleoporins

**Protein fibrils** protrude each side of complex - form cage-like structure on nuclear side, consist of nucleoporin (yeast 590 types, mammal 100 types)

Each pore, on average, imports 100 histone molecules per minute and exports 6 small ribosomal subunits. The formed protein also called nucleoporin

**Nucleus imports and exports macromolecules**

Nuclear envelope encloses nuclear DNA

Inner membrane contains binding sites for chromosomes and nuclear lamina

Outer nuclear membrane resembles ER membrane

Transcription factors enter into nucleus, RNA (once spliced) and ribosomal subunits are exported out of nucleus

Nuclear envelope perforated by pores, movement occurs in both directions through these pores

**Nuclear Pore Complexes (NPC)**

NPCs span the inner and outer nuclear membrane

- 3000–4000 in typical mammalian cell nucleus.
- Each pore, on average, imports 100 histone molecules per minute and exports 6 small ribosomal subunits. The formed protein also called nucleoporin

NPC are:

- large - 125 million Da
- complex-composed of more than 30 different proteins
- gated - Have diffusion limit of ~40 kDa. Larger proteins require active transport
- busy - every minute each NPC must transport 100 histone proteins, 6 small and large ribosome subunits, plus numerous other proteins and RNP complexes.
- traffic is bi-directional and highly regulated.
Mechanism of protein import: Protein contain NLS

Proteins selected for import into nucleus have a nuclear localisation signal (NLS) e.g.
-Pro-Pro-Lys-Lys-Lys-Arg-

Position of NLS in protein not important except needs to be on surface

NLS is recognized by cytosolic nuclear import receptors which bind to nuclear pore fibrils extending into cytosol

Pore opens and protein plus import receptor enter nucleus. Import receptor exported for re-use

Nuclear localization signals (NLS) direct nuclear proteins to the nucleus

Fusion of the T-Antigen NLS sequence to a cytosolic protein (pyruvate kinase), results in nuclear import of the cytosolic protein

Experiment shows that the NLS sequence is necessary and sufficient to direct nuclear import

a. Pyruvate kinase normally found in cytosol
b. Adding the -KKKRK- sequence results in the kinase localizing to the nucleus

Hypothesis: Receptors required for nuclear import.
Digitonin is detergent → permeabilizes plasma membrane → keep nucleus contain NPC → extracellular protein → enter cytosol → has NLS signal peptide → nucleus

Synthetic SV40 T-antigen NLS

Cytosolic proteins are required for nuclear transport

- NFT2 (nuclear transport factor 2)
- Some studies has found only β has import function
- Nuclear import receptors bind nuclear localization signals (α subunit) and nucleoporins (β subunit)

Active nuclear transport is driven by Ran

- Ran is a small GTPase- binds and hydrolyses guanine nucleotide triphosphate (GTP)
  - Ran exists in two conformational forms: Ran - GTP and Ran-GDP
  - Ran has weak GTPase activity that is stimulated by RanGAP (GTPase activating protein)
  - A guanine nucleotide exchange factor (GEF), called RCC1 stimulates the release of GDP and binding of GTP (higher concentration of GTP in the cell assures preferential binding of GTP)
  - The cycle of GTP binding, hydrolysis, release provides energy for nuclear transport
  - asymmetric localization of RanGAP and RCC1 assure directionality of transport

Ran is a small GTPase- binds and hydrolyses guanine nucleotide triphosphate (GTP)

Cytosol ER → translation to protein→ contain NLS → bind to importin→ import → nucleus

From digitonin-permeabilized cell system: found that Ran (a small G protein)

NFT2 (nuclear transport factor 2)

importin α and importin β → formed heterodimeric nuclear-import receptor → α bind to NLS (hydrophobic) of cargo; β bind to FG-nucleoporin

Active nuclear transport is driven by Ran

Importins transport protein containing Nuclear-Localizing Signal into the nucleus

Cytosolic proteins are required for nuclear transport

- NFT2 (nuclear transport factor 2)
- Some studies has found only β has import function
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Protein import to nucleus (nuclear import)
Conversion between the 2 states is triggered by 2 Ran-specific regulatory proteins

1. Nuclear guanine exchange factor (Ran-GEF)
   - Exchanges GDP for GTP, and converts Ran GDP to Ran GTP
   - Because Ran-GAP is in the cytosol & Ran-GEF is in the nucleus:
     - Cytosol contains Ran-GDP
     - Nucleus contains Ran-GTP

Mechanism of export from nucleus

Most of traffic moving out of nucleus consists of different types of RNA molecules

RNA moves through nuclear pore as complex of ribonucleoprotein (RNP)

Protein component of RNP contains a nuclear export signal (NES) that is recognized by export proteins

mRNA is bound by hnRNP only after fully spliced so only mature RNA is exported

Exportins transport proteins containing NES out of the nucleus

Export: ribosomal subunit, tRNA, to cytoplasm
Export protein contain Nucleus export signal (NES)
A least three type of NES:
Leucine rich
Two different sequence in two different heterogeneous ribonucleoprotein particales
Nucleus export has two mechanism : Ran dependent and Ran-independent
Most mRNAs are exported from the nucleus by a ran-independent mechanism

From immature to mature mRNA are associated with heterogeneous ribonucleoprotein particles (hnRNP); mRNA + hnRNP → also called heterogeneous nuclear nuclear RNA (hnRNA) or mRNP

Mature mRNA + associated specific hnRNP → messenger ribonucelar protein complex; mRNP

mRNP exporter: heterodimeric protein a large subunit NXF1(nuclear export factor 1) or TAP and a small subunit Nxt1(nuclear export transporter 1) The mRNA export receptor TAP/NXF1

TAP/Nxt1 complex interact with FG-domains of FG-nucleoporin

TAP/NXF1 exhibits low affinity RNA binding and is likely to interact with cellular mRNPs through protein-protein rather than protein-RNA interactions

Ran independent export

Tap/Nxt1 + mRNPs → complex→NPC pore →export→cytosol via Dbp5 provide the driving force

Dbp5: RNA helicase
RNA export pathways

- RNA binding protein (Adaptor)
- Exportins (Receptor)
- RNA binding protein
- Splicing factors
- TAP/NXF1
- CRM1
- Exp-t

- RNAs
- Cellular mRNA
- SS rRNA
- HIV RNA
- IRNA

Location:
- Nucleus
- Cytoplasm

- RNA binding protein (Adaptor)
- Exportins (Receptor)
- RNA binding protein
- Splicing factors
- TAP/NXF1
- CRM1
- Exp-t

Location:
- Nucleus
- Cytoplasm