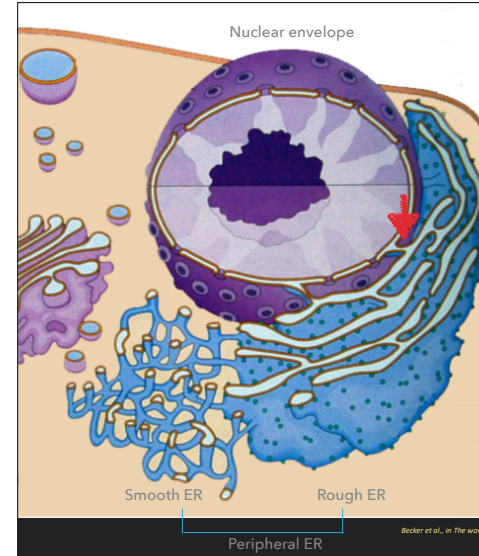


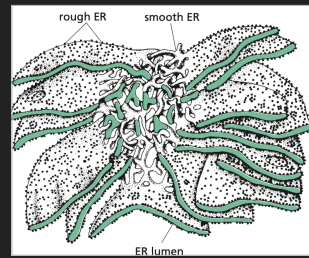
THE ENDOPLASMIC RETICULUM

Pr Christian Poüs - 2020-2024



Becker et al., in The world of the cell, 5th edition B. Cummings Ed.

THE ER IN THE CELL ORGANISATION



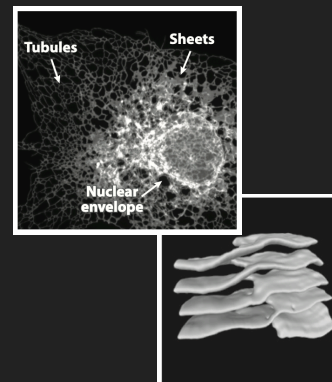
Alberts et al., in Molecular Biology of the Cell, Garland Science.



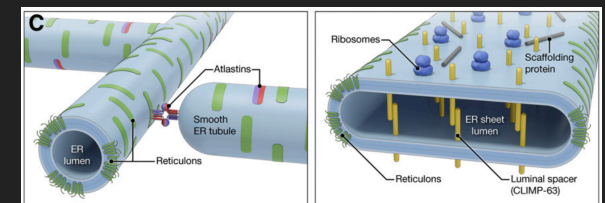
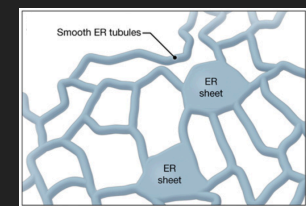
Stacked cisternae covered with ribosomes

- ✦ Single continuous membrane
- ✦ Different shapes associated to different functions
→ specific protein organisations

Becker et al., in The world of the cell, 5th edition B. Cummings Ed.

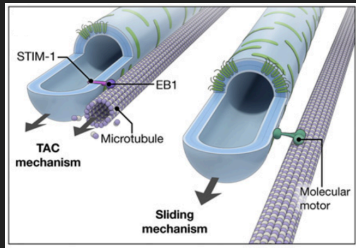


Westrate et al., Annu. Rev. Biochem., 2015, 84:791.



Goyal and Blackstone, BBA, 2013, 1833:2492

Membrane tubule network



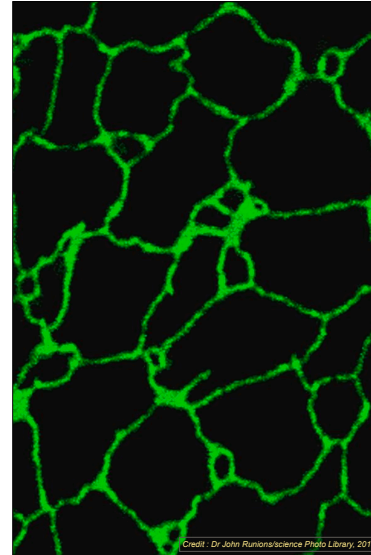
Goyal and Blackstone, *BBA*, 2013, 1833:2492

Microtubule and motor-dependent peripheral extension

Endoplasmic Reticulum
Microtubules

Dual fluorescence digital imaging of the dynamics of microtubules and endoplasmic reticulum in the lamella of a newt lung epithelial cell.

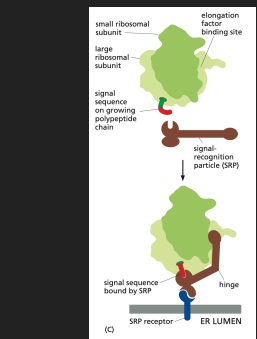
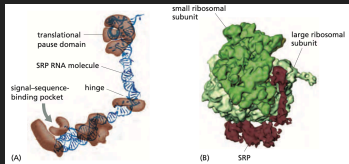
Clare M. Waterman-Storer and E.D. Salmon, 1998.



Credit: Dr John Runions/science Photo Library, 2018

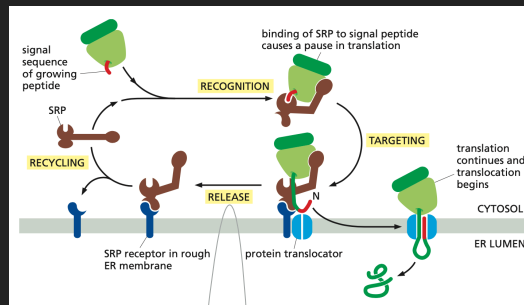
FONCTIONS OF THE ROUGH ER

PROTEIN BIOSYNTHESIS



THE SRP CYCLE

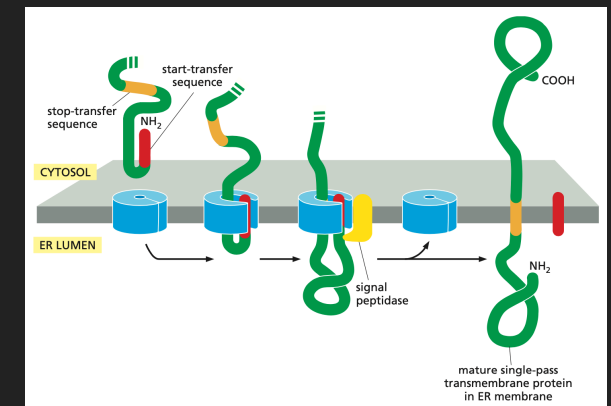
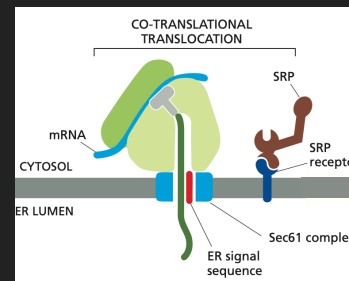
SRP = SIGNAL-RECOGNITION PARTICLE



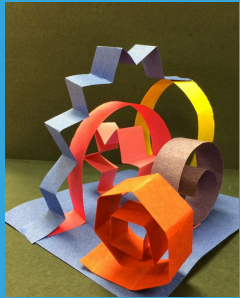
GDP+Pi GTP

Alberts et al., in *Molecular Biology of the Cell*, Garland Science.

PROTEIN TRANSLOCATION



Alberts et al., in *Molecular Biology of the Cell*, Garland Science.



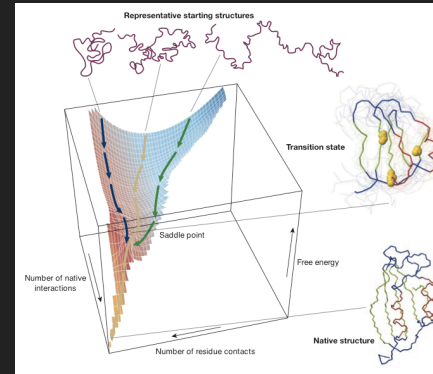
PROTEIN FOLDING & CHAPERONES

QUALITY CONTROL & UNFOLDED PROTEIN RESPONSE

PROTEIN FOLDING

QUALITY CONTROL

STEPS OF PROTEIN FOLDING



- ✦ Folding possibilities dictated by the AA sequence
- ✦ Competition between folding paths
- ✦ Folding stops when free energy reaches a minimum
- ✦ Folding steps:
 - hydrophobic sequences collapse
 - burial of electrostatic interactions
 - local folding of α -helices or β -strands

Typically 50-100 μ s

Keeping in a folding-competent state until the interacting partners contact

↓

Shielding by chaperones

Gelboin, Nature, 2003, 426:884

PROTEIN FOLDING CHAPERONES

QUALITY CONTROL

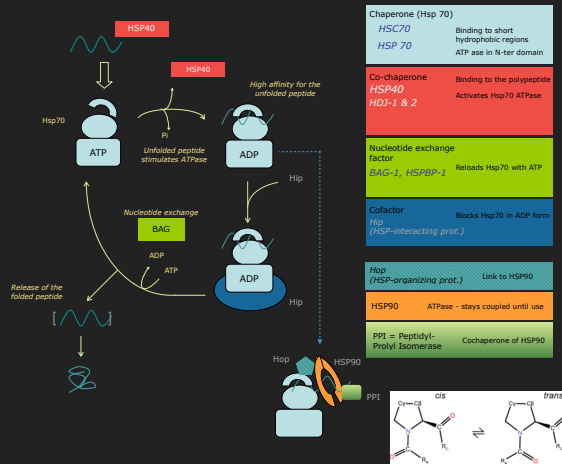
HYDROPHOBIC PEPTIDE CHAPERONES

ER environment:

- dense (~100 g/l)
- high Ca^{++} (5 μ M)
- oxidant properties (GSH/GSSG 1:1 vs 30:1 in the cytosol)

ER equivalent

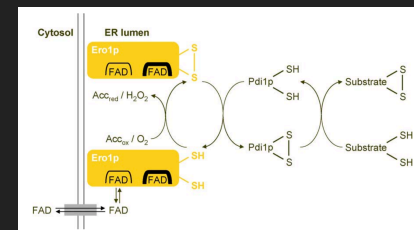
HSP 70 class	BiP/GRP78
HSP 40 class	ERdj1,5
BAG class	BAP
HSP90 class	GRP94
PPI class	Cyclophilin, FKBP



PROTEIN FOLDING CHAPERONES

QUALITY CONTROL

CONTROL OF DISULFIDE BRIDGE FORMATION BY OXYDOREDUCTASES

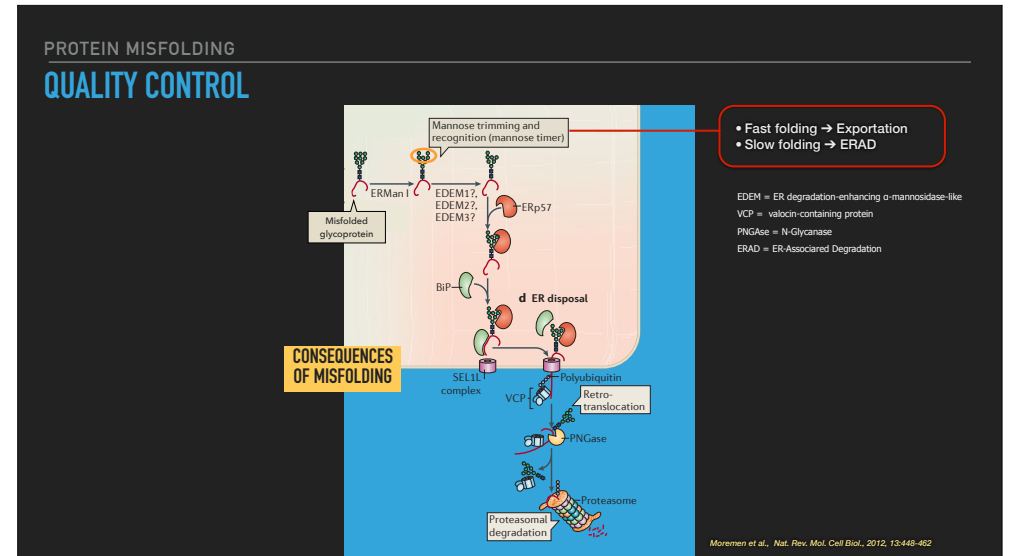
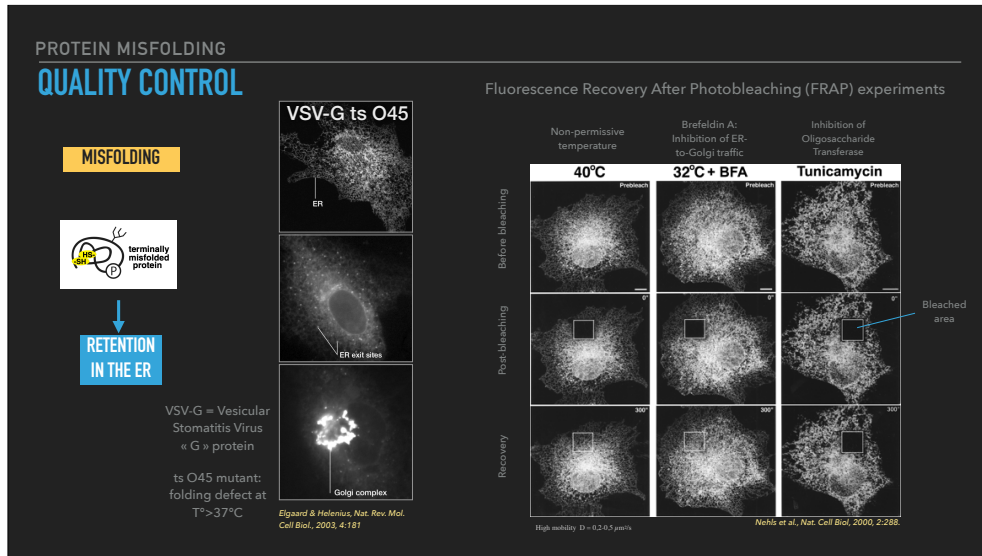
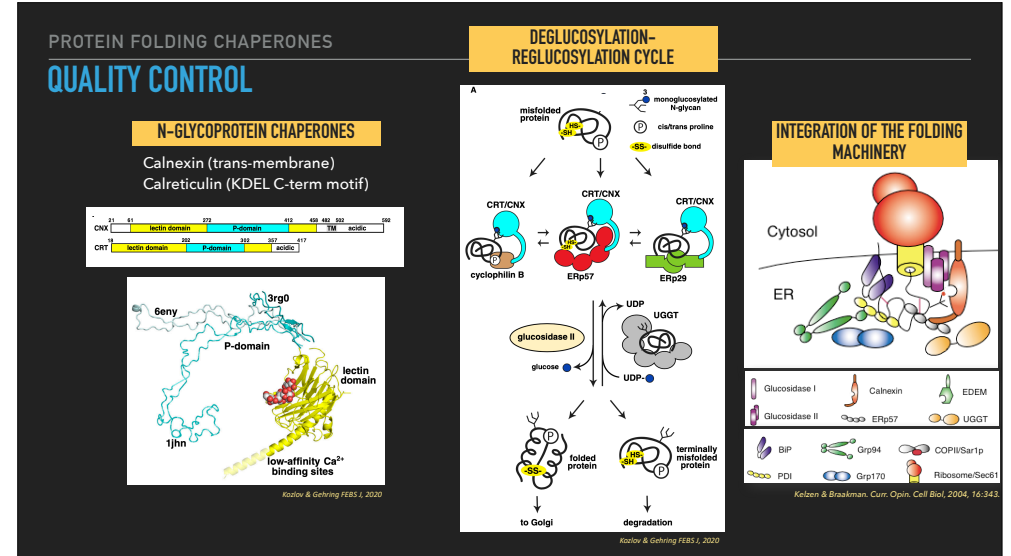
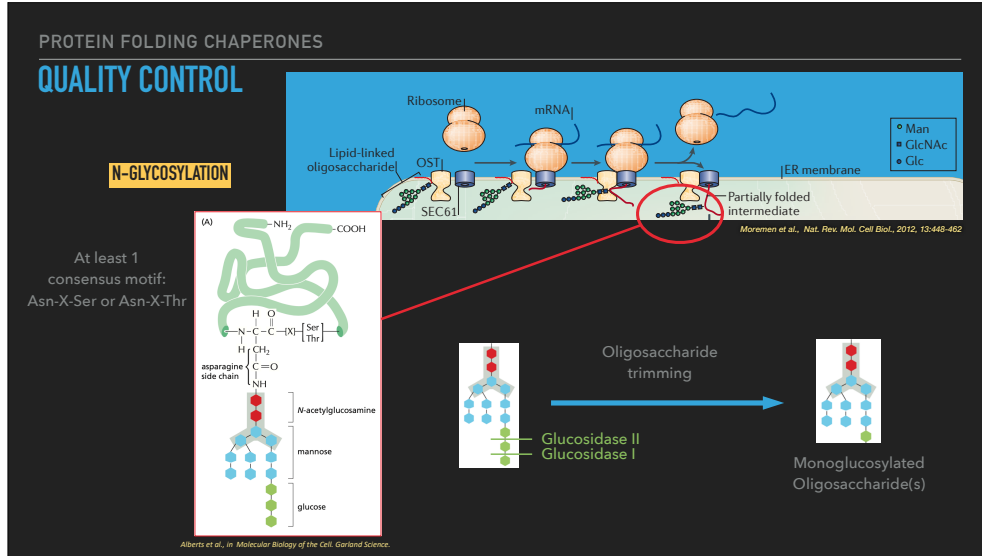


- ✦ Spontaneous S-S formation due to oxidative conditions
- ✦ Thiol protection by Protein Disulfide Isomerases (PDI)

Main chaperones:

- PDI
- ERp57

Schroder & Kaufman, Mol. Res. 2005, 5:69-79



PROTEIN MISFOLDING

UNFOLDED PROTEIN RESPONSE = UPR

4 Transducers

- IRE1
- PERK
- ATF6
- pCSP-12

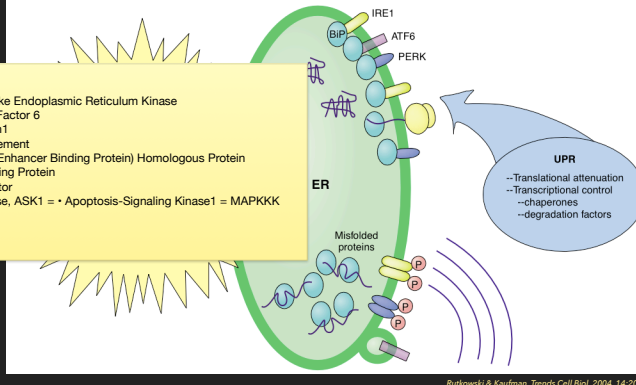
4 Compartments

- ER
- Golgi
- Cytoplasm
- Nucleus

4 Responses

- Transcription
- Translation
- ERAD
- Apoptosis

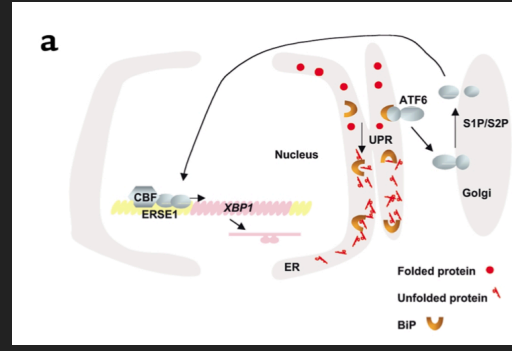
- Protein kinase R (PKR)-like Endoplasmic Reticulum Kinase
- Activating Transcription Factor 6
- Inositol Requiring protein1
- ER Stress (Response) Element
- CHOP= C/EBP (CCAAT/Enhancer Binding Protein) Homologous Protein
- XBP1= X-Box DNA-Binding Protein
- TRAF2 = Cytosolic adaptor
- JIK = JNK-inhibitory Kinase, ASK1 = Apoptosis-Signaling Kinase1 = MAPKKK



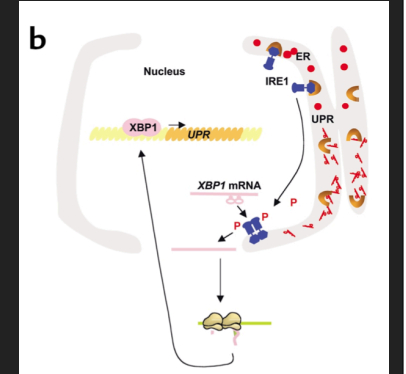
PROTEIN MISFOLDING

UNFOLDED PROTEIN RESPONSE

ATF6, ER-TO-GOLGI, TRANSCRIPTION



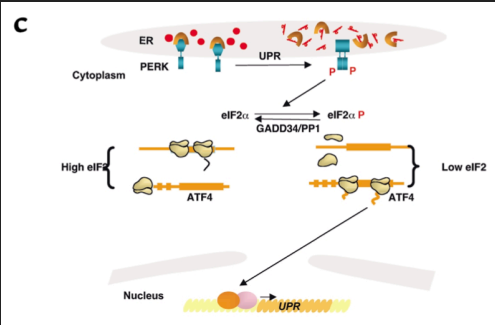
IRE1, NUCLEUS, TRANSCRIPTION



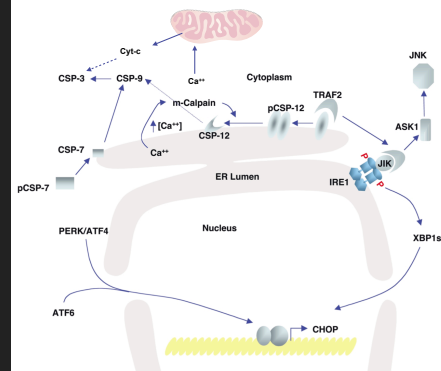
PROTEIN MISFOLDING

UNFOLDED PROTEIN RESPONSE

PERK, CYTOSOL, PROTEIN TRANSLATION



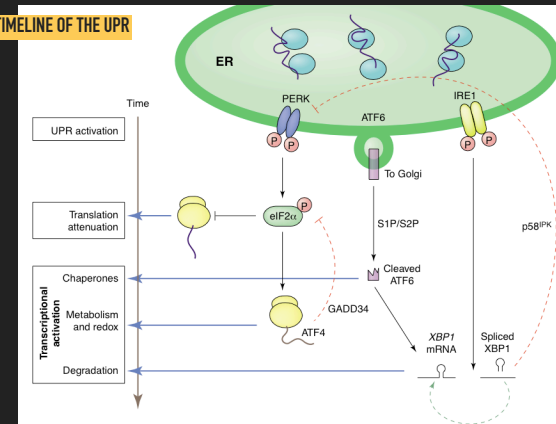
PROCASPASE 12, ENDOPLASMIC RETICULUM, APOPTOSIS

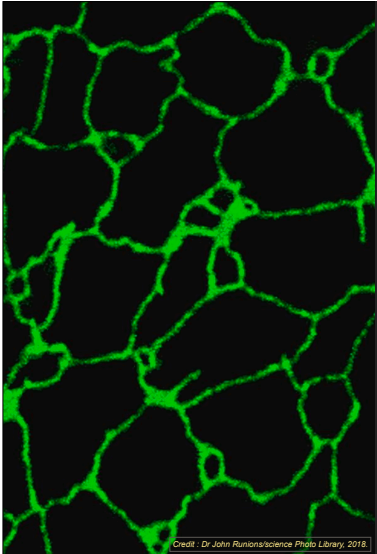


PROTEIN MISFOLDING

UNFOLDED PROTEIN RESPONSE

TIMELINE OF THE UPR





Credit : Dr John Runions/science Photo Library, 2018.

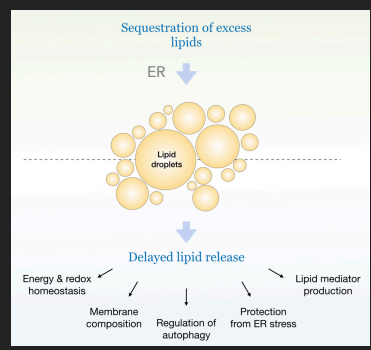
FONCTIONS OF THE SMOOTH ER

LIPID HOMEOSTASIS

LIPID BIOSYNTHESIS

LIPID HOMEOSTASIS

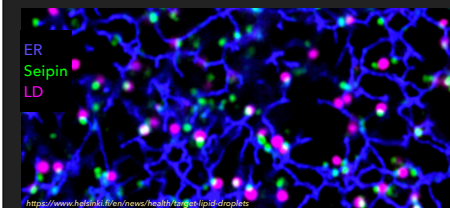
- Energy storage as triglycerides in Lipid Droplets
 - Balanced with lipid degradation
- Biosynthesis and regulation of new lipid bilayers
 - Glycerophospholipids
 - Sphingolipids
 - Cholesterol



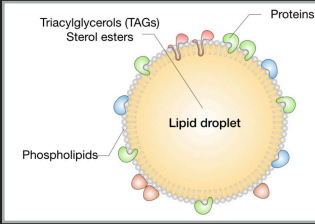
Jarc & Petan, Yale J. Biol. Med., 2019, 92:435.

LIPID BIOSYNTHESIS

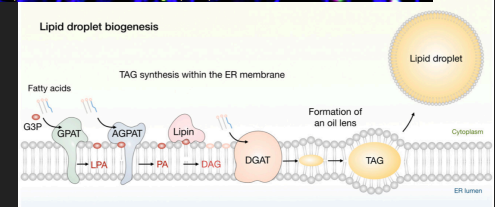
LIPID HOMEOSTASIS



<https://www.huffpost.com/en/news/health/science/lipid-droplets>



Decrease of surface tension in the cytosolic leaflet



Asymmetric protein recruitment and binding

Local asymmetry in phospholipid composition

Symmetrical surface tension

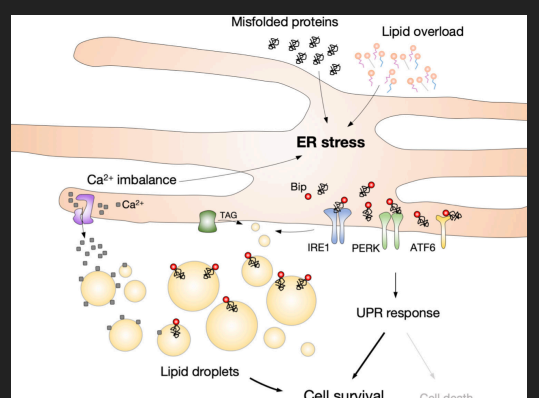
LD budding

Ozman & Carvalho, Nat. Rev. Mol. Cell Biol., 2019, 20:137.

LIPID BIOSYNTHESIS

LIPID HOMEOSTASIS

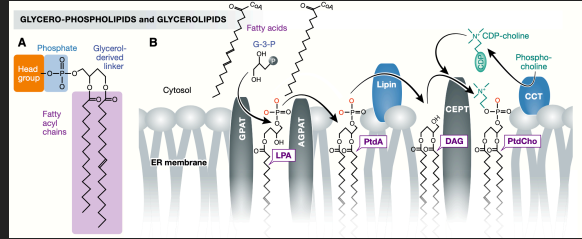
- Contributions to ER stress:
 - LDs buffer excess misfolded proteins → *pro-survival in the course of the UPR*
 - LDs buffer excess lipids → *decreased lipotoxicity*
 - LDs buffer cytosolic calcium released from the ER → *prevents signaling and mitochondria-mediated apoptosis*



Jarc & Petan, Yale J. Biol. Med., 2019, 92:435.

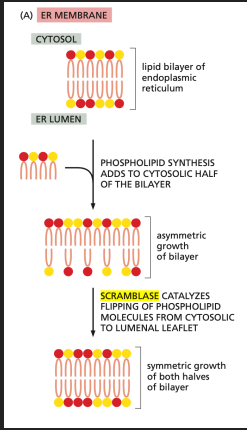
LIPID BIOSYNTHESIS

CYTOSOLIC LEAFLET OF THE ER MEMBRANE



Jacquemyn et al., EMBO Rep., 2017, 18:1905.

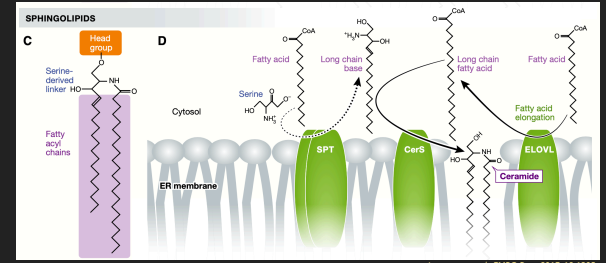
GPAT = Glycerol-3-Phosphate AcylTransferase
 AGPAT = AcylGlycerol-3-Phosphate AcylTransferase
 CEPT = Choline/Ethanolamine PhosphoTransferase
 CCT = CTP:phosphocholine CytidylylTransferase
 LPA = LysoPhosphatidic Acid
 PtdA = Phosphatidic Acid
 DAG = DiAcylGlycerol
 PtdCho = PhosphatidylCholine



Alberts et al., in Molecular Biology of the Cell, Garland Science.

LIPID BIOSYNTHESIS

CYTOSOLIC LEAFLET OF THE ER MEMBRANE

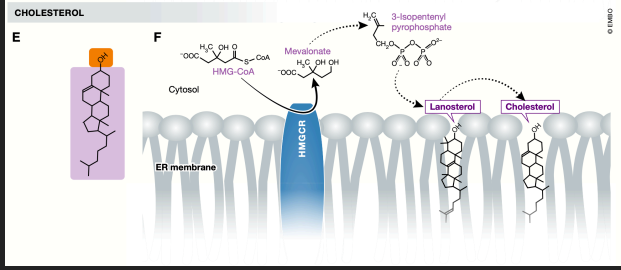


Jacquemyn et al., EMBO Rep., 2017, 18:1905.

SPT = Serine Palmitoyl Transferase
 CerS = Ceramide Synthase
 ELOVL = ELongation Of Very Long fatty acid

LIPID BIOSYNTHESIS

OUTER LEAFLET OF THE ER MEMBRANE

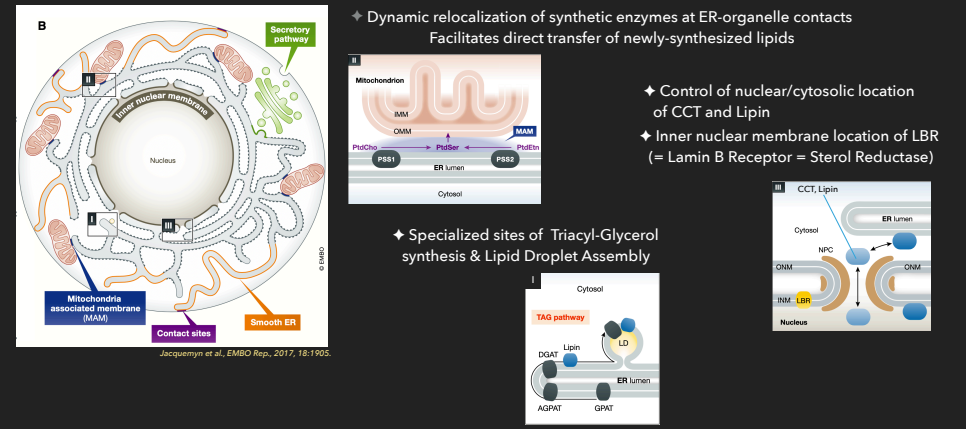


Jacquemyn et al., EMBO Rep., 2017, 18:1905.

HMGCR = HydroxyMethyl Glutaryl CoA Reductase

LIPID BIOSYNTHESIS

DYNAMIC LOCALIZATION OF SYNTHESIS LOCATIONS



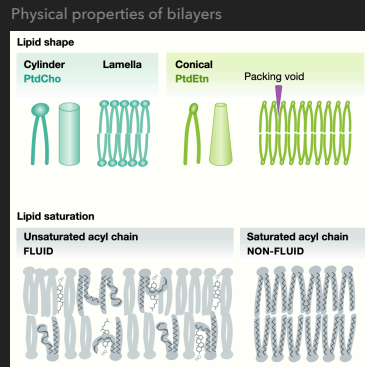
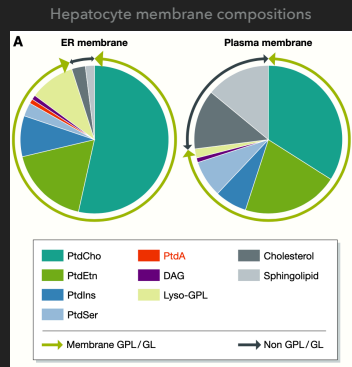
Jacquemyn et al., EMBO Rep., 2017, 18:1905.

Dynamic relocation of synthetic enzymes at ER-organelle contacts
 Facilitates direct transfer of newly-synthesized lipids

Control of nuclear/cytosolic location of CCT and Lipin
 Inner nuclear membrane location of LBR
 (= Lamin B Receptor = Sterol Reductase)

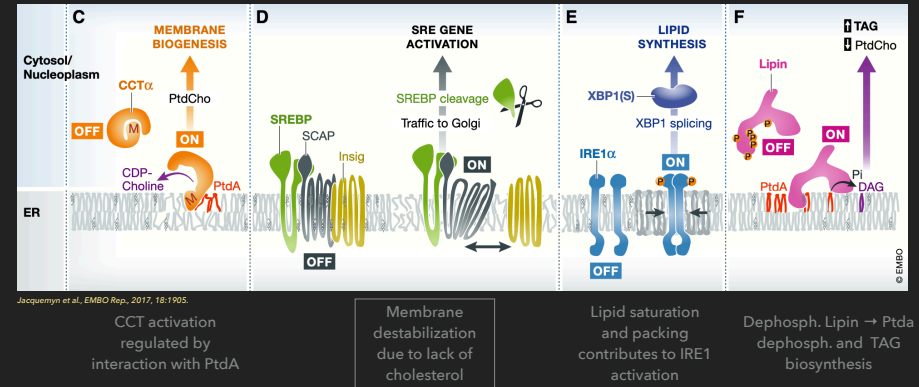
Specialized sites of Triacyl-Glycerol synthesis & Lipid Droplet Assembly

LIPID BIOSYNTHESIS
LIPID HOMEOSTASIS



Jacquemyn et al., EMBO Rep., 2017, 18:1905.

LIPID BIOSYNTHESIS
LIPID HOMEOSTASIS



Jacquemyn et al., EMBO Rep., 2017, 18:1905.

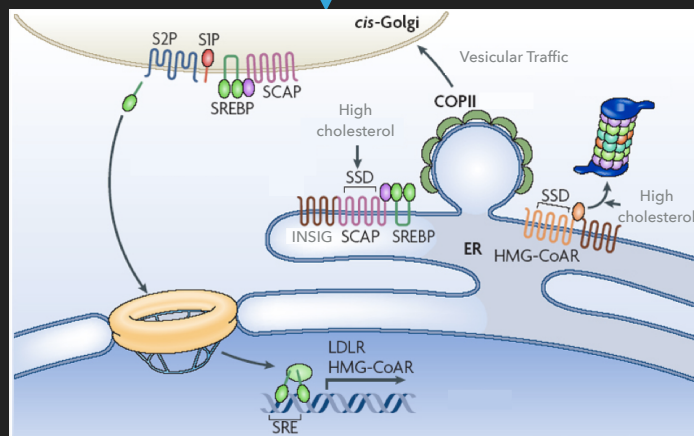
CCT activation regulated by interaction with PtdA

Membrane destabilization due to lack of cholesterol

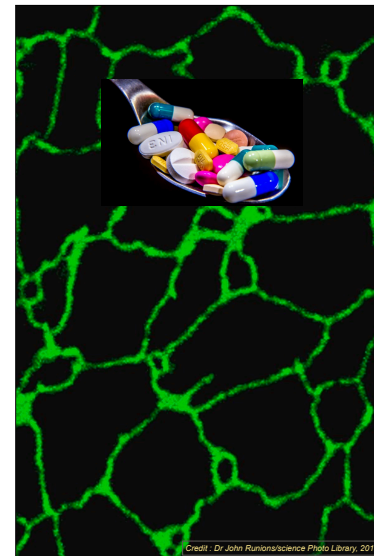
Lipid saturation and packing contributes to IRE1 activation

Dephosph. Lipin → PtdA dephosph. and TAG biosynthesis

LIPID BIOSYNTHESIS
LIPID HOMEOSTASIS



SSD = Sterol-Sensing Domain
SRE = Sterol-Responsive Element
SREBP = Sterol-Responsive Element Binding Protein
SCAP = SREBP Cleavage Activating Protein
INSIG = Insulin-Induced Gene

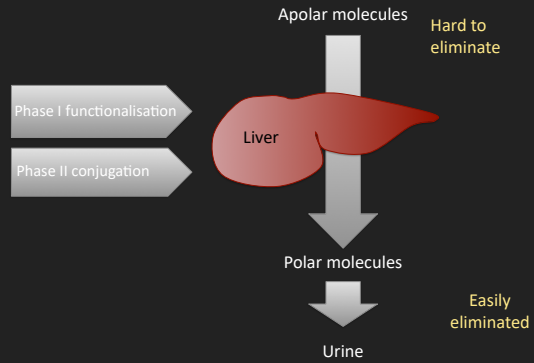


Credit: Dr. John Runions/science Photo Library, 2018.

FONCTIONS OF THE SMOOTH ER
XENOBIOTICS METABOLISM

FUNCTIONS OF THE SMOOTH ER

XENOBIOTICS METABOLISM

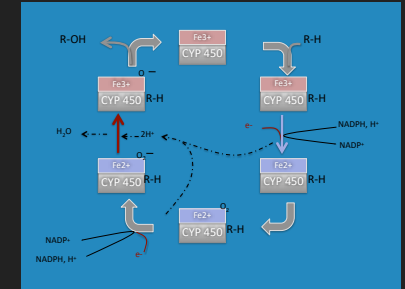
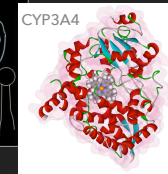
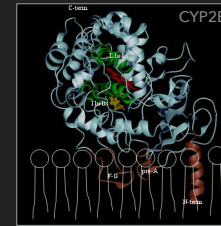
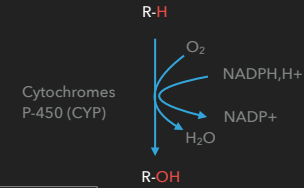


FUNCTIONS OF THE SMOOTH ER

XENOBIOTICS METABOLISM

PHASE I

Mono-oxygenations using molecular oxygen



FUNCTIONS OF THE SMOOTH ER

XENOBIOTICS METABOLISM

PHASE II

Conjugation with various substrates by specific enzymes

- ◆ Glucuronate
- ◆ Acetate
- ◆ Glutathion
- ◆ Sulfates
- ◆ Aminoacids

Integration with Phase I reactions

