traducción

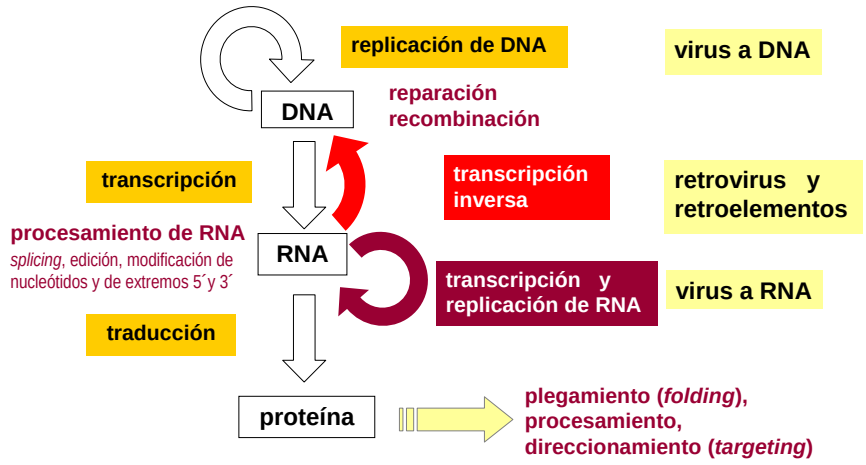
síntesis de proteínas (2)

modificaciones
co- y pos-traduccionales

direccionamiento de proteínas

1

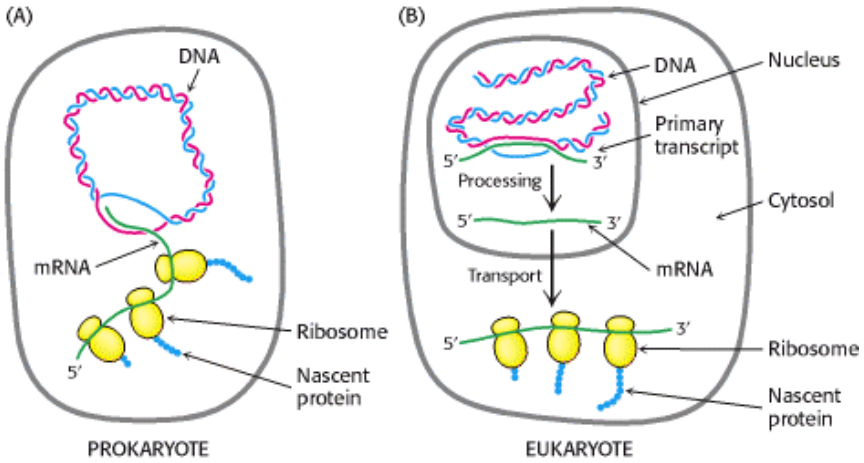
"Dogma central de la biología molecular"



2

Víctor Romanowski

transcripción y traducción
en el mismo o en diferentes compartimientos



3

Modificación de proteínas

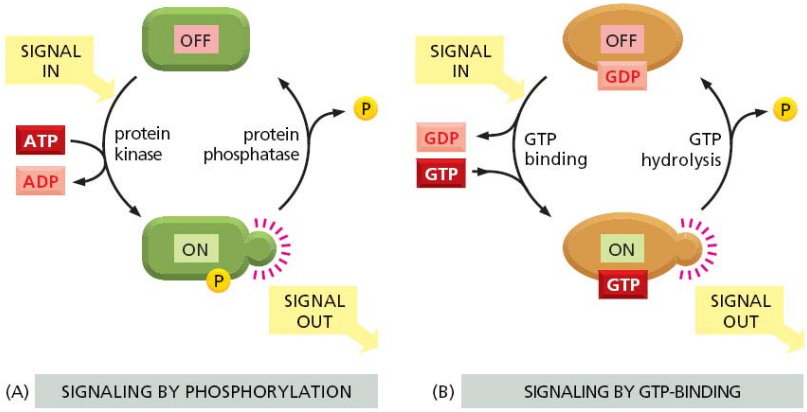
1. las proteínas sufren modificaciones post-traducionales (y co-traduccionales)

2. la actividad biológica puede depender de las modificaciones

3. la espectrometría de masas es uno de los mejores métodos para identificar las modificaciones

4

Modificación de proteínas ➡ covalente o no covalente ➡ actividad



A comparison of the two major intracellular signaling mechanisms in eucaryotic cells. In both cases, a signaling protein is activated by the addition of a phosphate group and inactivated by the removal of this phosphate. To emphasize the similarities in the two pathways, ATP and GTP are drawn as APPP and GPPP, and ADP and GDP as APP and GPP, respectively. The addition of a phosphate to a protein can also be inhibitory.

5

- Protein Post-translational Modifications

1. Folding and Processing of Proteins

-During translation proteins fold as they exit ribosome

-Some proteins can assume native 3D structure spontaneously

-Other proteins may require chaperones

6

Protein Post-translational Modifications

2. Amino-terminal and carboxyterminal modifications

-Cleavage of f-Met from bacterial proteins or Met from eukaryotic proteins. Other amino acids may be trimmed as well.

-Acetylation of Met or other N-terminal amino acids

-Removal of signal peptide for secreted or membrane proteins

-Removal of C-terminal amino acids.

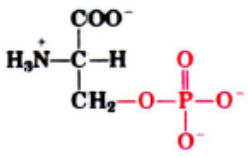
7

Protein Post-translational Modifications

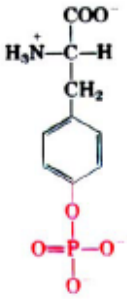
3. Modification of Individual Amino Acids

a. Phosphorylation

- Enzymatic reaction by specific kinases
- Usually on Ser, Thr, Tyr



Phosphoserine



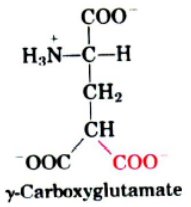
Phosphotyrosine

8

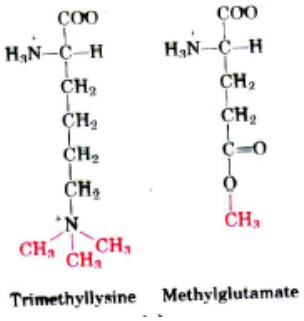
- Protein Post-translational Modifications

3. Modification of Individual Amino Acids

b. Carboxylation
Addition of extra carboxyl groups to Asp and Glu


γ-Carboxyglutamate

c. Methylation
Addition of methyl groups to Lys and Glu


Trimethyllysine Methylglutamate

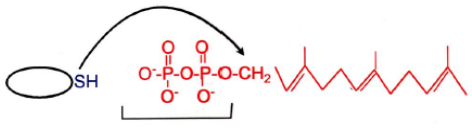
- Protein Post-translational Modifications

3. Modification of Individual Amino Acids

d. Isoprenylation

- Addition of an isoprenyl group to a protein at either the C-terminus or the N-terminus

- Derived from pyrophosphate intermediate in cholesterol biosynthesis



10

- Protein Post-translational Modifications

3. Modification of Individual Amino Acids

e. Addition of prosthetic groups

Covalently bound prosthetic group – required for activity
Example: Cytochrome C -- Heme group

11

Protein Post-translational Modifications

3. Modification of Individual Amino Acids

f. Proteolytic Processing
Some types of proteins are synthesized as a larger, inactive precursor protein and must be cleaved for activity

g. Formation of disulfide bonds
Spontaneous cross-linking at Cys residues
Brought into proximity by folding
Helps to stabilize 3D structure

12

- Protein Post-translational Modifications

3. Modification of Individual Amino Acids

h. Glycosylation (N)

-Addition of oligosaccharides to proteins

-Usually at Asn

-Sugars are transferred from dolichol-P

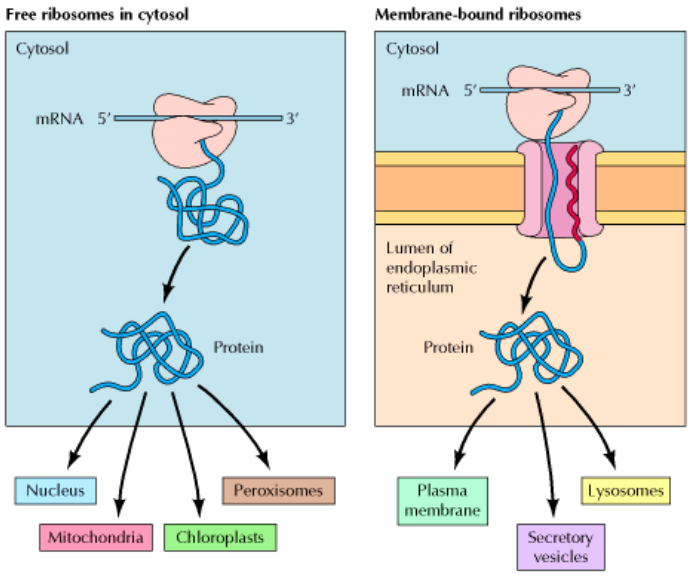
-Present in ER

13

Direccionamiento proteínas a diferentes compartimientos subcelulares

protein targeting

14

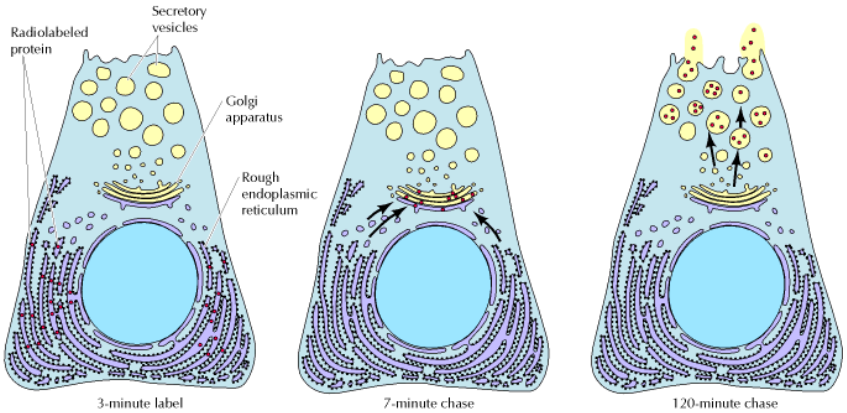


Overview of protein sorting In mammalian cells, the initial sorting of proteins to the ER takes place while translation is in progress. Proteins synthesized on free ribosomes either remain in the cytosol or are transported to the nucleus, mitochondria, chloroplasts, or peroxisomes. In contrast, proteins synthesized on membrane-bound ribosomes are translocated into the ER while their translation is in progress. They may be either retained within the ER or transported to the Golgi apparatus and, from there, to lysosomes, the plasma membrane, or the cell exterior via secretory vesicles.

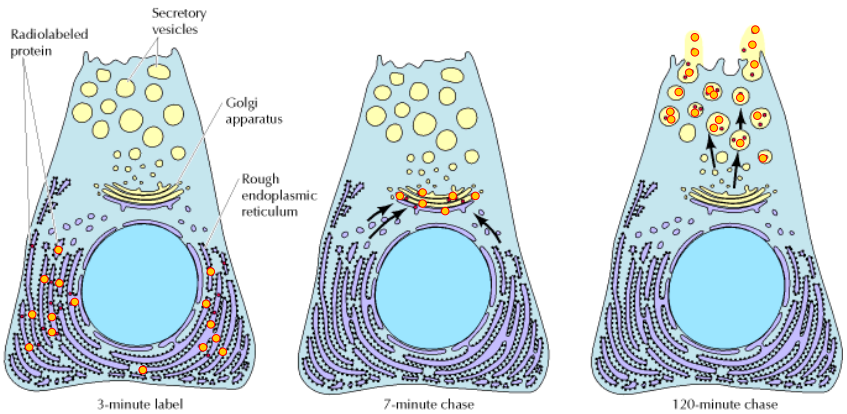
15

proteínas de secreción:
la vía secretoria
secretory pathway

16



The secretory pathway Pancreatic acinar cells, which secrete most of their newly synthesized proteins into the digestive tract, were labeled with radioactive amino acids to study the intracellular pathway taken by secreted proteins. After a short incubation with radioactive amino acids (3-minute label), autoradiography revealed that newly synthesized proteins were localized to the rough ER. Following further incubation with nonradioactive amino acids (a chase), proteins were found to move from the ER to the Golgi apparatus and then, within secretory vesicles, to the plasma membrane and cell exterior. 17



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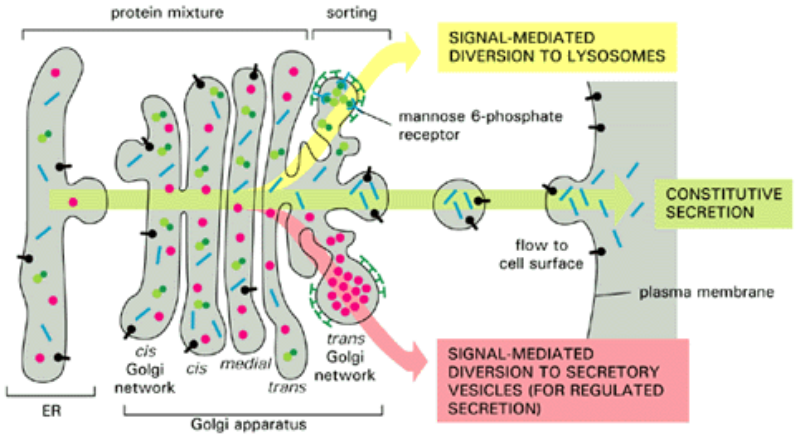
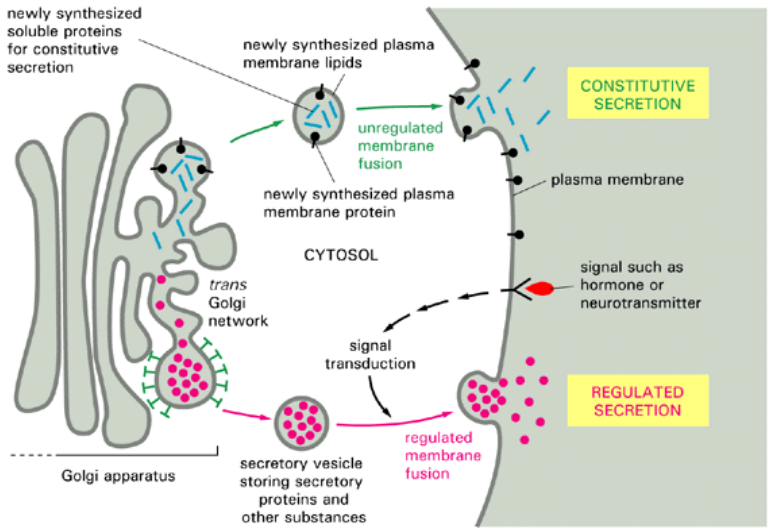

protein mixture
sorting
SIGNAL-MEDIATED DIVERSION TO LYSOSOMES
mannose 6-phosphate receptor
CONSTITUTIVE SECRETION
flow to cell surface
plasma membrane
cis Golgi network
cis
medial
trans
trans Golgi network
SIGNAL-MEDIATED DIVERSION TO SECRETORY VESICLES (FOR REGULATED SECRETION)
ER
Golgi apparatus

19


newly synthesized soluble proteins for constitutive secretion
newly synthesized plasma membrane lipids
CONSTITUTIVE SECRETION
unregulated membrane fusion
plasma membrane
newly synthesized plasma membrane protein
CYTOSOL
signal such as hormone or neurotransmitter
trans Golgi network
signal transduction
REGULATED SECRETION
regulated membrane fusion
secretory vesicle storing secretory proteins and other substances
Golgi apparatus

20

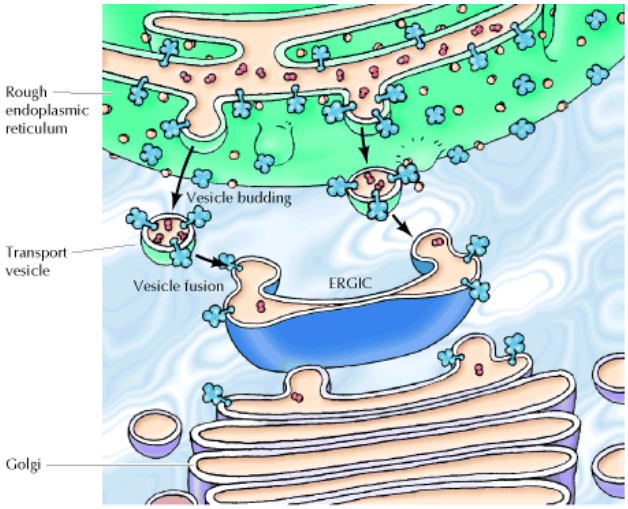
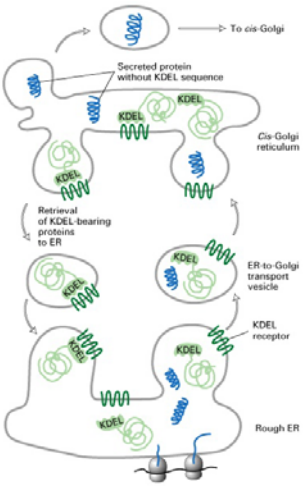


Figure 9.20. Vesicular transport from the ER to the Golgi Proteins and lipids are carried from the ER to the Golgi in transport vesicles that bud from the membrane of the ER and then fuse to form the vesicles and tubules of the ER-Golgi intermediate compartment (ERGIC). Lumenal ER proteins are taken up by the vesicles and released into the lumen of the Golgi. Membrane proteins maintain the same orientation in the Golgi as in the ER.

21

ER-resident proteins often are retrieved from the *cis*-Golgi



22

Lys-Asp-Glu-Leu (**KDEL**)
C-terminal → RER

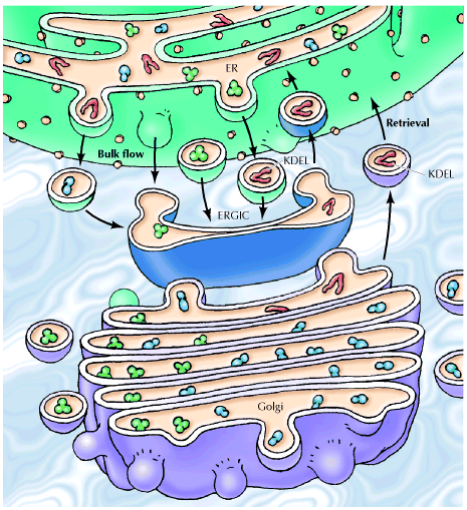
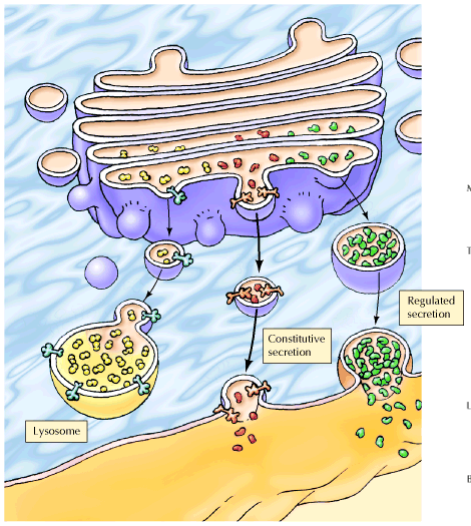


Figure 9.21. Retrieval of resident ER proteins Proteins destined to remain in the lumen of the ER are marked by the sequence Lys-Asp-Glu-Leu (KDEL) at their carboxy terminus. These proteins are exported from the ER to the Golgi in the nonselective bulk flow of proteins through the secretory pathway, but they are recognized by a receptor in the ER-Golgi intermediate compartment (ERGIC) or the Golgi apparatus and selectively returned to the ER.

23



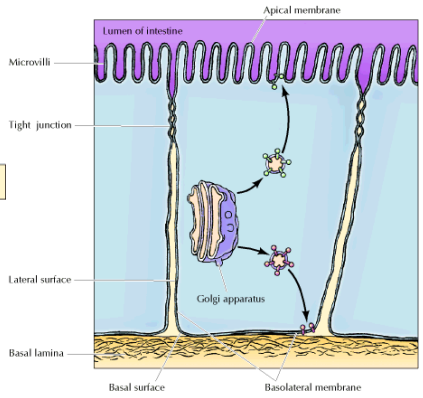
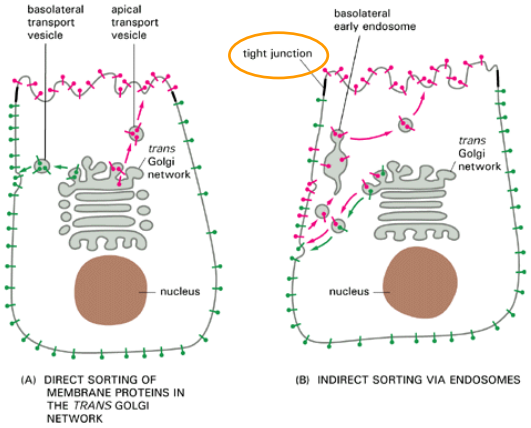


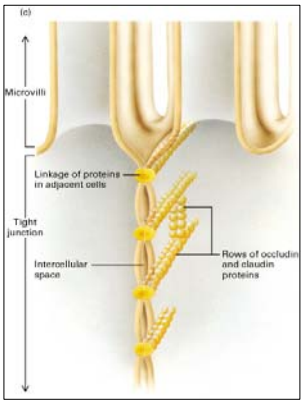
Figure 9.27. Transport from the Golgi apparatus Proteins are sorted in the *trans* Golgi network and transported in vesicles to their final destinations. In the absence of specific targeting signals, proteins are carried to the plasma membrane by constitutive secretion. Alternatively, proteins can be diverted from the constitutive secretion pathway and targeted to other destinations, such as lysosomes or regulated secretion from the cells. **Figure 9.28. Transport to the plasma membrane of polarized cells** The plasma membranes of polarized epithelial cells are divided into apical and basolateral domains. In this example (intestinal epithelium), the apical surface of the cell faces the lumen of the intestine, the lateral surfaces are in contact with neighboring cells, and the basal surface rests on a sheet of extracellular matrix (the basal lamina). The apical membrane is characterized by the presence of microvilli, which facilitate the absorption of nutrients by increasing surface area. Specific proteins are targeted to either the apical or basolateral membranes in the *trans* Golgi network. Tight junctions between neighboring cells maintain the identity of the apical and basolateral membranes by preventing the diffusion of proteins between these domains.

24

direccionamiento a superficie apical y basolateral

en células polarizadas (epitelios)





tight junctions
uniones de oclusión
o estancas

25

The Nobel Prize in Physiology or Medicine 1999

"for the discovery that proteins have intrinsic **signals** that govern their **transport and localization** in the cell"

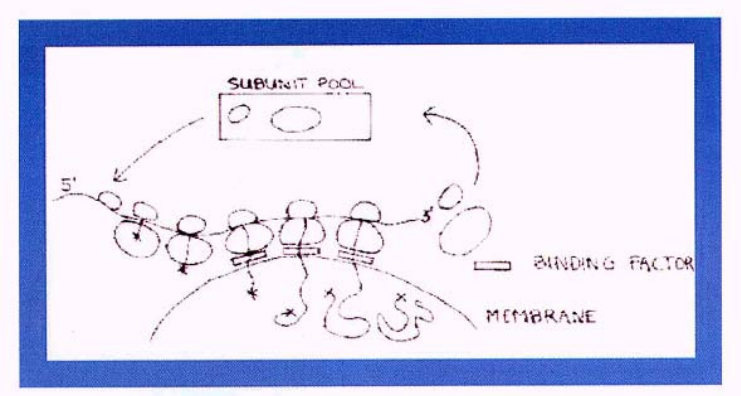
Günter Blobel

Rockefeller University, New York, NY, USA;
Howard Hughes Medical Institute

26

Signal hypothesis

1971: “Las proteínas secretadas al espacio extracelular contienen una señal intrínseca que las dirige hacia y a través de las membranas”



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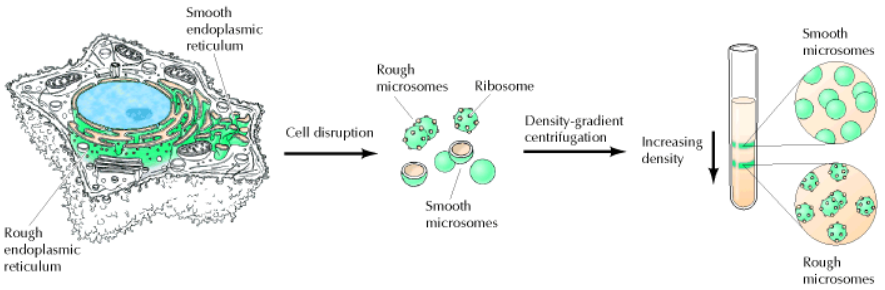
Signal hypothesis

- La traducción de poly(A) mRNA de células de mieloma (principalmente mRNA de IgG) en un sistema libre de células **sin vesículas microsomales** genera una **proteína 2-3 kDa mayor**.
- El mapa peptídico indica que la extensión se encuentra en el **amino** terminal

Milstein, C**. et al., Nature New Biology 239: 117-120, **1972

28

preparación de microsomas



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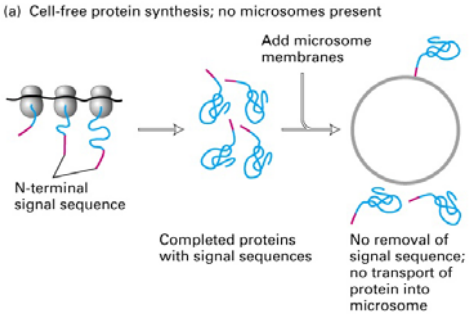
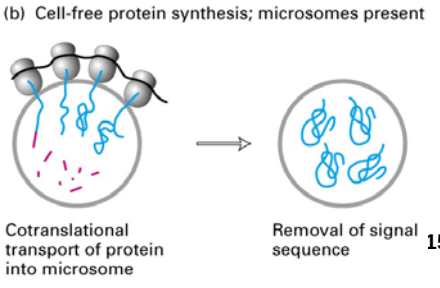


traducción *in vitro* en ausencia de microsomas

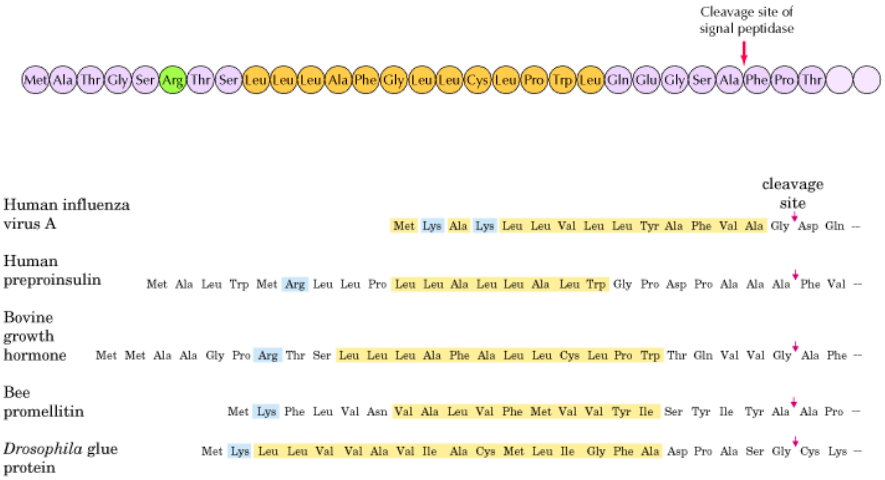


importación co-traduccional de las proteínas al RER:

traducción *in vitro* en presencia de microsomas

15

The signal sequence of growth hormone
Most signal sequences contain a stretch of hydrophobic amino acids, preceded by basic residues (e.g., arginine).



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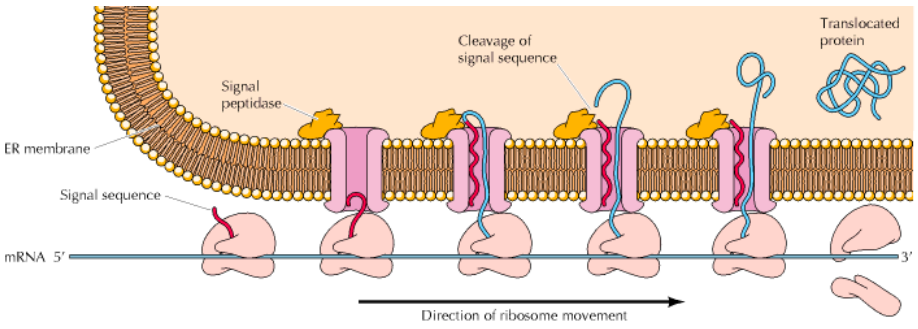
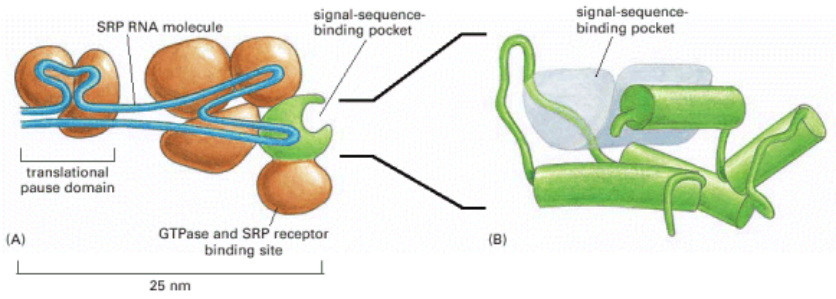


The role of signal sequences in membrane translocation Signal se-quences target the translocation of polypeptide chains across the plasma membrane of bacteria or into the endoplasmic reticulum of eukaryotic cells (shown here). The signal sequence, a stretch of hydrophobic amino acids at the amino terminus of the polypeptide chain, inserts into a membrane channel as it emerges from the ribosome. The rest of the polypeptide is then translocated through the channel and the signal sequence is cleaved by the action of signal peptidase, releasing the mature translocated protein.

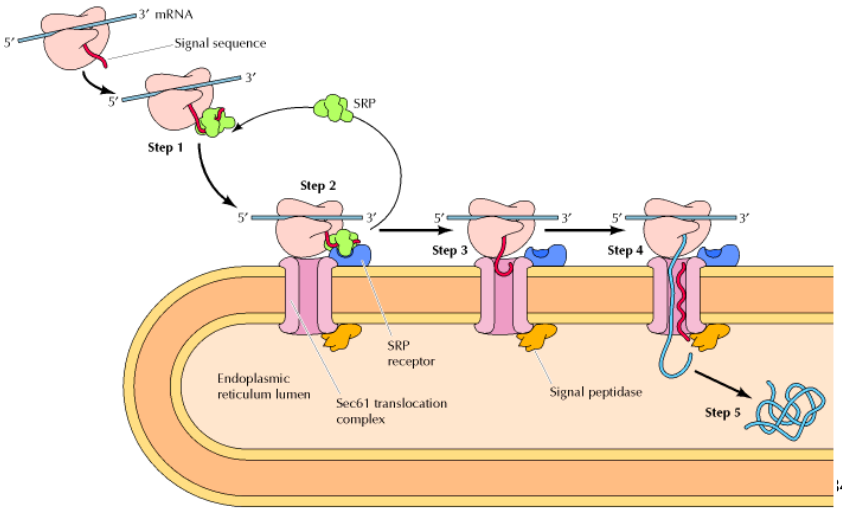
32

Estructura de la partícula de reconocimiento de la señal “signal recognition particle” (SRP)



33

Cotranslational targeting of secretory proteins to the ER Step 1: As the signal sequence emerges from the ribosome, it is recognized and bound by the signal recognition particle (SRP). Step 2: The SRP escorts the complex to the ER membrane, where it binds to the SRP receptor. Step 3: The SRP is released, the ribosome binds to a membrane translocation complex of Sec61 proteins, and the signal sequence is inserted into a membrane channel. Step 4: Translation resumes, and the growing polypeptide chain is translocated across the membrane. Step 5: Cleavage of the signal sequence by signal peptidase releases the polypeptide into the lumen of the ER.



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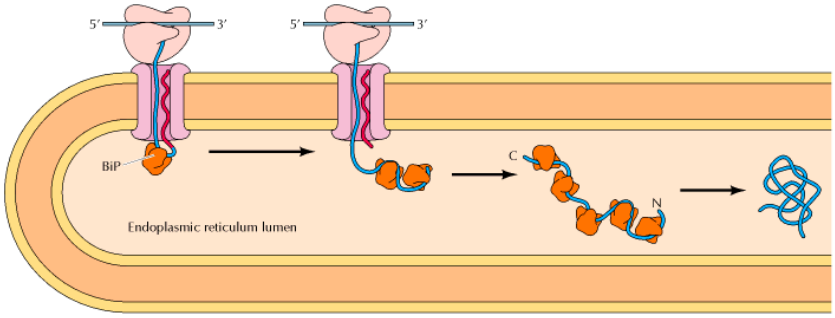
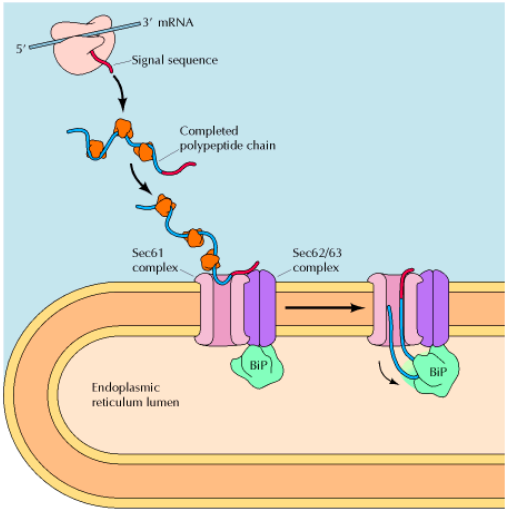


35

More unusual pathway for translocation of proteins into the ER

Figure 9.8. Posttranslational translocation of proteins into the ER Proteins destined for posttranslational import to the ER are synthesized on free ribosomes and maintained in an unfolded conformation by cytosolic chaperones. Their signal sequences are recognized by the Sec62/63 complex, which is associated with the Sec61 translocation channel in the ER membrane. The Sec63 protein is also associated with a chaperone protein (BiP), which acts as a molecular ratchet to drive protein translocation into the ER.



36

Chaperones

Protein family	Prokaryotes	Eukaryotes	Cell compartment
Hsp70	DnaK	Hsc73	Cytosol
		BiP	endoplasmic reticulum
		SSC1	mitochondria
		ctHsp70	Chloroplasts
Hsp60	GroEL	TriC	cytosol
		Hsp60	Mitochondria
		Cpn60	chloroplasts
Hsp90	HtpG	Hsp90	Cytosol
		Grp94	endoplasmic reticulum
		Hsc73	Cytosol

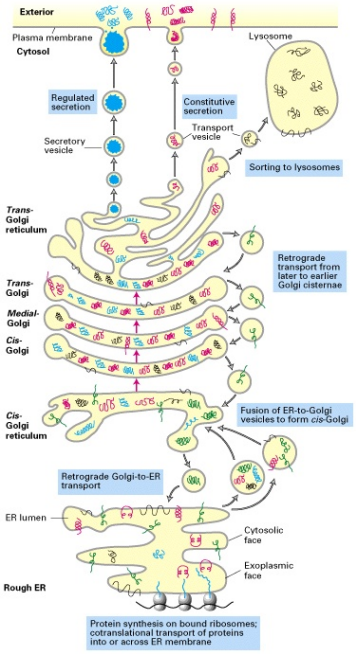
37

Espacio extracelular

trans Golgi

Cis Golgi

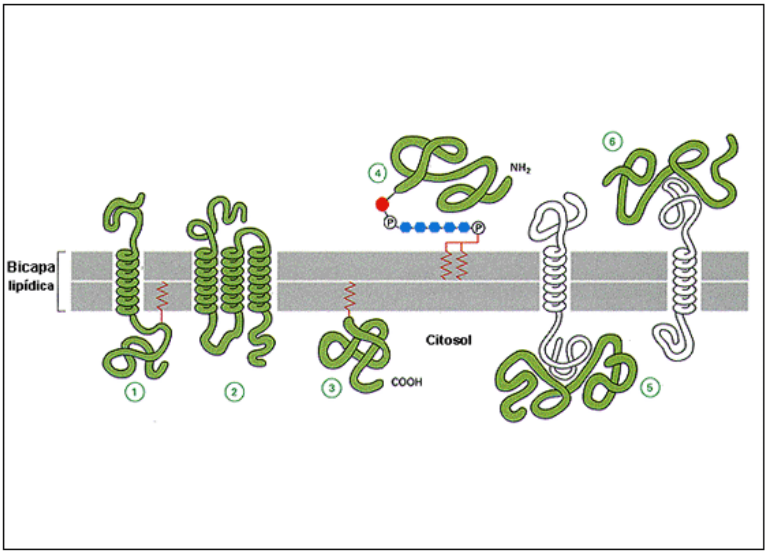
RE rugoso



ruta secretoria

38

proteínas de membrana



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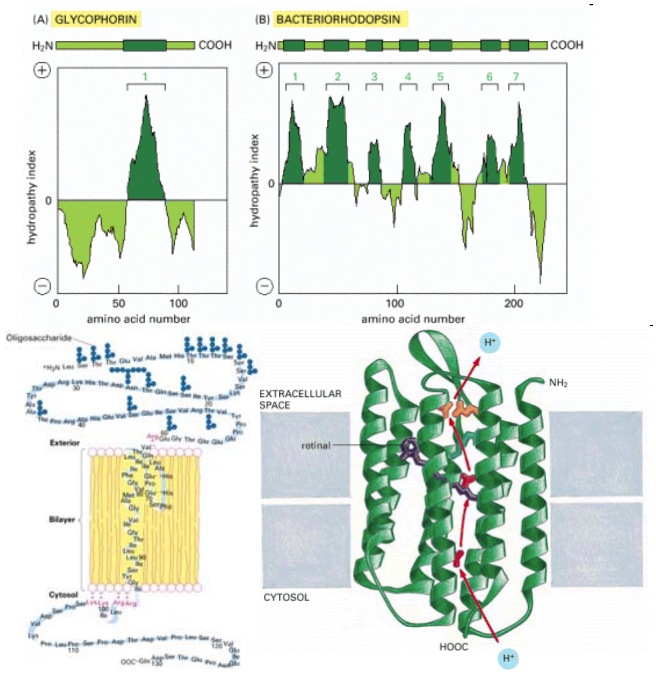
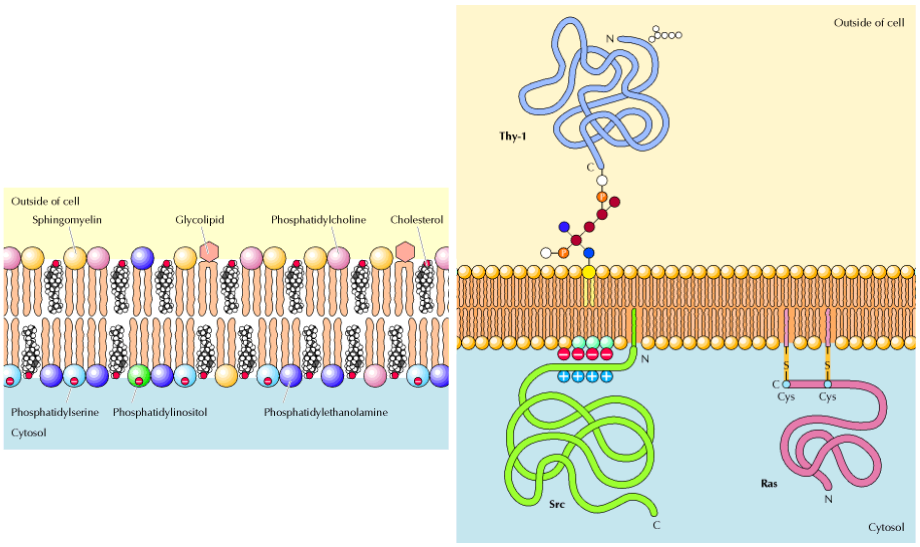


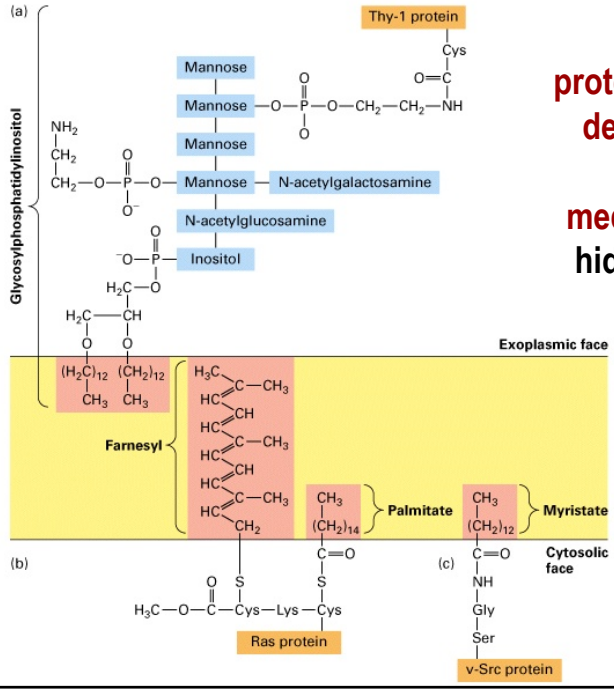
Figure 10-37. The three-dimensional structure of a bacteriorhodopsin molecule. The polypeptide chain **crosses the lipid bilayer seven times as α helices**. The location of the retinal chromophore *(purple)* and the probable pathway taken by protons during the light-activated pumping cycle are shown. The first and key step is the passing of a H+ from the chromophore to the side chain of aspartic acid 85 *(red,* located next to the chromophore) that occurs upon absorption of a photon by the chromophore. Subsequently, other H+ transfers—utilizing the hydrophilic amino acid side chains that line a path through the membrane—complete the pumping cycle and return the enzyme to its starting state. Color code: glutamic acid *(orange),* aspartic acid *(red),* arginine *(blue).* (Adapted from H. Luecke et al., *Science* 286:255–260, 1999.) Alberts 2002

40



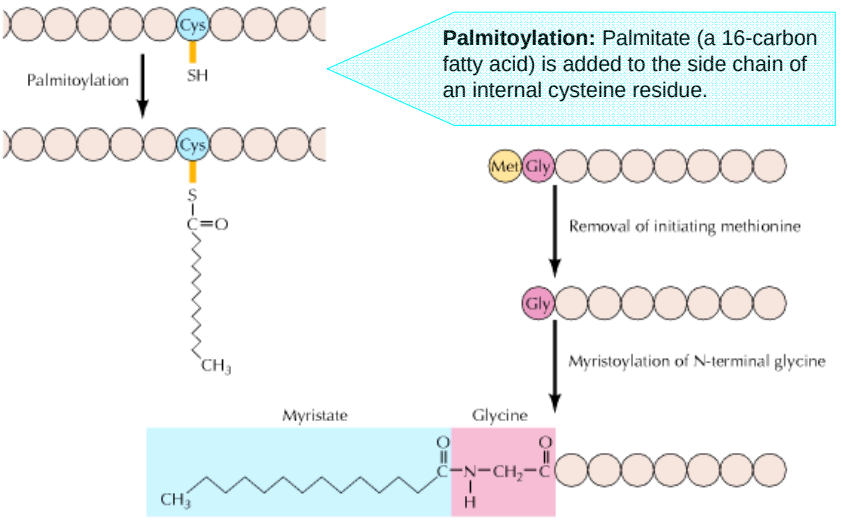
Examples of proteins anchored in the plasma membrane by lipids and glycolipids Some proteins (e.g., the lymphocyte protein Thy-1) are anchored in the outer leaflet of the plasma membrane by GPI anchors added to their C terminus in the endoplasmic reticulum. These proteins are glycosylated and exposed on the cell surface. Other proteins are anchored in the inner leaflet of the plasma membrane following their translation on free cytosolic ribosomes. The Ras protein illustrated is anchored by a prenyl group attached to the side chain of a C-terminal cysteine and by a palmitoyl group attached to a cysteine located five amino acids upstream. The Src protein is anchored by a myristoyl group attached to its N terminus. A positively charged region of Src also plays a role in membrane association, perhaps by interacting with the negatively charged head groups of phosphatidylserine.

41



Anclaje de proteínas integrales de la membrana plasmática mediante cadenas hidrocarbonadas

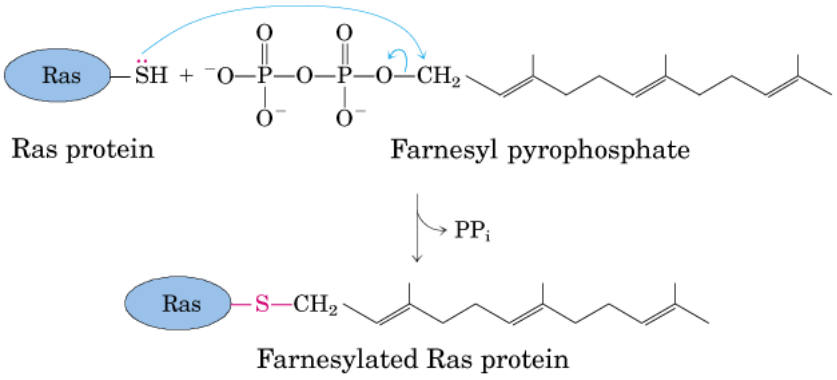
42



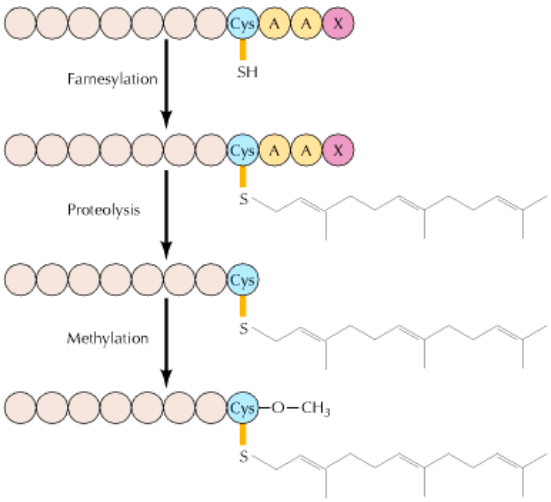
Palmitoylation: Palmitate (a 16-carbon fatty acid) is added to the side chain of an internal cysteine residue.

Addition of a fatty acid by **N-myristoylation:** The initiating methionine is removed, leaving glycine at the N terminus of the polypeptide chain. Myristic acid (a 14-carbon fatty acid) is then added.

43



44



Prenylation **of a C-terminal cysteine residue:** The type of prenylation shown affects Ras proteins and proteins of the nuclear envelope (nuclear lamins). These proteins terminate with a cysteine residue (Cys) followed by two aliphatic amino acids (A) and any other amino acid (X) at the C terminus. The first step in their modification is addition of the 15-carbon farnesyl group to the side chain of cysteine (farnesylation). This step is followed by proteolytic removal of the three C-terminal amino acids and methylation of the cysteine, which is now at the C terminus.

45

After insertion into the ER membrane, some proteins are transferred to a GPI anchor

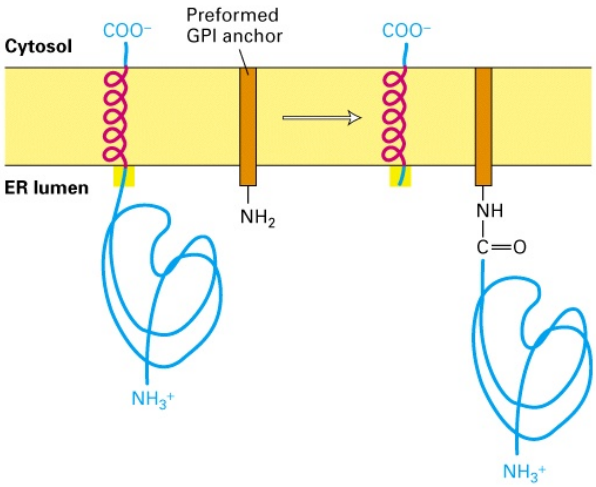
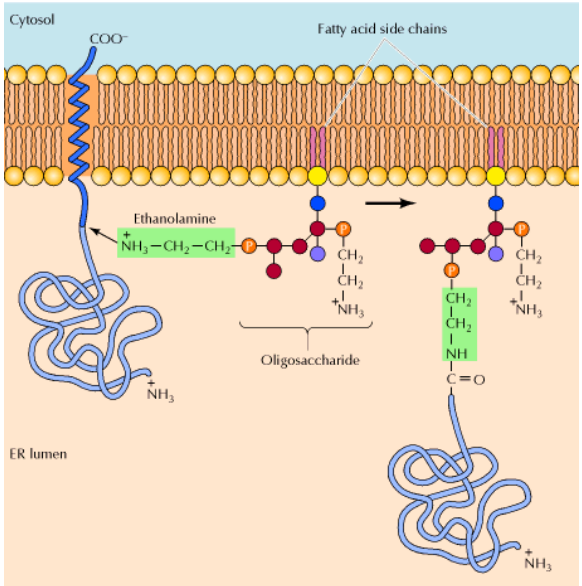


Figure 17-25

46

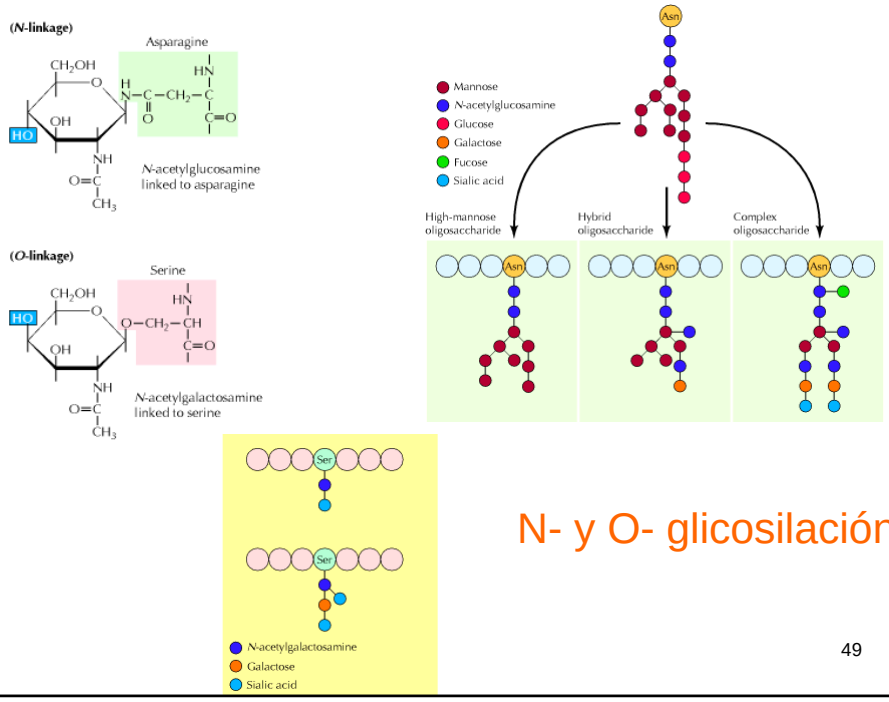


Addition of GPI anchors: Glycosylphosphatidylinositol (GPI) anchors contain two fatty acid chains, an oligosaccharide portion consisting of inositol and other sugars, and ethanolamine. The GPI anchors are assembled in the ER and added to polypeptides anchored in the membrane by a carboxy-terminal membrane- spanning region. The membranespanning region is cleaved, and the new carboxy terminus is joined to the NH2 group of ethanolamine immediately after translation is completed, leaving the protein attached to the membrane by the GPI anchor.

47

glicosilación de proteínas

48



N- y O- glicosilación

49

ABO blood type

is determined by two glycosyltransferases

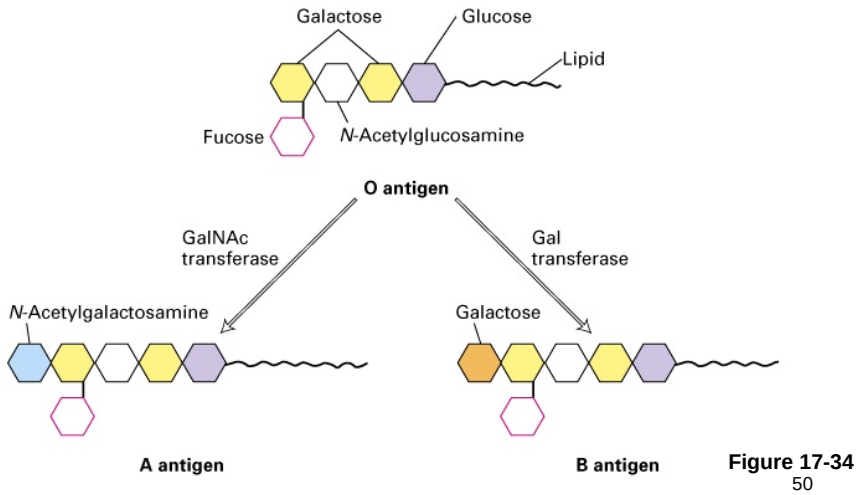
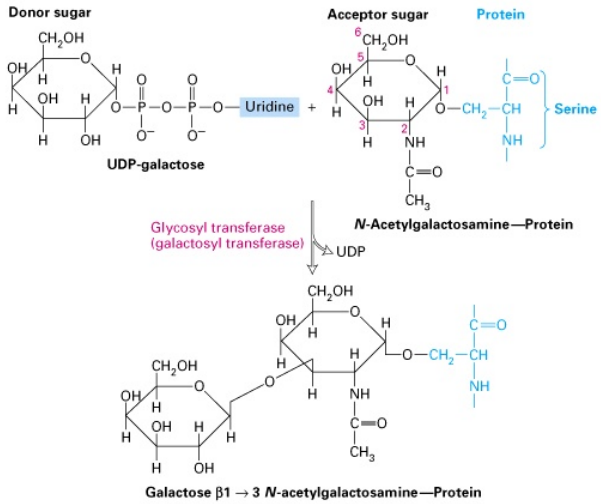


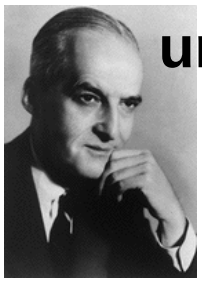
Figure 17-34

50

Las **glicosiltransferases** adicionan azúcares en forma específica utilizando **nucleótidos-azúcares** como dadores



51



uridina-difosfato-glucosa
UDPG

Luis Federico Leloir (1906-1987)

Premio Nobel de Química (1970)

Luis F. Leloir

Two decades of research on the biosynthesis of saccharides

Nobel Lecture, 11 December, 1970

52

340 1970 LUIS F. LELOIR

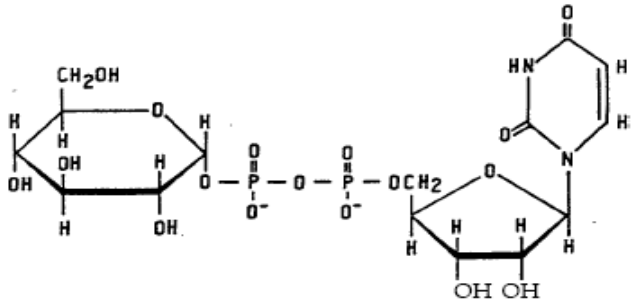
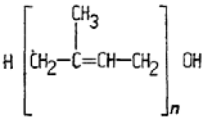


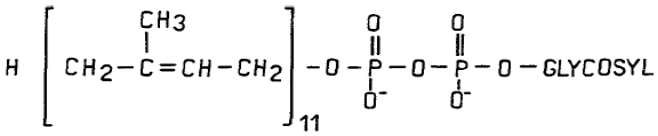
Fig. 1. Uridine diphosphate glucose (UDPG).

10. R.Caputto, L.F.Leloir, R.E.Trucco, C.E.Cardini and A.C.Paladini, *Arch.Biochem.*, 18(1948) 201.
9. R.Caputto, L.F.Leloir, C.E.Cardini. and A.C.Paladini, *J.Biol;Chem.*, 184(1950) 333.
12. C.E.Cardini, A. C. Paladini, R.Caputto and L.F.Leloir, *Nature*, 165(1950) 191.
48. E.Recondo, M.Dankert and L.F.Leloir, *Biochem.Biophys.Res.Commun.*, 12(1963) 204

53

Lipid Intermediates





UDP–glucose + DMP → DMP–glucose + UDP (22)

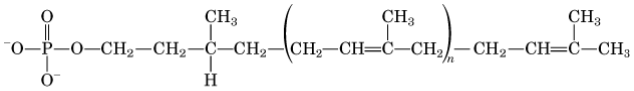
DMP–glucose + E → glucose–E + DMP (23)

glucose–E → glucose + E (24)

In these equations DMP stands for dolichol monophosphate and E for an endogenous acceptor believed to be a protein.

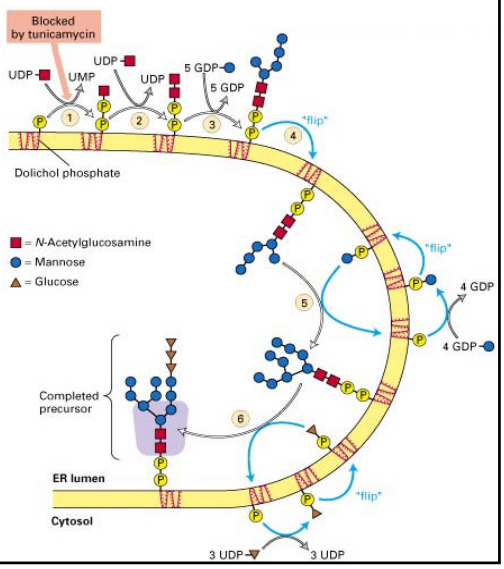
A.Wright, M.Dankert, P.Fennesey and P.W.Robbins ,*Proc.Natl.Acad.Sci.(U.S.)*, 57 (1967) 1798.
N. H. Behrens and L. F. Leloir, *Proc. Natl.Acad.Sci. (U.S.)*, 66 (1970) 153.

54



Dolichol phosphate
(n = 9–22)

A common
preformed N-linked oligosaccharide
is added to many proteins
in the **rough ER**



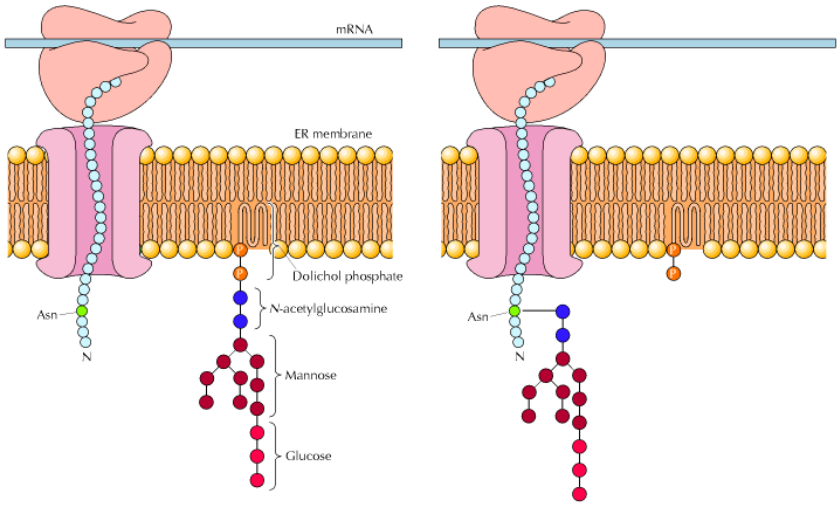
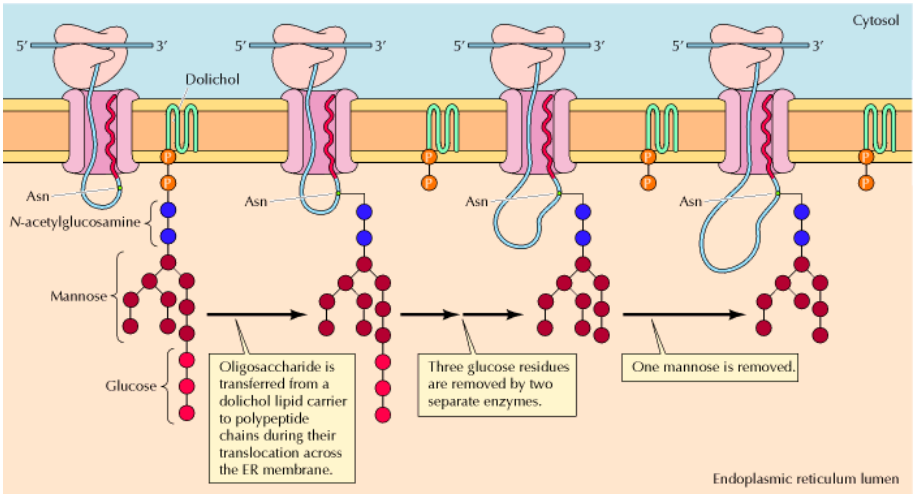


Figure 7.26. Synthesis of *N*-linked glycoproteins The first step in glycosylation is the addition of an oligosaccharide consisting of 14 sugar residues to a growing polypeptide chain in the endoplasmic reticulum (ER). The oligosaccharide (which consists of two *N*-acetylglucosamine, nine mannose, and three glucose residues) is assembled on a lipid carrier (dolichol phosphate) in the ER membrane. It is then transferred as a unit to an acceptor asparagine residue of the polypeptide.



57

Science, **298**, 1790-1793 (2002)

N-Linked Glycosylation in *Campylobacter jejuni* and Its Functional Transfer into *E. coli*

Michael Wacker,[1]* Dennis Linton,[2]* Paul G. Hitchen,[3] Mihai Nita-Lazar,[1] Stuart M. Haslam,[3] Simon J. North,[3] Maria Panico,[3] Howard R. Morris,[3,4] Anne Dell,[3] Brendan W. Wren,[2] Markus Aebi[1]†

N-linked protein glycosylation is the most abundant posttranslation modification of secretory proteins in eukaryotes. A wide range of functions are attributed to glycan structures covalently linked to asparagine residues within the asparagine-X-serine/threonine consensus sequence (Asn-Xaa-Ser/Thr). We found an N-linked glycosylation system in the bacterium *Campylobacter jejuni* and demonstrate that a functional N-linked glycosylation pathway could be transferred into *Escherichia coli*. Although the bacterial N-glycan differs structurally from its eukaryotic counterparts, the cloning of a universal N-linked glycosylation cassette in *E. coli* opens up the possibility of engineering permutations of recombinant glycan structures for research and industrial applications.

58

Disulfide bonds are formed and rearranged in the ER lumen

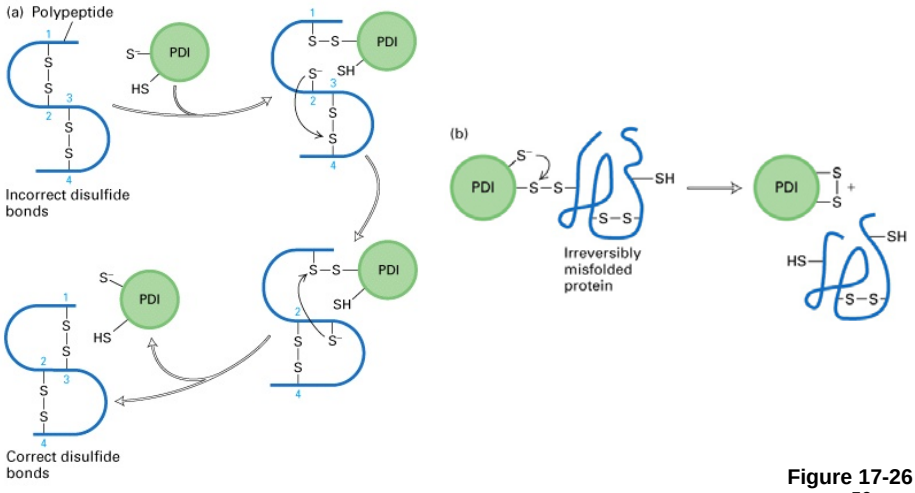
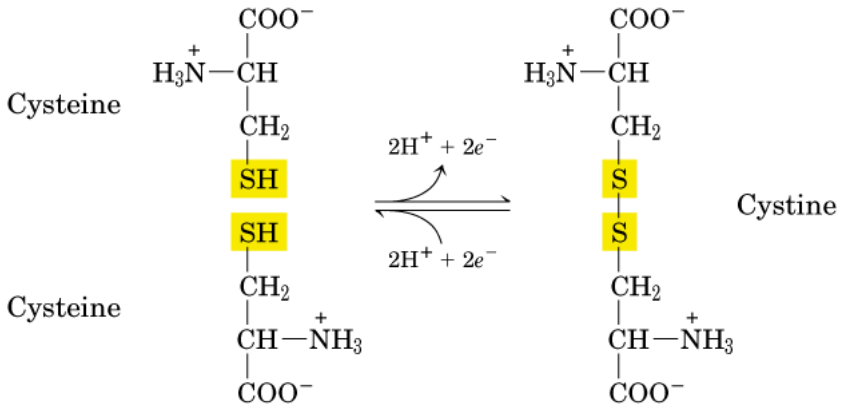
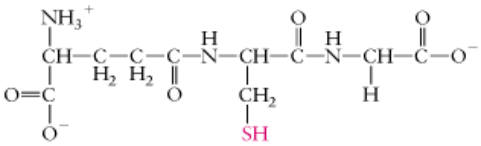


Figure 17-26

59



60



glutathione (GSH)

The **GSH:GSSG** ratio is over **50:1** in the **cytosol**; oxidized GSSG in the cytosol is reduced by the enzyme glutathione reductase, using electrons from the potent reducing agent NADPH
Thus, **cytosolic proteins** in bacterial and eukaryotic cells **do not utilize the disulfide bond** as a stabilizing force because the high GSH:GSSG ratio would drive the system in the direction of Cys SH and away from Cys S-S Cys.

$$NADPH + H^+ + GSSG \longrightarrow NADP^+ + 2\ GSH$$

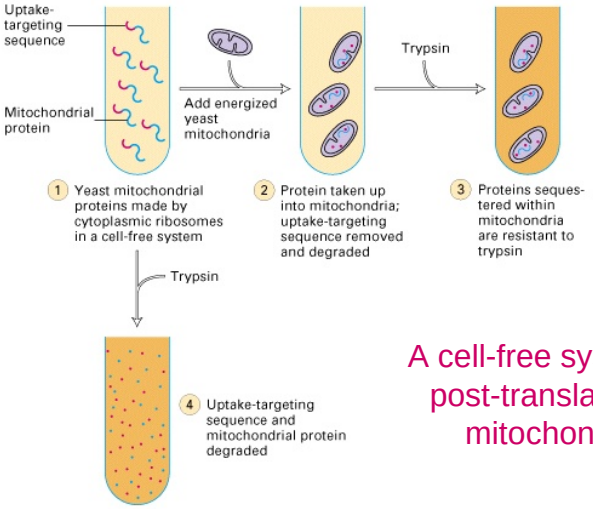
61

Post-translational modifications and quality control in the rough ER

- Newly synthesized polypeptides in the membrane and lumen of the ER undergo five principal modifications
  - Formation of disulfide bonds
  - Proper folding
  - Addition and processing of carbohydrates
  - Specific proteolytic cleavages
  - Assembly into multimeric proteins

62

Direccionamiento postraduccional de proteínas sintetizadas en citosol



A cell-free system for studying post-translational uptake of mitochondrial proteins

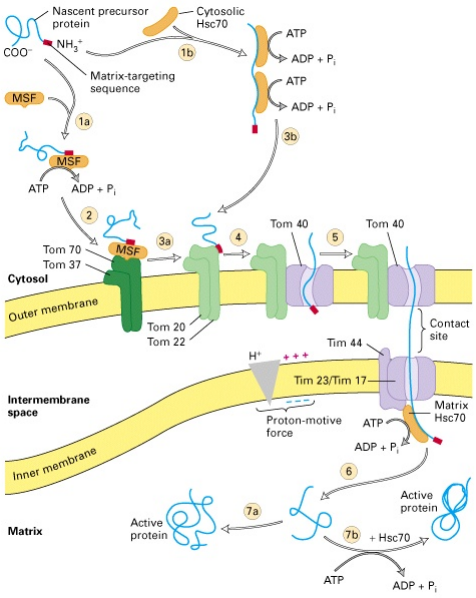
63

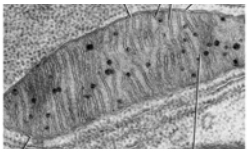
¿Qué elementos son requeridos para el direccionamiento mitocondrial?

- Una o más señales en la proteína
- Un receptor que reconozca la señal y direccione la proteína a la membrana correcta
- Una maquinaria de translocación, un canal
- Energía para abrir la compuerta y translocar la proteína

• Chaperonas para desplegar la proteína ya sintetizada

64



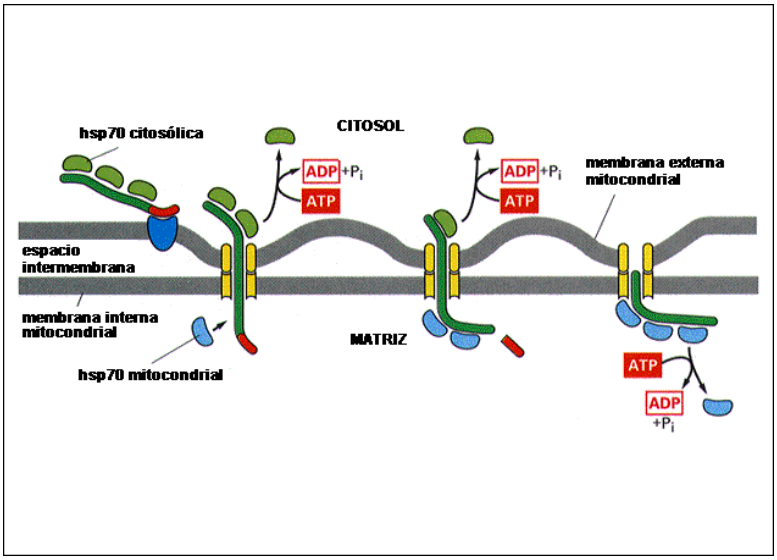


emplea

ENERGIA	CHAPERONAS
•ATP en el citosol, • fuerza protón motriz a través de la membrana interna • ATP en la matriz	•citosólicas y •Matriz mitocondrial

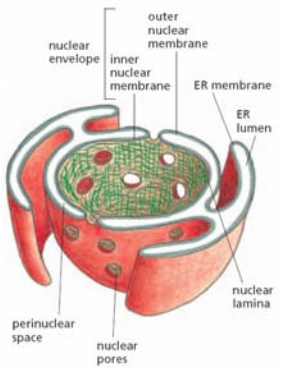
65

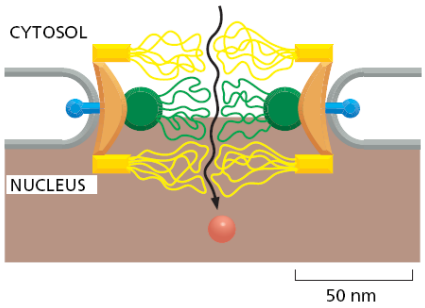
direccionamiento a mitocondrias



66

Poros nucleares
(NPC: Nuclear Pore Complex)

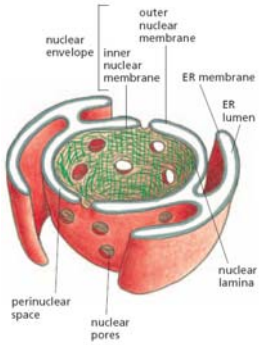


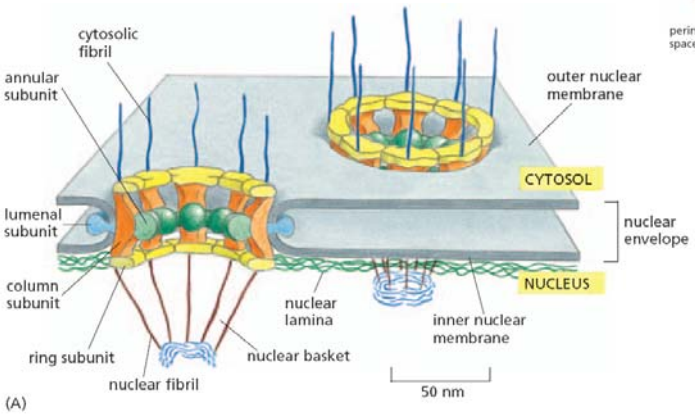


size of molecules
that enter nucleus
by free diffusion

size of macromolecules
that enter nucleus
by active transport

Poros nucleares
(NPC: Nuclear Pore Complex)





size of macromolecules
that enter nucleus
by active transport

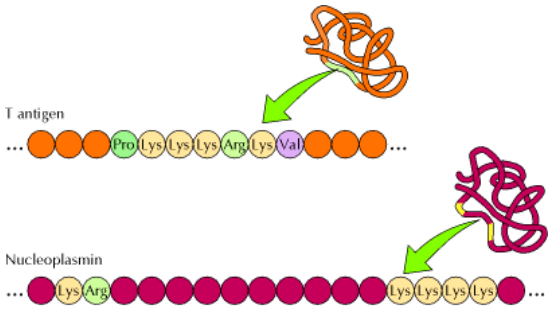
¿Qué elementos son requeridos para la entrada al núcleo?

- Una **REGION SEÑAL** en la proteína (no es clivada!!)
- Un receptor que reconozca la señal y direccione la proteína
- Una maquinaria de translocación, un canal
- Energía para translocar la proteína

69

Importación al núcleo: señal de localización nuclear NLS

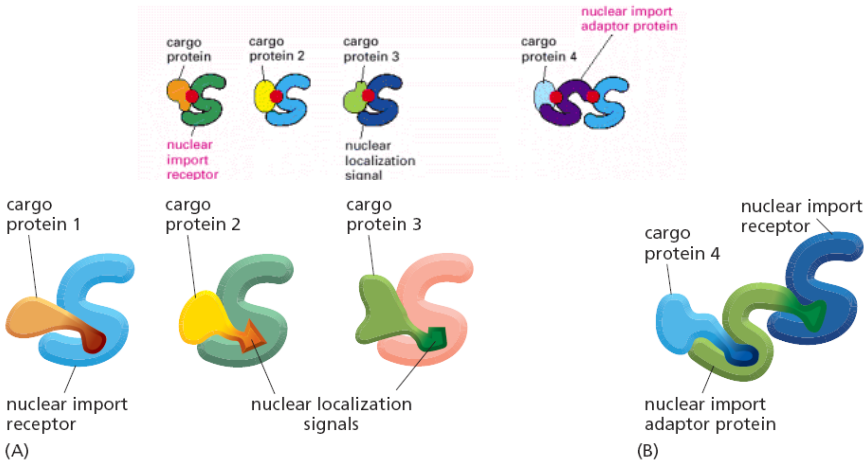
(señales con un bloque de varios aminoácidos básicos y señales bipartitas)



Nuclear localization signals: The T antigen nuclear localization signal is a single stretch of amino acids. In contrast, the nuclear localization signal of nucleoplasmin is bipartite, consisting of a Lys-Arg sequence followed by a Lys-Lys-Lys-Lys sequence located ten amino acids farther downstream

70

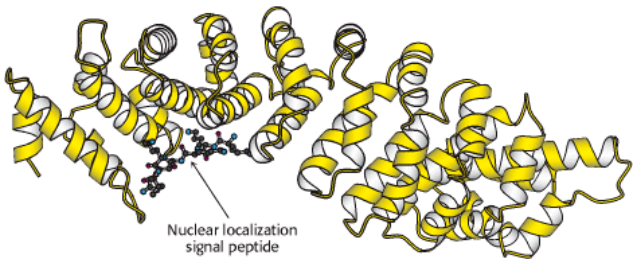
Proteínas transportadoras: reconocen NLS



Nuclear import receptors. (A) Many nuclear import receptors bind both to nucleoporins and to a nuclear localization signal on the cargo proteins they transport. Cargo proteins 1, 2, and 3 in this example contain different nuclear localization signals, which causes each to bind to a different nuclear import receptor. (B) Cargo protein 4 shown here requires an adaptor protein to bind to its nuclear import receptor. The adaptors are structurally related to nuclear import receptors and recognize nuclear localization signals on cargo proteins. They also contain a nuclear localization signal that binds them to an import receptor

71

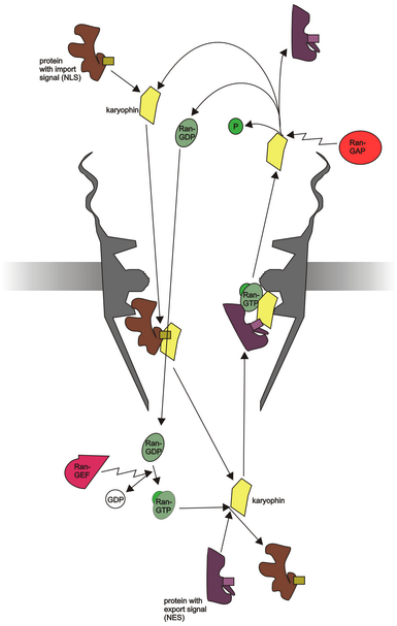
Transporte de polipéptidos al núcleo: **importina**



Protein Targeting Signal Recognition. The structure of the nuclear localization signal-binding protein **α-karyopherin** (also known as **α-importin**) with a nuclear localization signal peptide bound to its major recognition site.

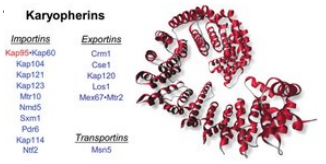
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=nuclear+localization+signal+AND+stryer%5Bbook%5D+AND+215912%5Buid%5D&rid=stryer.figgrp.1705

72

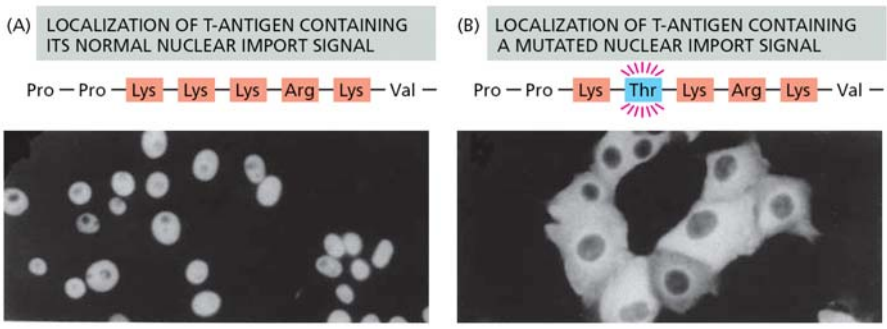


Transporte de polipéptidos al núcleo: **importina**

The entry and exit of large molecules from the cell nucleus is tightly controlled by the nuclear pore complexes (NPCs). Although small molecules can enter the nucleus without regulation, macromolecules such as RNA and proteins require association with karyopherins called importins to enter the nucleus and exportins to exit.



Importación al núcleo: señal de localización nuclear NLS



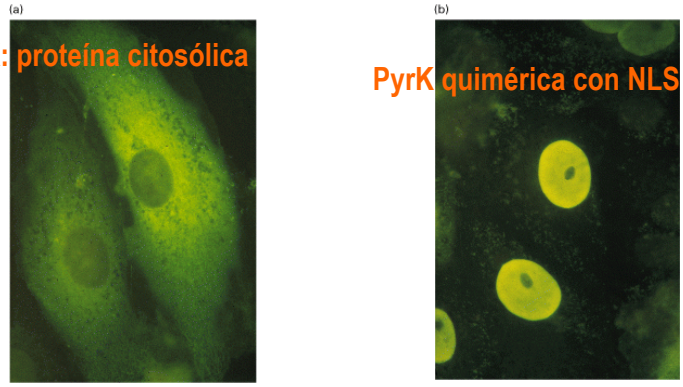
The function of a nuclear localization signal. Immunofluorescence micrographs showing the cellular location of SV40 virus T-antigen containing or lacking a short peptide that serves as a nuclear localization signal. (A) The normal T-antigen protein contains the lysine-rich sequence indicated and is imported to its site of action in the nucleus, as indicated by immunofluorescence staining with antibody against the T-antigen. (B) T-antigen with an altered nuclear localization signal (a threonine replacing a lysine) remains in the cytosol. (From D. Kalderon, B. Roberts, W. Richardson, and A. Smith, *Cell* 39:499–509, 1984. © Elsevier.)

74

Importación al núcleo:
señal de localización nuclear NLS

PyrK: proteína citosólica

PyrK quimérica con NLS de SV40

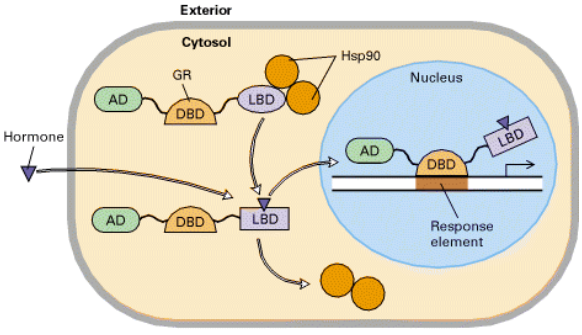


Demonstration that the nuclear-localization signal (NLS) of the SV40 large T-antigen can direct a cytoplasmic protein to the cell nucleus. (a) Normal pyruvate kinase, visualized by immunofluorescence after treating cultured cells with a specific antibody, is localized to the cytoplasm. (b) A chimeric pyruvate kinase protein, containing the SV40 NLS at its N-terminus, is directed to the nucleus. The chimeric protein was expressed from a transfected engineered gene produced by fusing a viral gene fragment encoding the SV40 NLS to the pyruvate kinase gene. [From D. Kalderon et al., 1984, *Cell* **39:**499; courtesy Dr. Alan Smith.]

75

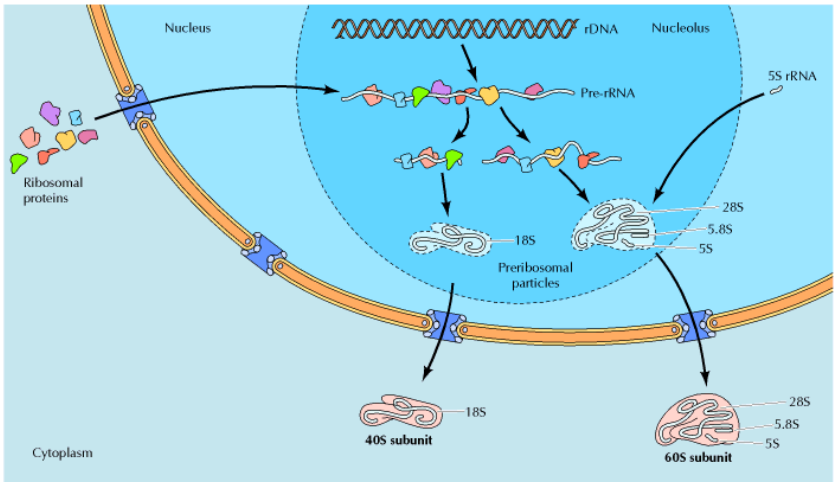
Importación al núcleo: exposición de NLS
cambio conformacional por unión a un ligando

(traslocación del receptor de glucocorticoides ➡ activación de la transcripción)



Model of hormone-dependent gene activation by the glucocorticoid receptor (GR). In the absence of hormone, GR is bound in a complex with Hsp90 in the cytoplasm via its ligand-binding domain (light purple). When hormone is present, it diffuses through the plasma membrane and binds to the GR ligand-binding domain, causing a conformational change in the ligand-binding domain that releases the receptor from Hsp90. The receptor with bound ligand is then translocated into the nucleus where its DNA-binding domain (orange) binds to response elements, allowing the activation domain (green) to stimulate transcription of target genes

76



Ribosome assembly Ribosomal proteins are imported to the nucleolus from the cytoplasm and begin to assemble on pre-rRNA prior to its cleavage. As the pre-rRNA is processed, additional ribosomal proteins and the 5S rRNA (which is synthesized elsewhere in the nucleus) assemble to form preribosomal particles. The final steps of maturation follow the export of preribosomal particles to the cytoplasm, yielding the 40S and 60S ribosomal subunits.

77

señales de direccionamiento:

en un bloque o en varias partes

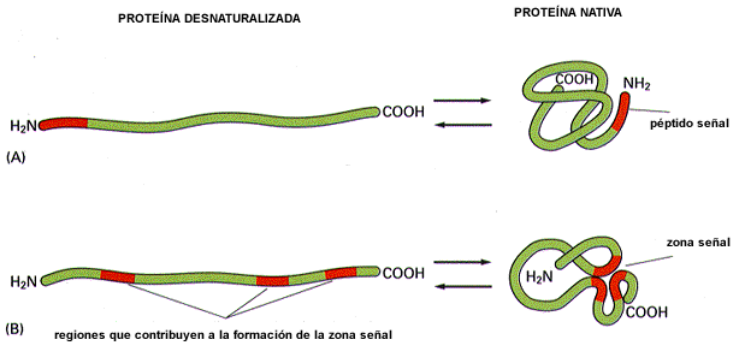


Figure 12-8. Two ways in which a sorting signal can be built into a protein. (A) The signal resides in a single discrete stretch of amino acid sequence, called a signal sequence, that is exposed in the folded protein. Signal sequences often occur at the end of the polypeptide chain (as shown), but they can also be located internally. (B) A signal patch can be formed by the juxtaposition of amino acids from regions that are physically separated before the protein folds (as shown). Alternatively, separate patches on the surface of the folded protein that are spaced a fixed distance apart can form the signal.

78

Señales de direccionamiento de proteínas

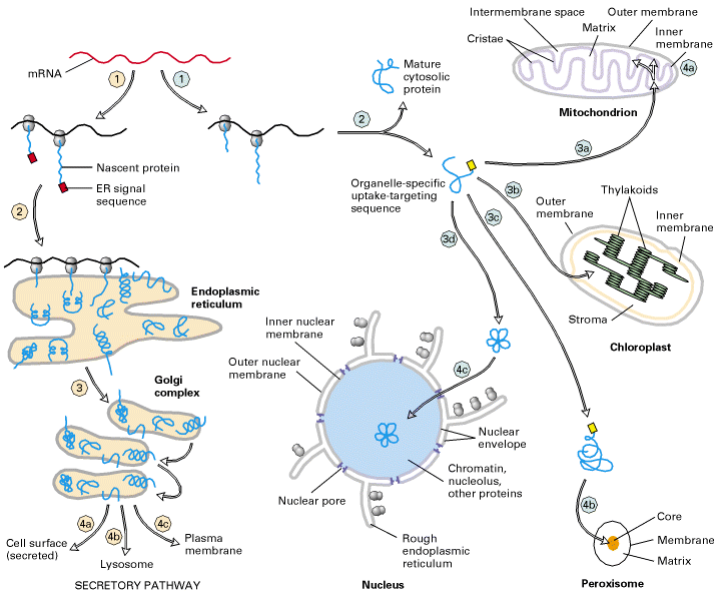
Table 12–3 Some Typical Signal Sequences

FUNCTION OF SIGNAL SEQUENCE	EXAMPLE OF SIGNAL SEQUENCE
Import into nucleus	-Pro-Pro-Lys-Lys-Lys-Arg-Lys-Val-
Export from nucleus	-Leu-Ala-Leu-Lys-Leu-Ala-Gly-Leu-Asp-Ile-
Import into mitochondria	$^{+}H_3N$-Met-Leu-Ser-Leu-Arg-Gln-Ser-Ile-Arg-Phe-Phe-Lys-Pro-Ala-Thr-Arg-Thr-Leu-Cys-Ser-Ser-Arg-Tyr-Leu-Leu-
Import into plastid	$^{+}H_3N$-Met-Val-Ala-Met-Ala-Met-Ala-Ser-Leu-Gln-Ser-Ser-Met-Ser-Ser-Leu-Ser-Leu-Ser-Ser-Asn-Ser-Phe-Leu-Gly-Gln-Pro-Leu-Ser-Pro-Ile-Thr-Leu-Ser-Pro-Phe-Leu-Gln-Gly-
Import into peroxisomes	-Ser-Lys-Leu-COO^{-}
Import into ER	$^{+}H_3N$-Met-Met-Ser-Phe-Val-Ser-Leu-Leu-Leu-Val-Gly-Ile-Leu-Phe-Trp-Ala-Thr-Glu-Ala-Glu-Gln-Leu-Thr-Lys-Cys-Glu-Val-Phe-Gln-
Return to ER	-Lys-Asp-Glu-Leu-COO^{-}

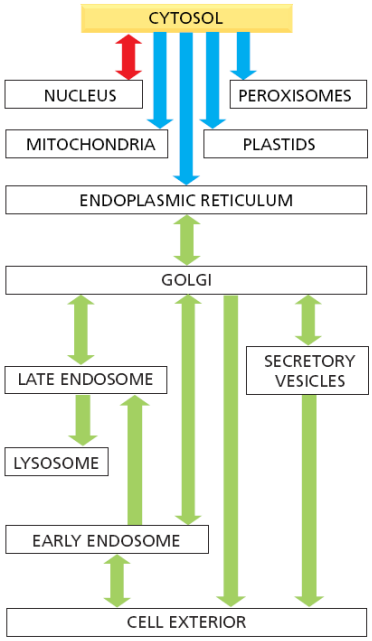
Some characteristic features of the different classes of signal sequences are highlighted in color. Where they are known to be important for the function of the signal sequence, positively charged amino acids are shown in *red* and negatively charged amino acids are shown in *green*. Similarly, important hydrophobic amino acids are shown in *white* and important hydroxylated amino acids are shown in *blue*. $^{+}H_3N$ indicates the N-terminus of a protein; COO^{-} indicates the C-terminus.

79

Direccionamiento de proteínas



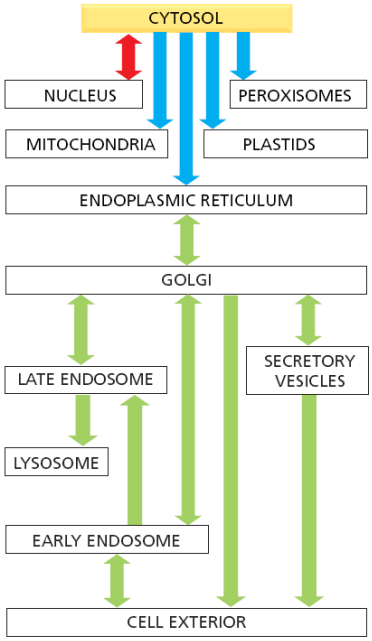
80



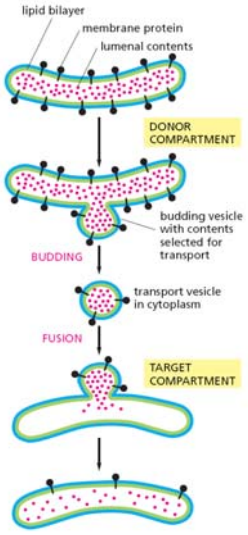
Direccionamiento de proteínas

KEY:
= gated transport
= transmembrane transport
= vesicular transport

81

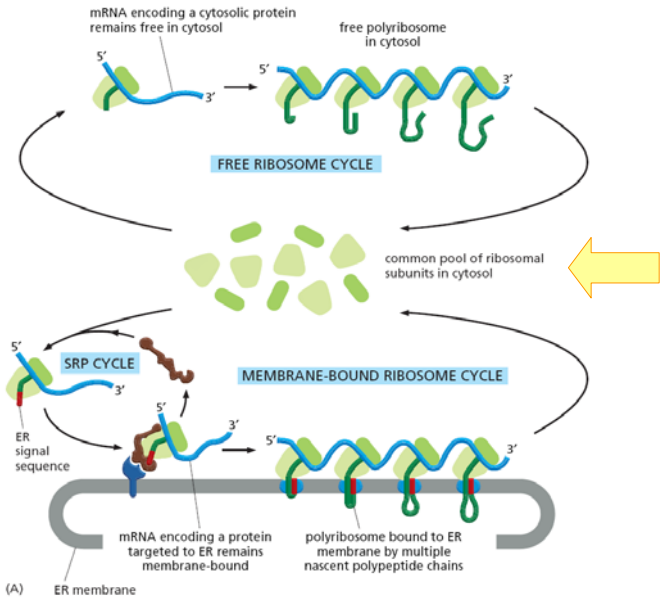


Direccionamiento de proteínas



82

pool de subunidades ribosómicas



83