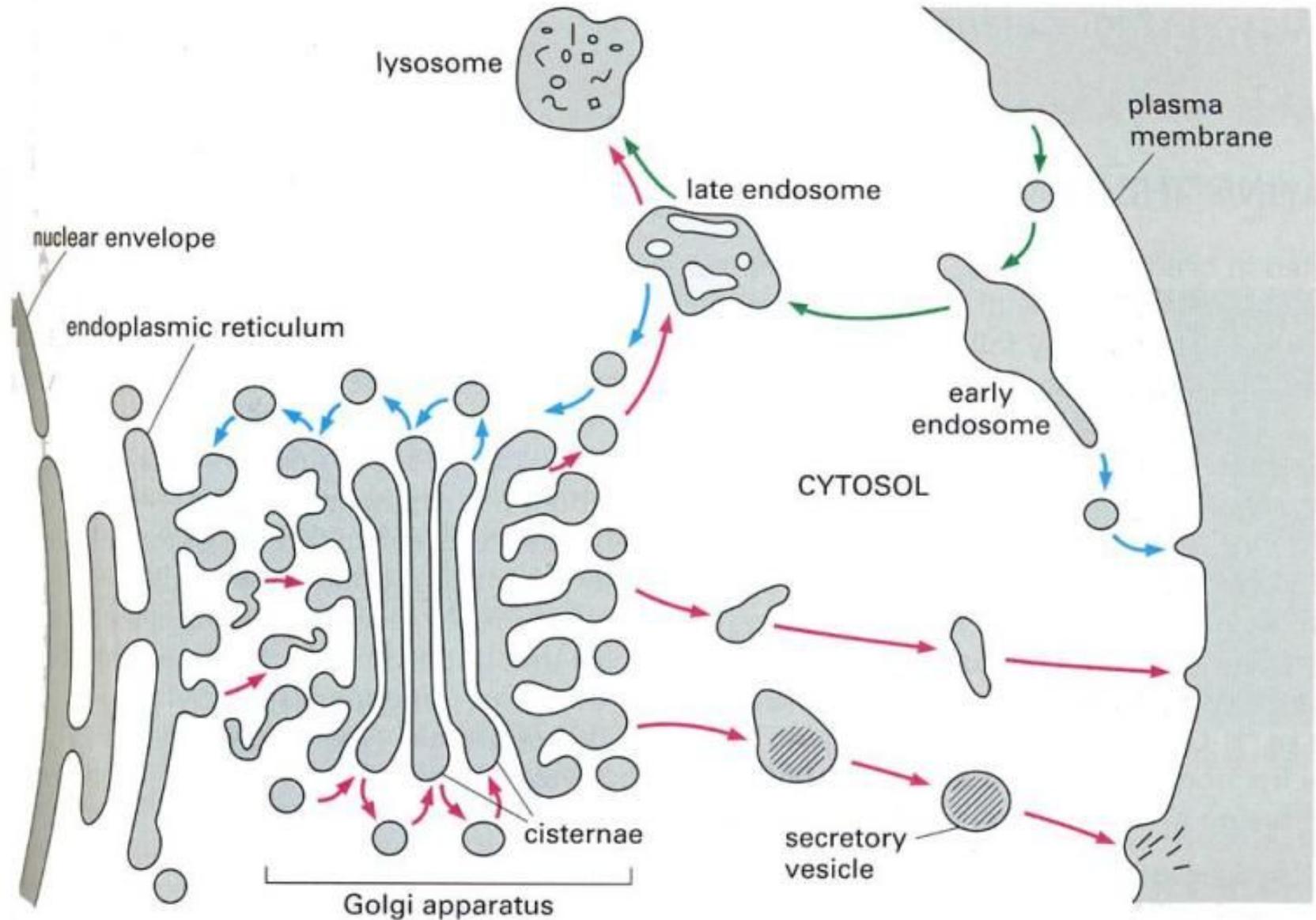


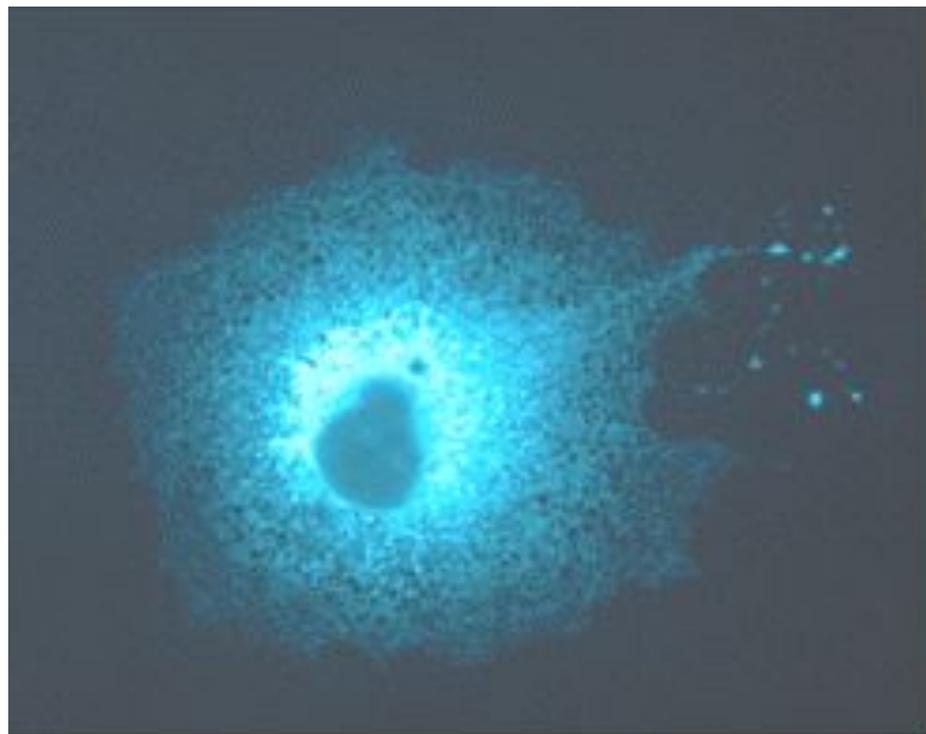
Мембранные органеллы



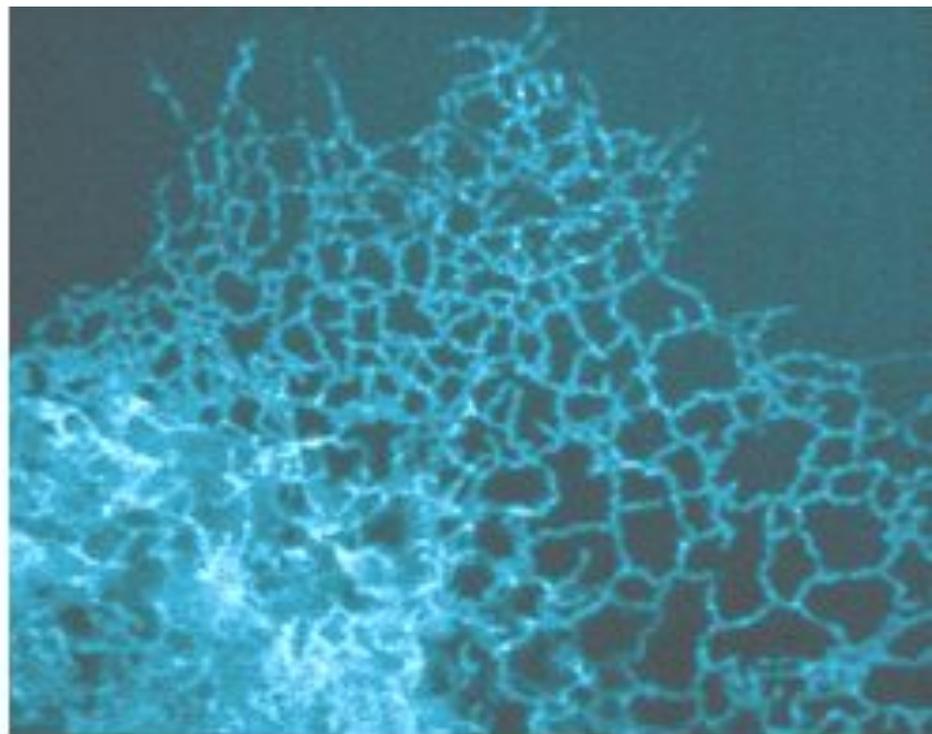
Соотношение различных типов мембран

% от всех мембран		
Тип мембраны	гепатоцит 5000 мкм ³	Экзокринная клетка поджелудочной железы 1000 мкм ³
Общий объем мембран	110,000 мкм²	13,000 мкм²
Плазматическая мембрана	2	5
Гр. ЭПР	35	60
Гл. ЭПР	16	<1
Аппарат Гольджи	7	10
Митохондрии		
Наружная мембрана	7	4
Внутренняя мембрана	32	17
Внутренняя мембрана ЯО	0.2	3
Секреторные везикулы	not determined	3
Лизосомы	0.4	not determined
Пероксисомы	0.4	not determined
Эндосомы	0.4	not determined

Эндоплазматический ретикулум

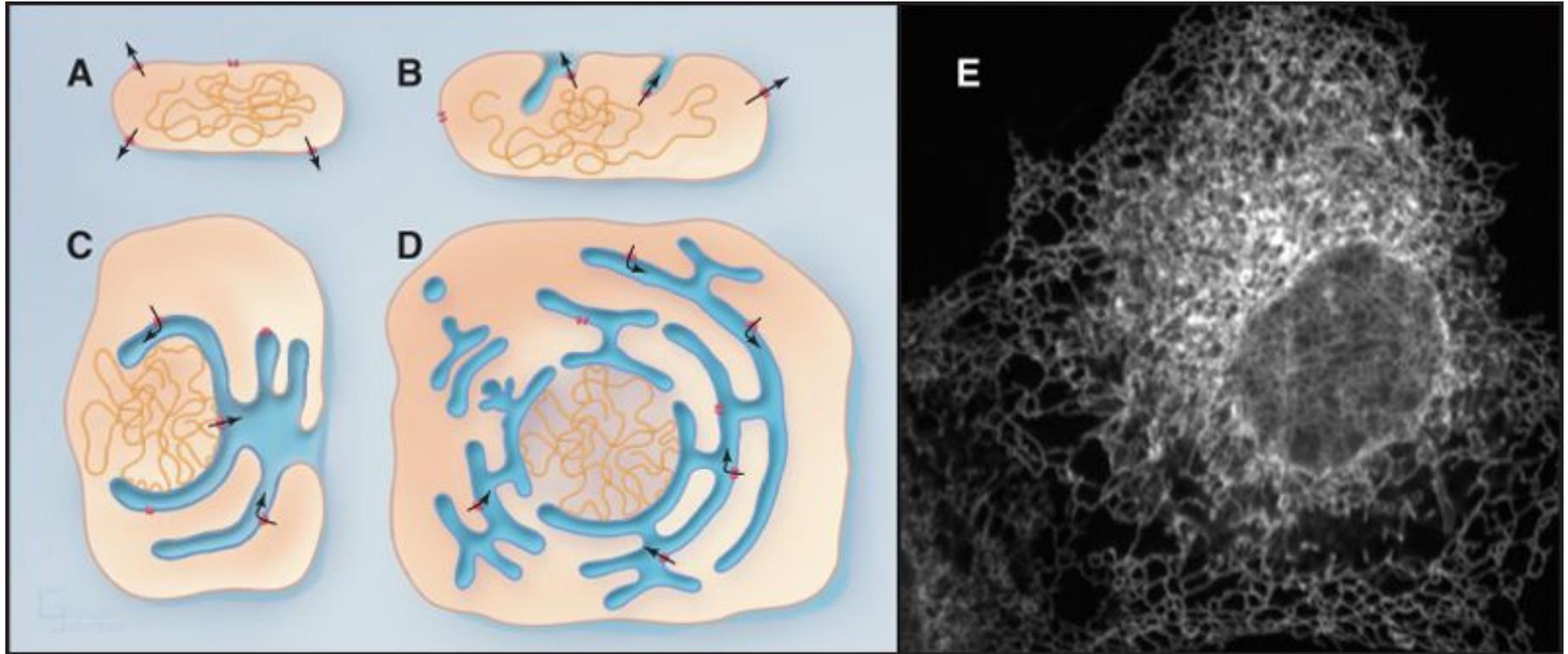


10 μm



2 μm

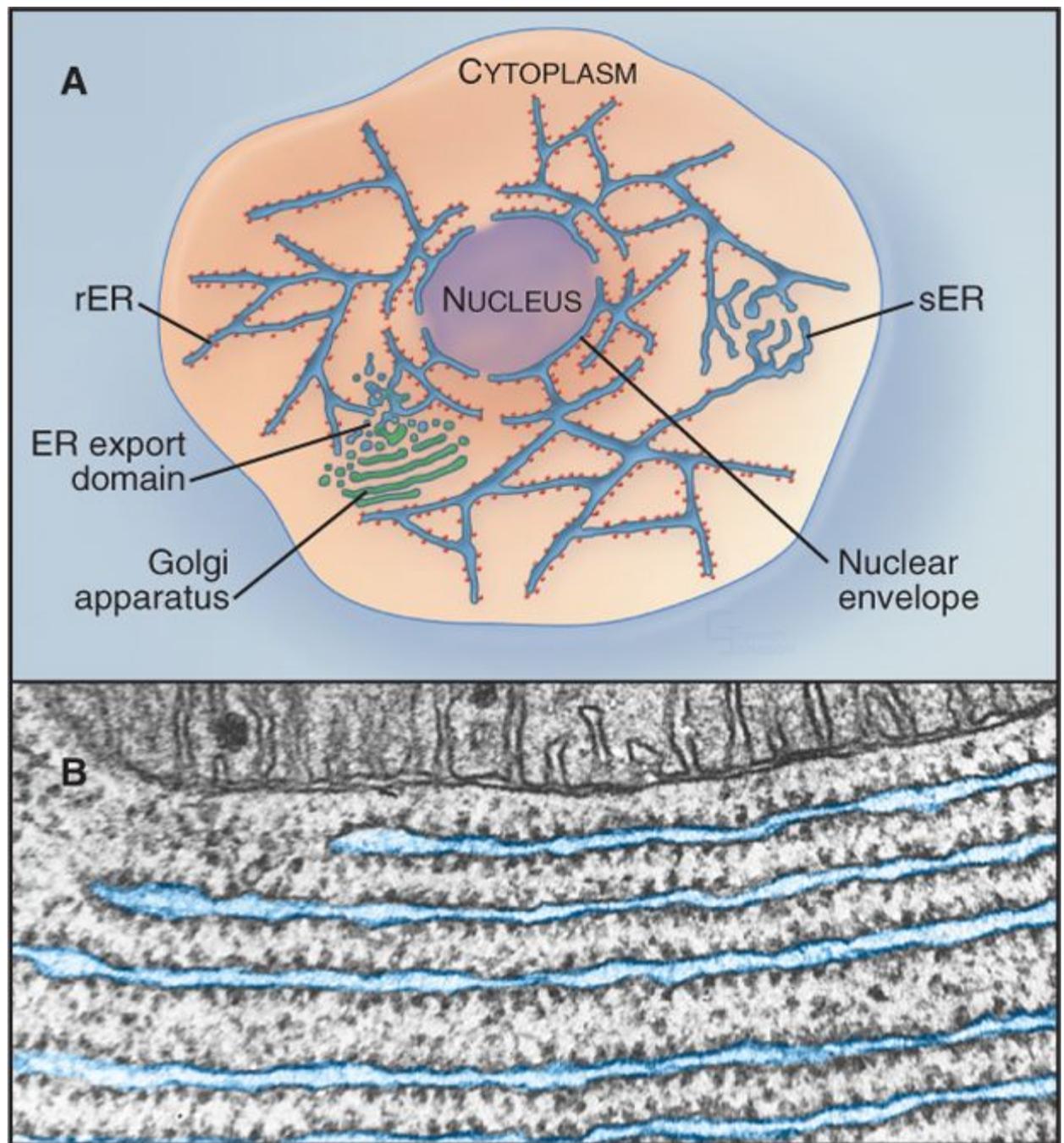
Эндоплазматический ретикулум



Субдомены ЭТР

+

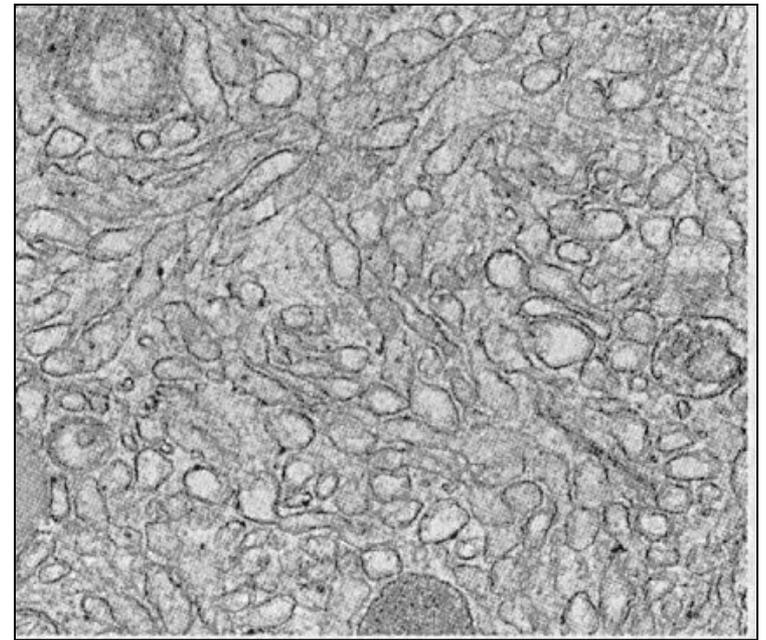
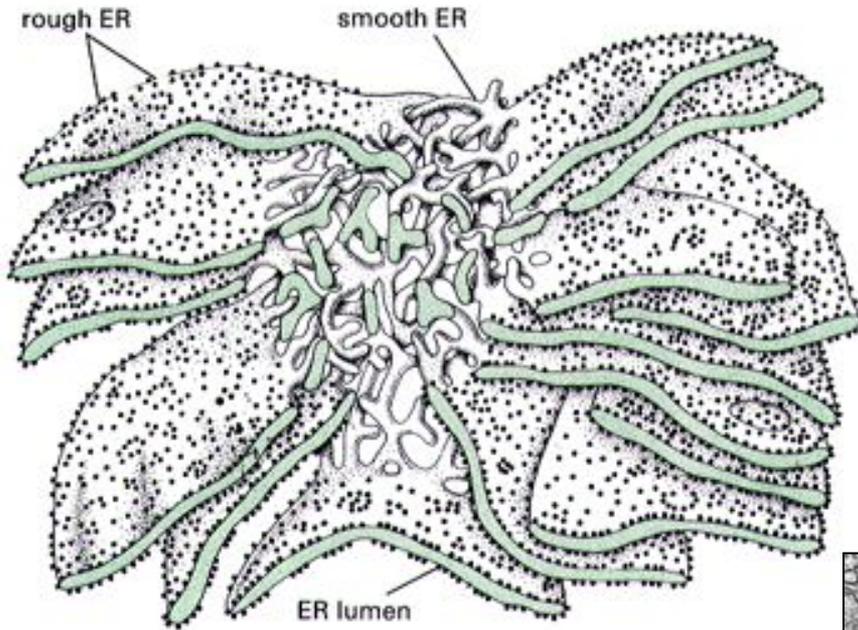
Пероксисомы
Липидные капли
Контактные сайты



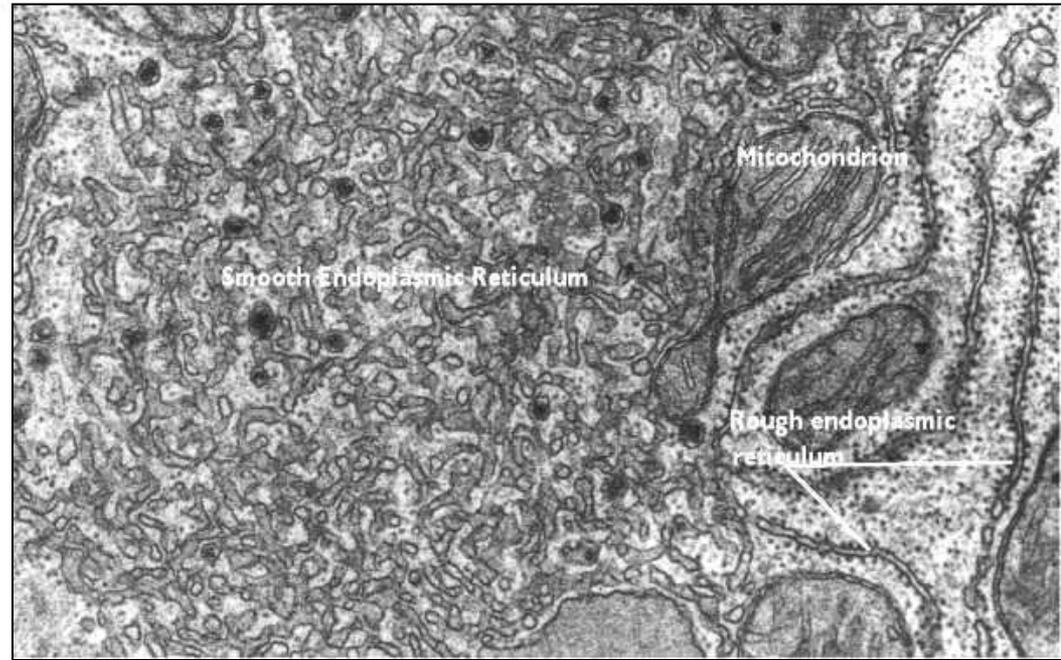
Субдомены ЭПР

субдомены	функции	белки
Гр. ЭПР	Синтез белков Транслокация Складывание и олигомеризация Первичное гликозилирование и др. модификации Деградация Образование мембран	Sec61 complex, TRAP, TRAM, BiP Oligosaccharide transferase PDI, Calnexin, Calreticulin, EDEМ, Derlin1
Гл. ЭПР	Детоксикация Метаболизм липидов Метаболизм стероидов Метаболизм гема Депозит Са Метаболизм гликогена	Семейство цитохром Р450 HMG-CoA reductase Cytochrome b(5) IP ₃ receptors
Экспортный домен	Экспорт белков и липидов в секреторный путь	Sar1p, Sec12p, Sec16p
Ядерная оболочка	Транспорт: ядерные поры Заякоривание хроматина	POM121, GP210 Lamin B receptor
Контактные зоны	Транспорт липидов	LTPs

Гладкий ЭТР микросомы

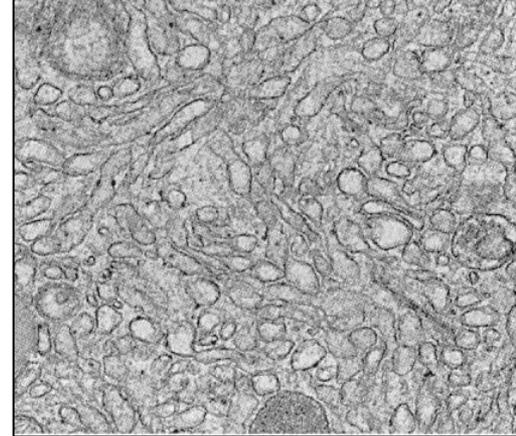


- Детоксикация
- Метаболизм липидов
- Метаболизм стероидов
- Метаболизм гема
- Депозит Са
- Метаболизм гликогена

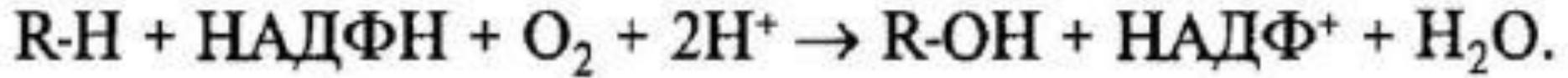




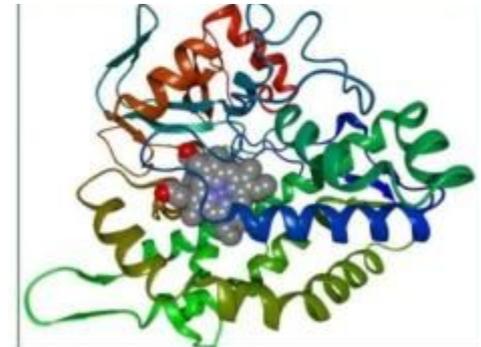
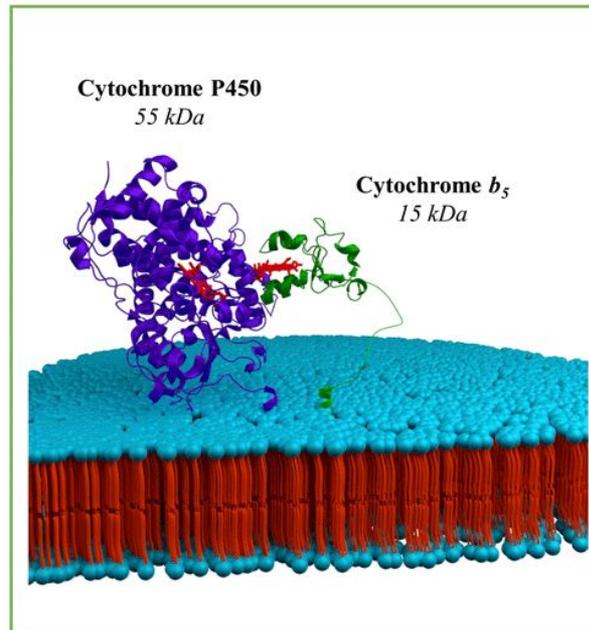
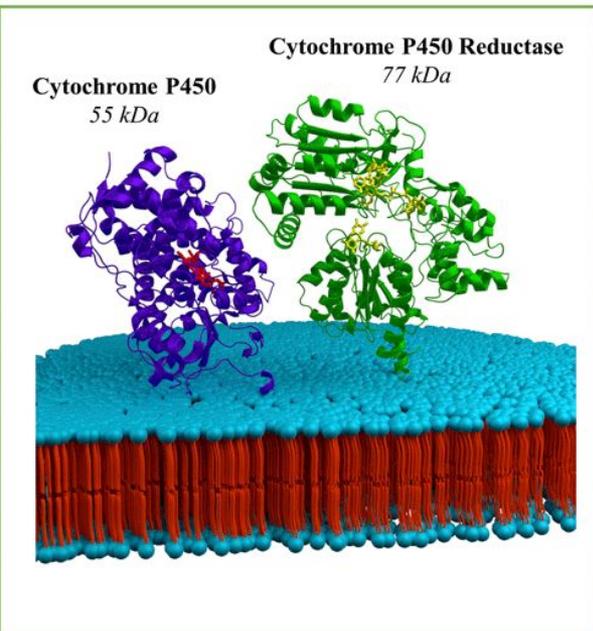
Детоксикация



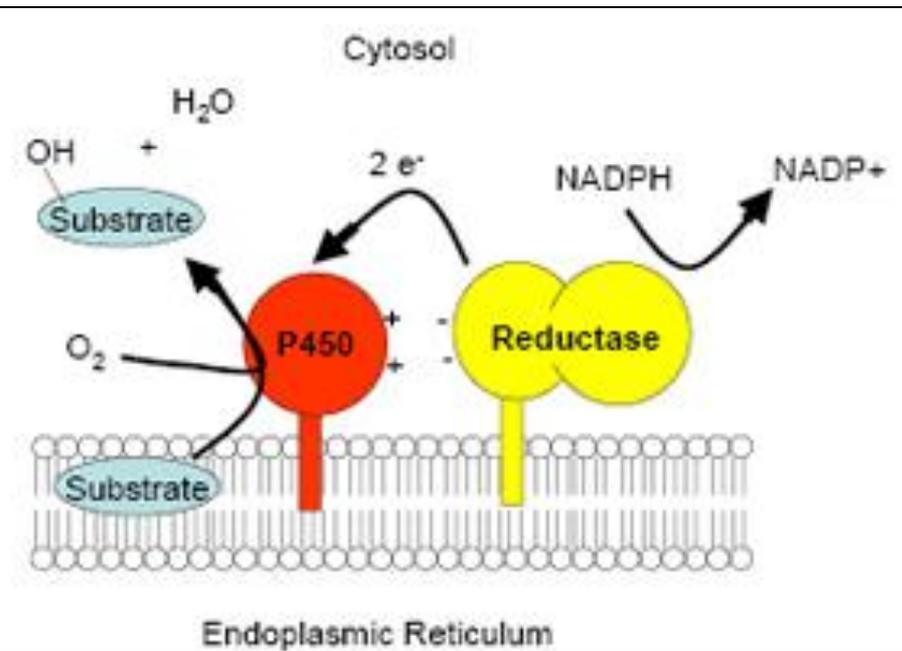
Монооксигеназные реакции



Ко-факторы НАДФН НАДН Р450-редуктаза Р450



Детоксикация



Электронтранспортные цепи ЭПР

1 цепь включает:

1) цитохром P₄₅₀, имеет центры связывания для O₂ и гидрофобного субстрата; 2) NADPH-цитохром P₄₅₀-редуктазу, содержащую коферменты FAD и FMN; 3) NADPH+H⁺ – донор e⁻ и H⁺ в этой электрон-транспортной цепи; 4) O₂.

2 цепь включает:

1) цитохром P₄₅₀; 2) фермент NADH-цитохром b₅-редуктазу, коферментом которой является FAD; 3) цитохром b₅ – гемопротейн, переносящий e⁻ от NADH-цитохром b₅-редуктазы на цитохром P₄₅₀; 4) NADH + H⁺ – донор e⁻ и H⁺; 5) O₂.

Цитохром P₄₅₀ один атом O₂ включает в молекулу субстрата, а 2-й восстанавливает с образованием H₂O за счет переноса e⁻ и H⁺ от NADPH+H⁺ при участии цитохром P₄₅₀-редуктазы (или от NADH+H⁺ с помощью цитохром b₅-редуктазы и цитохрома b₅).

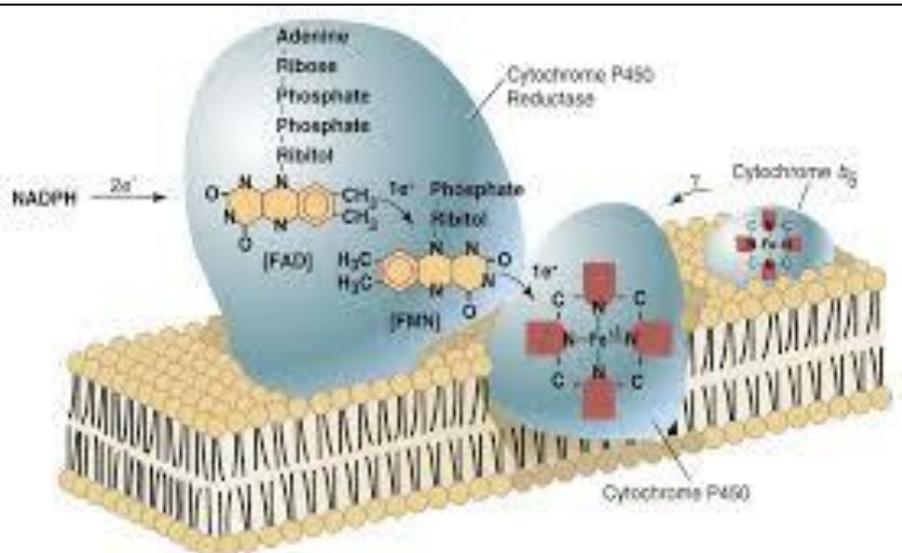
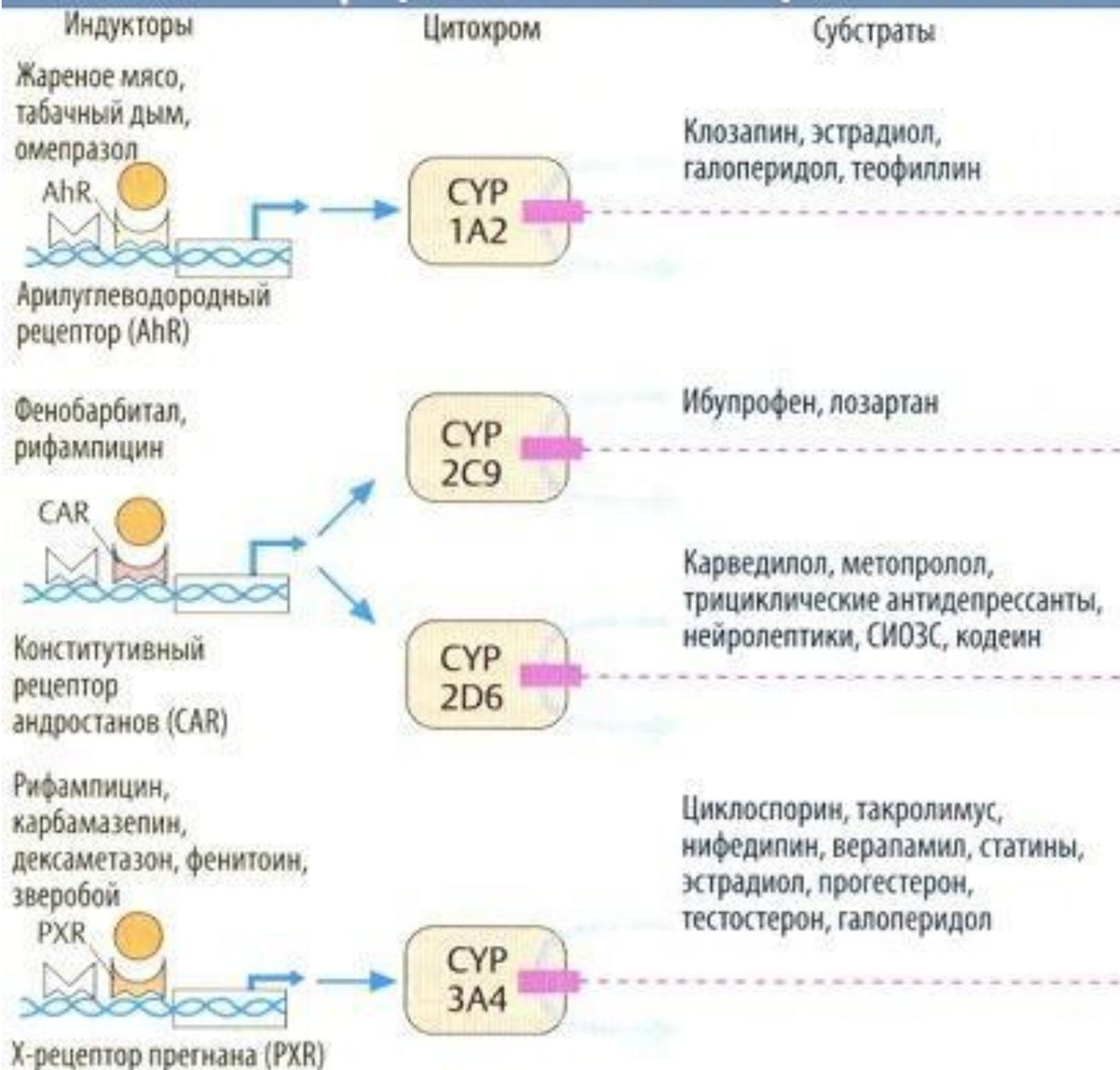


Figure 11.5. Components of the endoplasmic reticulum (microsomal) cytochrome P450 system.

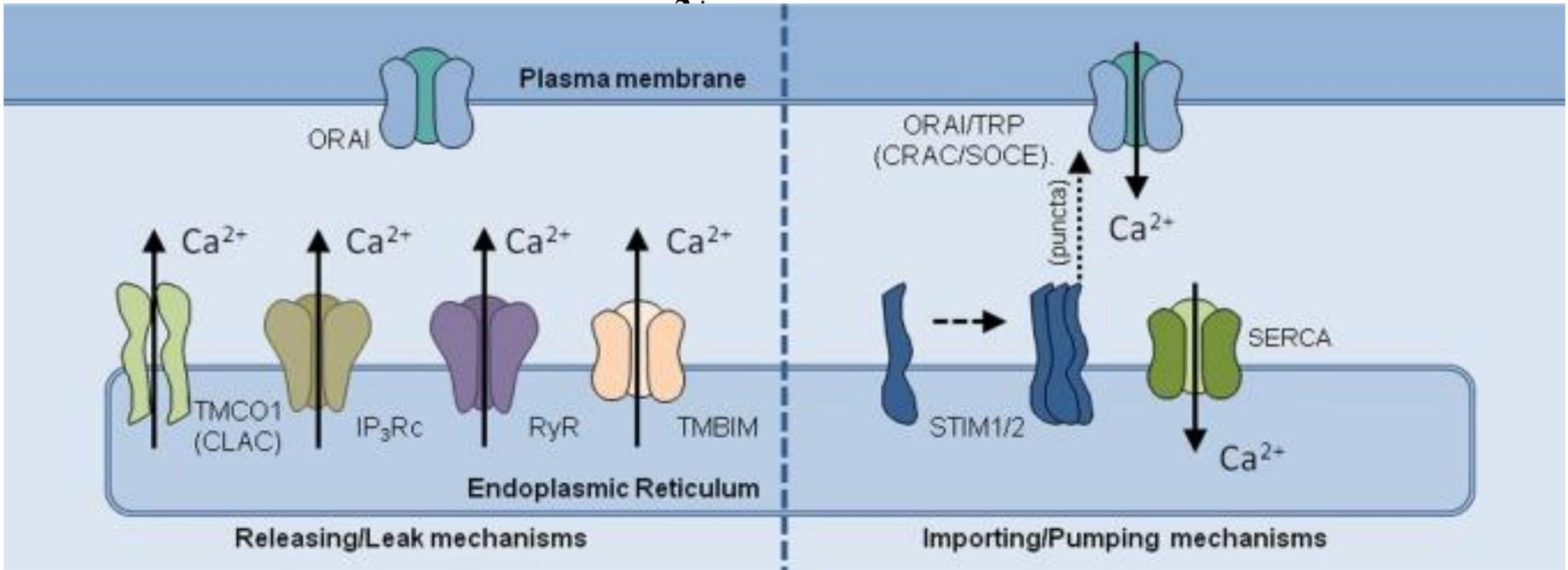
Семейство супергенов P450

Семейство	Функции	Состав
CYP1	метаболизм лекарств и стероидов (особенно эстрогена)	3 подсемейства, 3 гена, 1 псевдоген
CYP2	метаболизм лекарств и стероидов	13 подсемейств, 16 генов, 16 псевдогенов
CYP3	метаболизм лекарств и стероидов (включая тестостерон)	1 подсемейство, 4 гена, 2 псевдогена
CYP4	метаболизм арахидоновой кислоты	6 подсемейств, 12 генов, 10 псевдогенов
CYP5	синтез тромбксана A₂	1 подсемейство, 1 ген
CYP7	биосинтез желчных кислот, участие в метаболизме стероидов	2 подсемейства, 2 гена
CYP8	<i>различные</i>	2 подсемейства, 2 гена
CYP11	биосинтез стероидов	2 подсемейства, 3 гена
CYP17	биосинтез стероидов, 17-альфа гидроксилаза	1 подсемейство, 1 ген
CYP19	биосинтез стероидов (ароматаза, синтезирующая эстроген)	1 подсемейство, 1 ген
CYP20	не установлены	1 подсемейство, 1 ген
CYP21	биосинтез стероидов	2 подсемейства, 1 ген, 1 псевдоген
CYP24	биодegradация витамина D	1 подсемейство, 1 ген
CYP26	гидроксилирование ретиноловой кислоты	3 подсемейства, 3 гена
CYP27	<i>различные</i>	3 подсемейства, 3 гена
CYP39	7-альфа-гидроксилирование 24-гидроксихолестерола	1 подсемейство, 1 ген
CYP46	холестерол 24-гидроксилаза	1 подсемейство, 1 ген
CYP51	биосинтез холестерина	1 подсемейство, 1 ген, 3 псевдогена

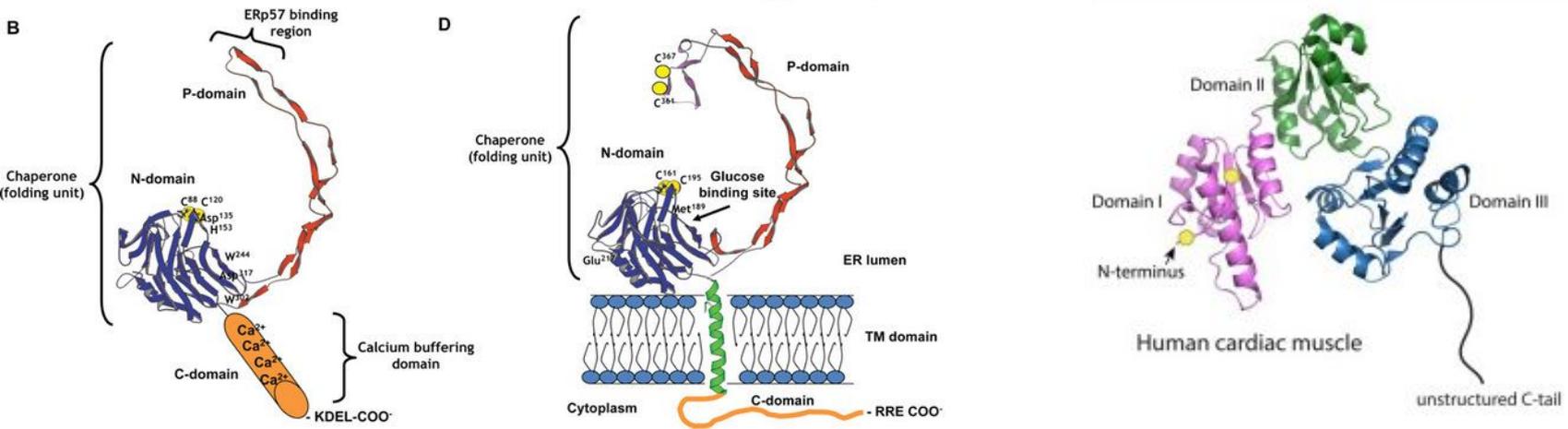
Изоферменты цитохрома P450



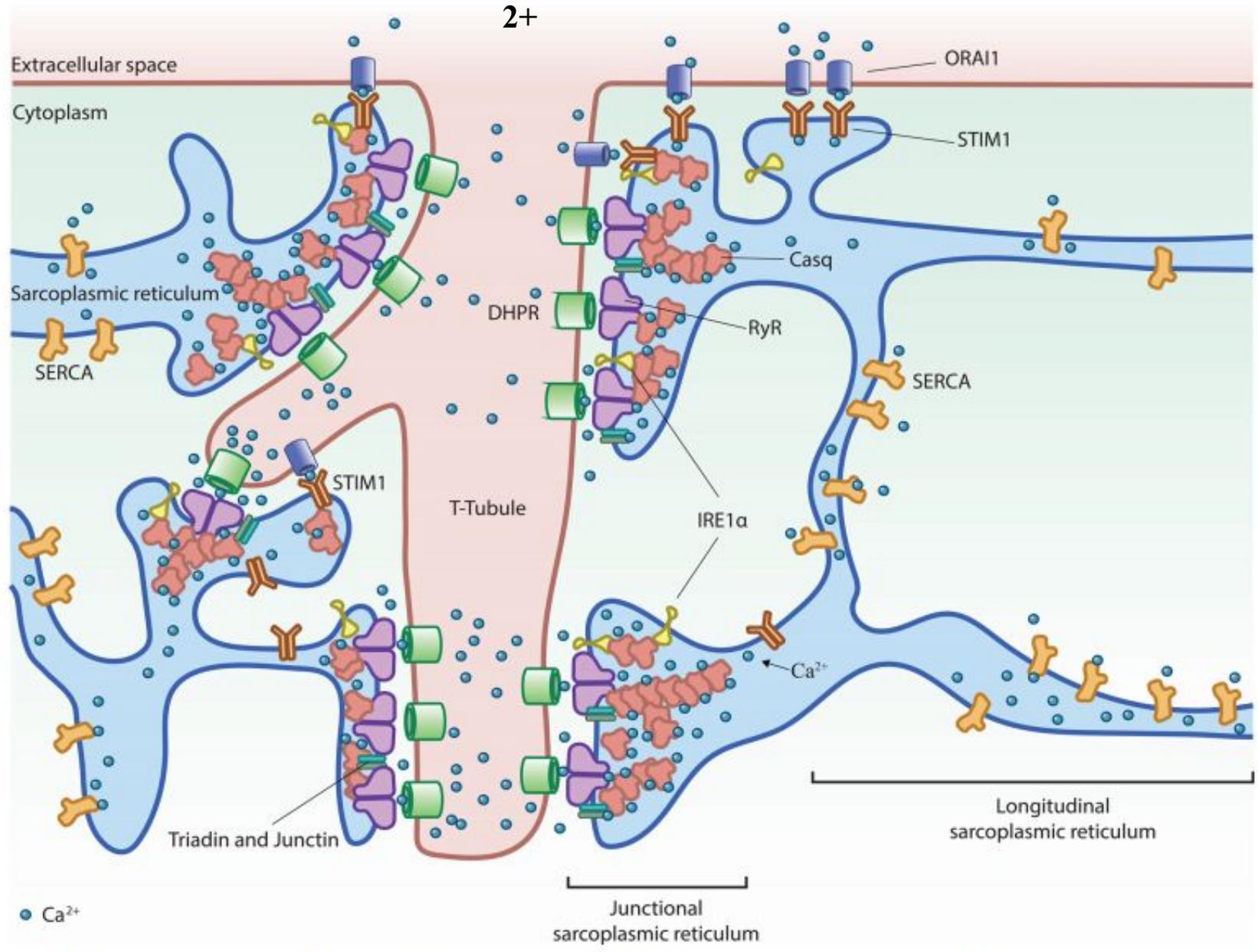
Депозитиране на Са



Калретикулин Калнексин Калсеквестрин

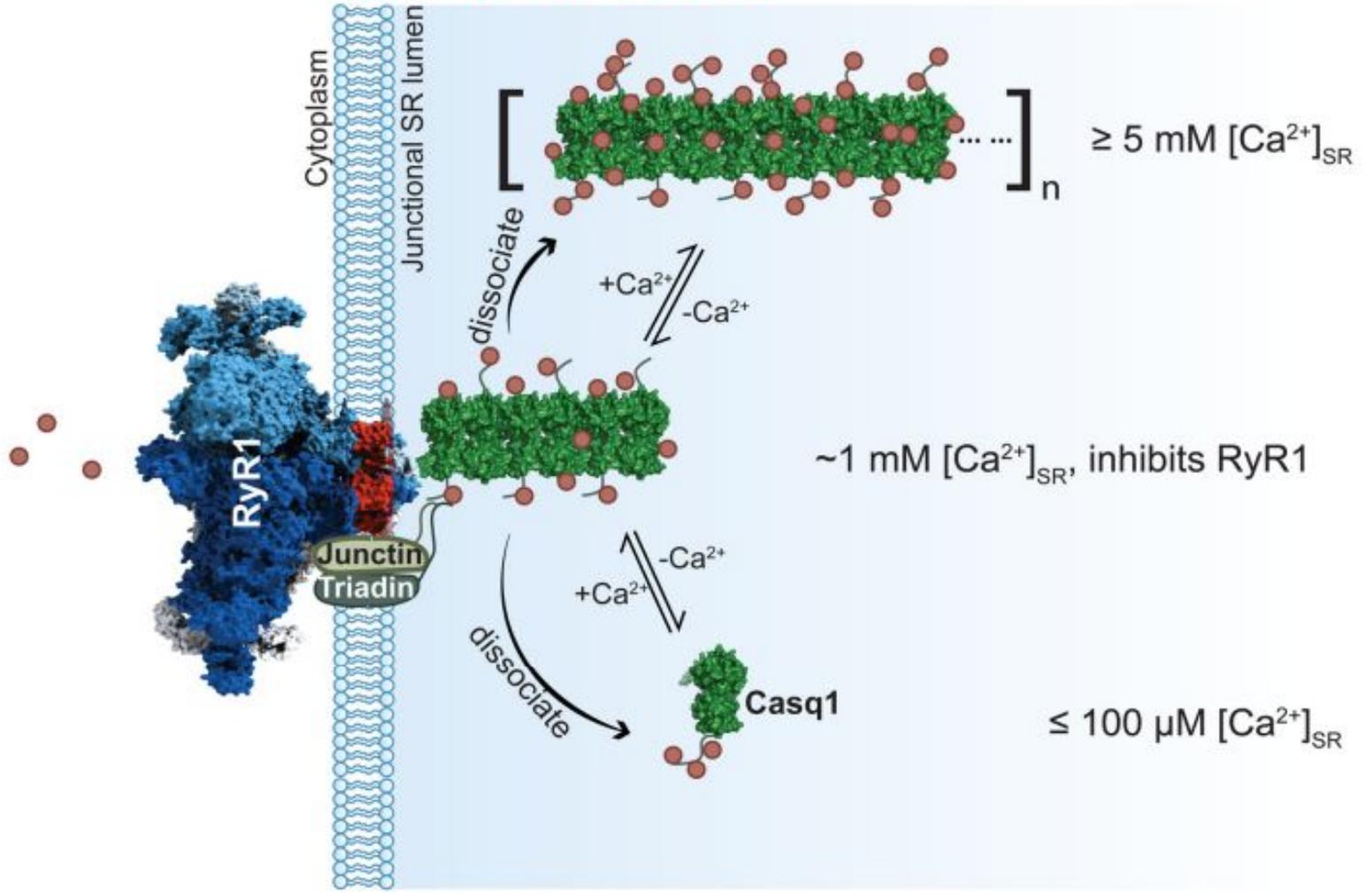


Депозит Са²⁺

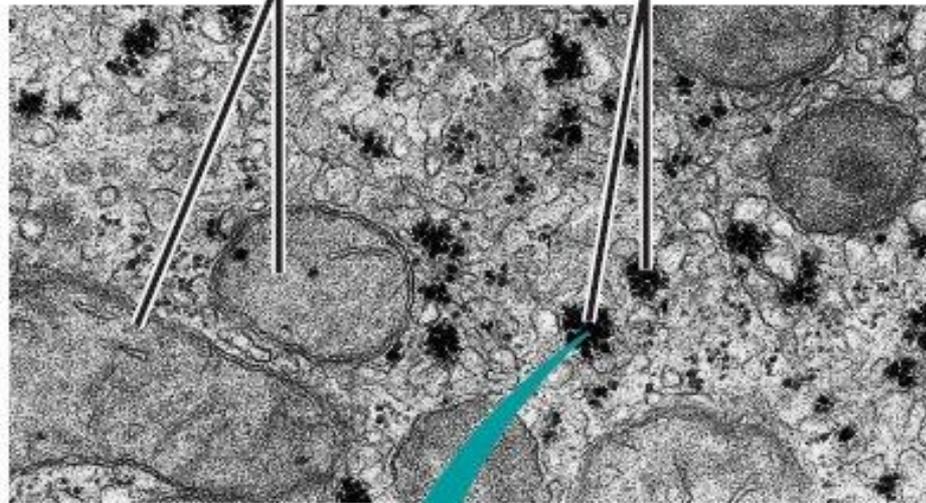


Депозит Ca^{2+}

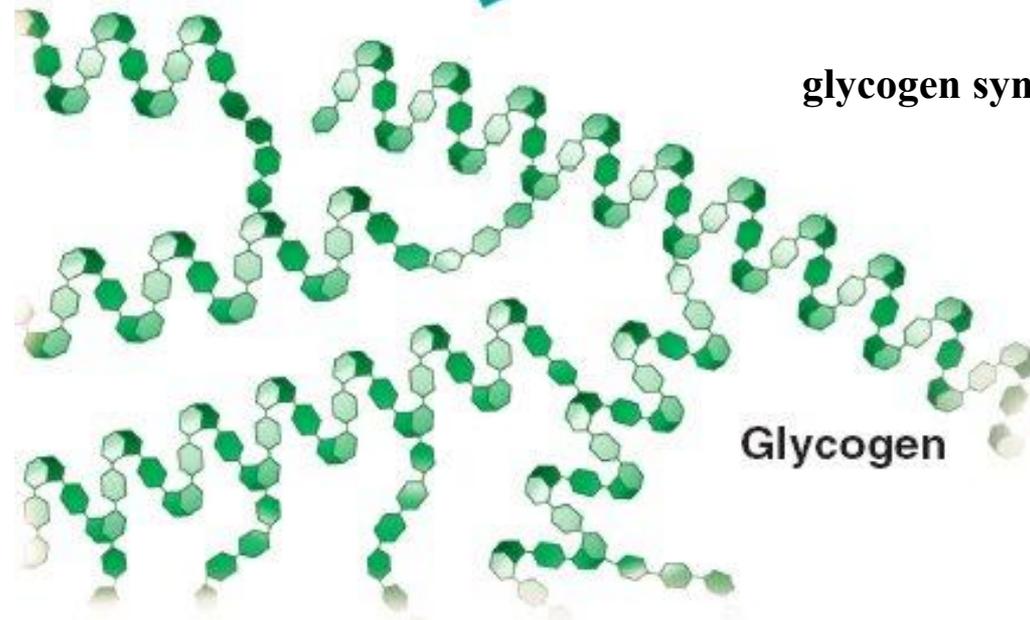
Skeletal muscle



Mitochondria Glycogen granules



0.5 μm



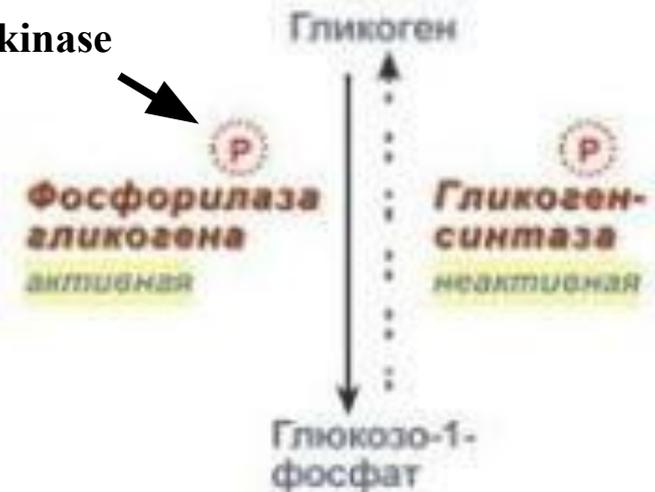
glycogen synthase kinase

ПОКОЙ или ОТДЫХ



При синтезе гликогена оба фермента дефосфорилированы

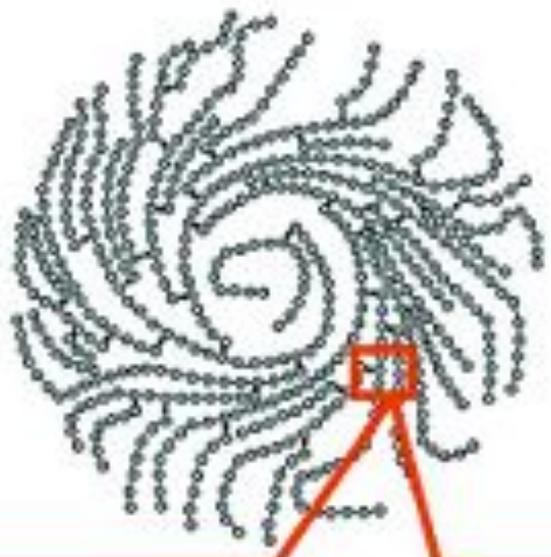
ФИЗИЧЕСКАЯ РАБОТА



При расщеплении гликогена оба фермента фосфорилированы

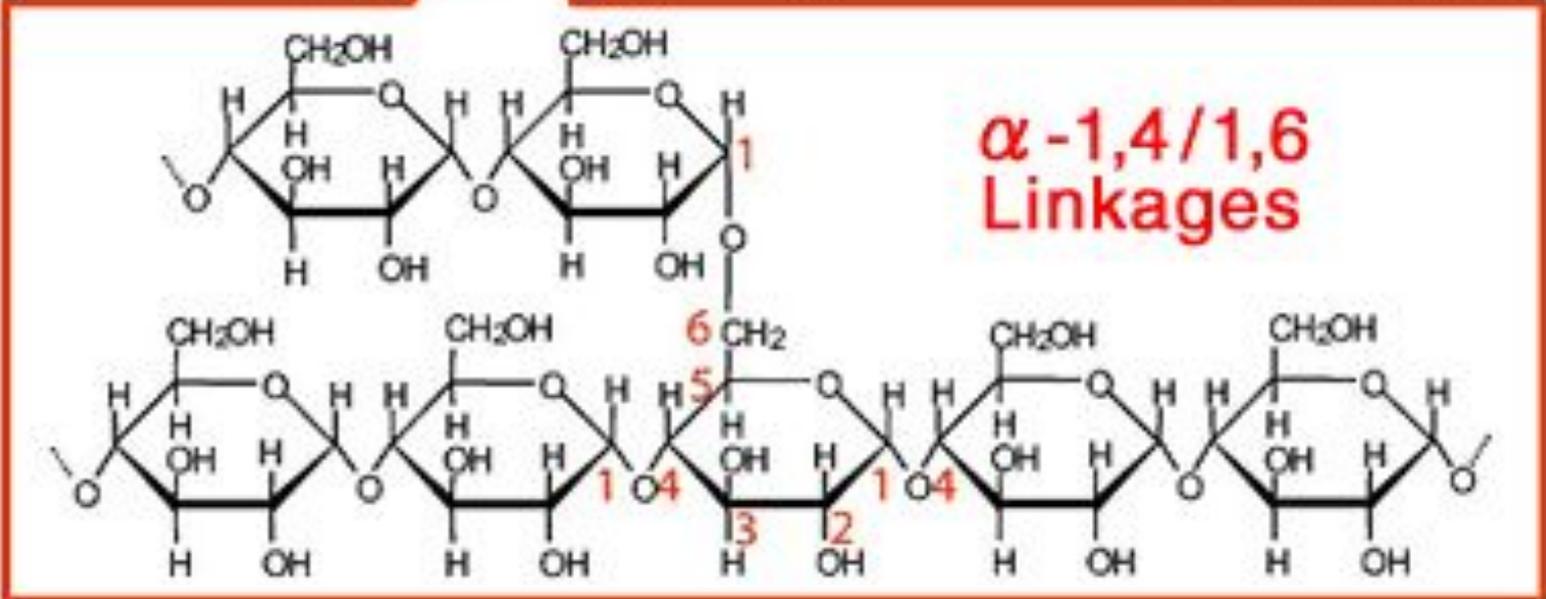
Синтез гликогена.

ГЛИКОГЕНСИНТАЗА
ГЛЮКАНТРАНСФЕРАЗА



20 ~ 50nm

● : Glucose



Синтез гликогена.

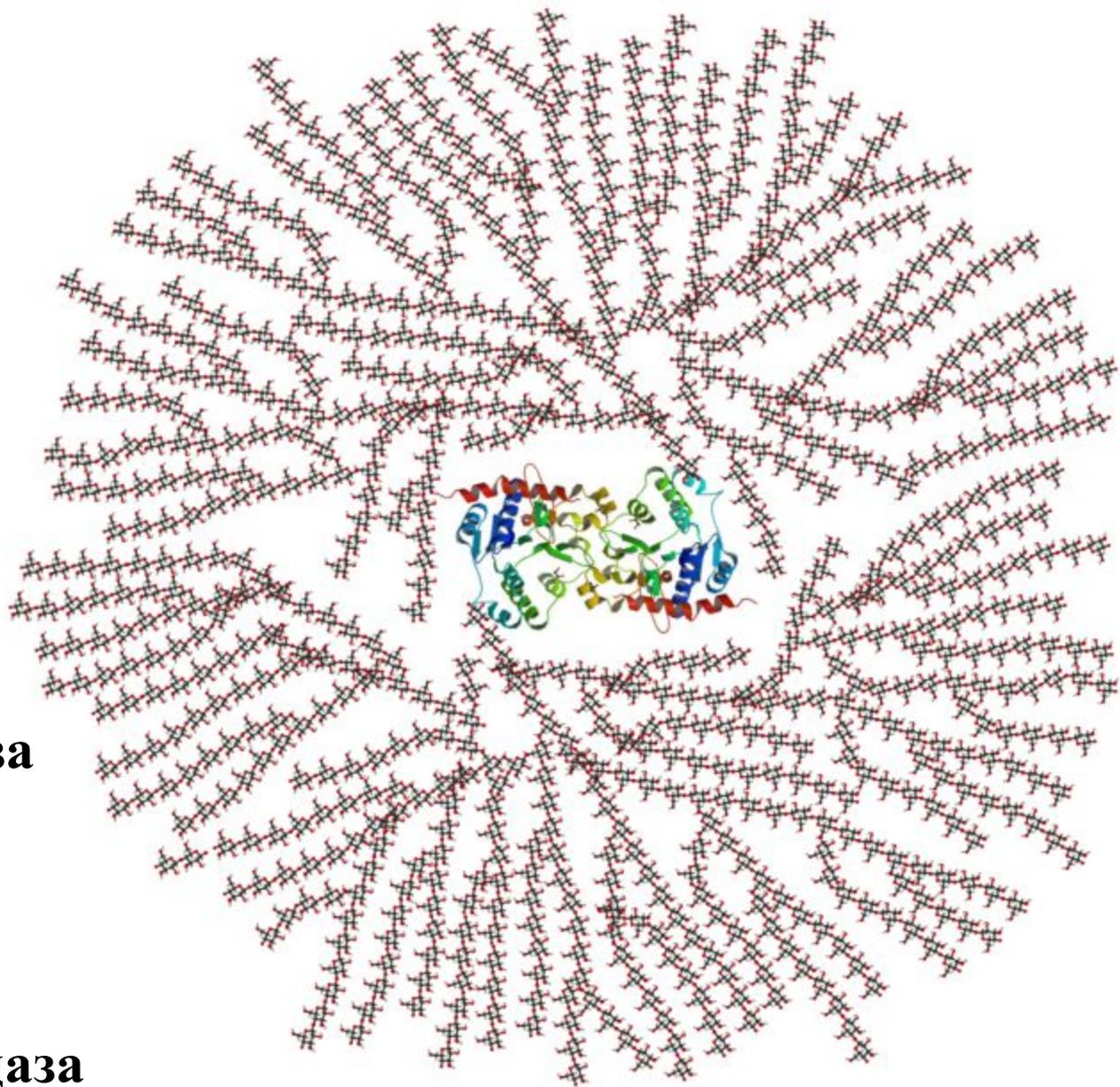
ГЛИКОГЕНИН

ГЛИКОГЕНСИНТАЗА

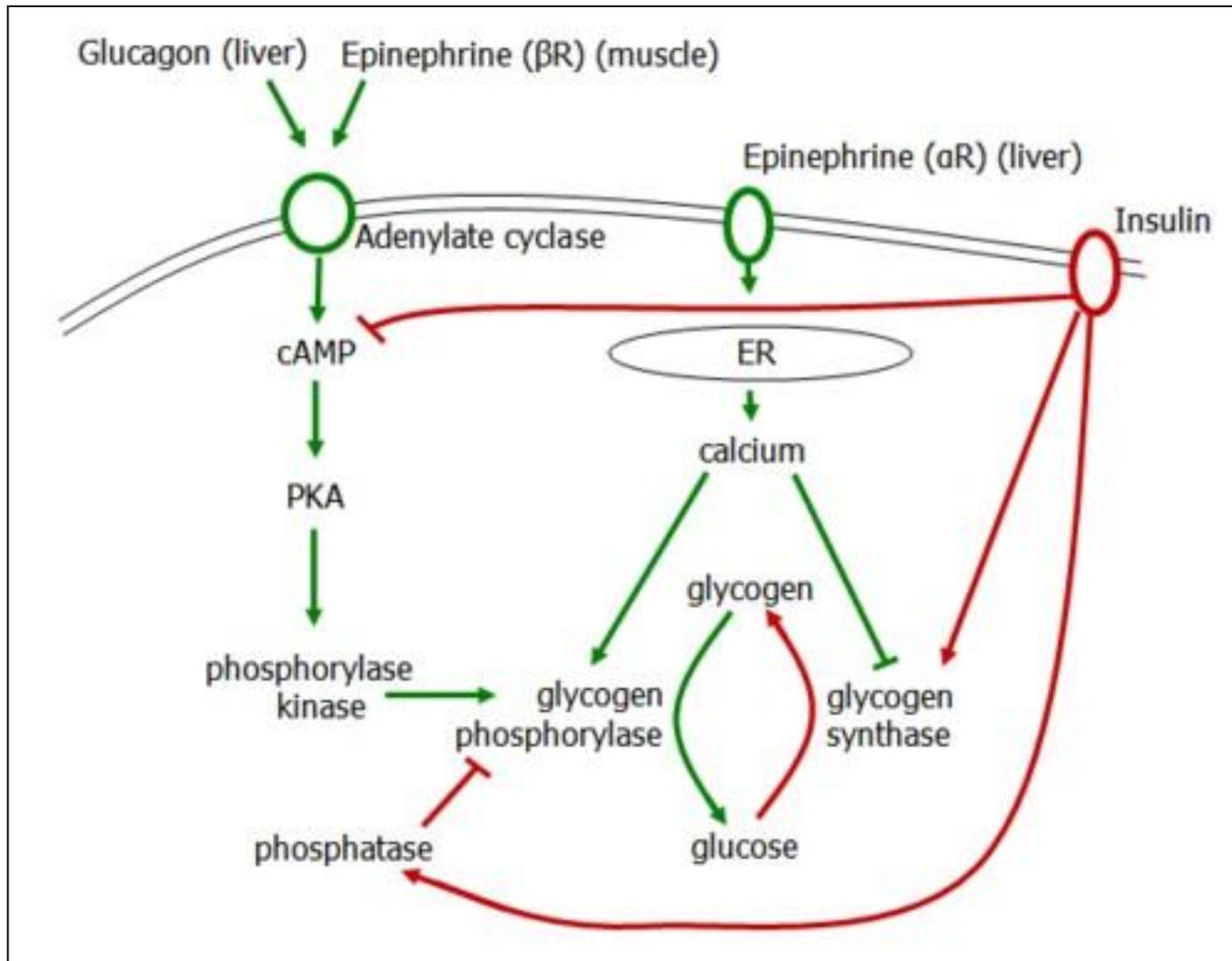
ГЛИКОГЕНФОСФОРИЛАЗА

ГЛЮКАНТРАНСФЕРАЗА

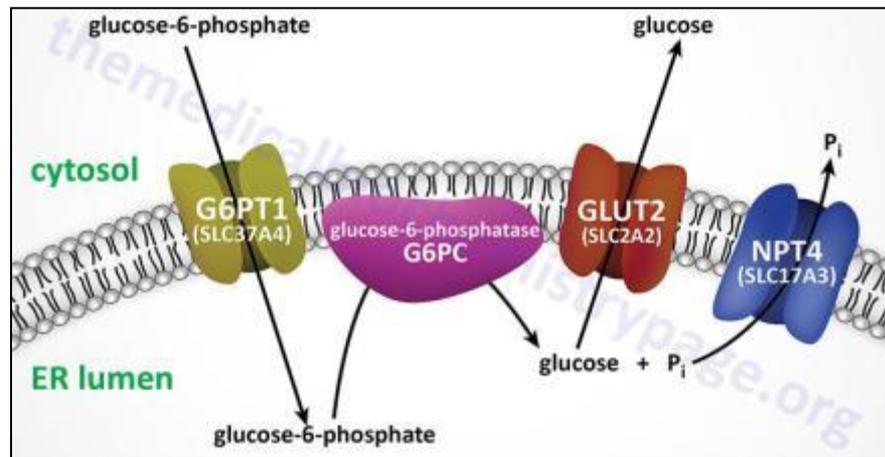
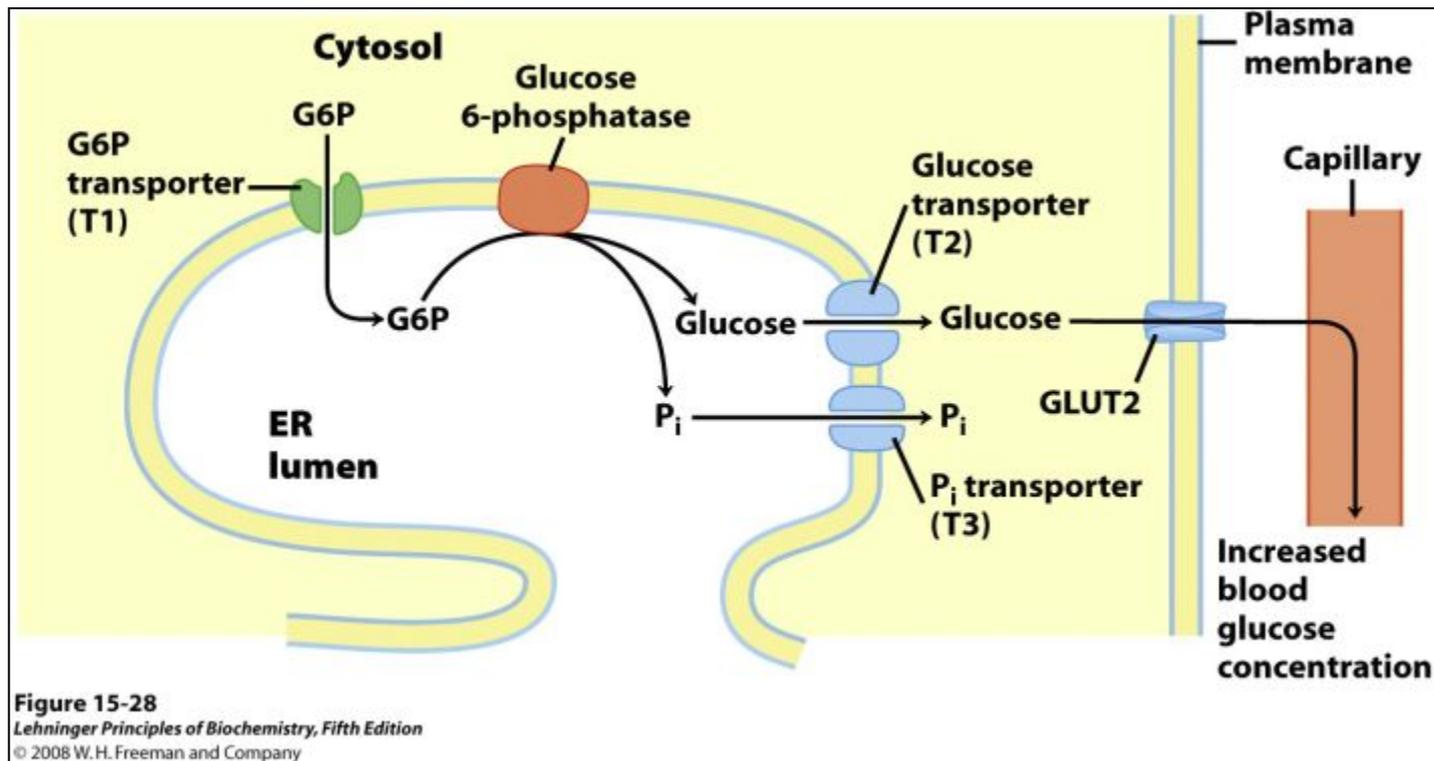
АМИЛО- α 1,6-ГЛЮКОЗИДАЗА



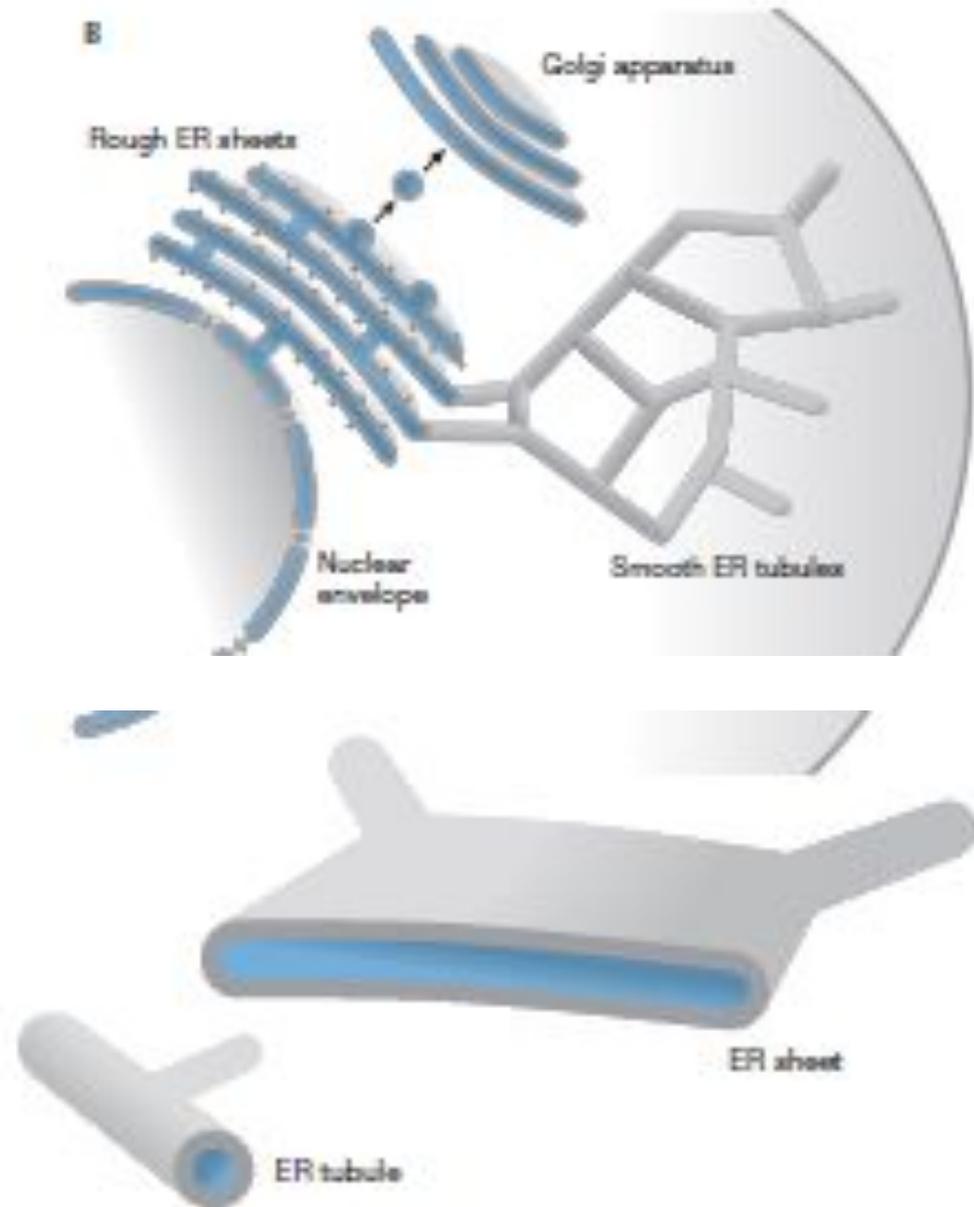
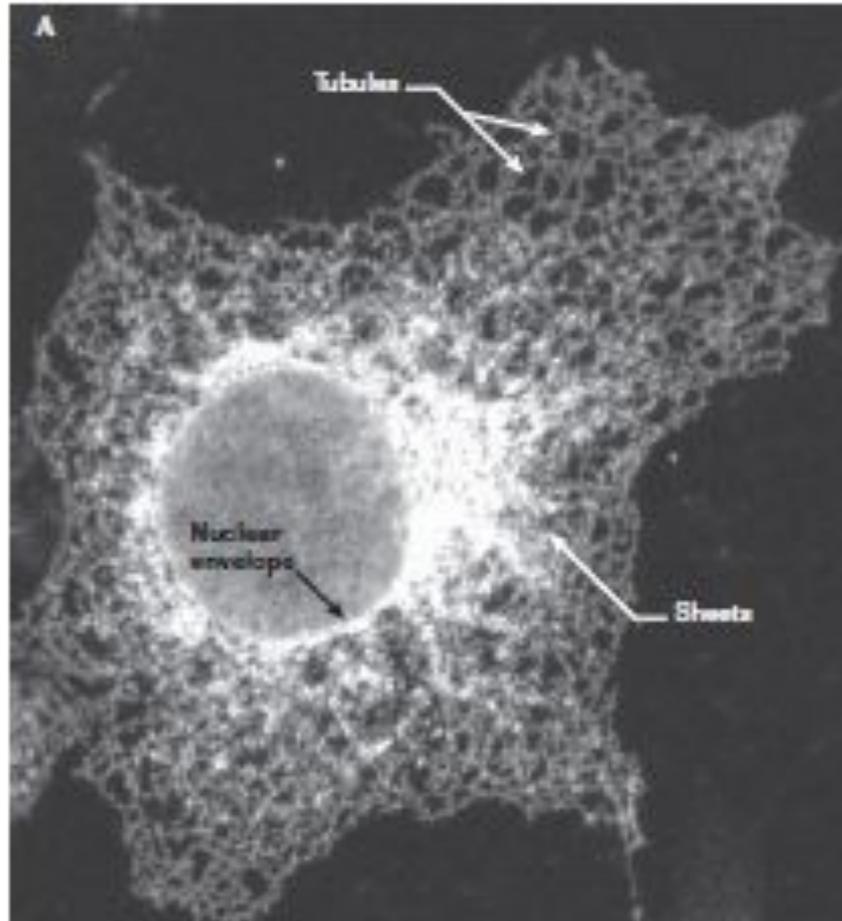
Регуляция синтеза гликогена



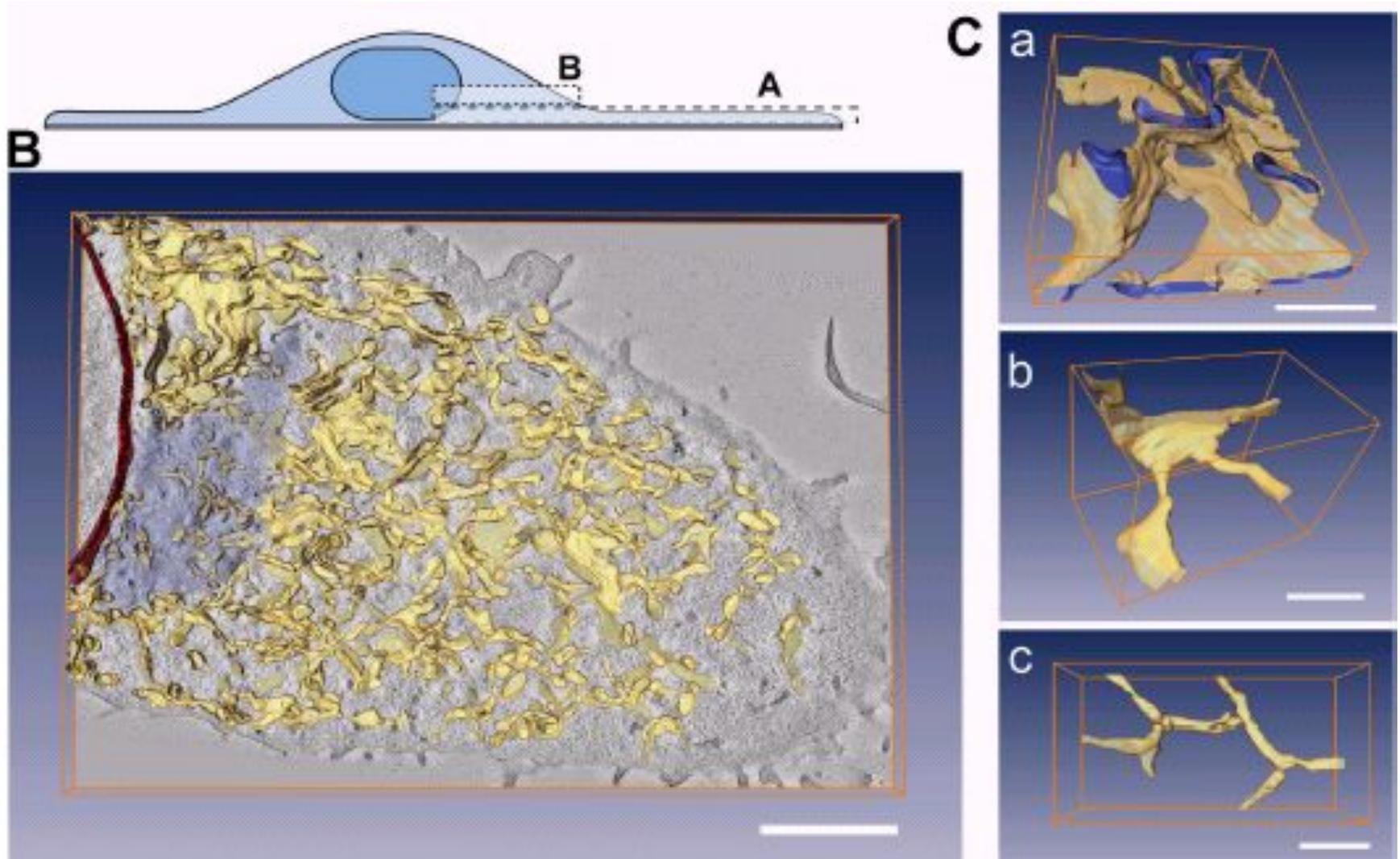
ЭПР и синтез гликогена

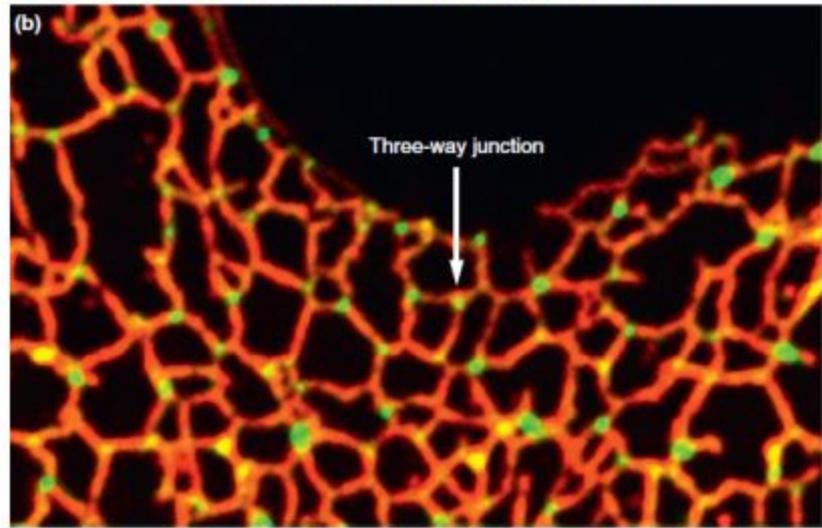
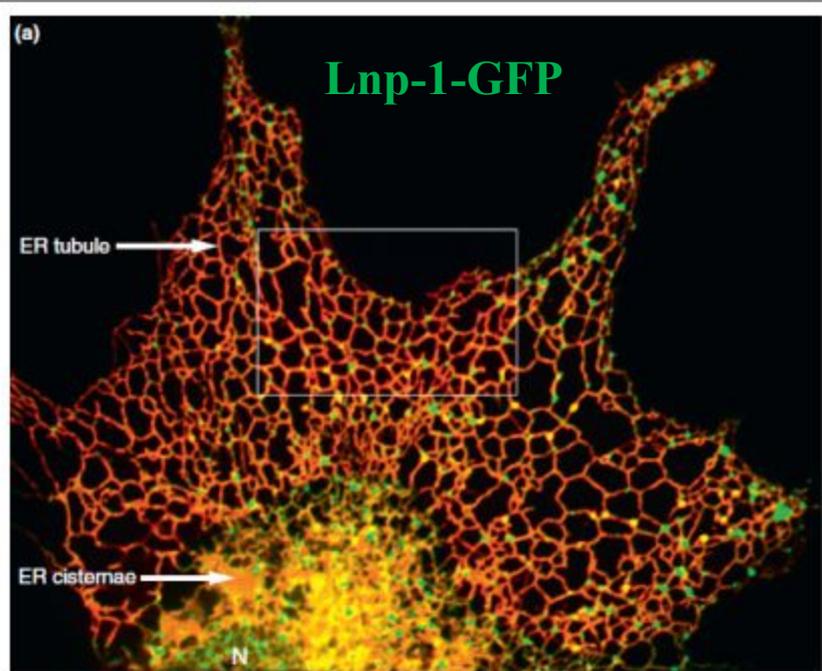


Форма ЭТР.

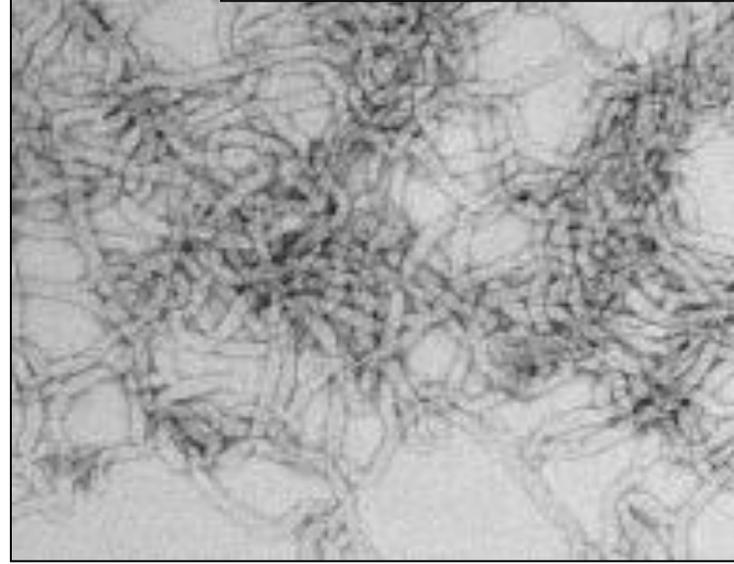
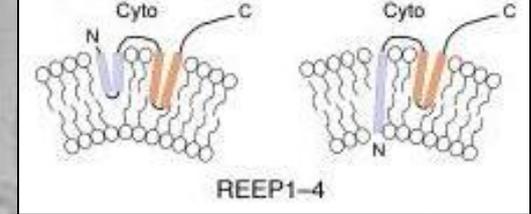


Форма ЭТР.





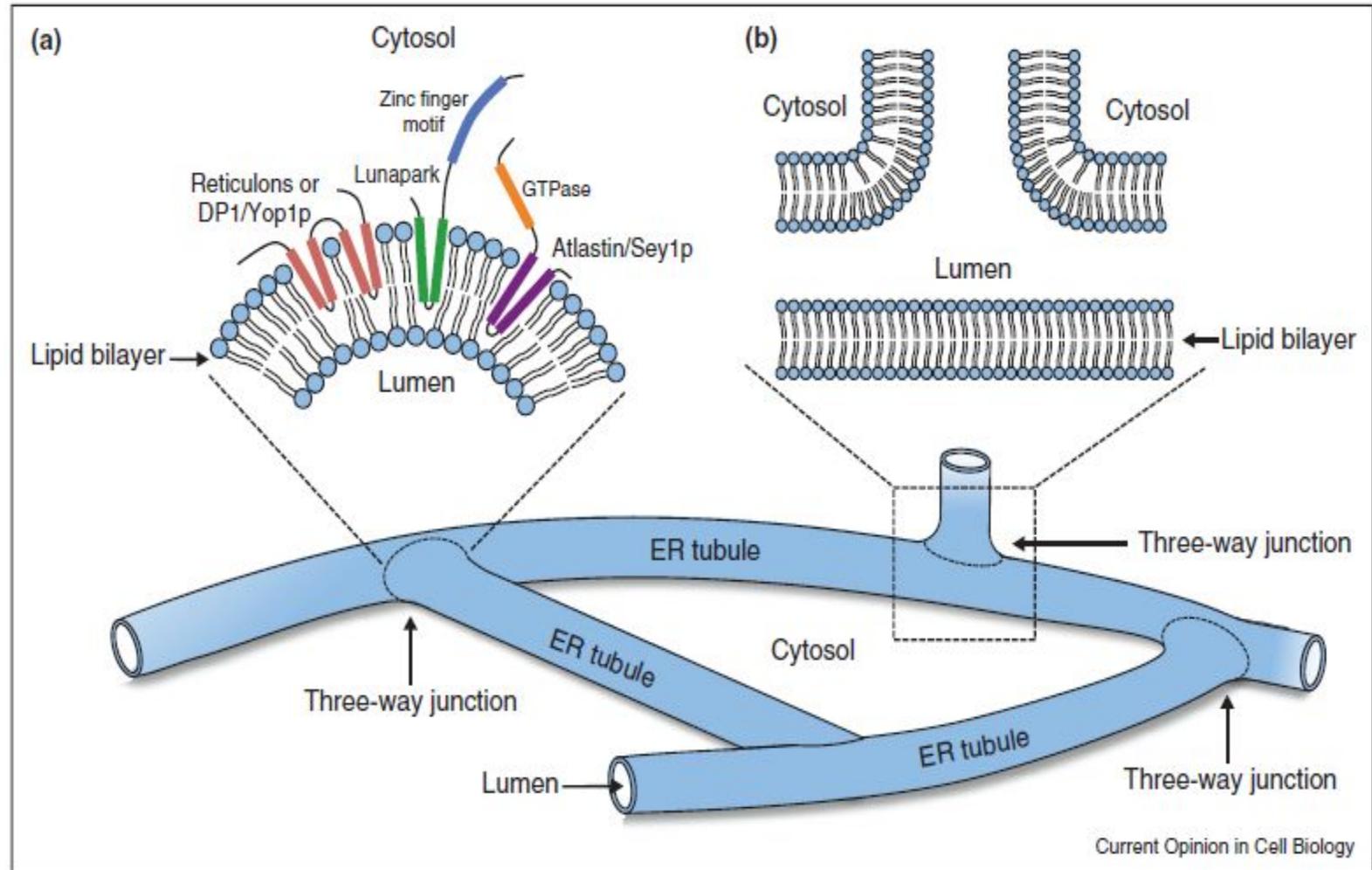
Current Opinion in Cell Biology



DP1/REEP/Yop1 ретикулони

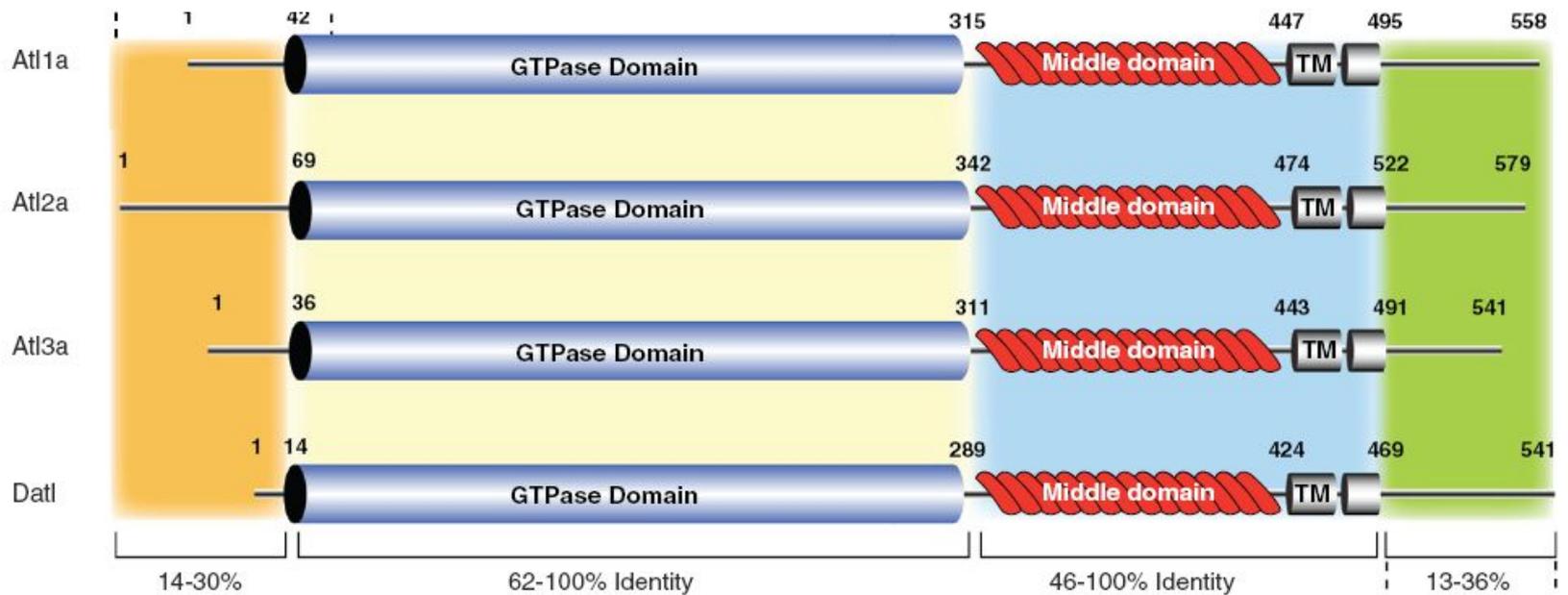
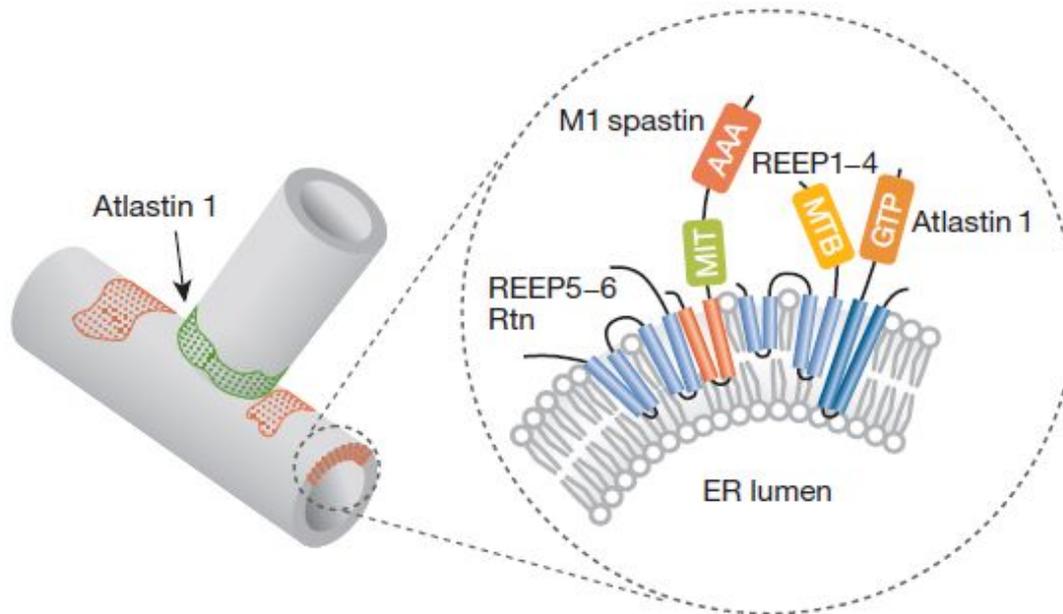
The ER network. (a) The ER network of COS-7 cells is labeled with mCherry-KDEL (red) and the junctions are labeled with Lnp1-GFP (green). Also marked: nucleus (N), ER cisternae and ER tubules. (b) The box area marked in the top panel is magnified below. Interconnected ER tubules form a network with three-way junctions marked by Lnp1-GFP.

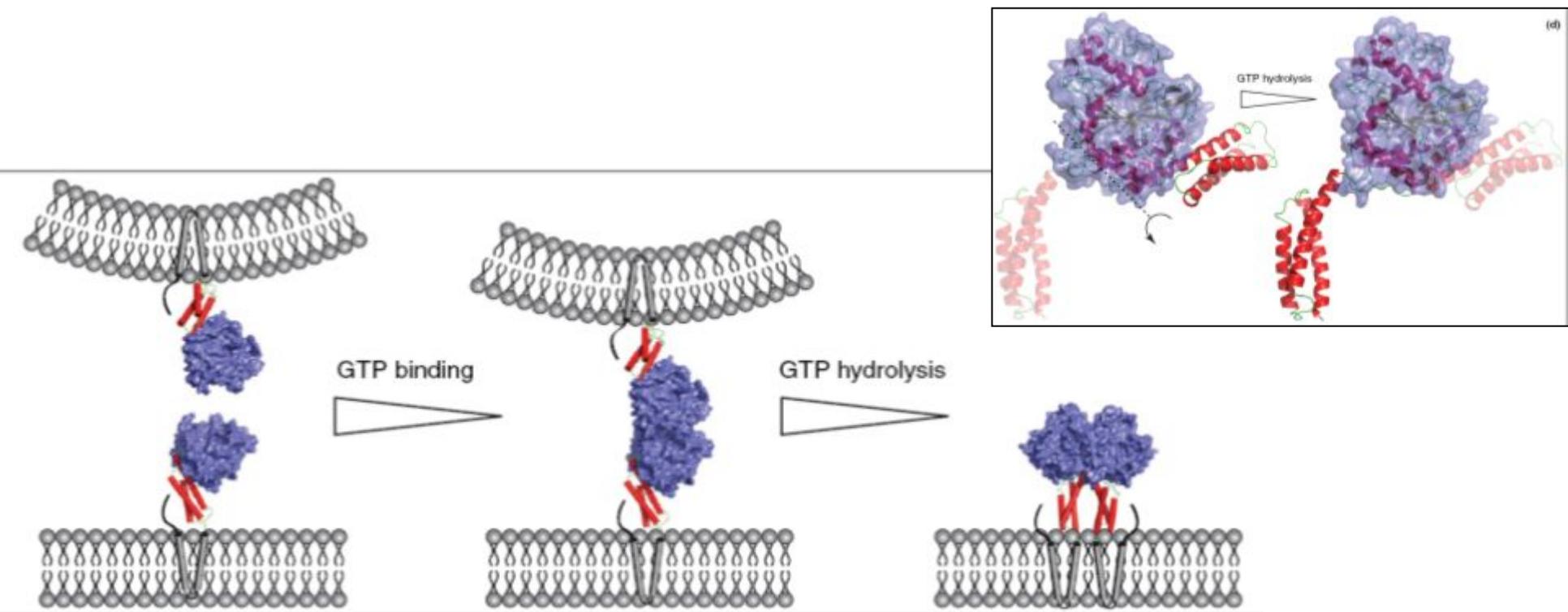
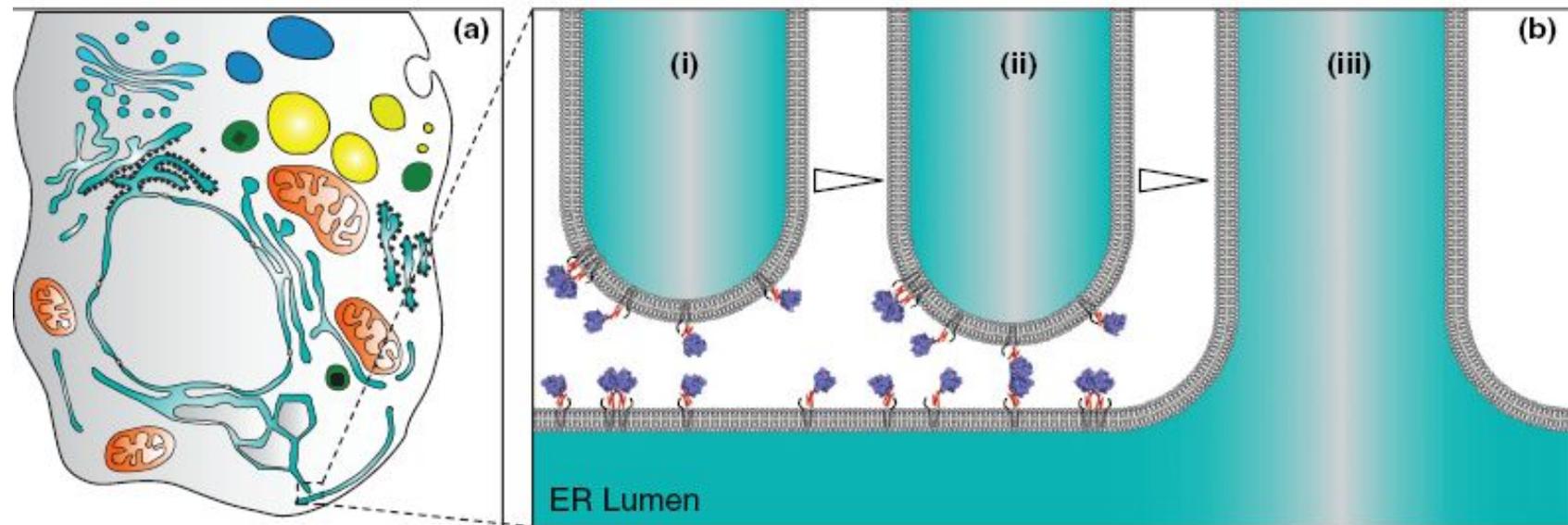
Figure 2



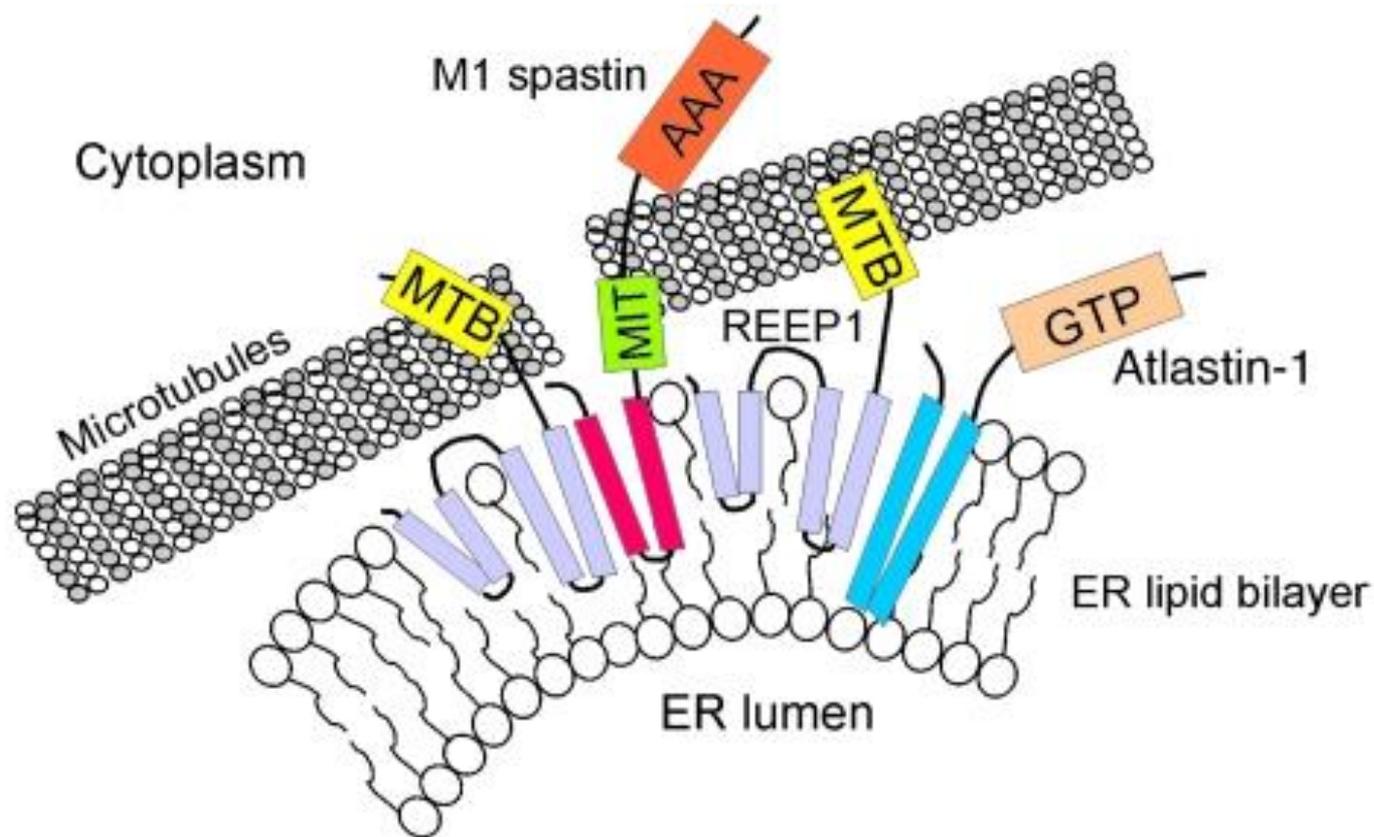
Schematic diagram of the ER shaping proteins at three-way junctions. **(a)** Membrane topology around a three-way junction where reticulons (coral), DP1/Yop1p (coral), Lunapark (green and blue) and atlastin (purple and orange) insert into the outer leaflet of the phospholipid bilayer from the cytosolic side of the membrane. **(b)** A cross-section view of a three-way junction.

Атластин

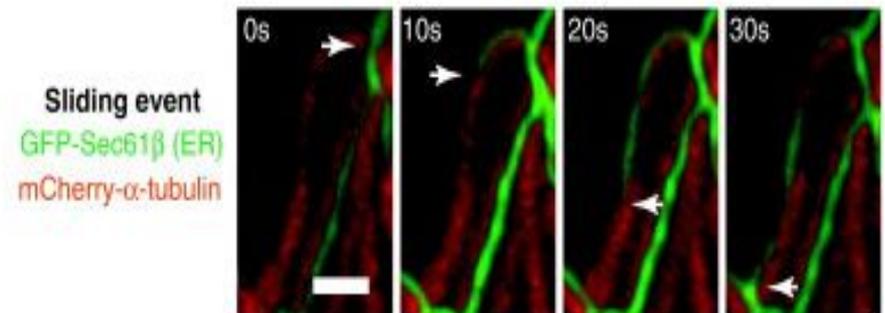
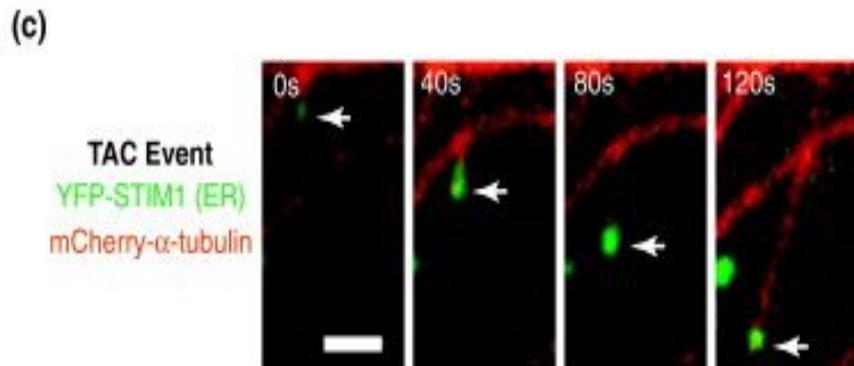
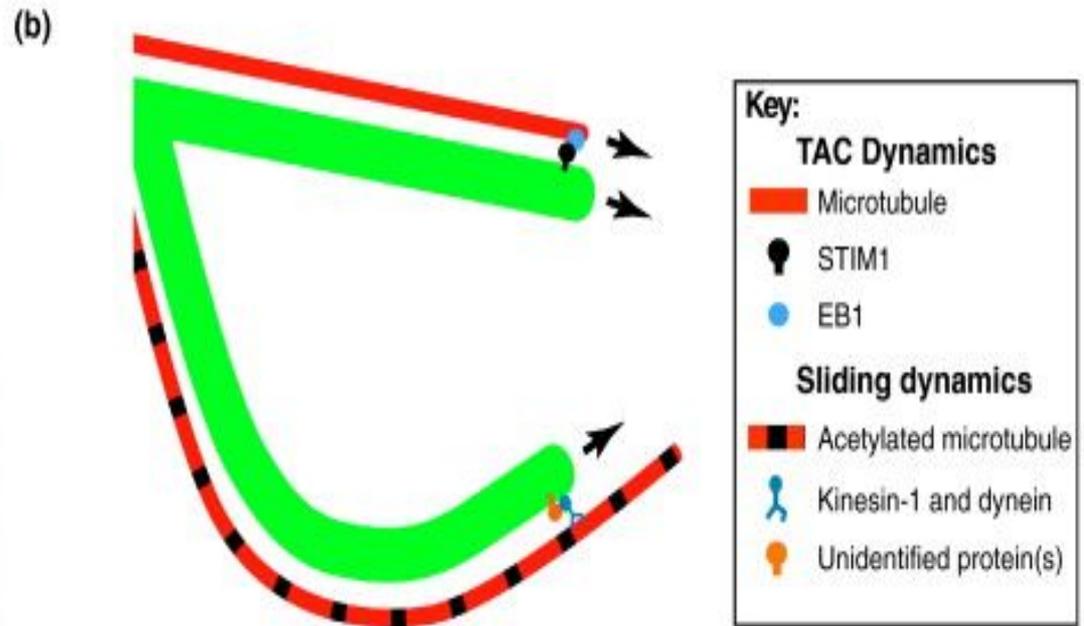
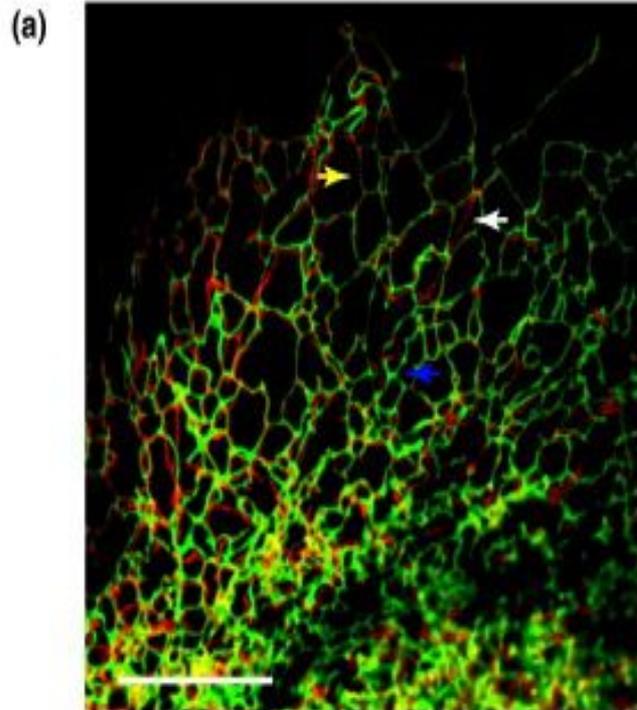




Взаимодействие с микротрубочками

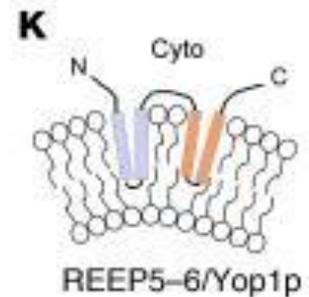


TAC - tip attachment complex

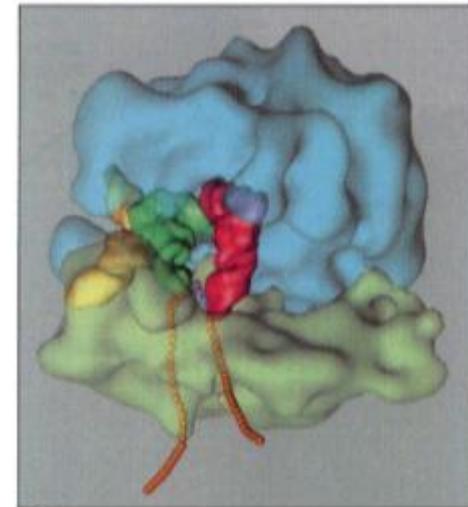
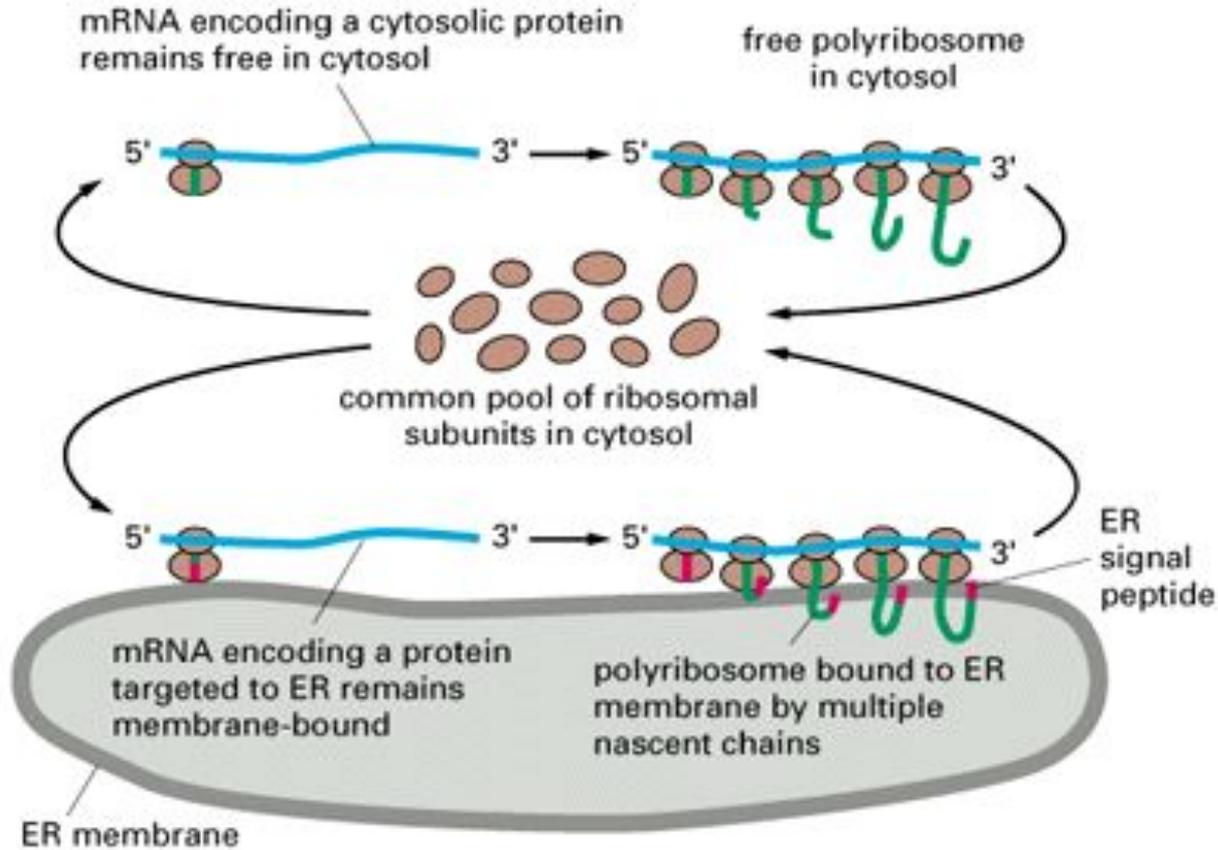


Форма ЭПР.

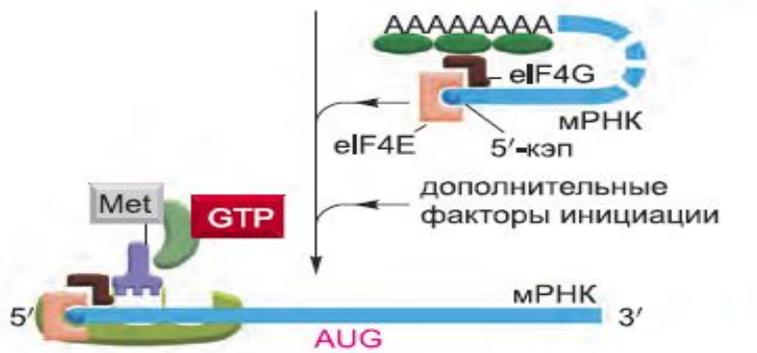
Белки	животные	дрожжи	растения
Пласты	Climp63, p180, kinectin, органеллы		
Слияние тубул	Atlastin	Sey1 p	RHD3
Образование тубул	Reticulons DP1 Lunapark family Lnp1p STIM1 (TAC) Rab10	RTN1 Yop1p She3p, Myo4p	Reticulons DP1
Рост ЭПР	TAC (STIM1, EB1) кинезин спастин		



Гранулярный ЭТР. Синтез белка.



(B)



дополнительные факторы инициации



ИНИЦИАТОРНАЯ тРНК ДВИГАЕТСЯ ВДОЛЬ РНК В ПОИСКАХ ПЕРВОГО КОДОНА AUG



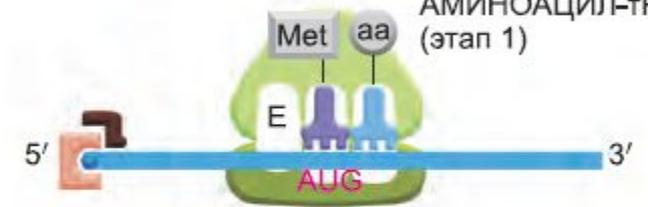
ДИССОЦИАЦИЯ eIF2 И ДРУГИХ ФАКТОРОВ ИНИЦИАЦИИ



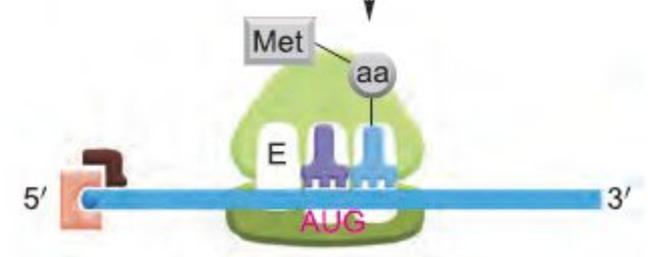
ПРИСОЕДИНЕНИЕ БОЛЬШОЙ СУБЧАСТИЦЫ РИБОСОМЫ



ПРИСОЕДИНЕНИЕ АМИНОАЦИЛ-тРНК (этап 1)



ОБРАЗОВАНИЕ ПЕРВОЙ ПЕПТИДНОЙ СВЯЗИ (этап 2)



и т. д.

Сигнальная последовательность

Function of Signal Peptide

Example of Signal Peptide

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-

Retain in lumen of ER

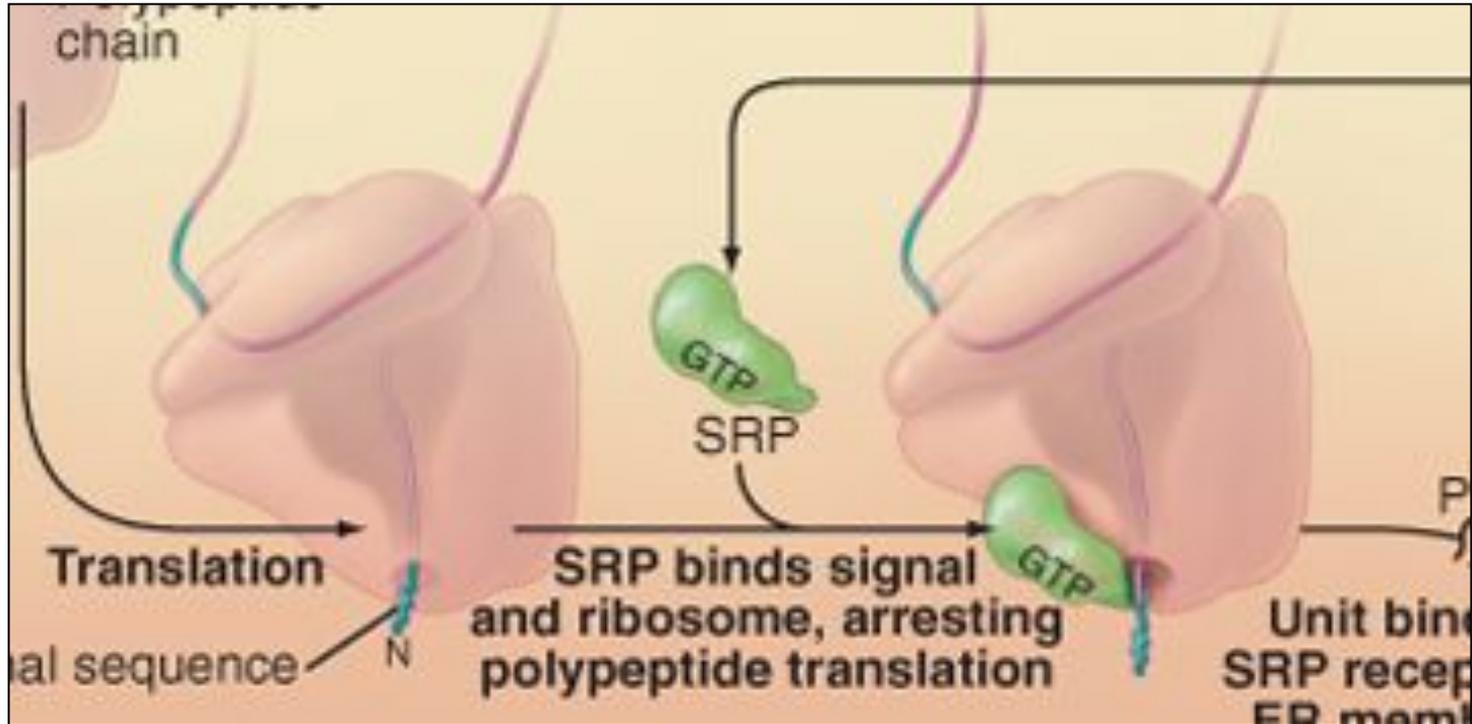
-Lys-Asp-Glu-Leu-COO $^-$

белок	последовательность
Preproalbumin	Met-Lys-Trp-Val-Thr-Phe-Leu-Leu-Leu-Leu-Phe-Ile-Ser-Gly-Ser-Ala-Phe-Ser ↓ Arg . . .
Pre-IgG light chain	Met-Asp-Met-Arg-Ala-Pro-Ala-Gln-Ile-Phe-Gly-Phe-Leu-Leu-Leu-Leu-Phe-Pro-Gly- Thr-Arg-Cys ↓ Asp . . .
Prelysozyme	Met-Arg-Ser-Leu-Leu-Ile-Leu-Val-Leu-Cys-Phe-Leu-Pro-Leu-Ala-Ala-Leu-Gly ↓ Lys . . .

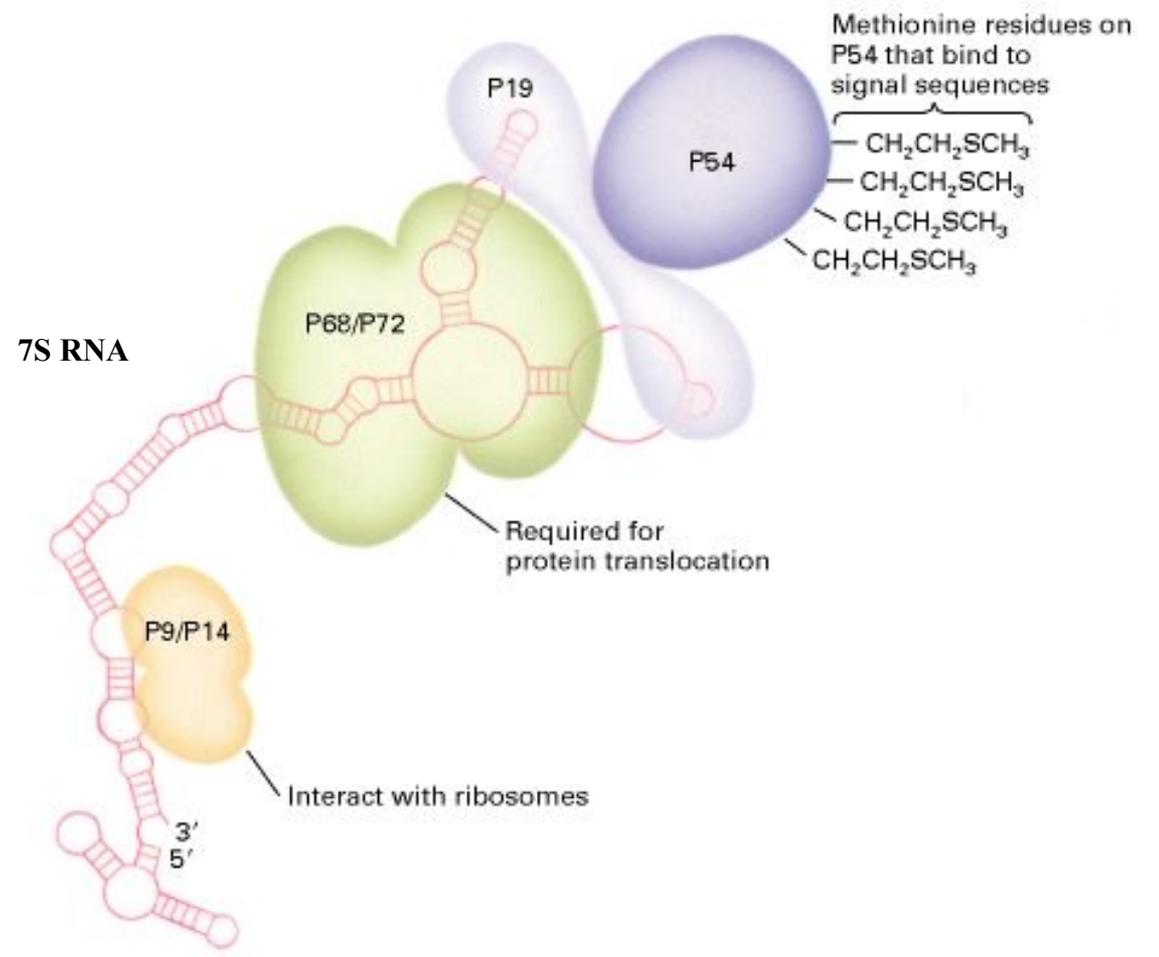
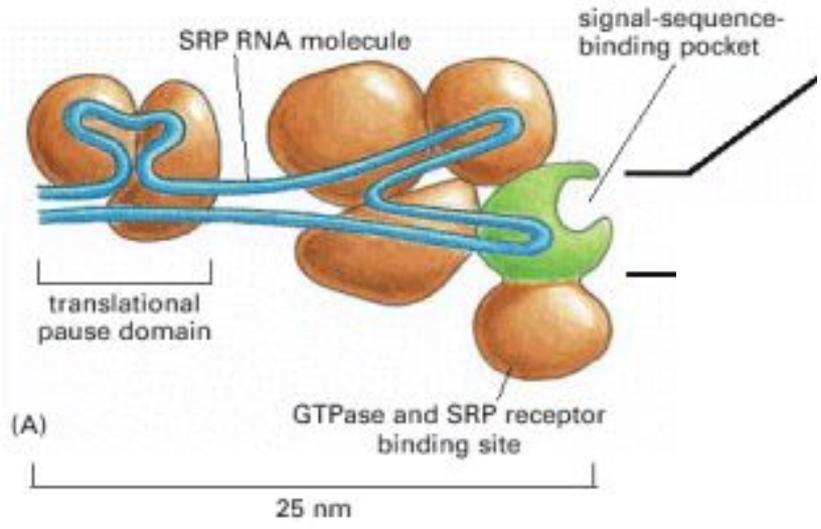
Сигнальная последовательность

Protein	Signal Sequence	Length	Charge
BiP	MKLSLVAAMLLLLSAARA	18	+1
Apo-A1	MKAAVLT LAVLFLTGSQA	18	+1
TGF- β 2	MHYCVLSAFLILHLVTVAL	19	0
Interferon γ	MKYTSYILAFQLCIVLG	17	+1
Glucagon	MKSIYFVAGLFVMLVQQ	19	+1
Choriogonadotropin	MEMFQGLLLLLLLLLSMGGTWA	20	-1
EGF-receptor	MRPSGTAGAALLALLAALCPRA	24	+1
Growth hormone	MATGSRTSLLLAFGLLCLPWLQ EGSA	26	+1

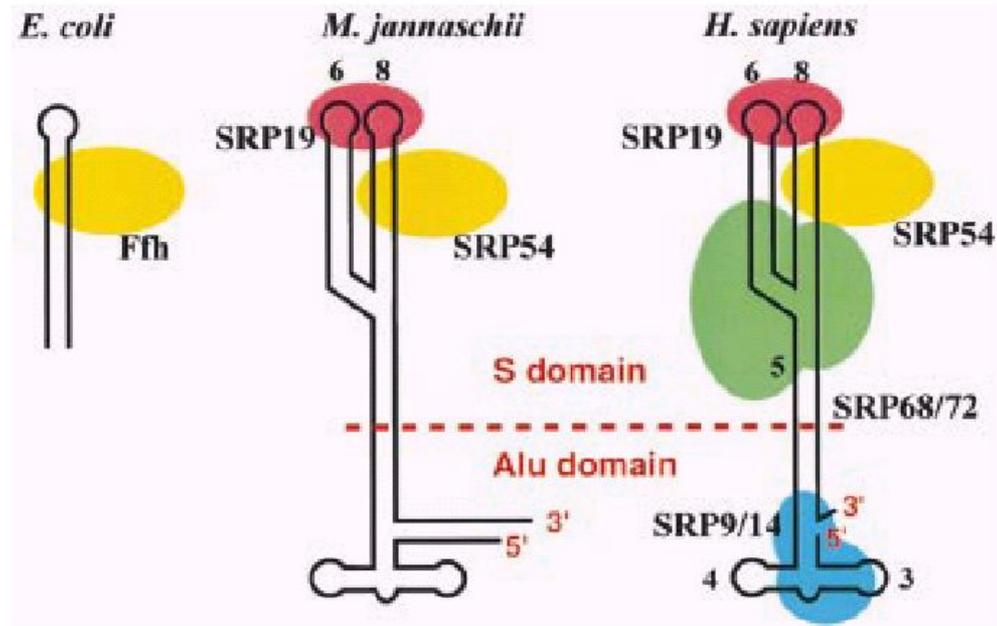
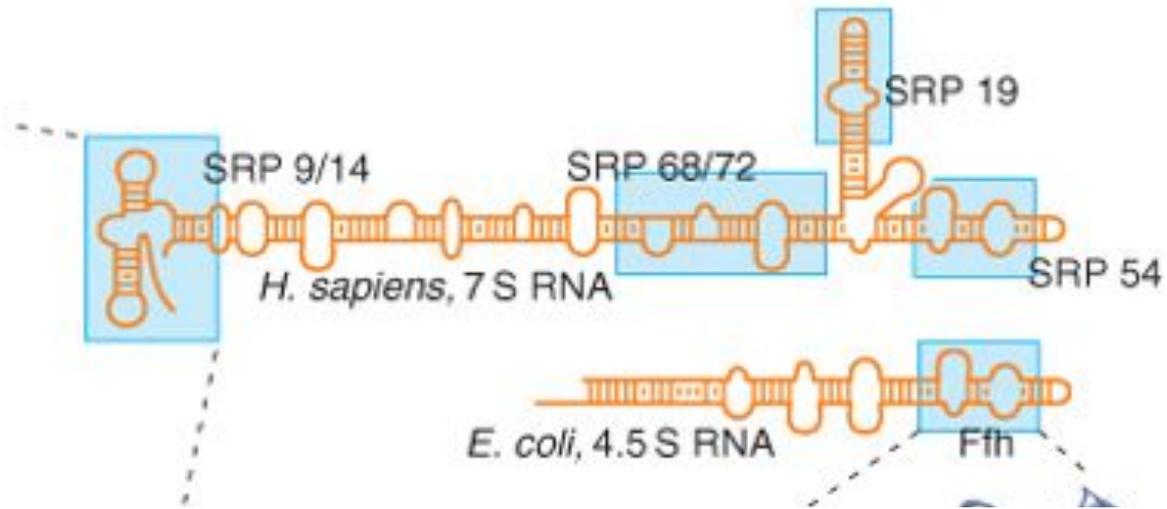
SRP-signal recognition particle



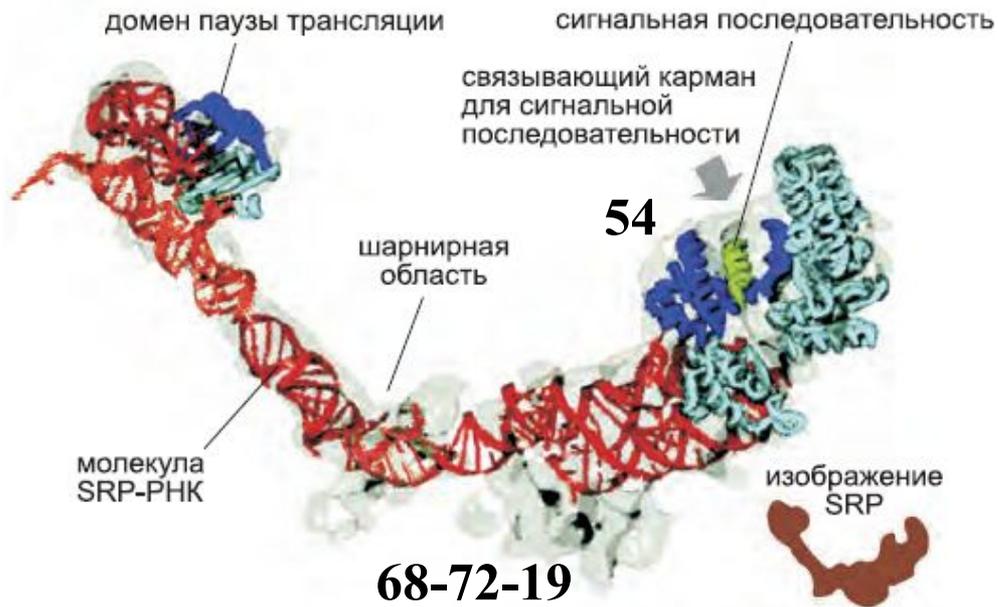
SRP-signal recognition particle



SRP

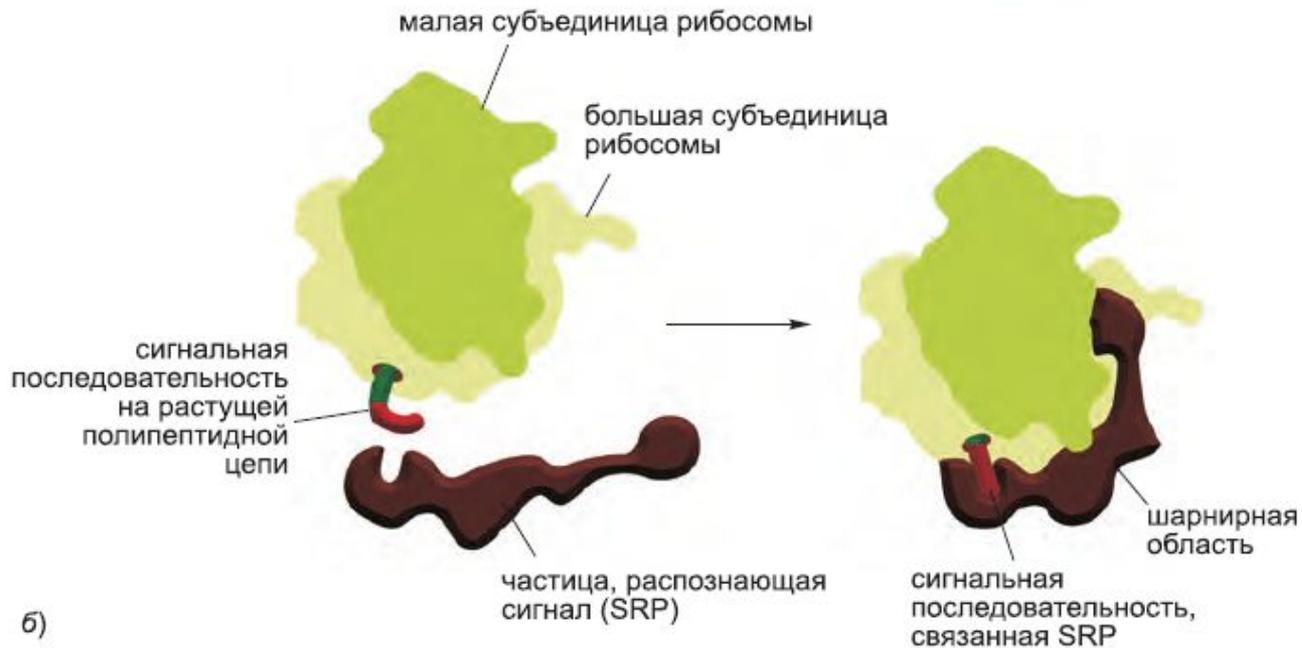


19-14

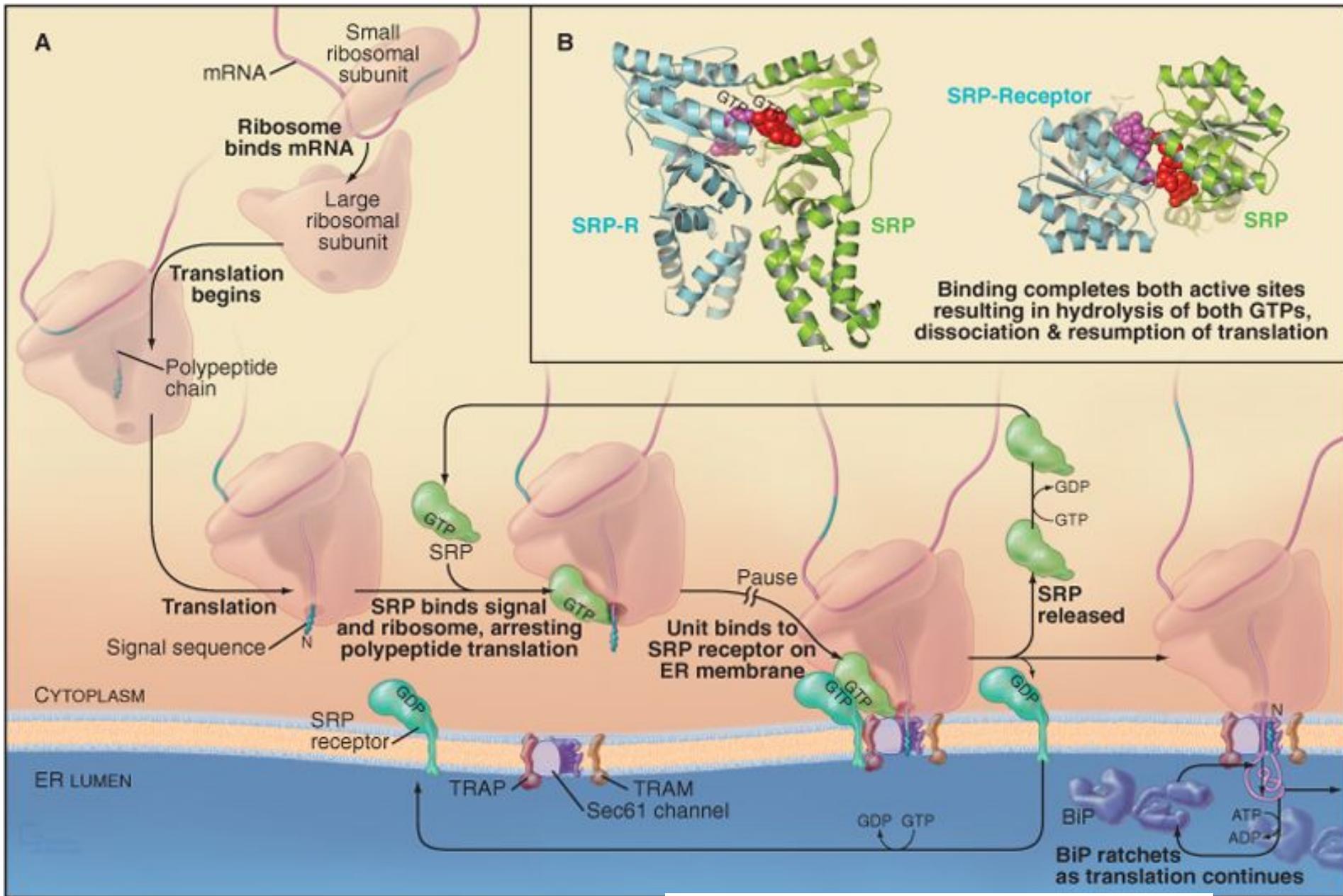


а)

68-72-19



б)



translocon-associated protein

Bio **translocating chain-associating membrane protein**

Sec61

α

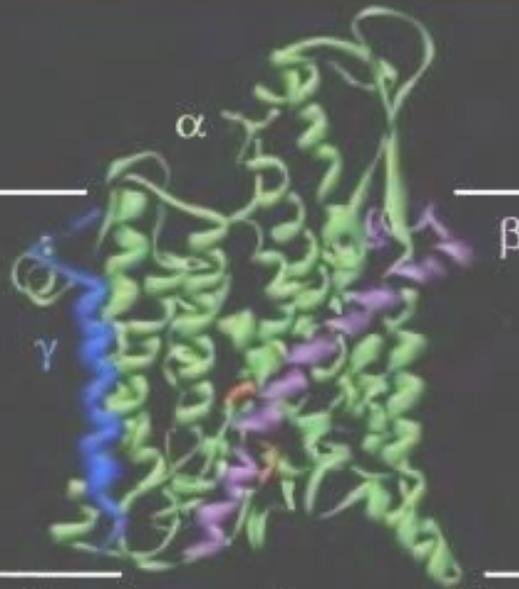
β

γ

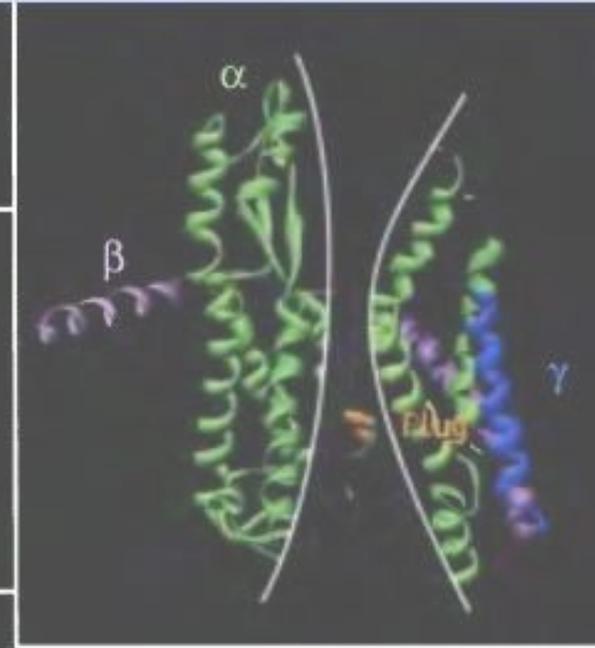
ЦИТОЗОЛЬ

МЕМБРАНА

ВНЕКЛЕТОЧНОЕ
ПРОСТРАНСТВО



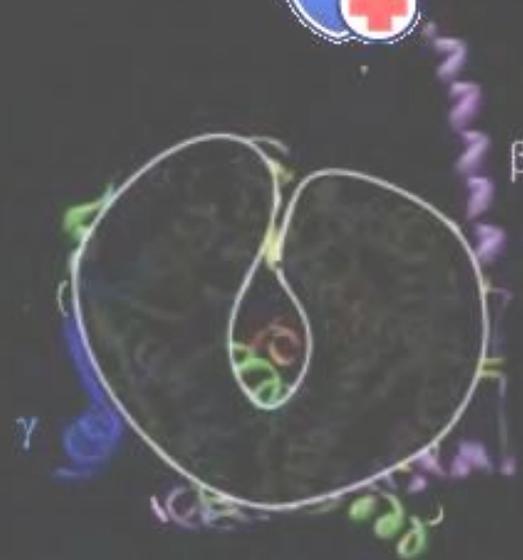
40 Å



90°



ВИД
СО СТОРОНЫ ЦИТОЗОЛЯ



www.bionet.ru



Sec

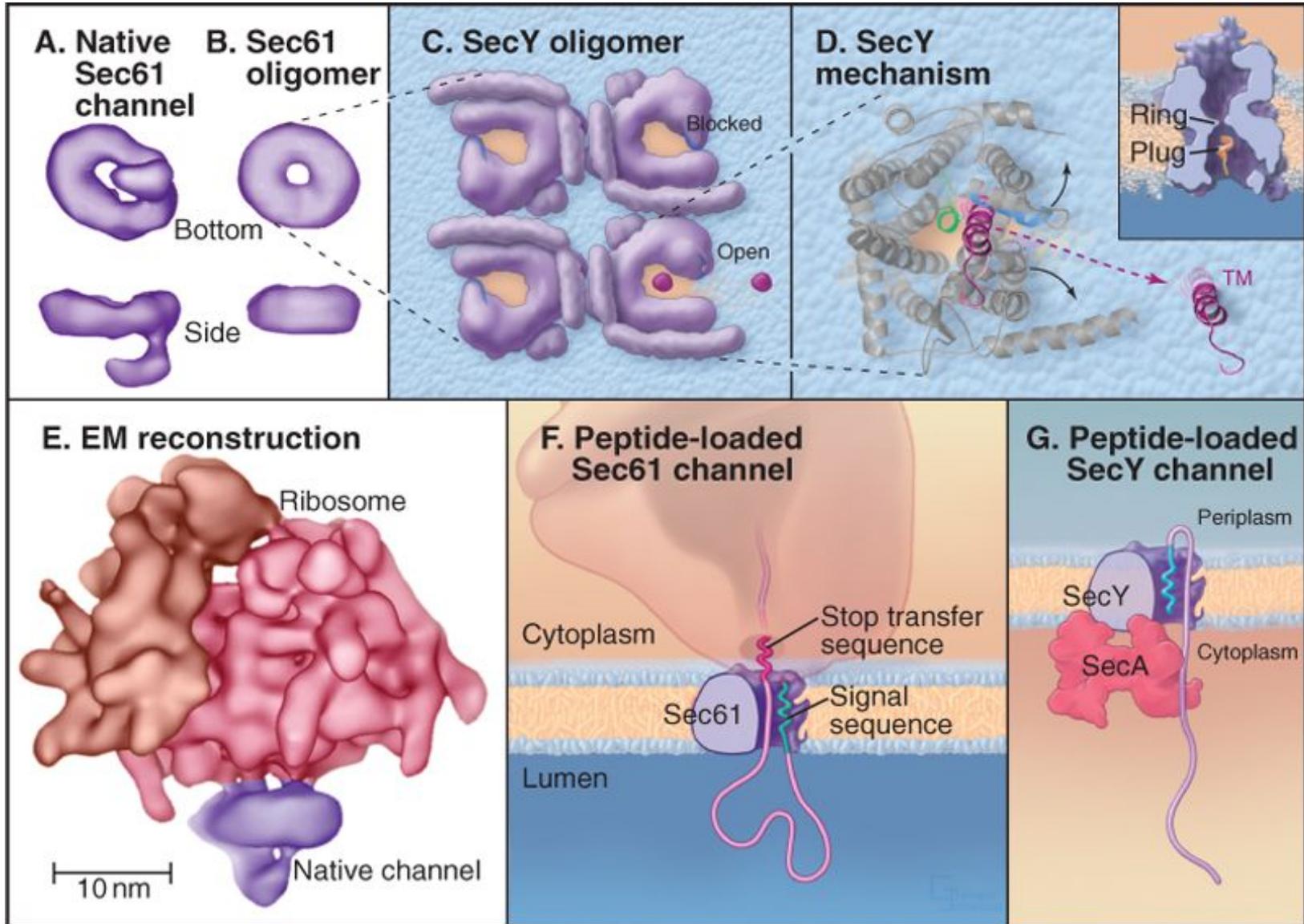
Y

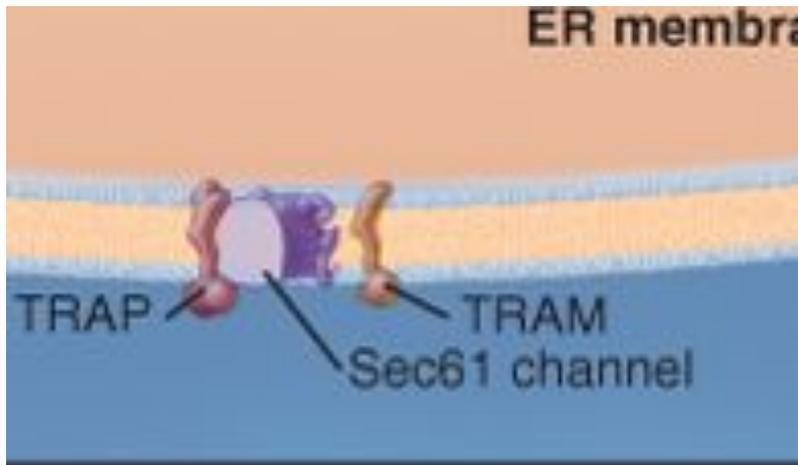
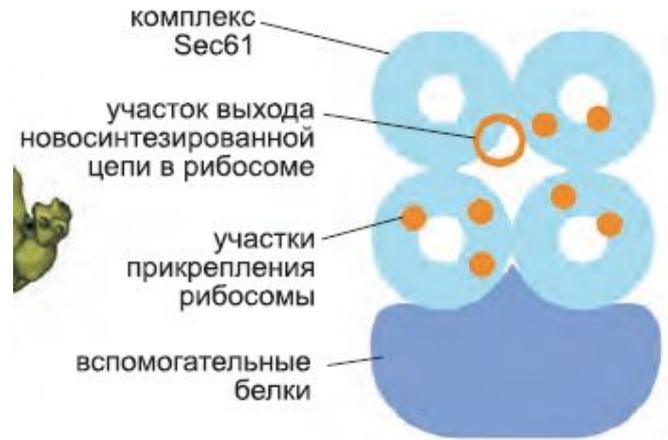
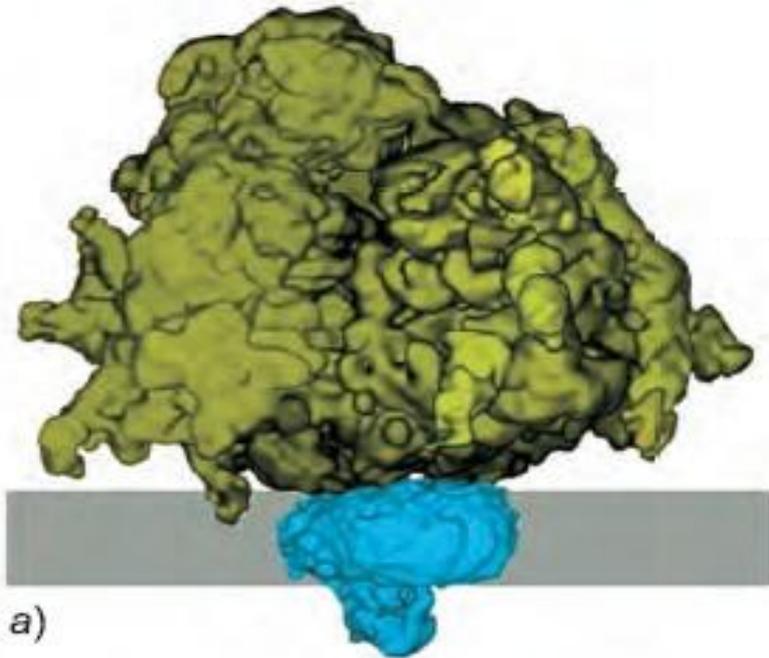
E

G

$\alpha\beta\gamma$

Котрансляционный перенос



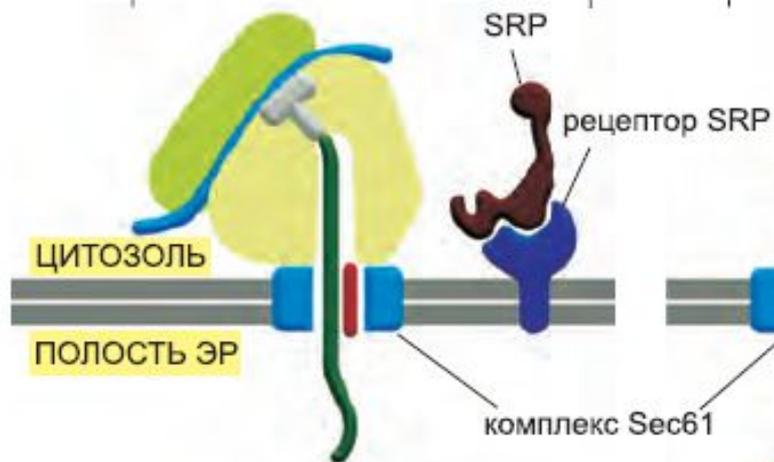


TRAP TRAM p180 Sec62, Sec63

**translocating chain-associating
membrane protein**

translocon-associated protein

КОТРАНСЛЯЦИОННЫЙ ПЕРЕНОС

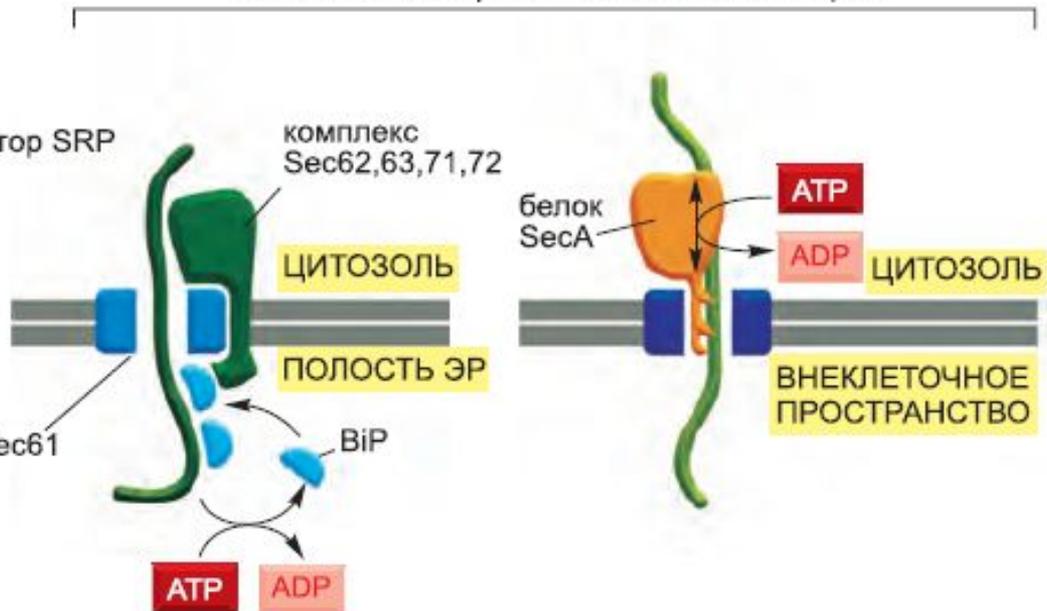


БАКТЕРИИ

АРХЕИ

ЭУКАРИОТЫ

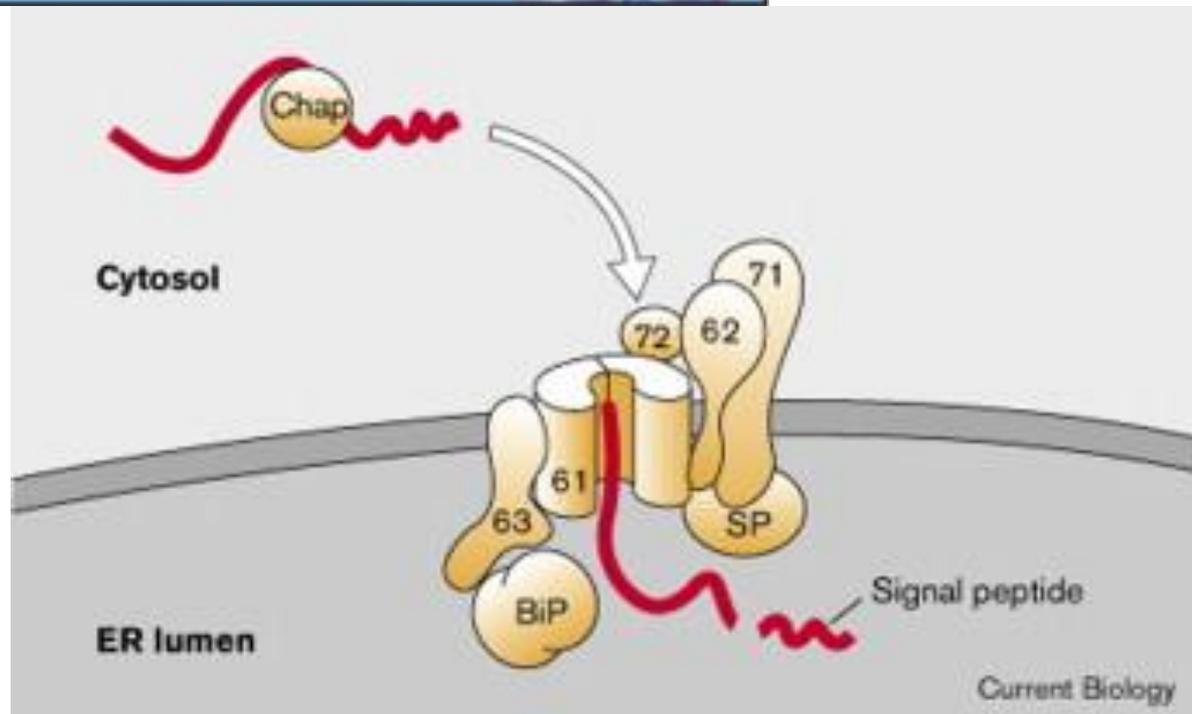
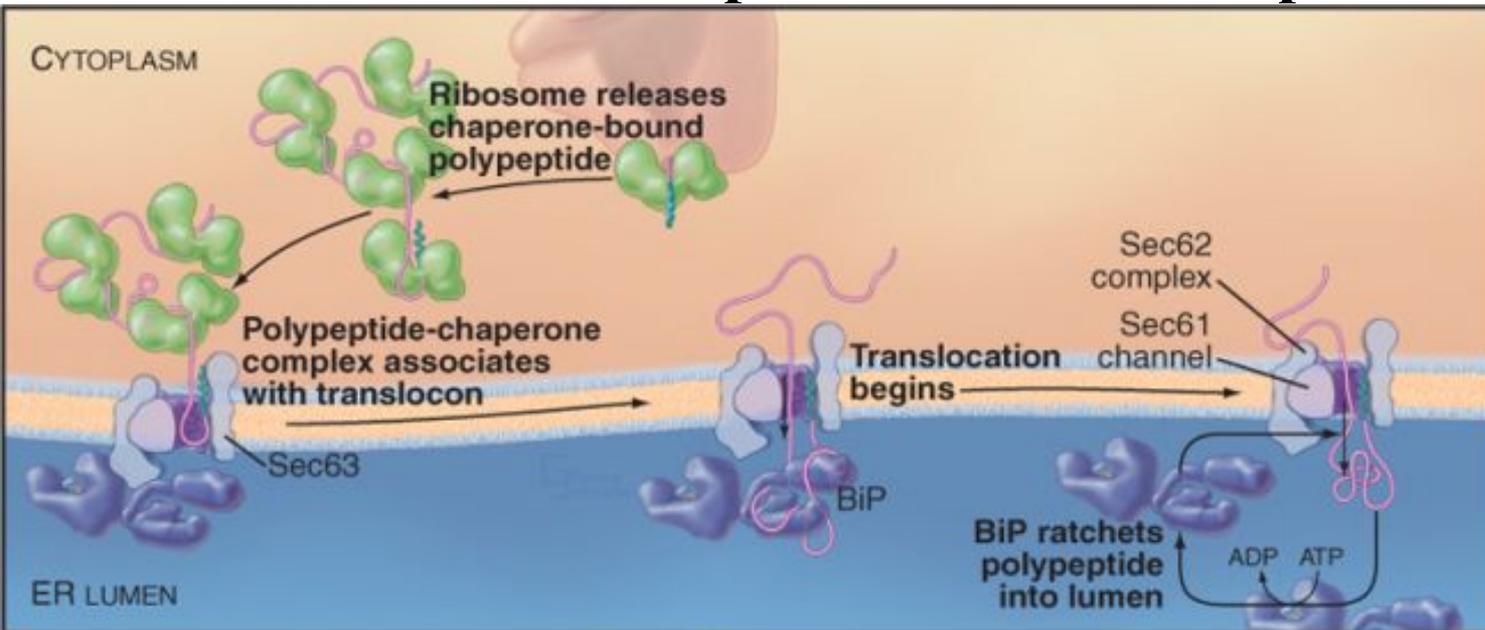
ПОСТТРАНСЛЯЦИОННАЯ ТРАНСЛОКАЦИЯ



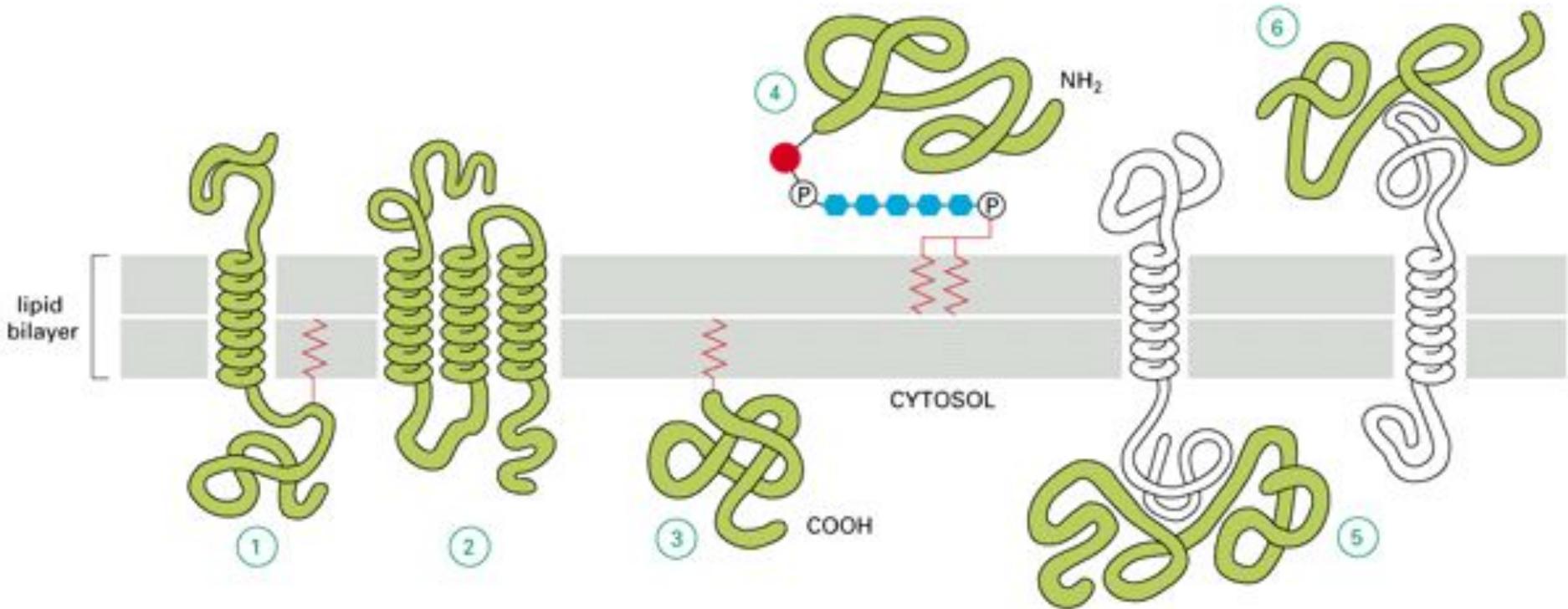
ЭУКАРИОТЫ

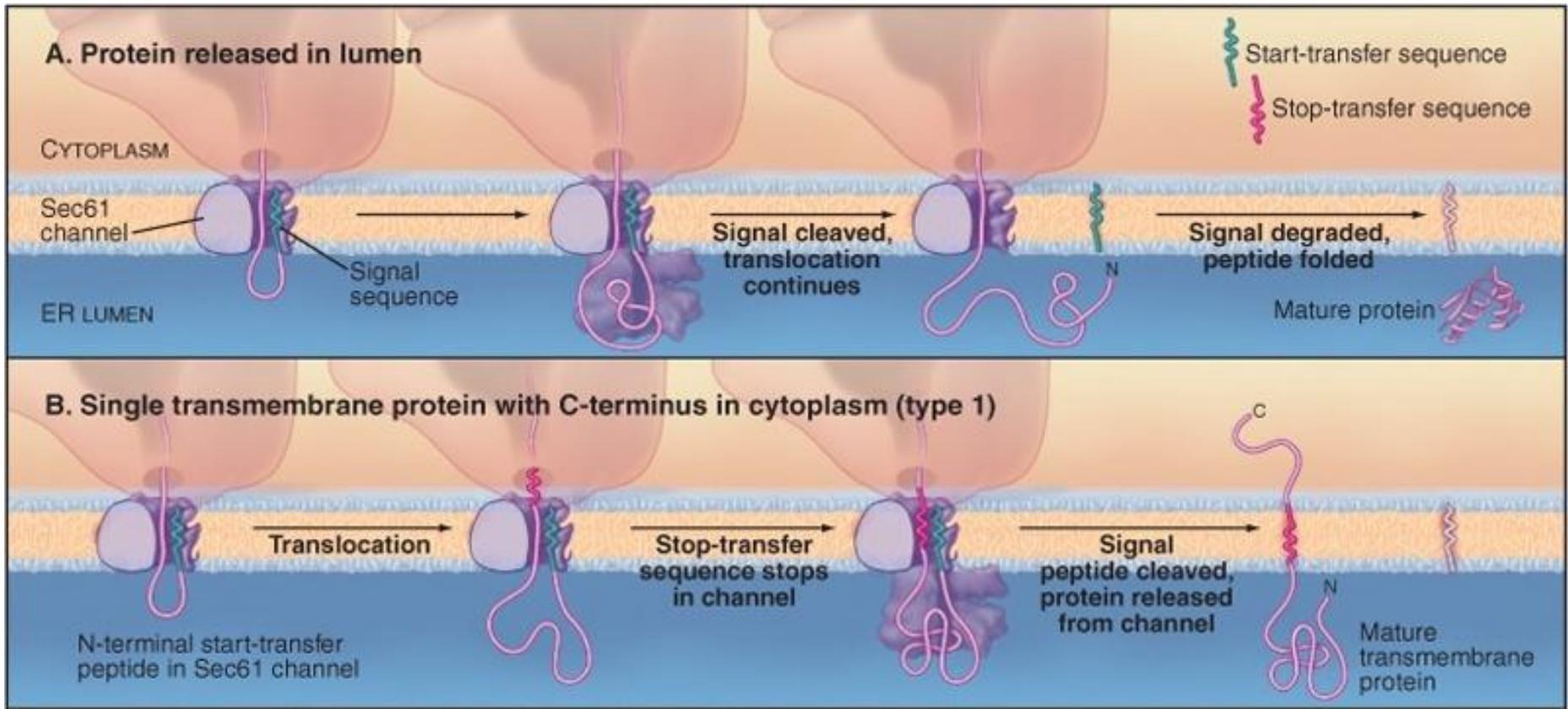
БАКТЕРИИ

Посттрансляционный перенос

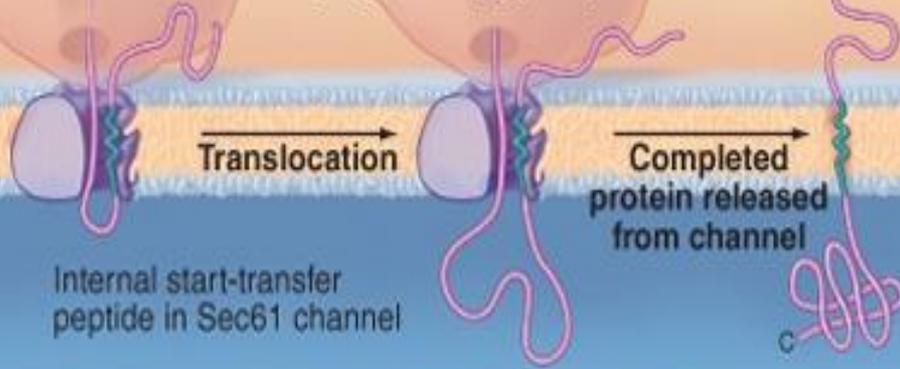


Белки мембран

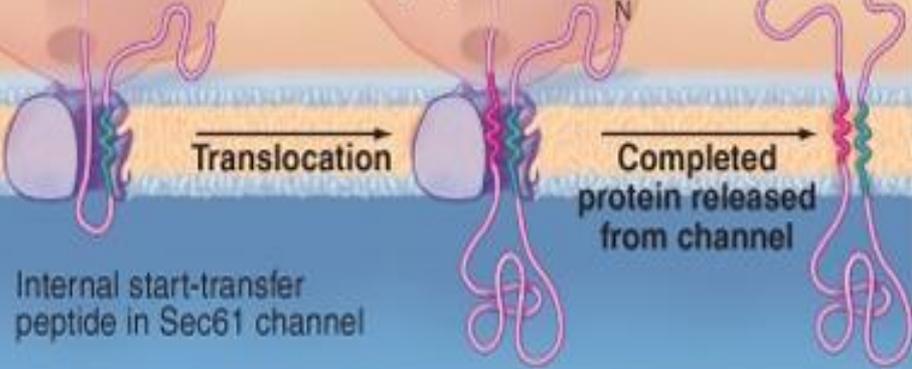




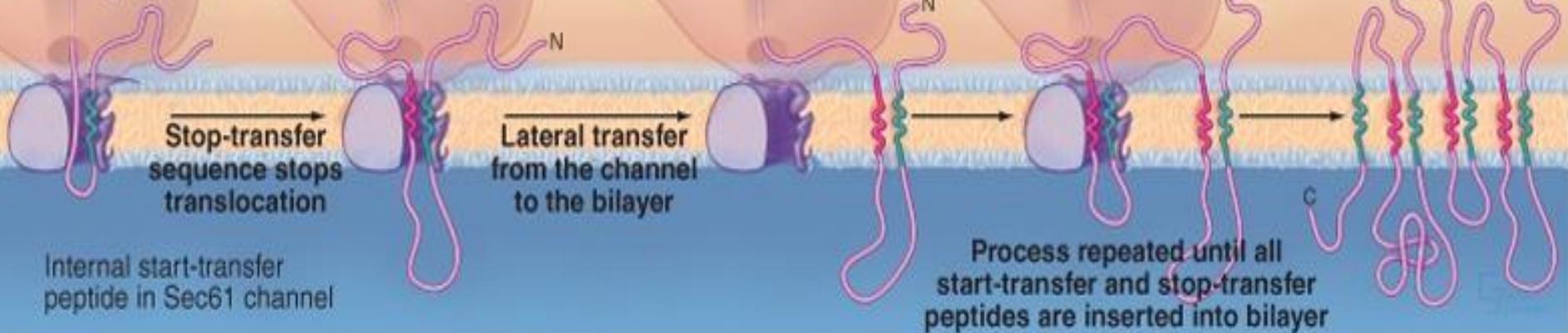
D. Single transmembrane protein with N-terminus in cytoplasm (type 2)

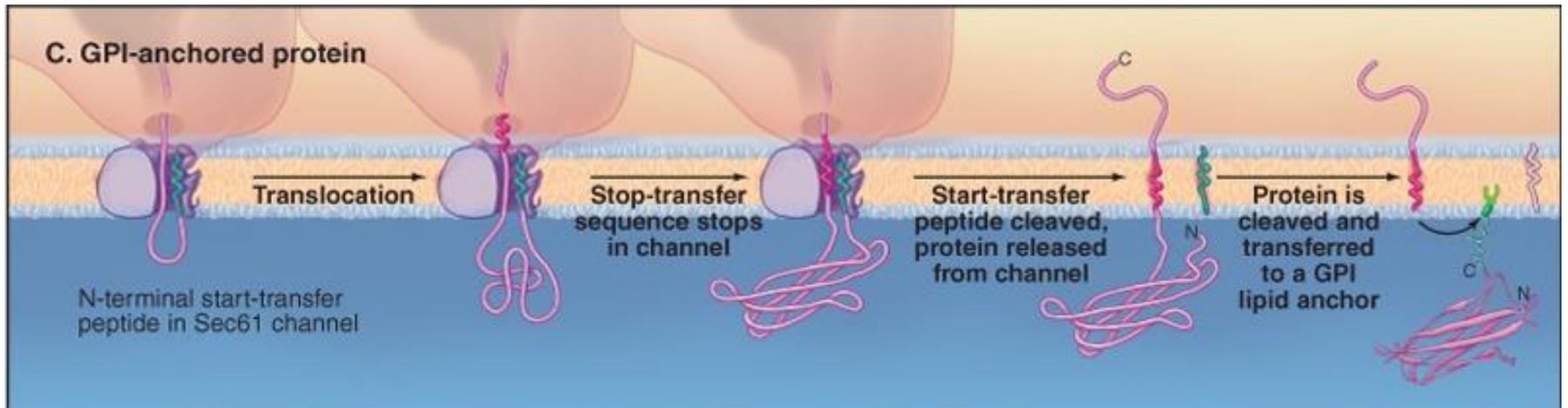


E. Two transmembrane-containing protein with N-terminus in cytoplasm

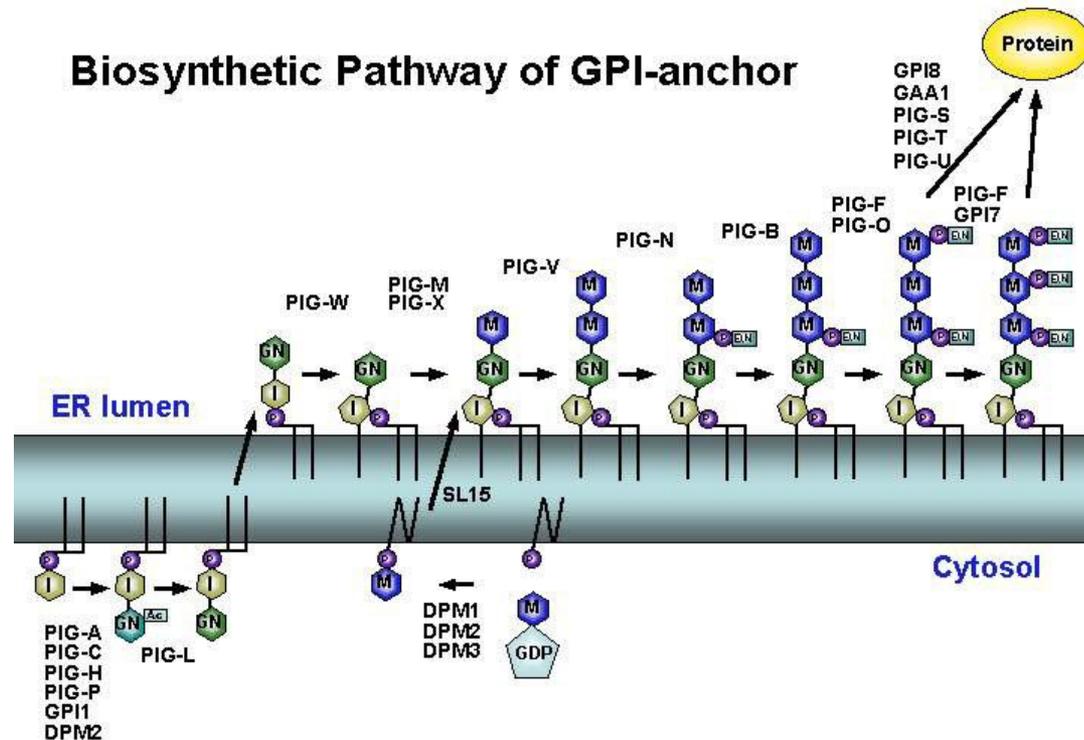


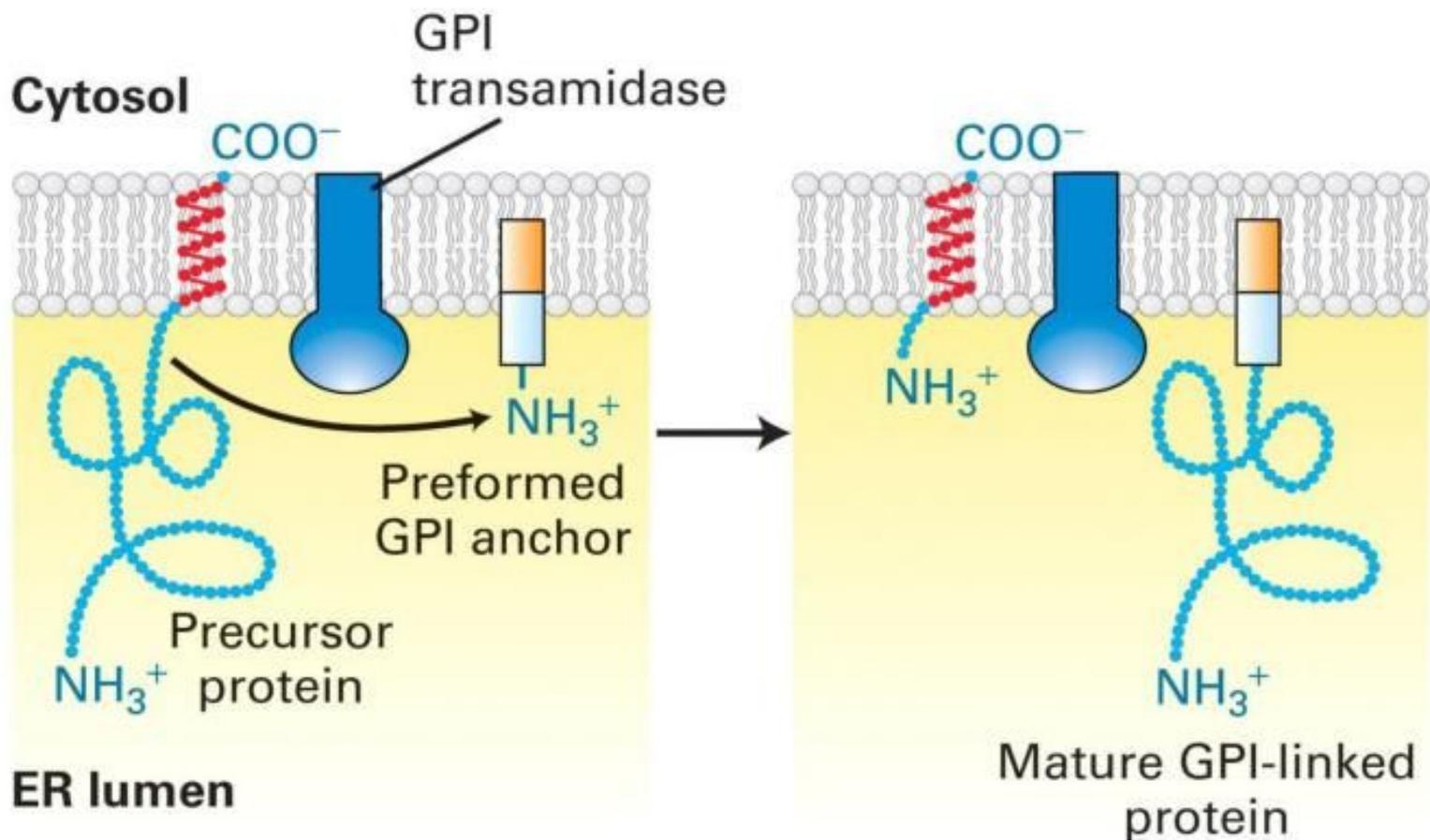
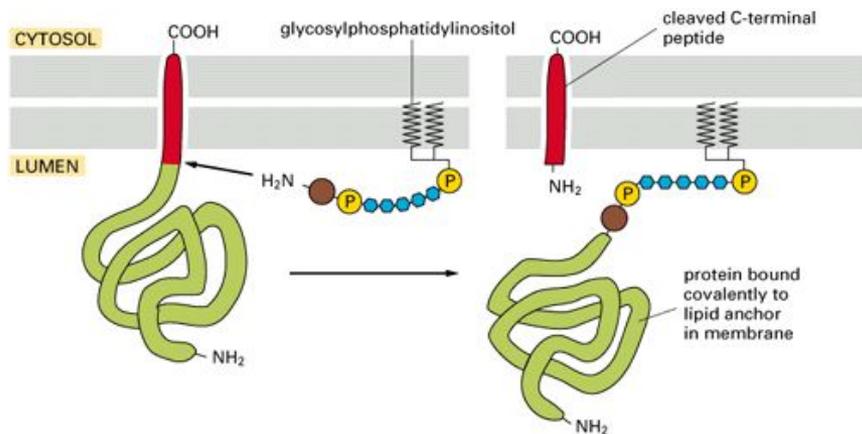
F. Multiple transmembrane protein



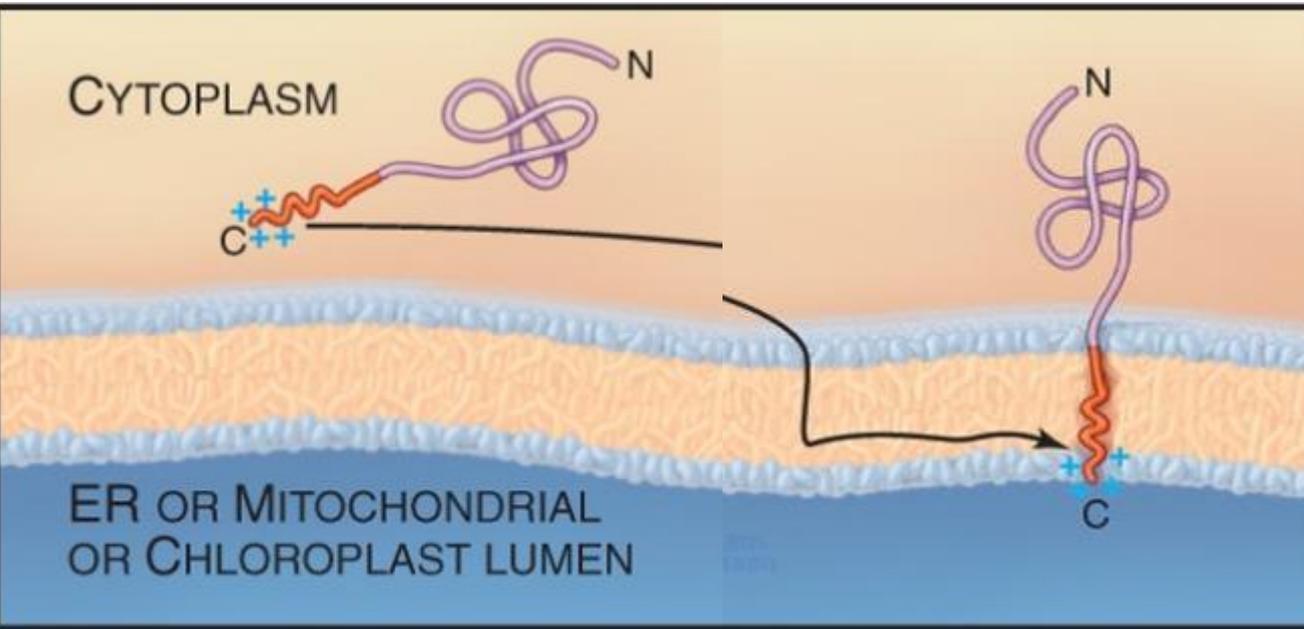


Biosynthetic Pathway of GPI-anchor



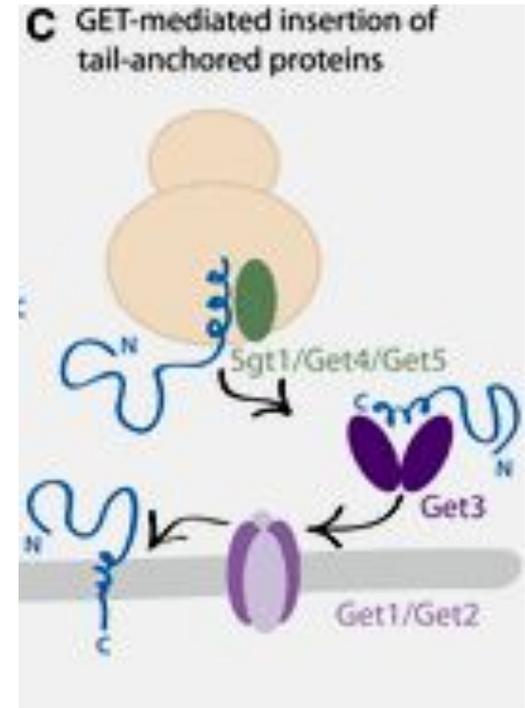


C-tail-anchored proteins (tail-anchored proteins)



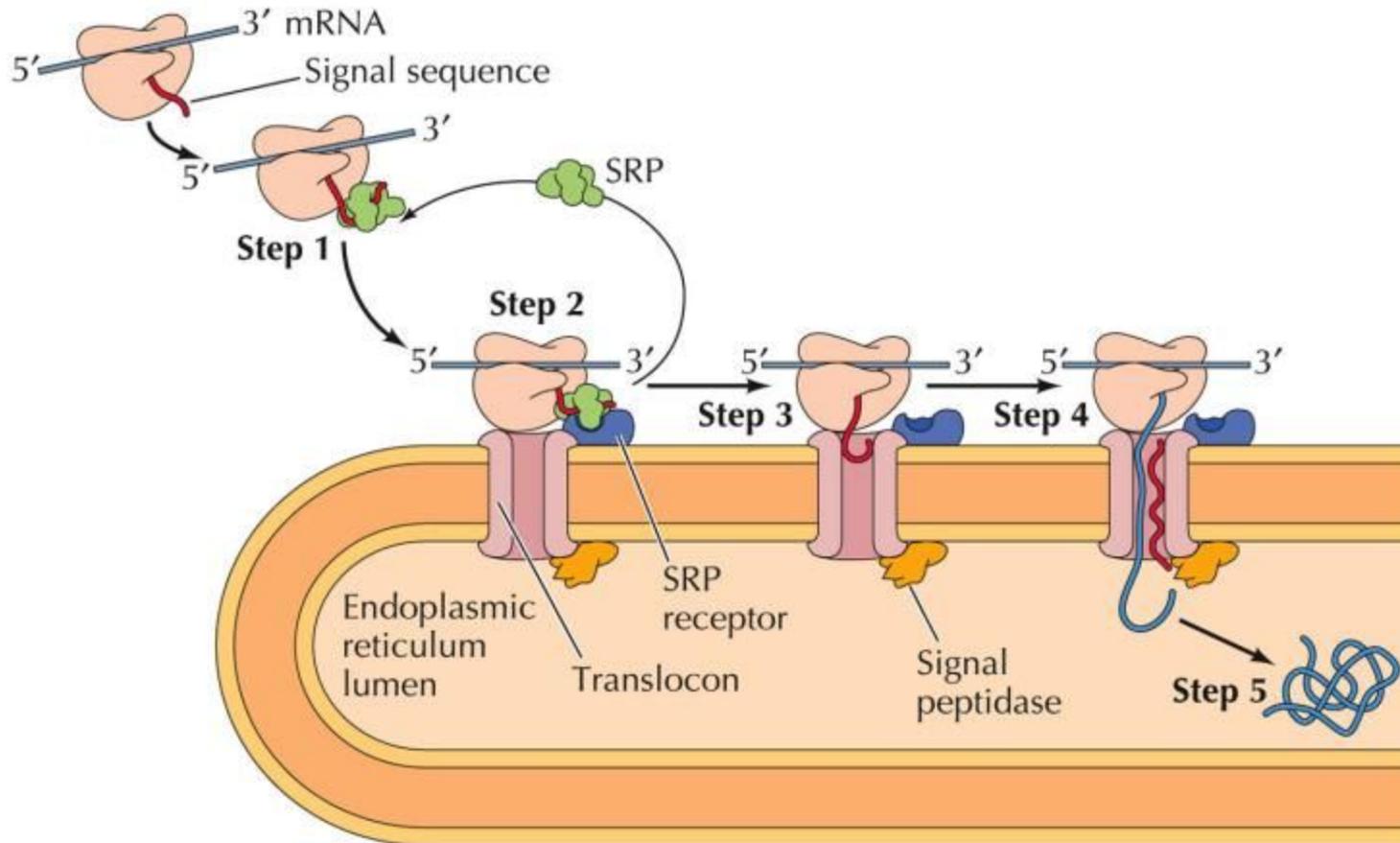
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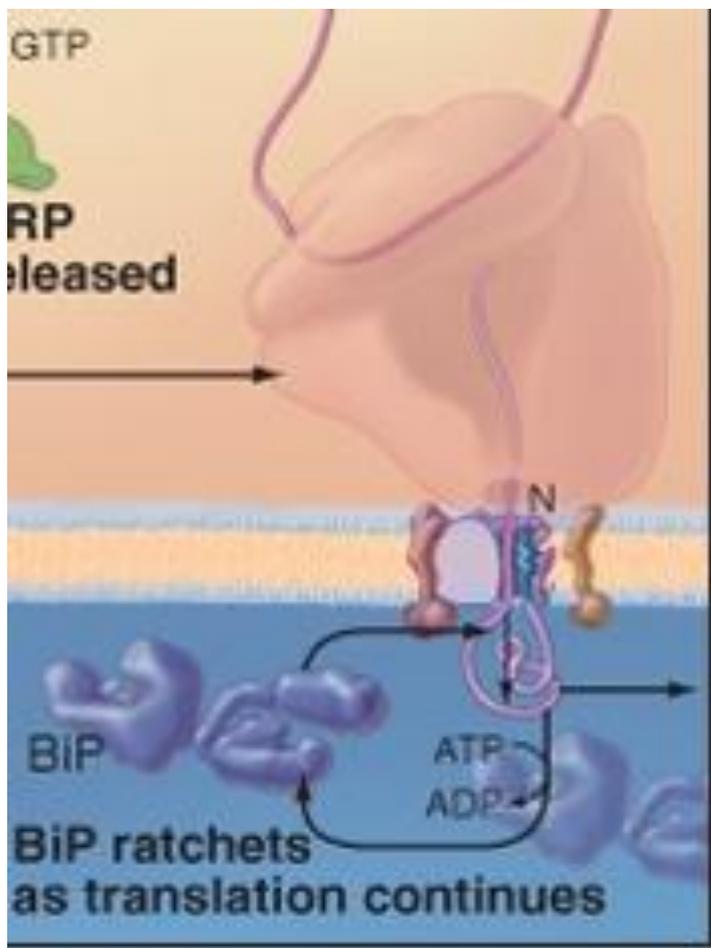
Golgi-to-ER trafficking



Target SNAREs (syntaxin), Vesicle SNAREs (synaptobrevin), Giantin (Golgi tethering protein), Sec61 γ , Sec61 β , Cytochrome b(5), Heme oxygenase I and II, UBC 6 (ER degradation), Bcl-2, Bax, Tom5, Tom6

Сигнальная пептидаза





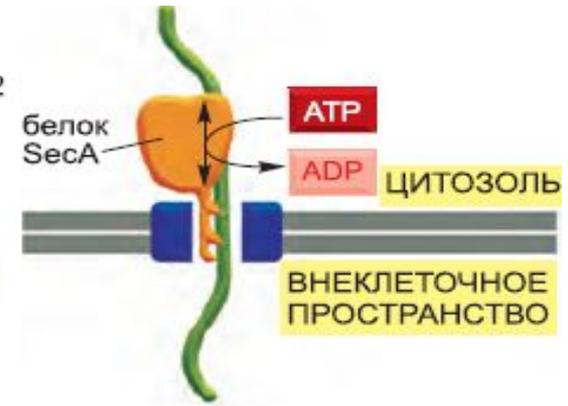
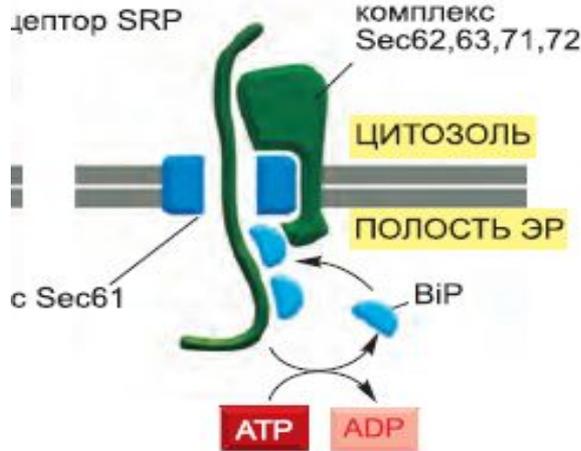
BiP Hsp70

олигосахаридтрансфераза

Гликозидазы 1, 2

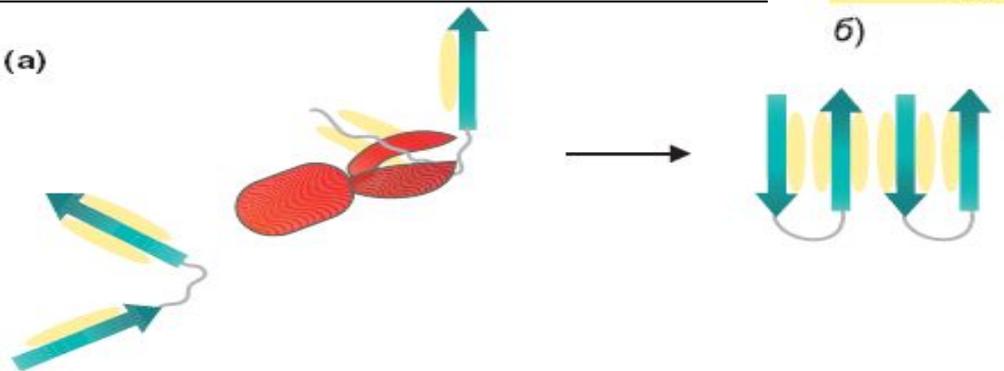
PDI-протеиндисульфидизомераза

Ero1p

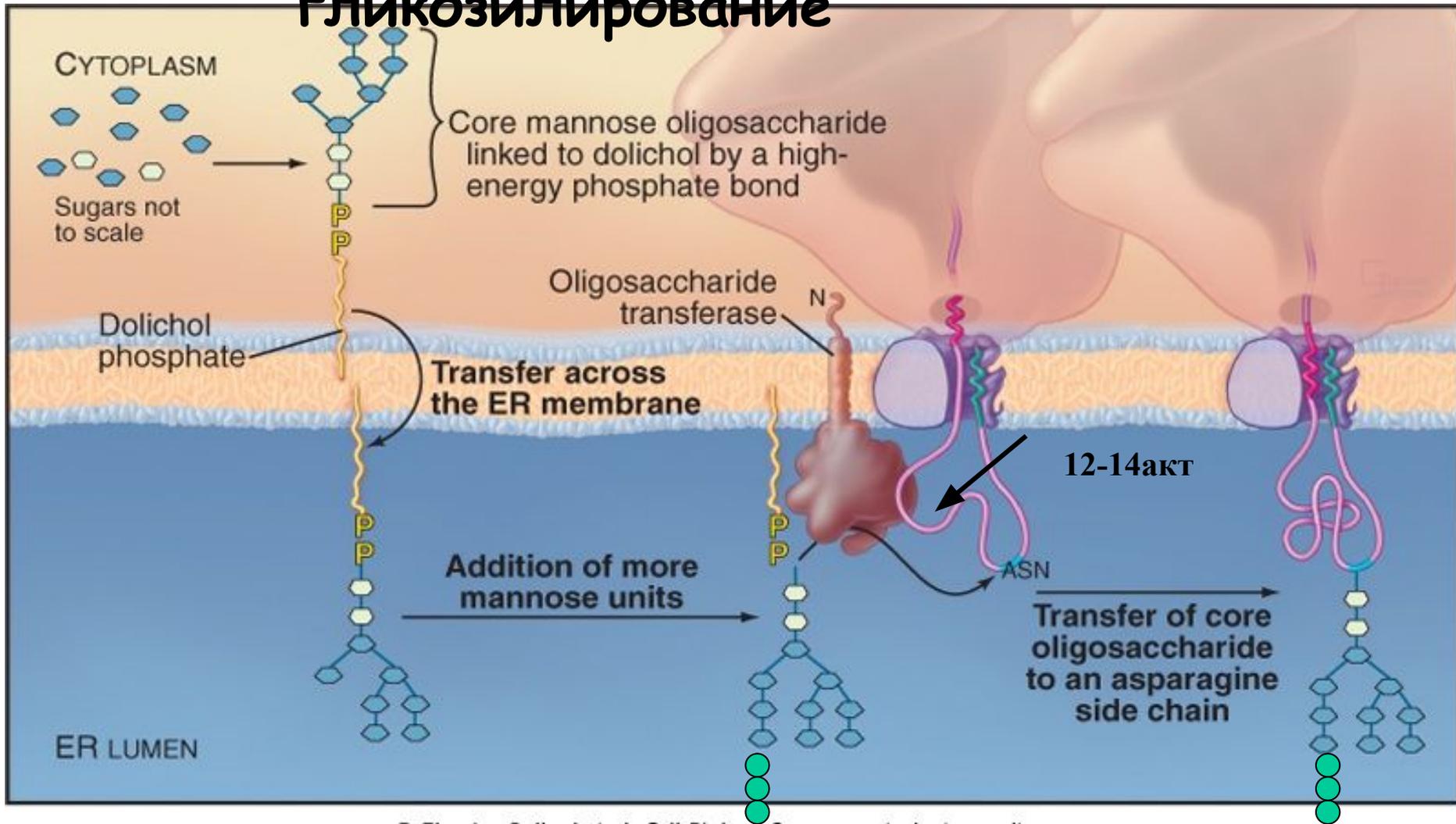


ЭУКАРИОТЫ

БАКТЕРИИ



Первичное гликозилирование

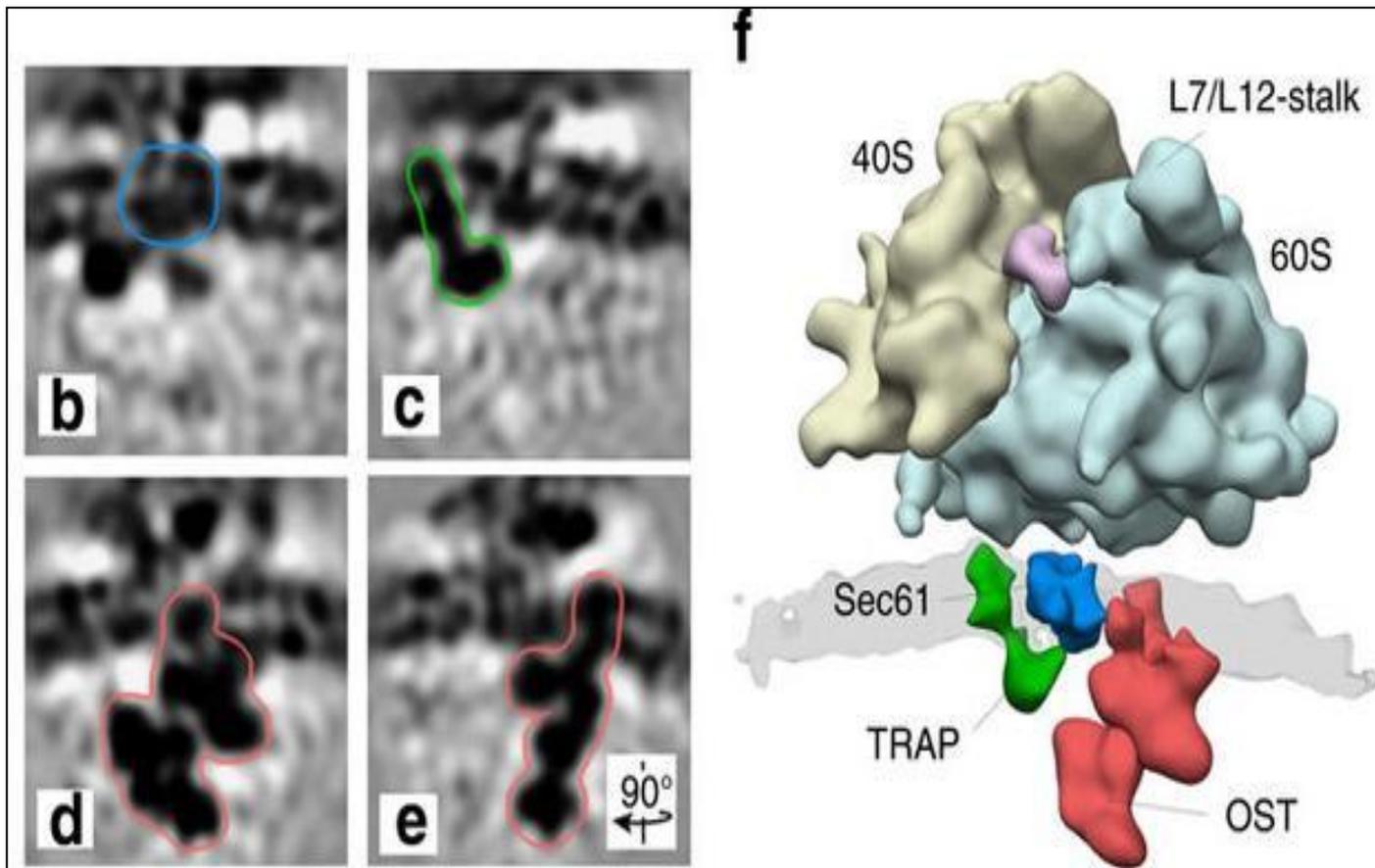


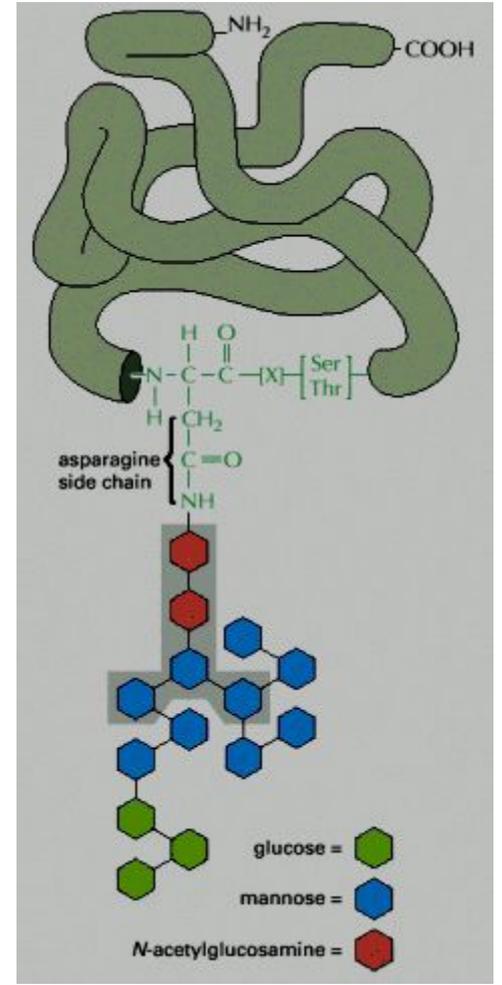
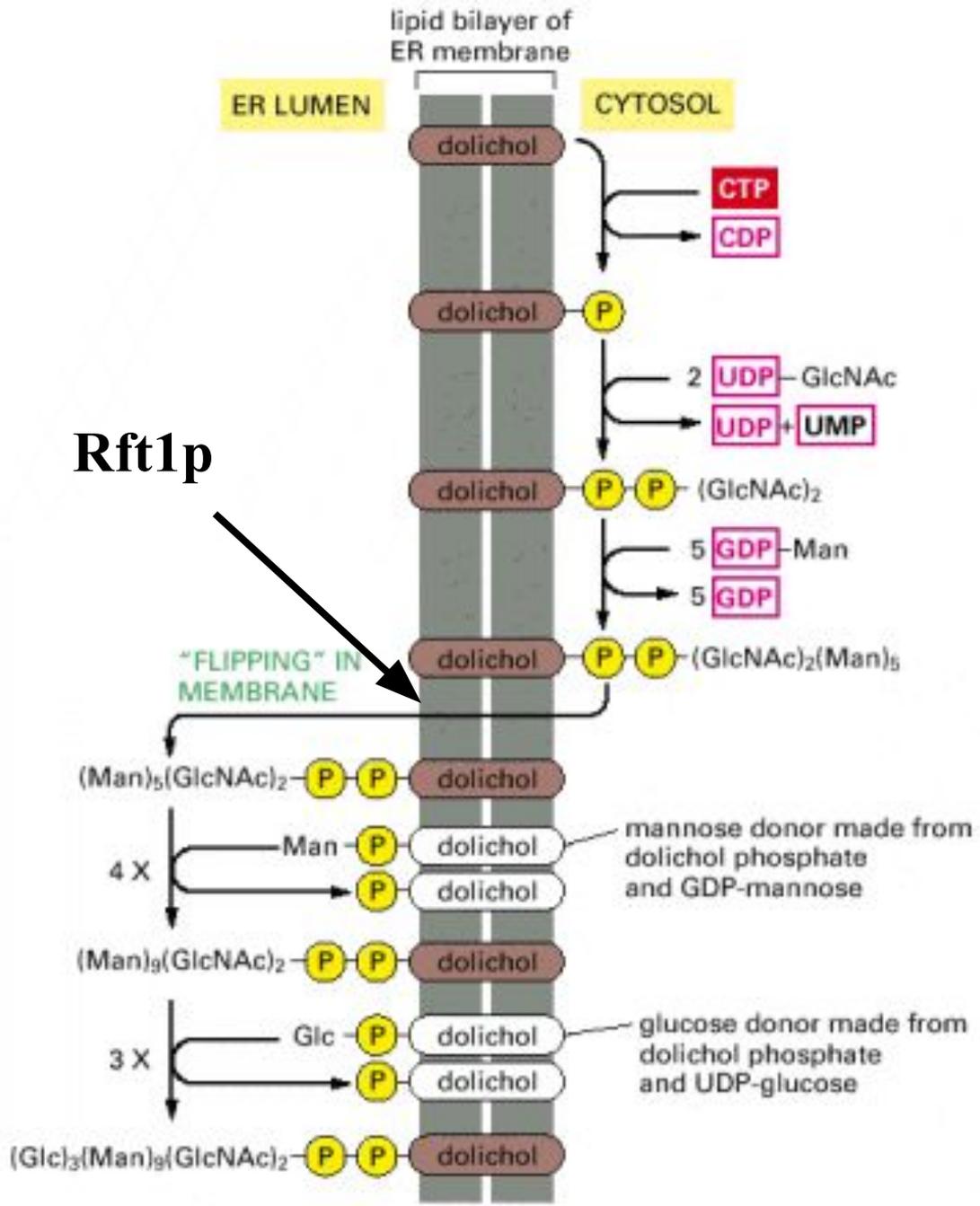
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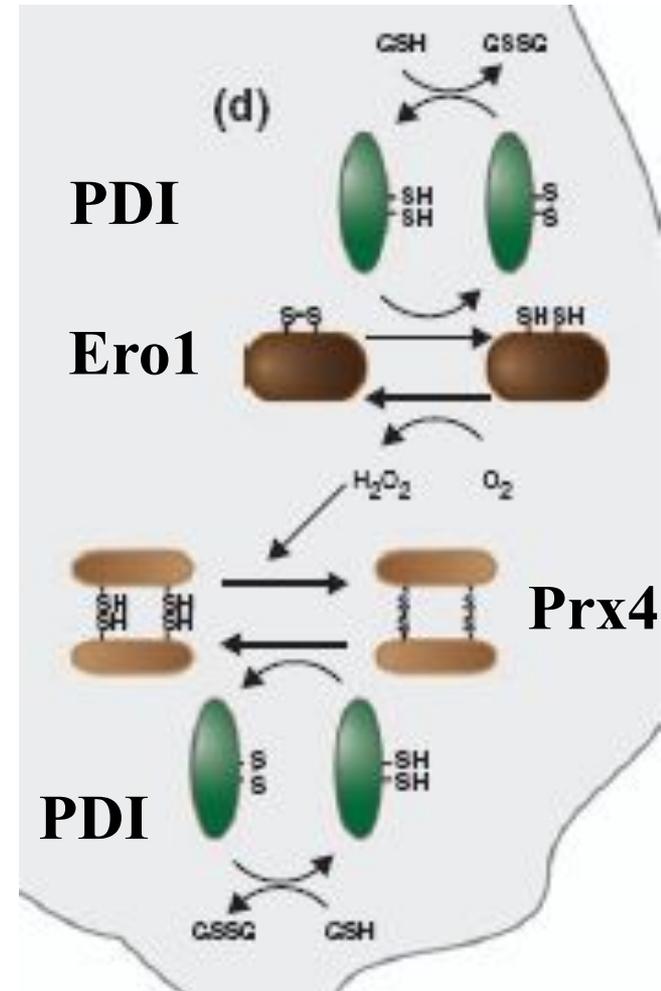
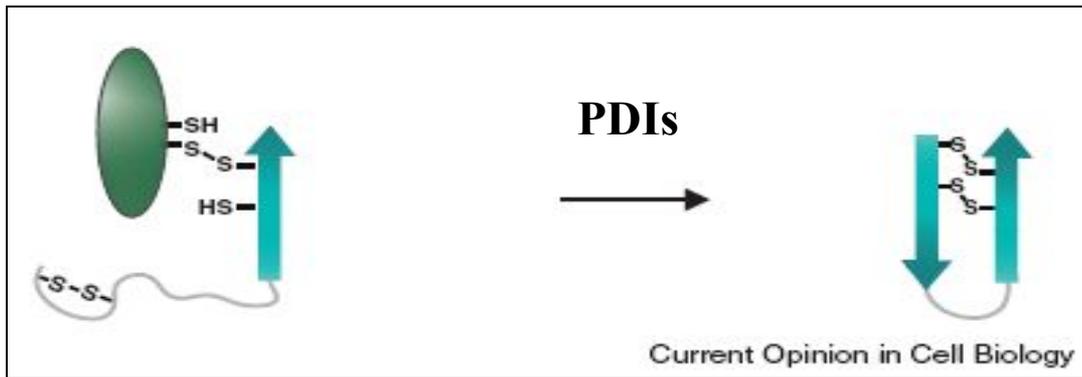
Asn-X-Ser/Thr

Олигосахарилтрансферазный комплекс





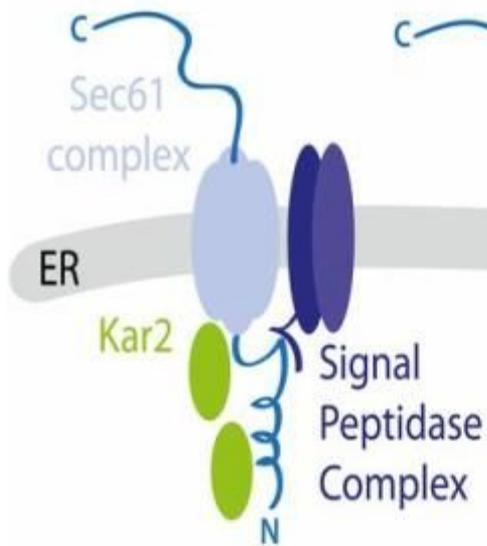
Образование дисульфидных связей



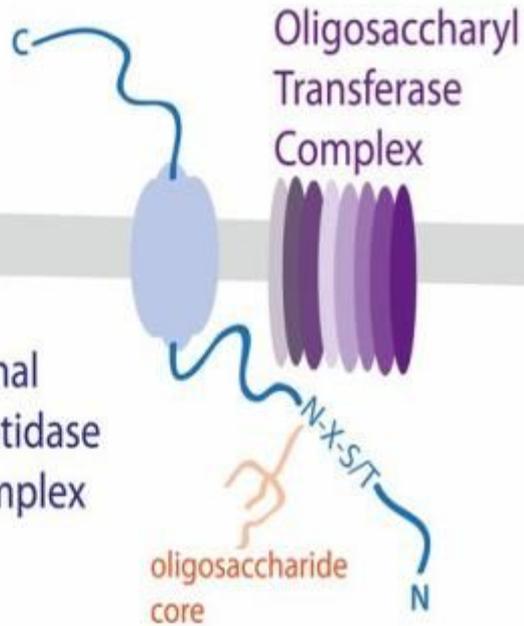
Summary of function and disease relevance of ER chaperones, co-chaperones and folding enzymes

Protein	Localization	Function	Knockout mouse model	Diseases
GRP78/BiP	ER lumen ER transmembrane Cell surface Nucleus	Chaperone, Ca ²⁺ -binding, ER stress sensor, UPR regulator Anti-apoptosis	Embryonic lethality at E3.5 due to failure of embryo peri-implantation	Cancer Alzheimer's disease Parkinson's disease Prion diseases Atherosclerosis
SIL1	ER lumen	Co-chaperone, nucleotide exchange factor for GRP78	Woozy mouse associated with cerebellar purkinje cell degeneration and ataxia	Marinesco-Sjögren syndrome
GRP94/gp96	ER lumen Cell surface transmembrane	Chaperone, Ca ²⁺ -binding Anti-apoptosis Tumor immunity	Embryonic lethality	Cancer Prion diseases Autoimmune disease
GRP170/ ORP150	ER lumen	Chaperone, potential nucleotide exchange factor for GRP78	Embryonic lethality	Alzheimer's disease
GRP58/ ERp57	ER lumen Nucleus Cytosol	Thio-oxidoreductase to catalyze disulfide bond formation of glycoprotein	Embryonic lethality (traditional knockout); <i>Grp58</i> ^{-/-} B cells are defective in antigen presentation (conditional knockout in B cells).	Prion diseases Alzheimer's disease
PDI	ER lumen Cell surface	Thio-oxidoreductase to catalyze disulfide bond formation	N.D.	Alzheimer's disease Parkinson's disease

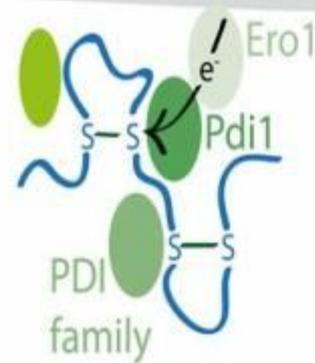
A signal peptide cleavage



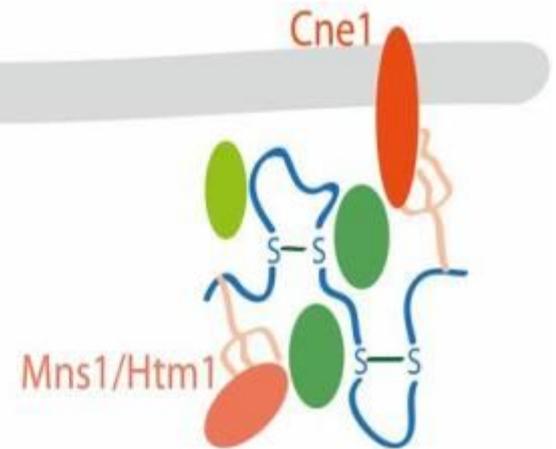
B N-linked glycosylation



C Disulfide bond formation

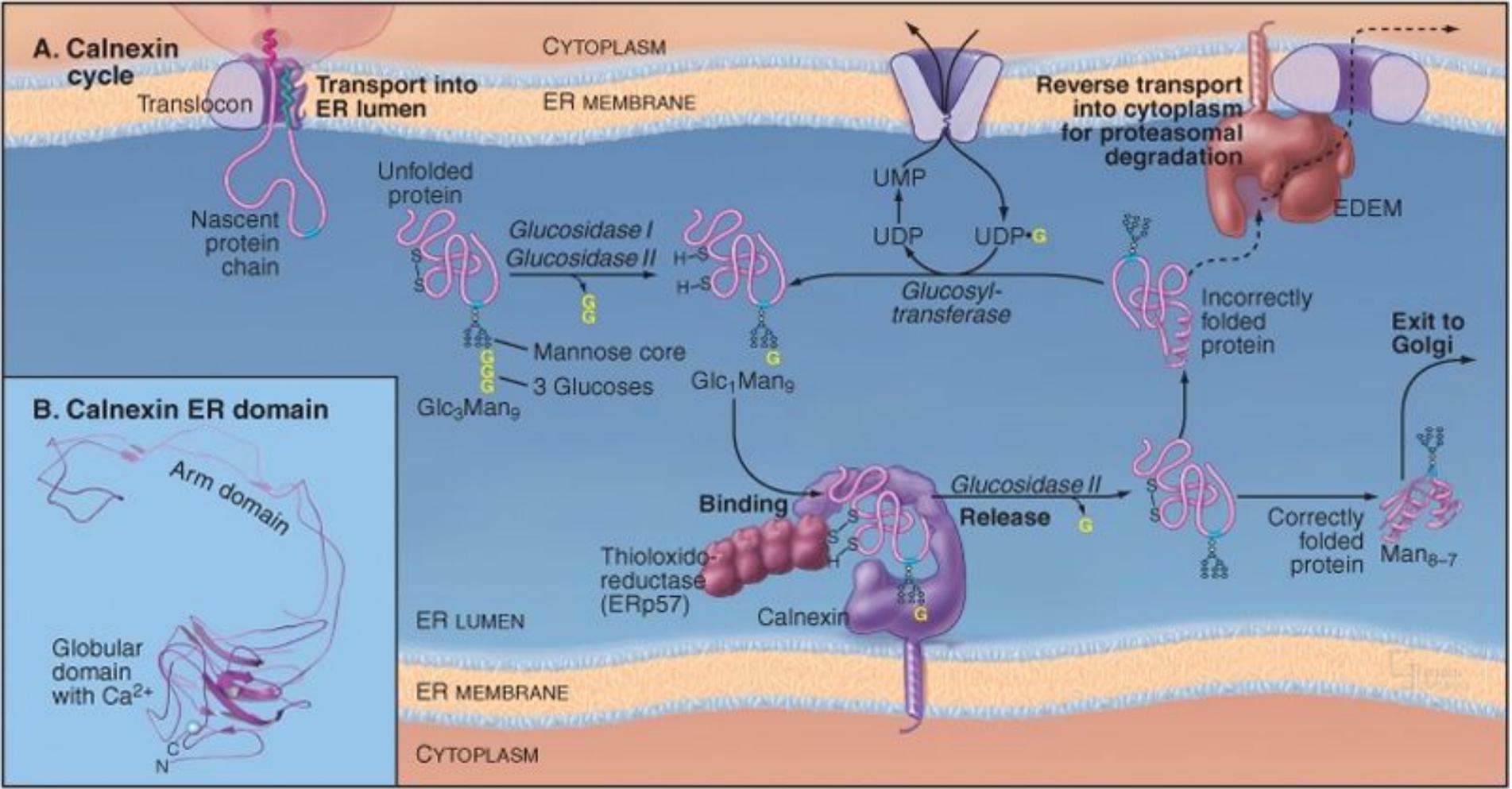


D Glycosidase trimming and protein folding



ERAD – ЭПР-ассоциированная деградация белков

sec61



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Glc, glucose; Man, mannose; UDP, uridine diphosphate; UMP, uridine monophosphate.)

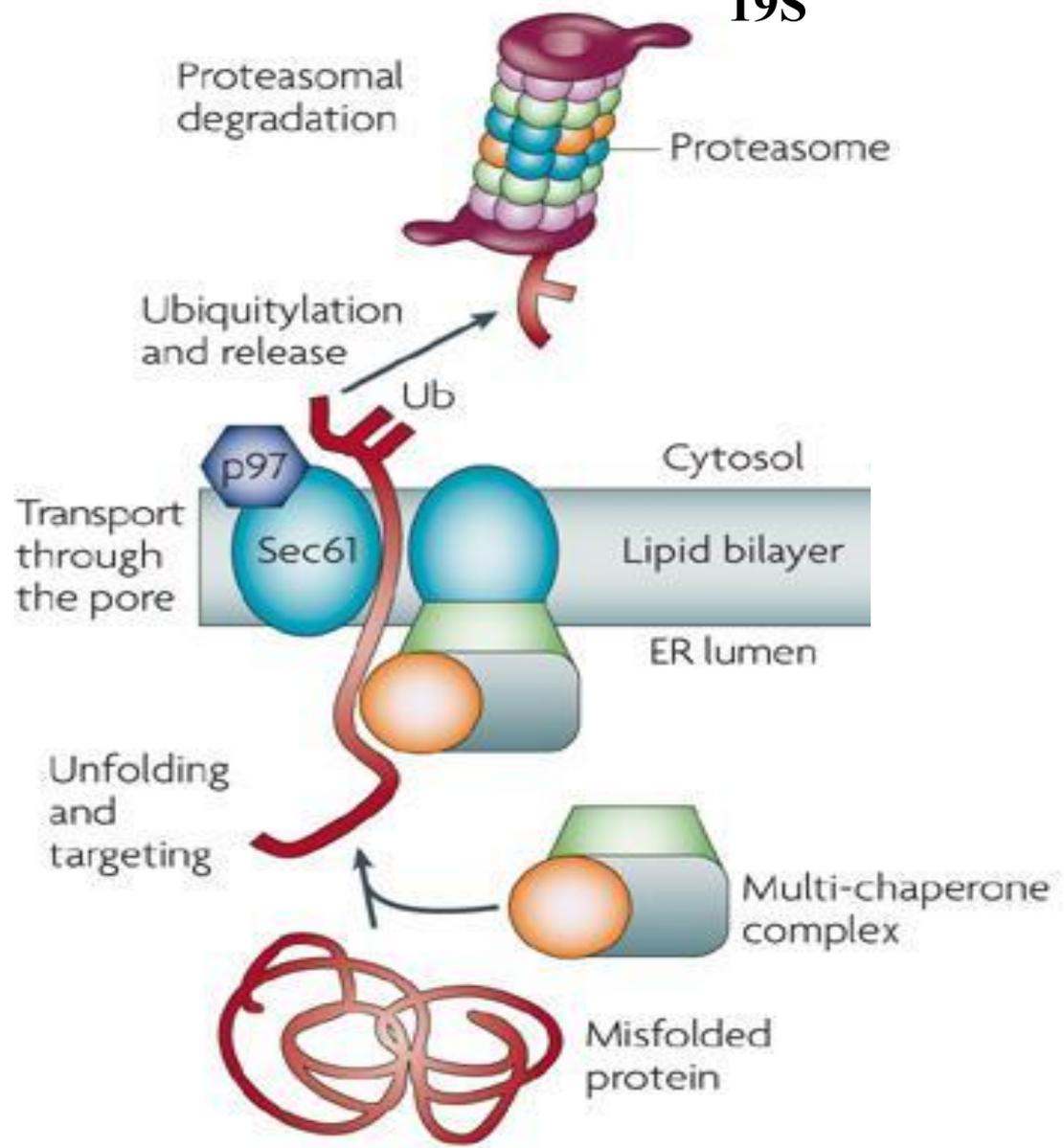
Протеиндисульфидизомераза – ERp57

EDEM – ER degradation-enhancing alfa-mannosidase-like protein

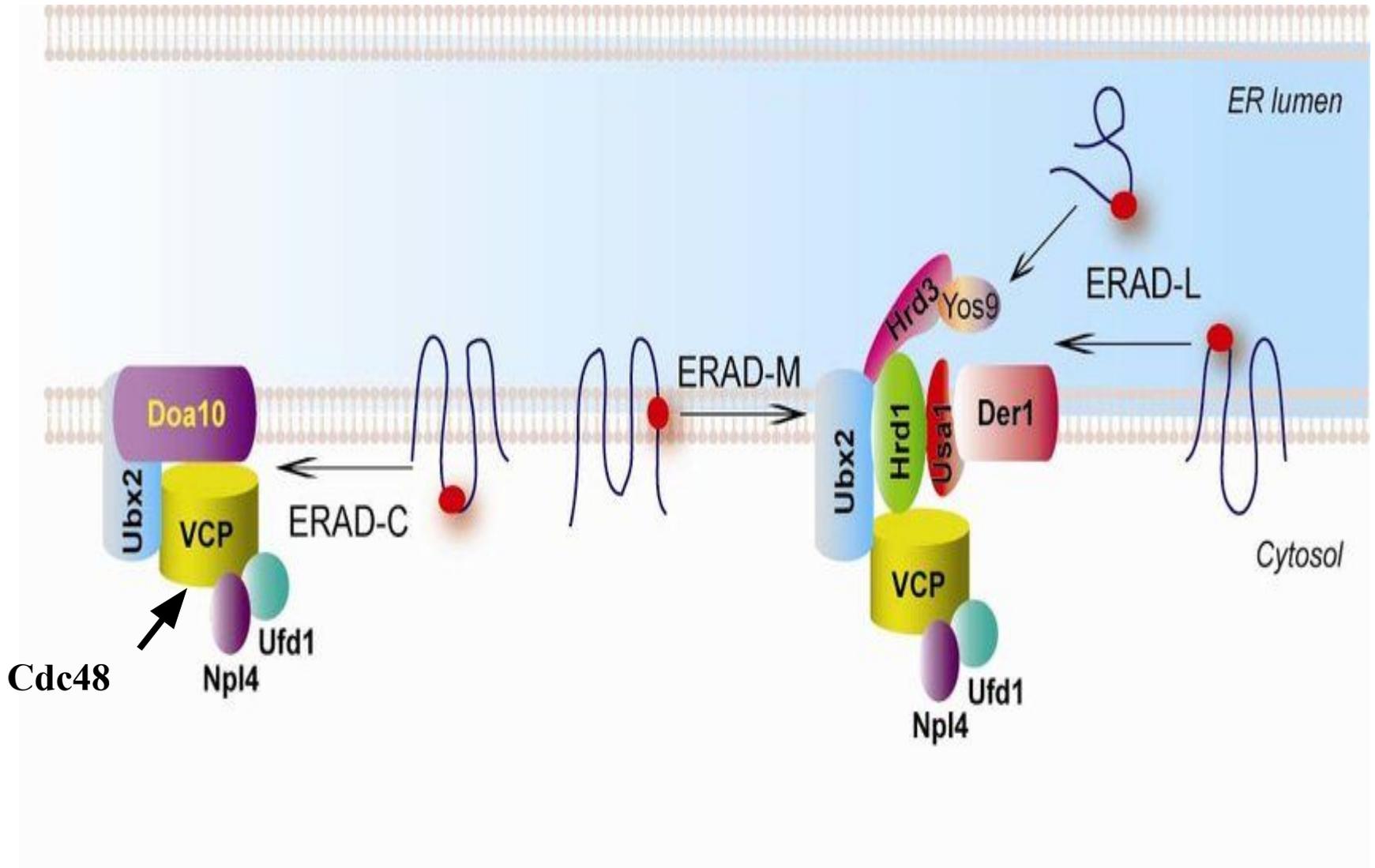
EDEM – ER degradation-enhancing alpha-mannosidase-like protein

a Misfolded proteins

19S

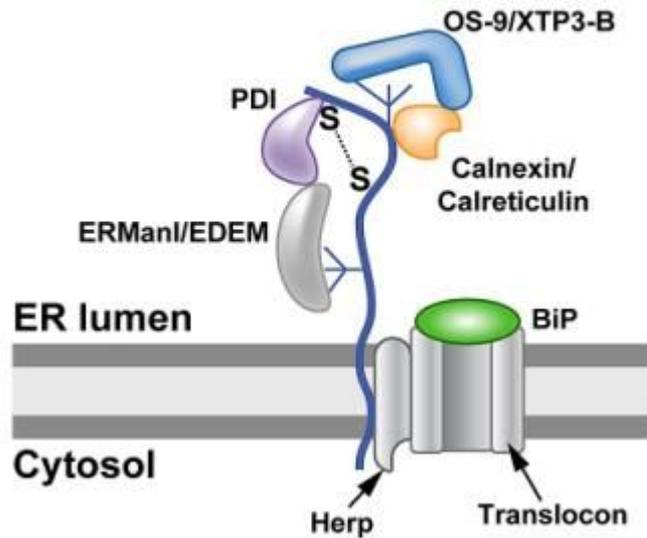


Endoplasmic-reticulum-associated protein degradation (ERAD)



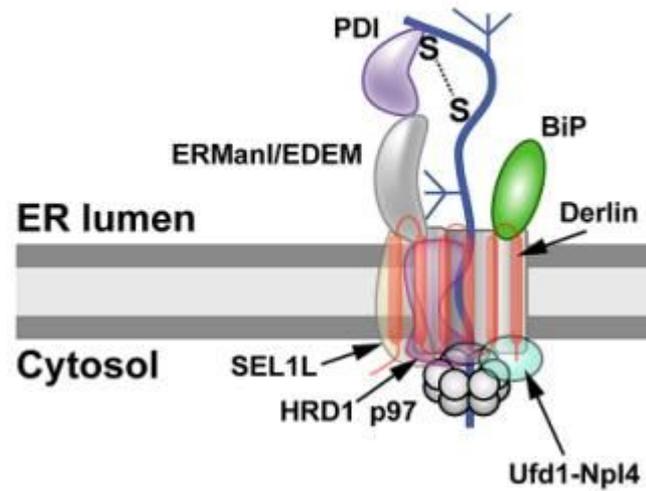
A

Recognition



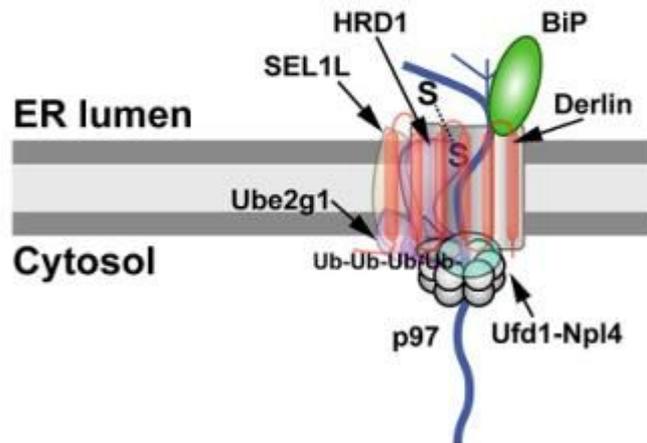
B

Retrotranslocation



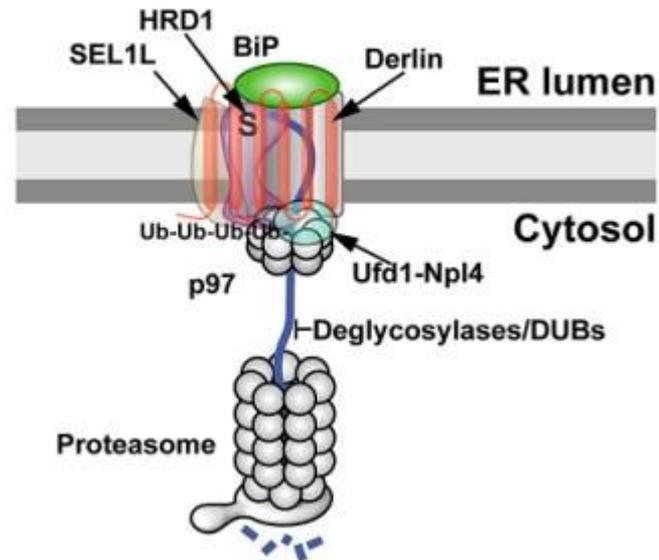
C

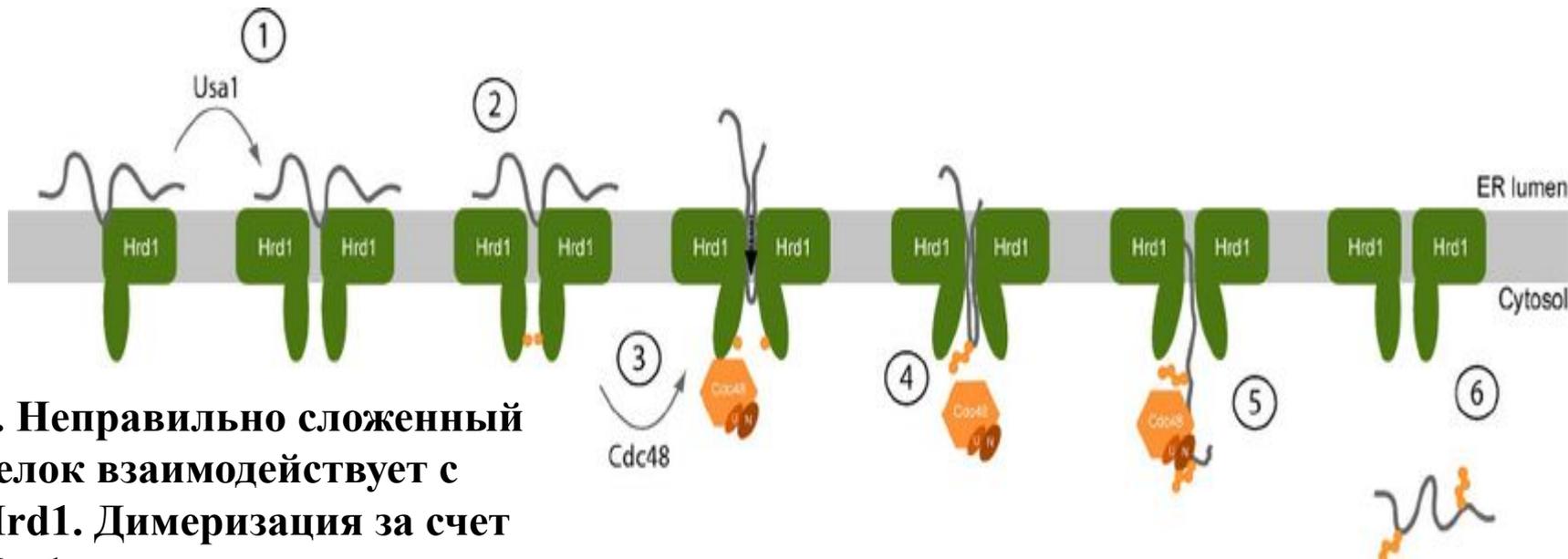
Ubiquitination



D

Proteasomal Degradation





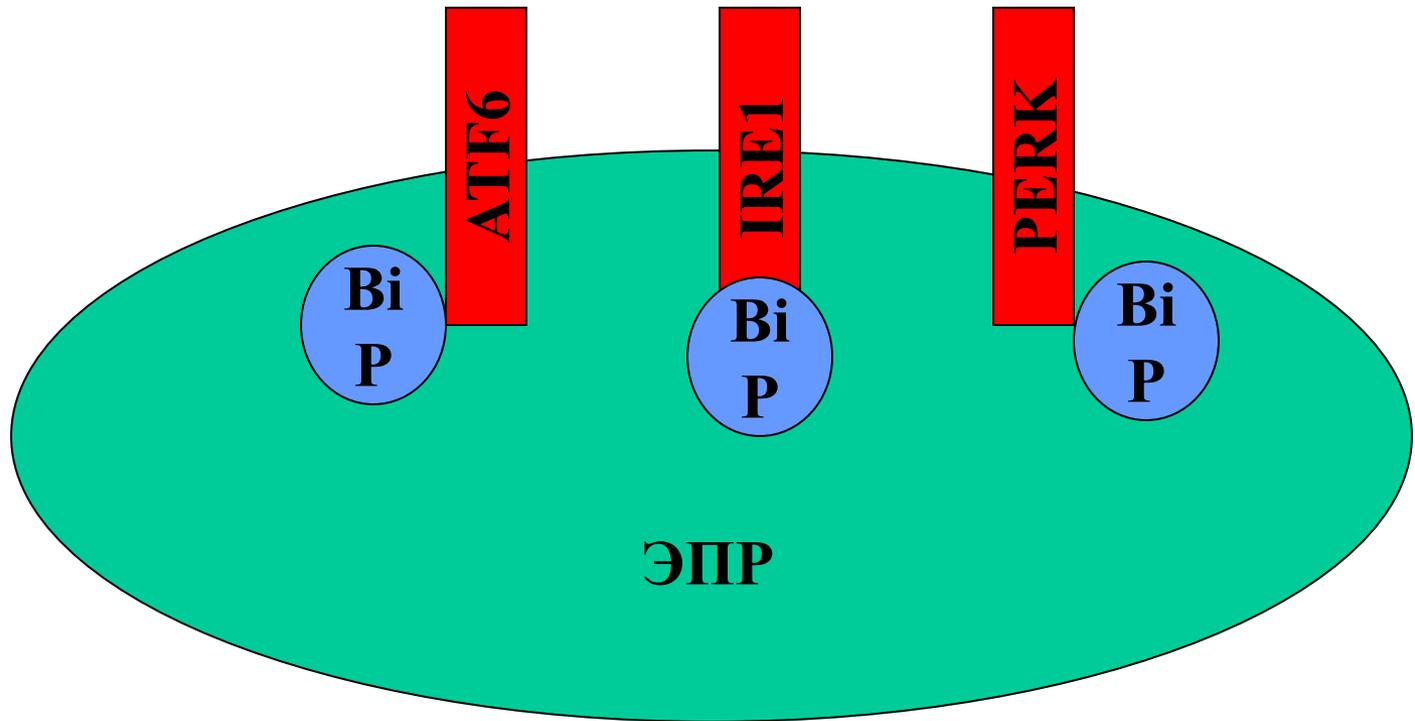
1. Неправильно сложенный белок взаимодействует с Hrd1. Димеризация за счет Usa1

2-3. Hrd1 самоубиквитинируется, что приводит к связыванию Cdc48 АТФ-азного комплекса (Cdc48 кофакторы Npl4 и Ufd1)

4. Гидролиз АТФ Cdc48 вызывает конформационные изменения Hrd1, что стимулирует транслокацию

5. Hrd1 убиквитинирует субстрат.

6. Hrd1 убиквитинирует субстрат.



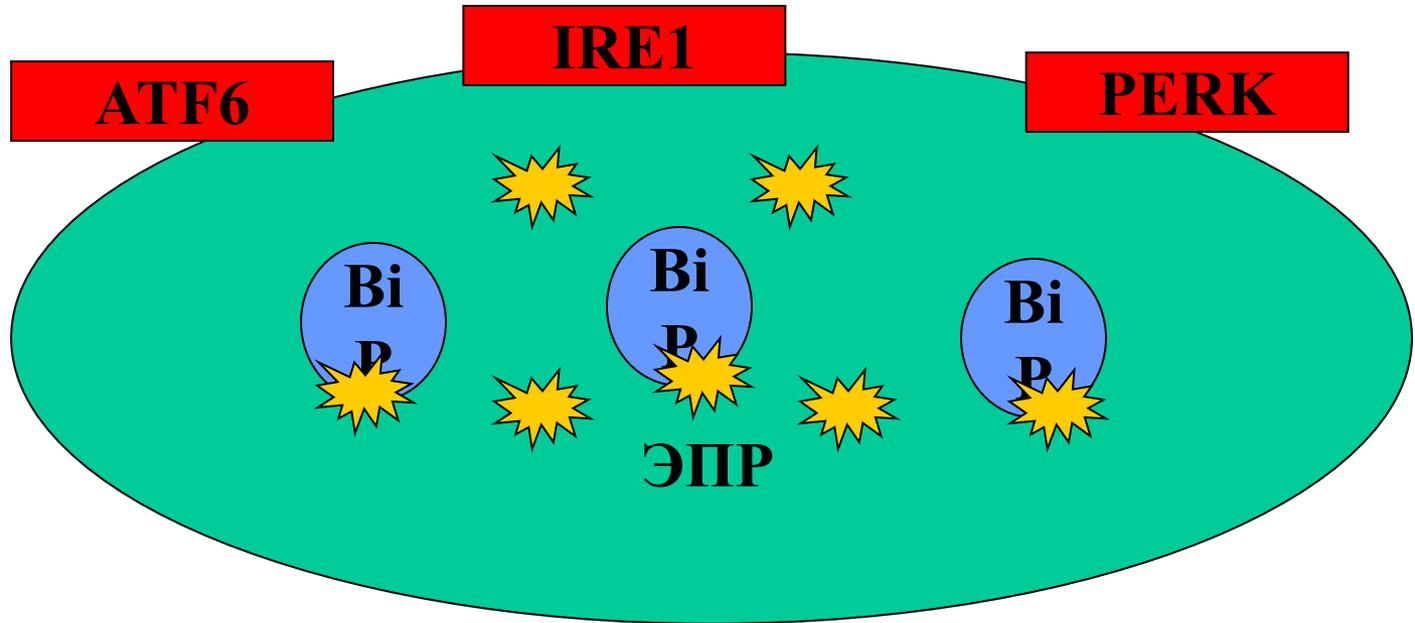
UPR unfolded protein response

ATF6 (activating transcription factor 6)

IRE1 (inositol requiring 1),

PERK/PEK (PKR-like endoplasmic reticulum kinase/pancreatic eIF2a kinase),

bZIP (basic leucine zipper) domain-containing transcription factors



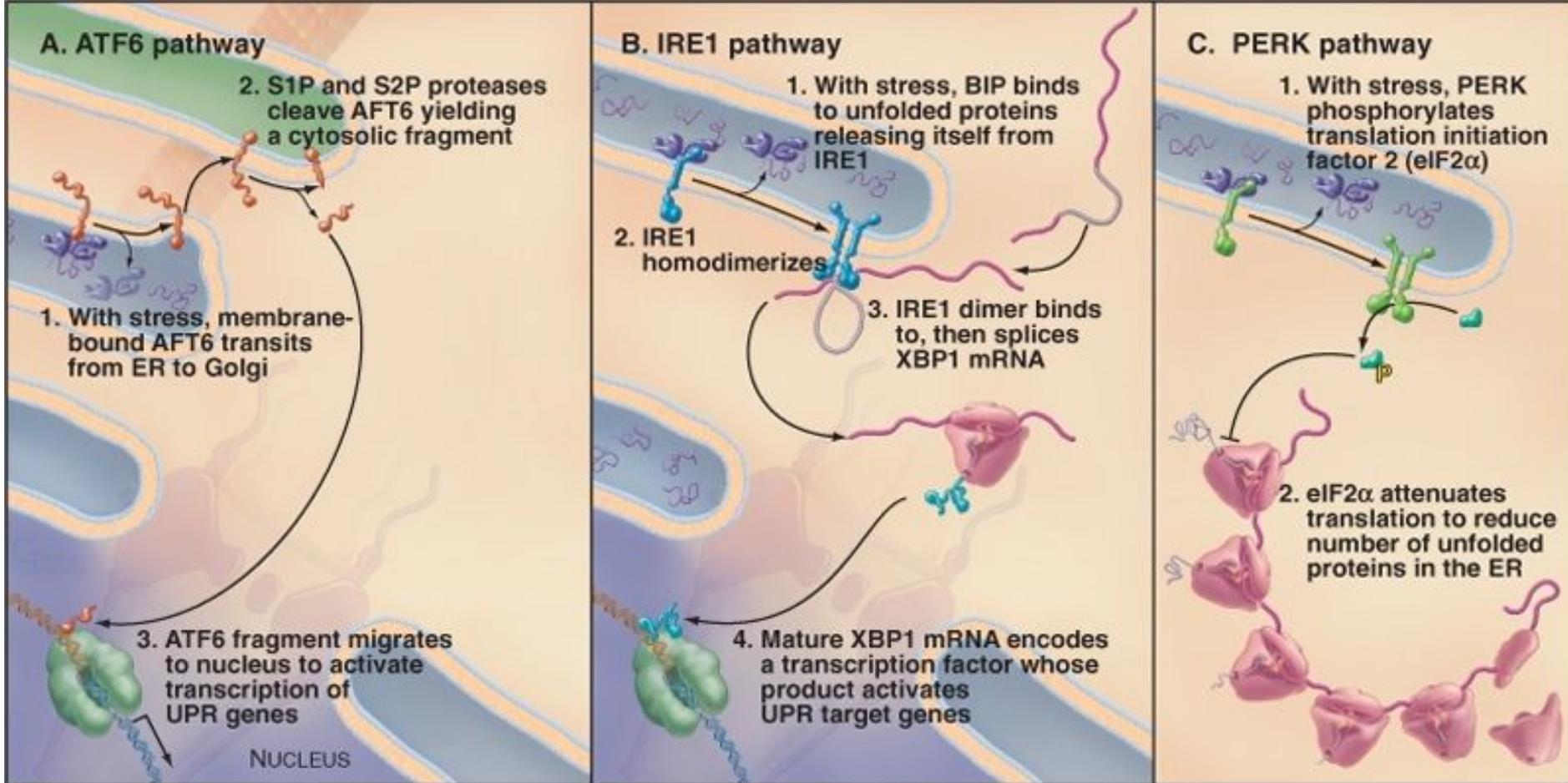
UPR unfolded protein response

ATF6 (activating transcription factor 6)

IRE1 (inositol requiring 1),

PERK/PEK (PKR-like endoplasmic reticulum kinase/pancreatic eIF2a kinase),

bZIP (basic leucine zipper) domain-containing transcription factors



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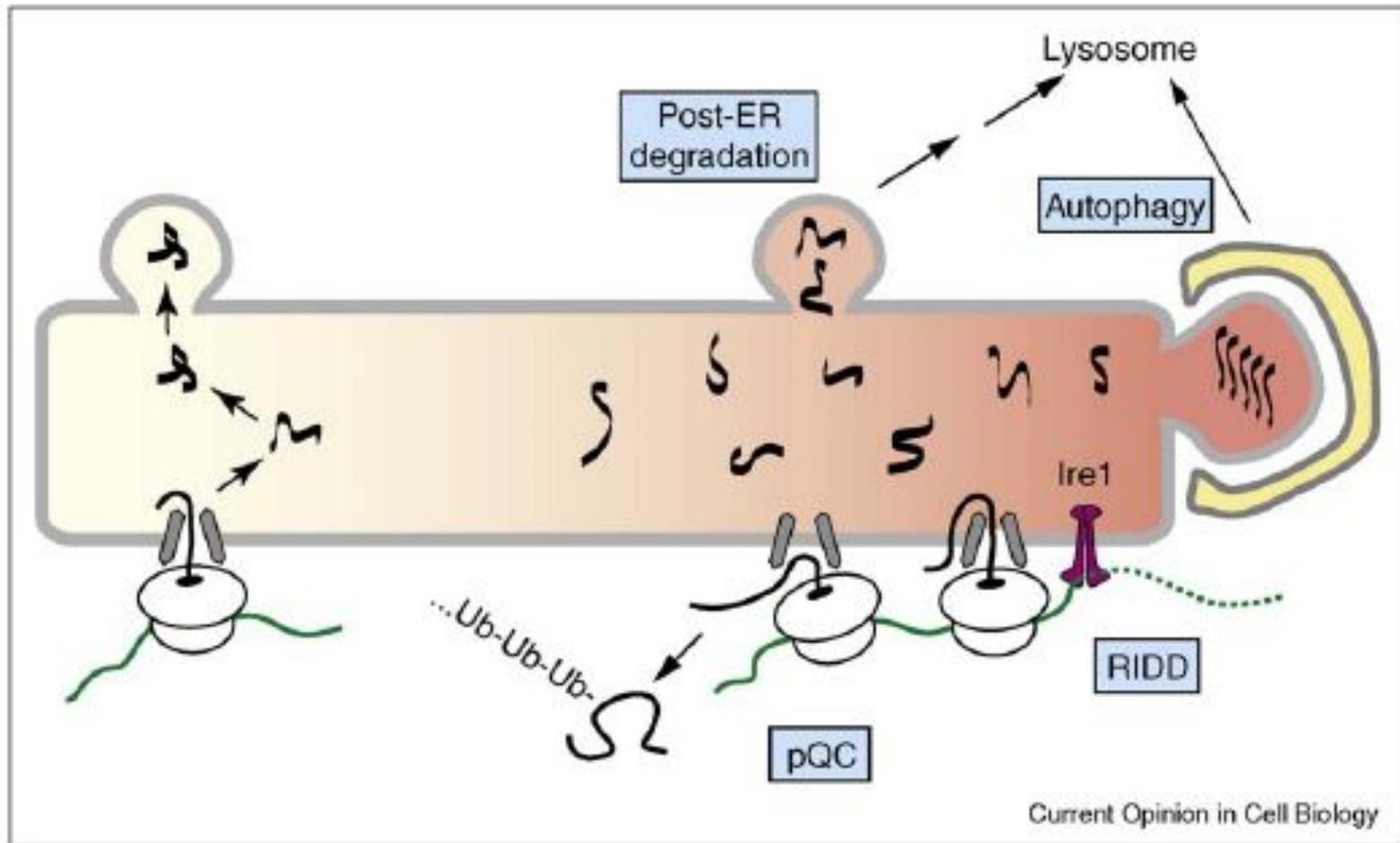
UPR unfolded protein response

ATF6 (activating transcription factor 6)

IRE1 (inositol requiring 1),

PERK/PEK (PKR-like endoplasmic reticulum kinase/pancreatic eIF2 α kinase),

bZIP (basic leucine zipper) domain-containing transcription factors



Pathways of stress-dependent quality control. During particularly severe ER stress, several pathways of quality control that may not operate during normal conditions become important for limiting protein misfolding in the ER. Pre-emptive quality control (pQC) involves reduced translocation of certain protein that are instead routed into the cytosol for degradation. Regulated Ire1-dependent degradation (RIDD) mediates degradation of select ER-bound mRNAs. Some misfolded proteins may be degraded by post-ER pathways involving vesicular trafficking to the lysosome. Autophagy can sequester whole sections of the ER containing misfolded or aggregated proteins.