MUNI
PHARM

Biologie

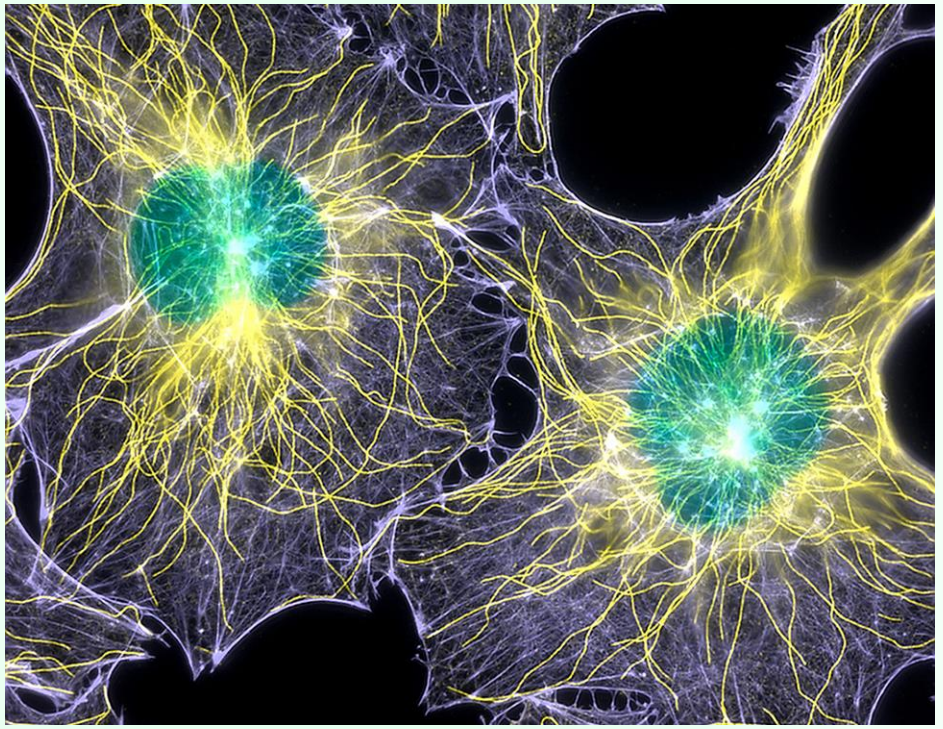
4. Membránové organely I.

Doc. RNDr. Jan Hošek, Ph.D.
hosek@mail.muni.cz

Ústav molekulární farmacie
FaF MU

Strukturní organizace eukaryotické buňky

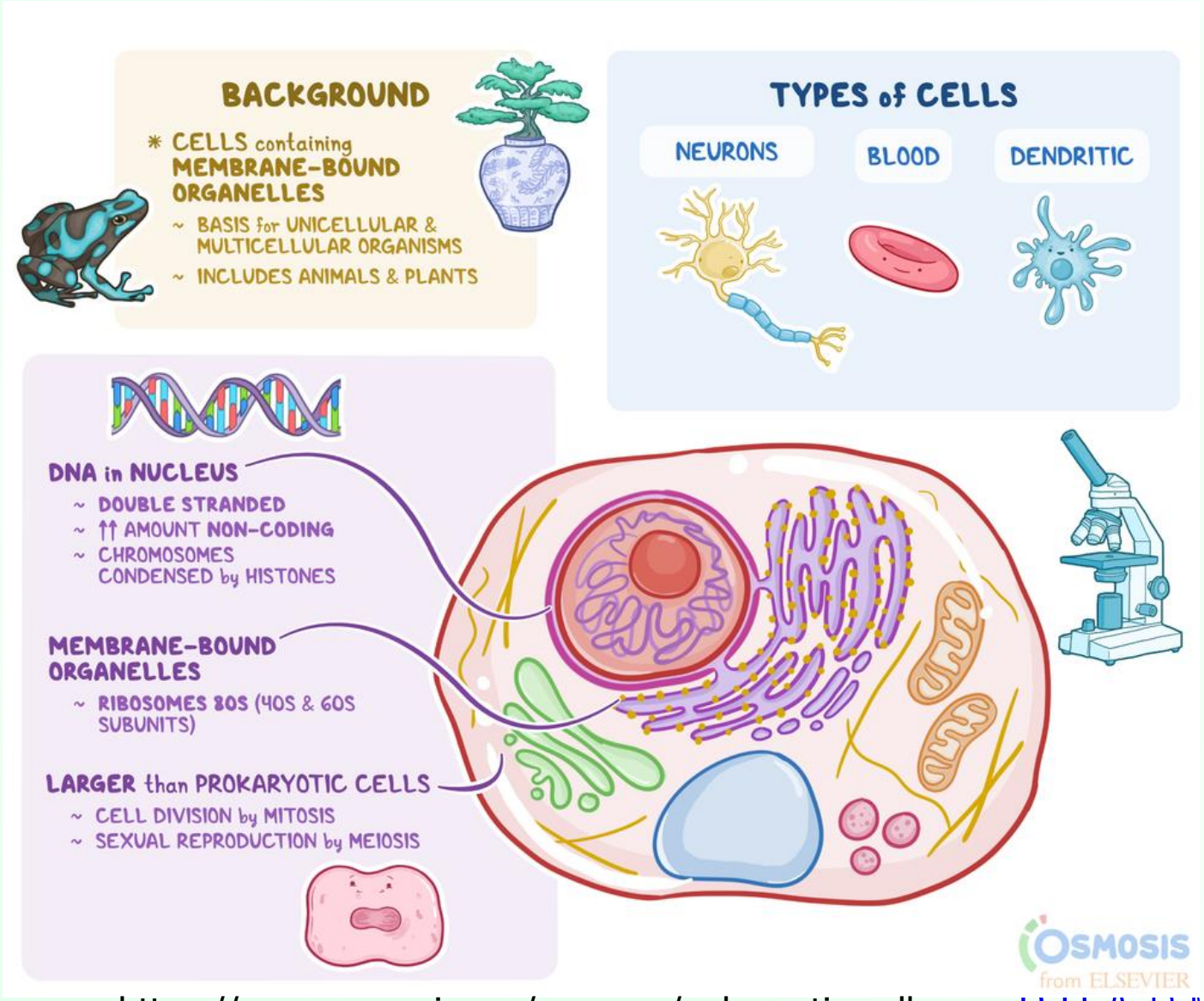
- každá buňka je složitý hierarchický systém
- hlavními stavebními prvky jsou proteiny, nukleové kyseliny, polysacharidy a lipidy
- jejich prostorovou organizací vznikají buněčné organely
- samy organely mají víceúrovňovou organizaci



MUNI PHARM

Rozdělení buněčných struktur

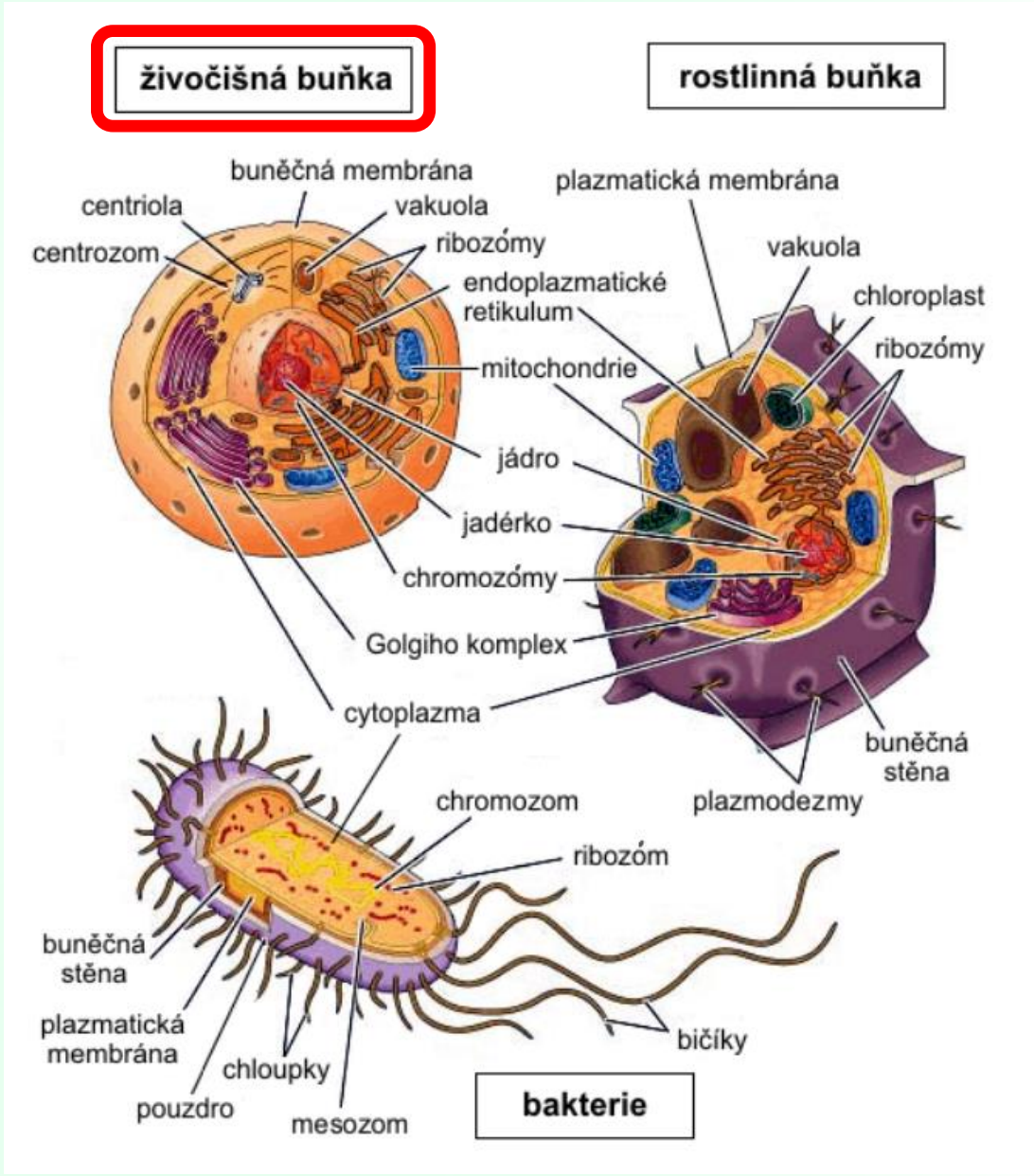
- membránové struktury
- fibrilární struktury
- genofory
- základní cytoplazma
- ribozómy
- buněčné inkluze



https://www.osmosis.org/answers/eukaryotic-cell

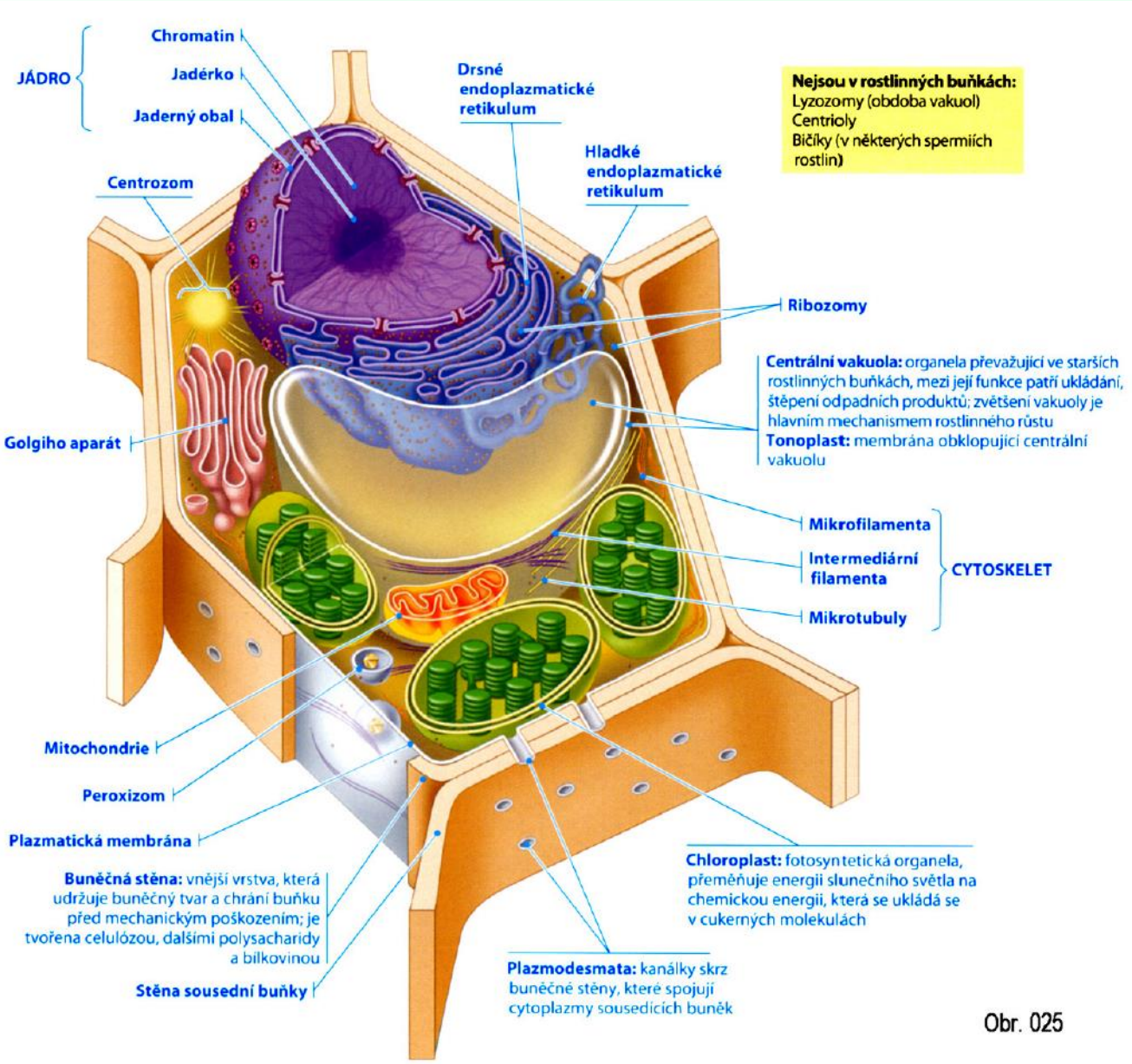
Čím se liší eukaryota od prokaryot?
Rychlé připomenutí…

	PROKARYOTA	EUKARYOTA
Stavba buňky	jednoduchá	komplikovaná
Jádro	nemají jádro (pouze nukleoid)	mají plnohodnotné jádro
Chromosom	pouze jeden kruhový	jeden i více lineárních
Geny	bez intronů	obsahují introny a exony
Kompartmentace / Organely	pouze nemembránové	membránové i nemembránové



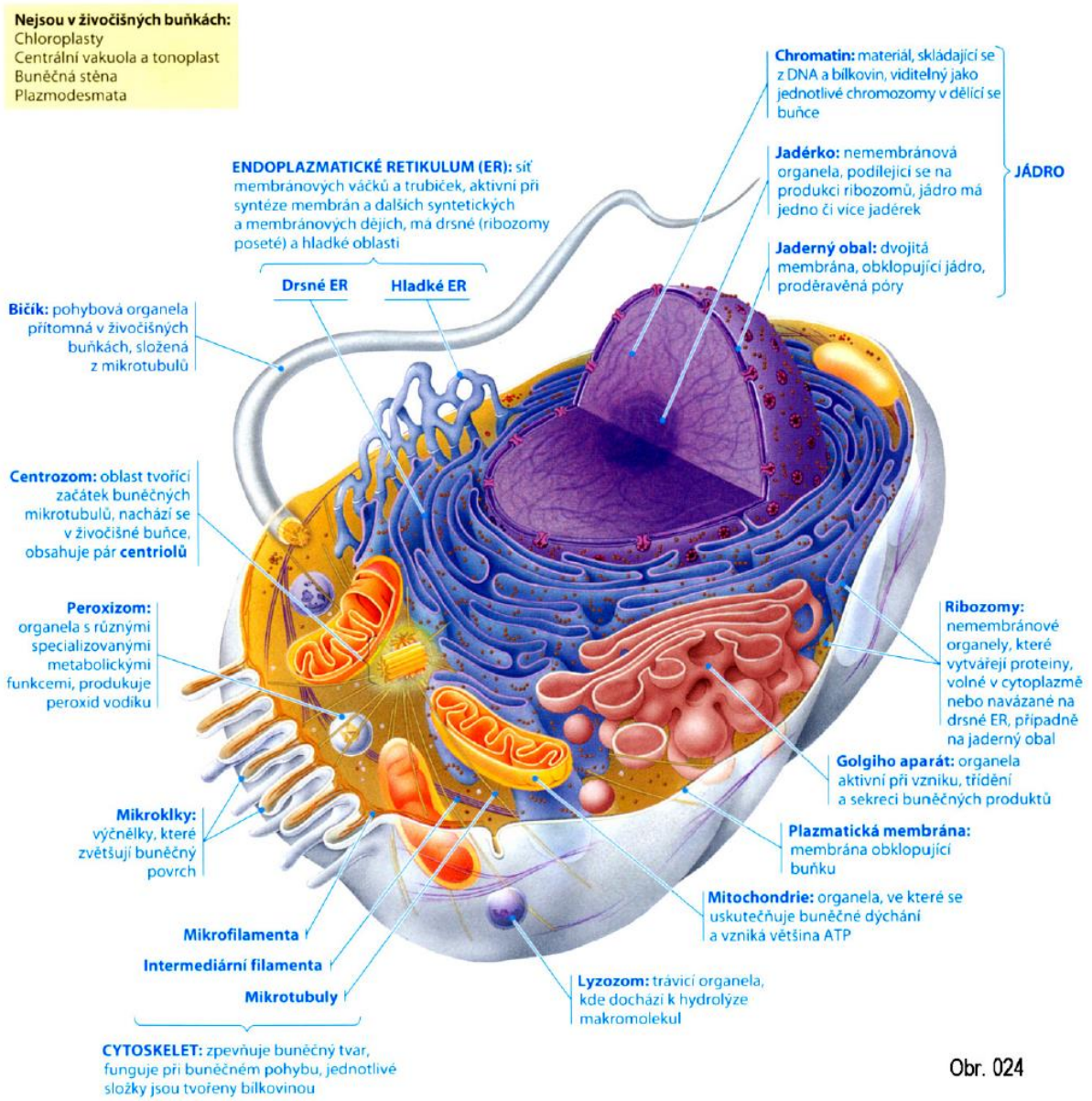
https://eluc.ikap.cz/verejne/lekce/2

Rostlinná buňka



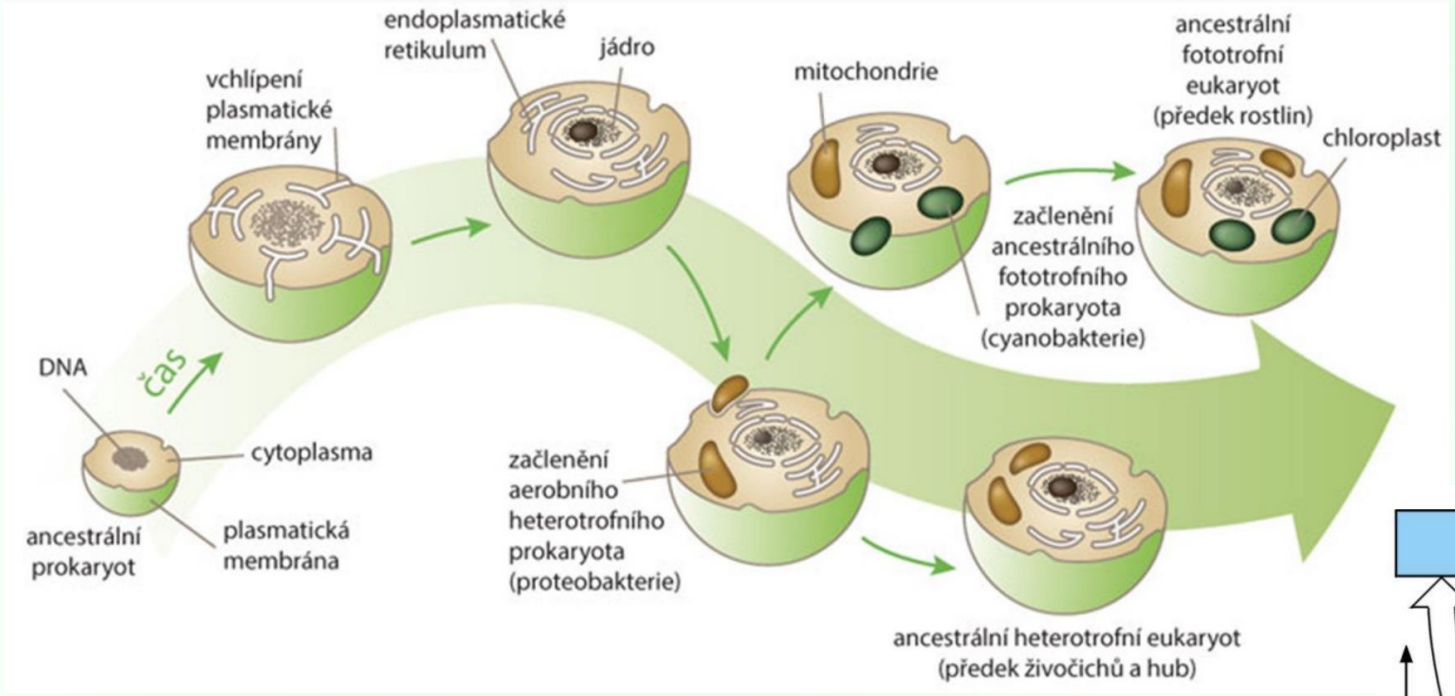
Obr. 025

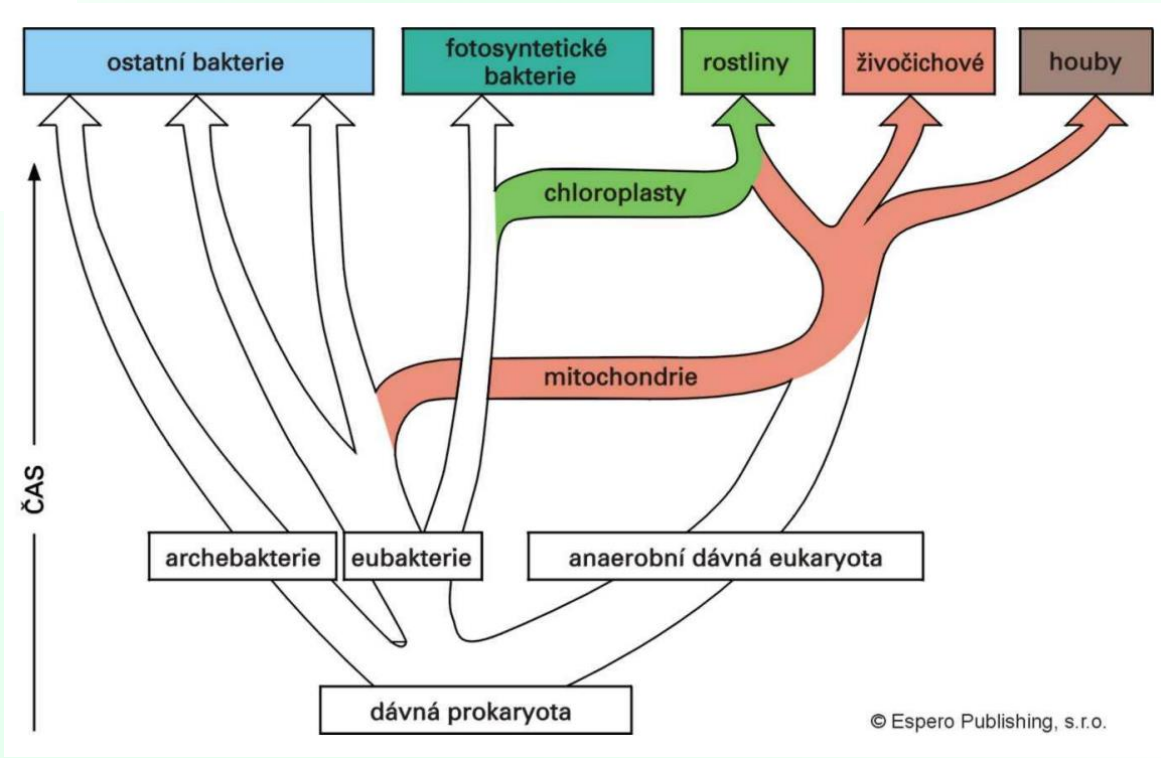
Živočišná buňka



Obr. 024

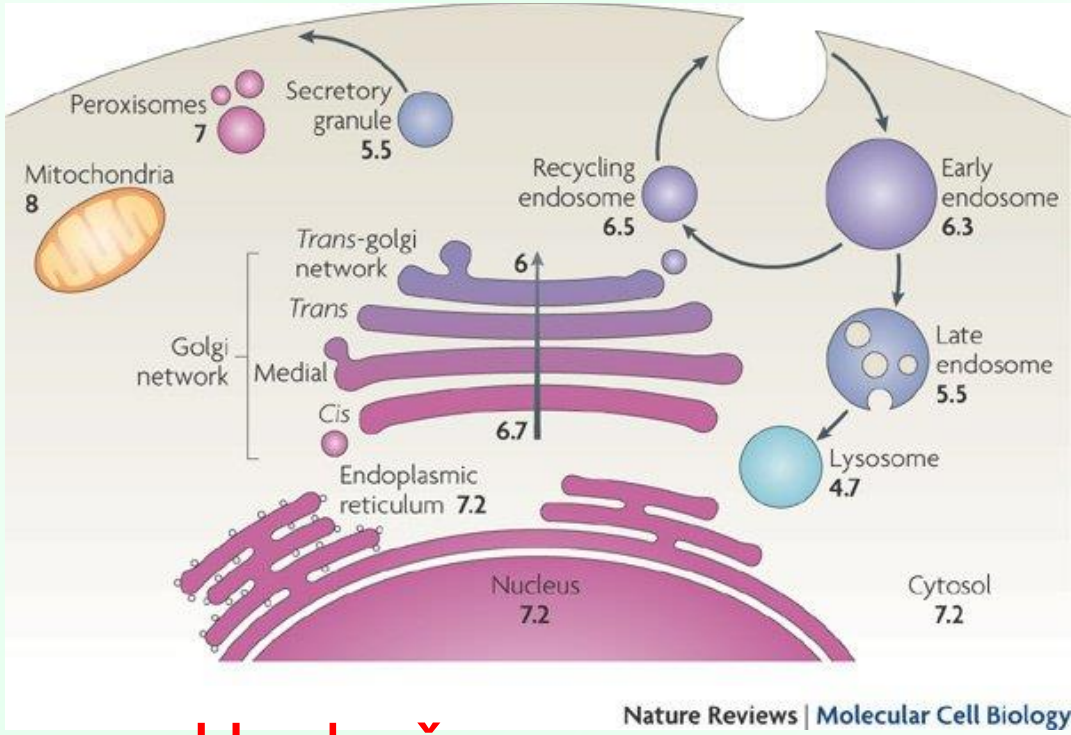
Kompartmentace – teorie endosymbiózy





Proč buňka potřebuje organely?

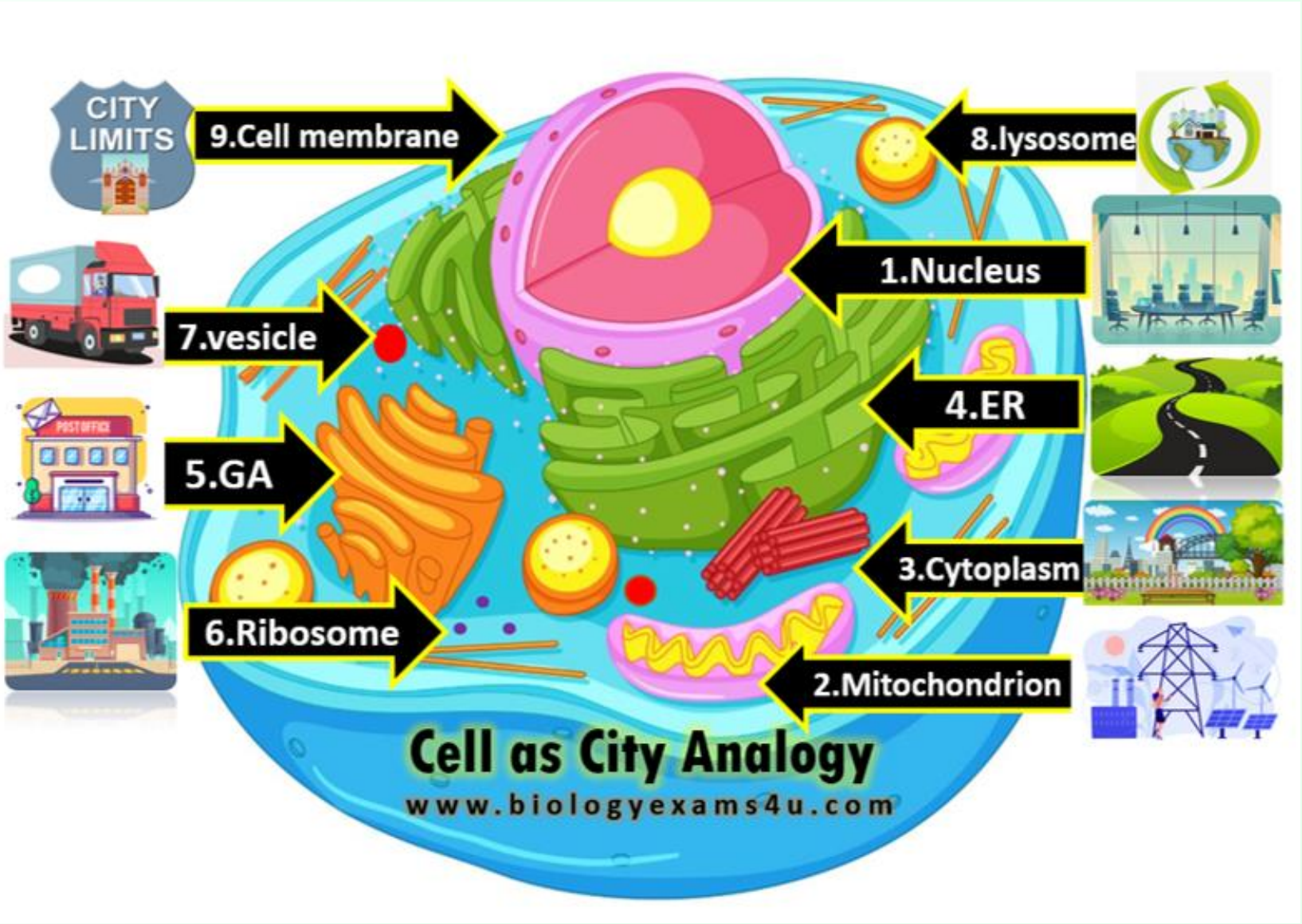
- Organely udržují různé koncentrace látek různých částech buňky. Nejvíc důležité je udržování gradientů koncentrace iontů na protilehlých stranách mebrány. Ve správný okamžik pak buňka může spustit influx nebo transport.
- Každý biochemický proces je výhodné udržet ve specifickém prostředí a za určité koncentrace. Šlo by to i bez nich, energetické a metabolické přeměny by nebyly tak efektivní nebo by byly pomalé a nebo by některé vůbec biochemicky nemohly probíhat. Odpadní látky by také zbytečně interagovali s DNA a jinými užitečnými molekulami uvnitř buňky.



pH v buňce

MUNI PHARM

Buňka jako město či továrna



https://prezi.com/hqun2aj4kqa5/cell-analogy-a-factory/

https://www.biologyexams4u.com/2022/12/cell-city-analogy-learn-cell-parts.html

MUNI PHARM

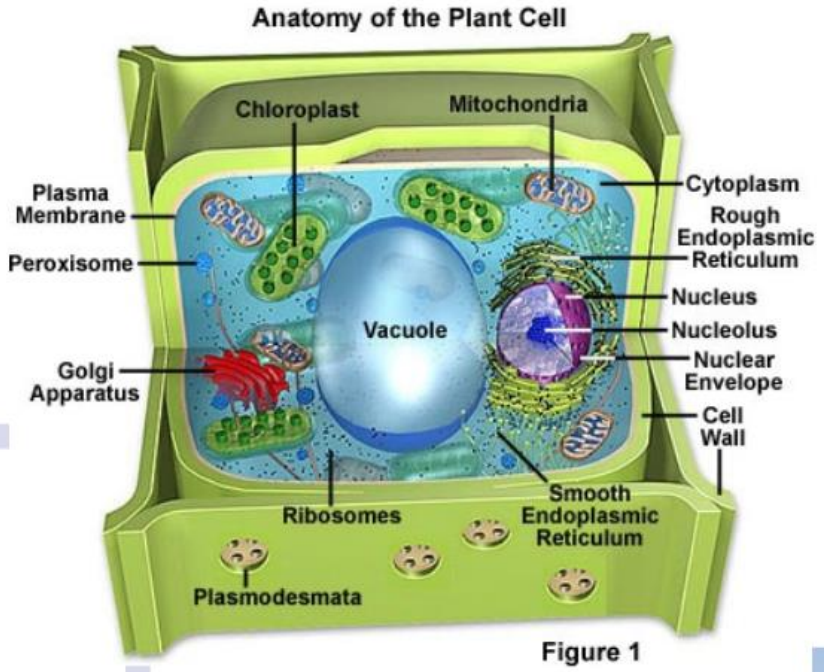


Figure 1

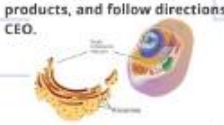
MUNI PHARM

Plant Cell Analogy: A Factory

By: Rachel Canzoneri, Megan McGee, and Angie Florimbio

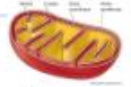
Ribosomes
Factory Workers

Ribosomes are one of the smallest organelles in the cell. They make proteins, and are located on the endoplasmic reticulum (ER). These ribosomes are similar to the factory workers, since they both create products, and follow directions from the nucleus/ CEO.



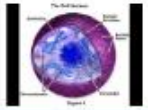

Mitochondria
Local Power Plant

In a cell, "mighty mitochondria" produces energy-rich molecules. Like the local power plant that provides power to most parts of the factory, mitochondria powers and produces energy in a cell.



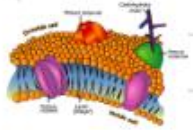

Nucleus
The CEO

The nucleus is the part of the cell that controls and directs all of the activity. Like the CEO of the factory, who makes all the major decisions and is responsible for most activity, the nucleus and CEO are clearly similar.



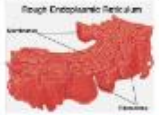

Cell Membrane
Doors of the Factory

The cell membrane is similar to the doors of the factory. In a cell, the cell membrane is part of the outer lining, and it controls what comes in and out, like the doors of the factory allow people to enter and leave.




Rough Endoplasmic Reticulum (Rough ER)
Assembly Line

The rough ER is where the ribosomes are located. So, it's where proteins, and other molecules, are made. Therefore, the rough ER is like the factory's assembly line, because it's where the ribosomes make the proteins, or where the workers make the products.




Golgi Bodies
Shipping Department

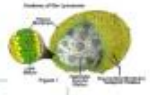
The golgi body is located near the cell membrane. It's responsible for grouping vesicles, finalizing them, and shipping them elsewhere. A shipping department is like the golgi body because it takes the final product and ships to where they need to go. Therefore, the golgi body is like our shipping department.


Cytoplasm:
Floors of the Factory

Cytoplasm is the jelly-like fluid that takes up most of the space in the cell, besides the organelles. Like the floors of the factory, it's where everything happens and it takes up quite a lot of space.


Lysosomes
Maintanence Crew

In a cell, lysosome are responsible for breaking waste down, and handle the movement of trash and waste. Therefore, lysosomes are like the maintenance crew or janitors, because both handle waste and general trash.

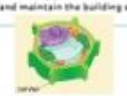



Vacuole
Storage Area

The large, central vacuole is one of the cell's biggest organelles. It stores water and nutrients. This is very similar to the way the factory's storage closet stores tools, machines, and other supplies.

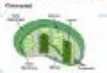

Cell Wall
Structure/Walls of the Factory

The cell wall is the outermost lining of the cell. Found only in plant cells, it protects the cell and maintains it's shape. Like the cell wall, the walls of the factory protect the factory workers,protection, and maintain the building structure.




Chloroplast
Solar-powered Rooftop

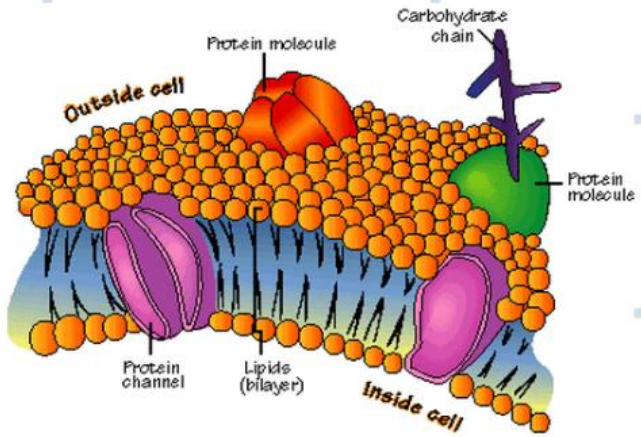
Since plants don't eat food, they use chloroplast to transform energy they absorb from the sun for the cell to use in a process called photosynthesis. Since solar power panels absorb light from the sun and transform the energy to power the factory, chloroplast and the solar-powered rooftop of the factory are very analogus to each other.




MUNI PHARM

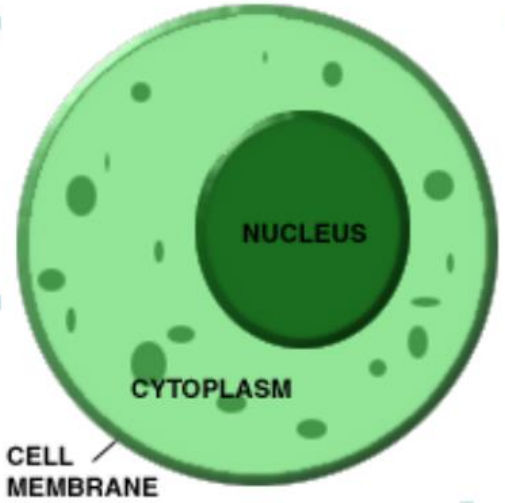
Cell Membrane
Doors of the Factory

The cell membrane is similar to the doors of the factory. In a cell, the cell membrane is part of the outer lining, and it controls what comes in and out, like the doors of the factory allow people to enter and leave.



Cytoplasm:
Floors of the Factory

Cytoplasm is the jelly-like fluid that takes up most of the space in the cell, besides the organelles. Like the floors of the factory, it's where everything happens and it takes up quite a lot of space.



Nucleus

The CEO

The nucleus is the part of the cell that controls and directs all of the activity. Like the CEO of the factory, who makes all the major decisions and is responsible for most activity, the nucleus and CEO are clearly similar.

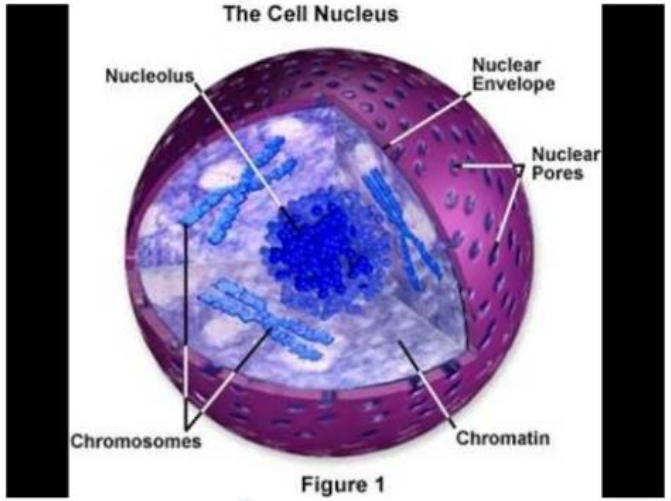
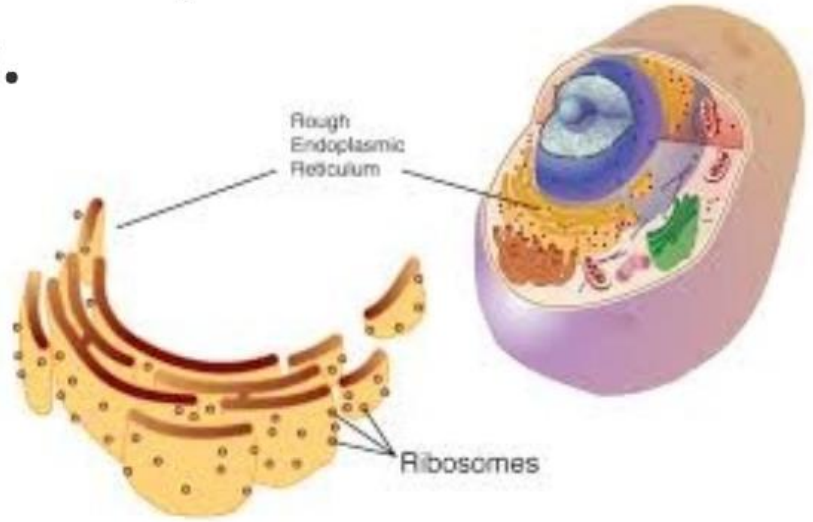


Figure 1

Ribosomes

Factory Workers

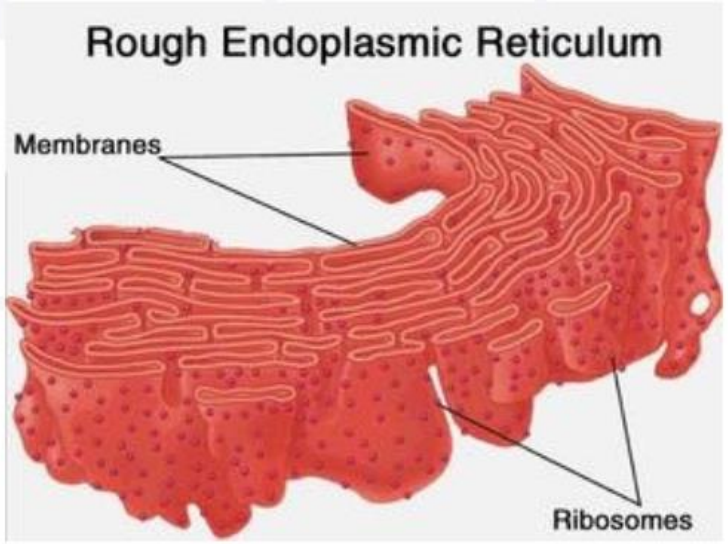
Ribosomes are one of the smallest organelles in the cell. They make proteins, and are located on the endoplasmic reticulum (ER). These ribosomes are similar to the factory workers, since they both create products, and follow directions from the nucleus/ CEO.



Rough Endoplasmic Reticulum (Rough ER)

Assembly Line

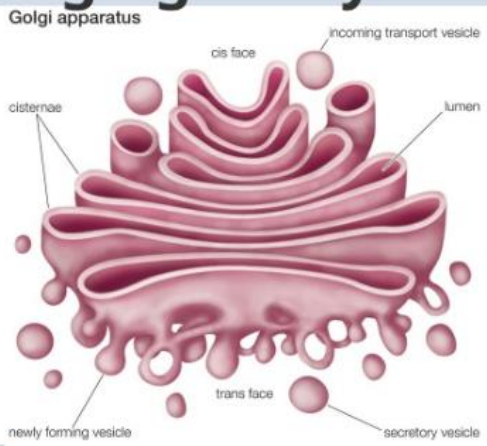
The rough ER is where the ribosomes are located. So, it's where proteins, and other molecules, are made. Therefore, the rough ER is like the factory's assembly line, because it's where the ribosomes make the proteins, or where the workers make the products.



Golgi Bodies

Shipping Department

The golgi body is located near the cell membrane. It's responsible for grouping vesicles, finalizing them, and shipping them elsewhere. A shipping department is like the golgi body because it takes the final product and ships to where they need to go. Therefore, the golgi body is like our shipping department.

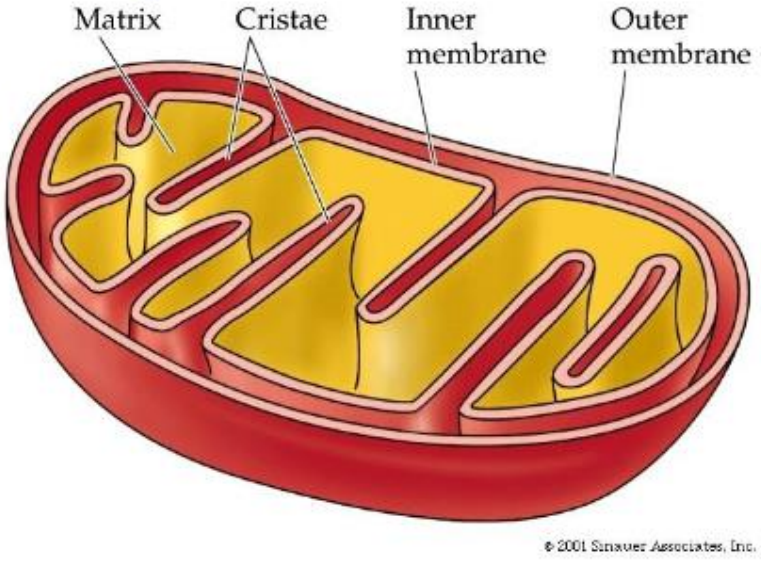


MUNI PHARM

Mitochondria

Local Power Plant

In a cell, "mighty mitochondria" produces energy-rich molecules. Like the local power plant that provides power to most parts of the factory, mitochondria powers and produces energy in a cell.



MUNI PHARM

Lysosomes

Maintanence Crew

In a cell, lysosome are responsible for breaking waste down, and handle the movement of trash and waste. Therefore, lysosomes are like the maintenance crew or janitors, because both handle waste and general trash.

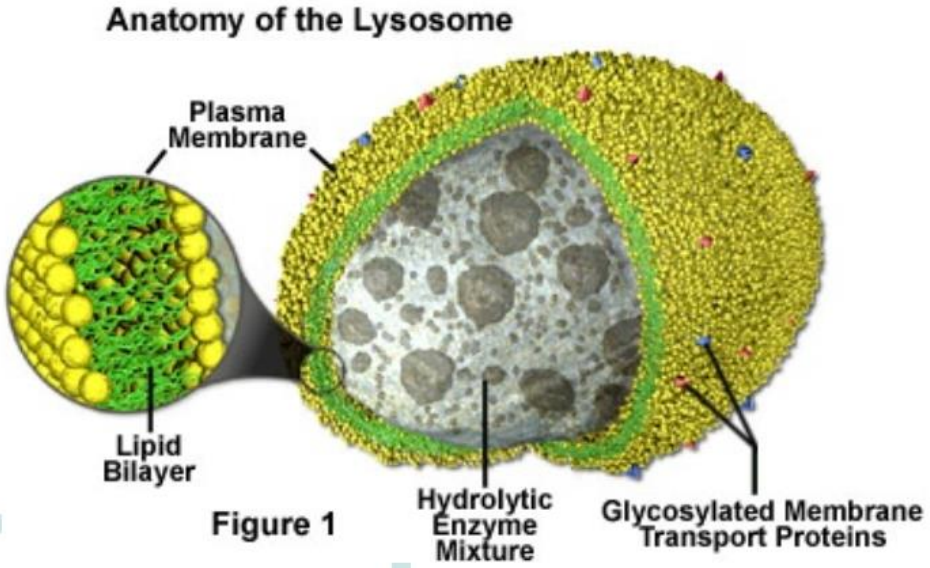


Figure 1

MUNI PHARM

Vacuole

Storage Area

The large, central vacuole is one of the cell's biggest organelles. It stores water and nutrients. This is very similar to the way the factory's storage closet stores tools, machines, and other supplies.

Plant Cell Central Vacuole

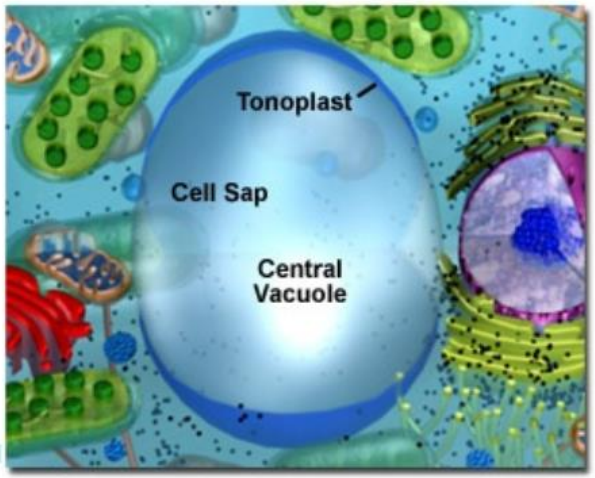


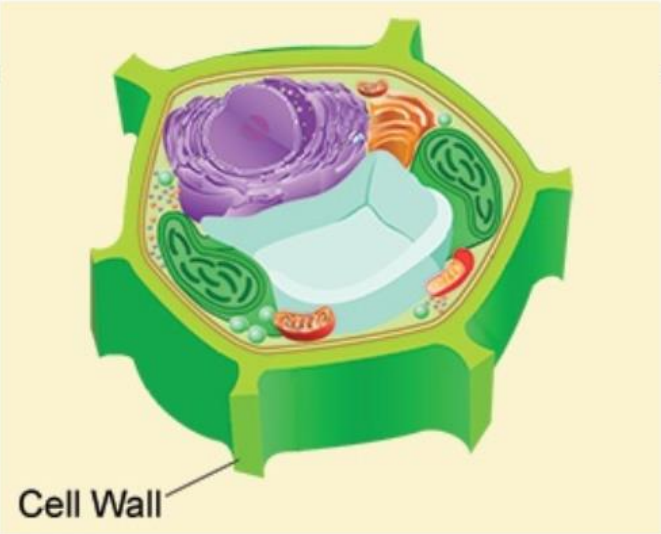
Figure 1

MUNI PHARM

Cell Wall

Structure/Walls of the Factory

The cell wall is the outermost lining of the cell. Found only in plant cells, it protects the cell and maintains it's shape. Like the cell wall, the walls of the factory protect the factory workers,protection, and maintain the building structure.

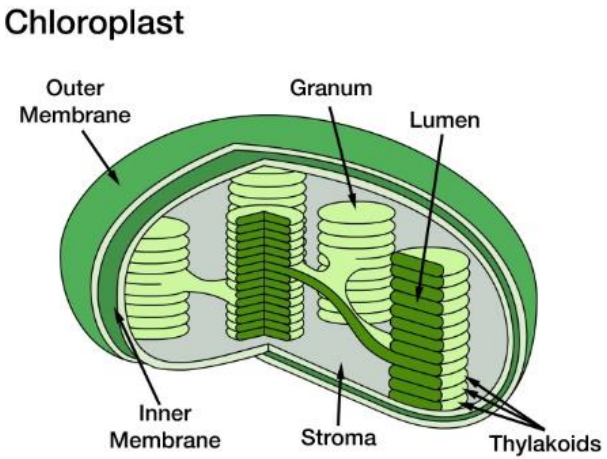


MUNI PHARM

Chloroplast

Solar-powered Rooftop

Since plants don't eat food, they use chloroplast to transform energy they absorb from the sun for the cell to use in a process called photosynthesis. Since solar-power panels absorb light from the sun and transform the energy to power the factory, chloroplast and the solar-powered rooftop of the factory are very analogus to each other.



MUNI PHARM

Homeostasis Scenario

Cell

Problem: The vacuole is too full of water and nutrients.

Solution: The vacuole stops taking in water and the other organelles take the water when -needed. Once the vacuole isn't at maximum capacity, the cell can start absorbing water again.

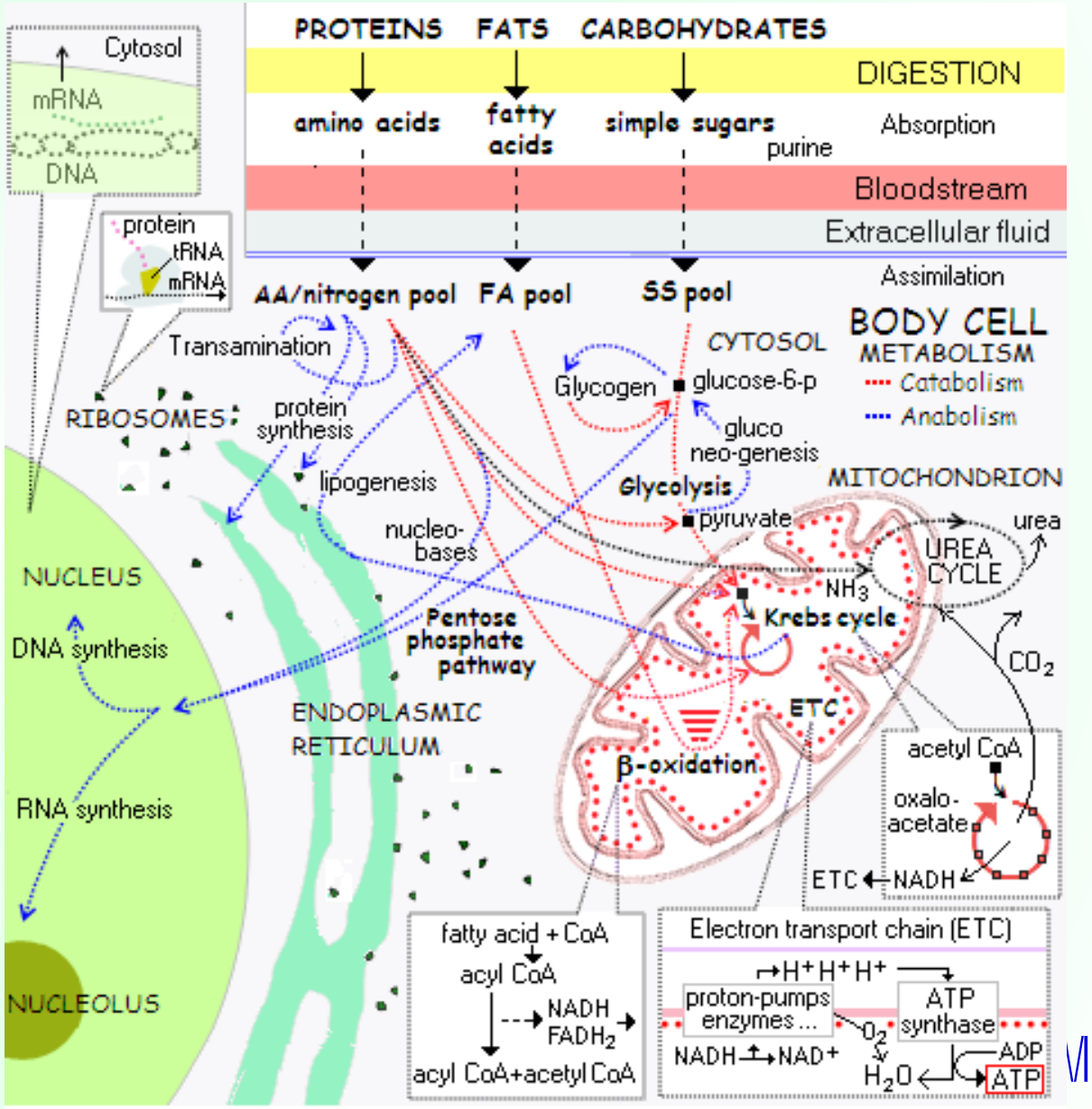
Factory

Problem: The storage area is overflowing with tools and other supplies.

Solution: Production is put on hold until most of the supplies are shipped out or used. Production can then be resumed because there is space in the storage area.

Metabolická síť organel

- Každá organela má svoji úlohu
- Mezi organelami probíhá intenzivní výměna látek a energie

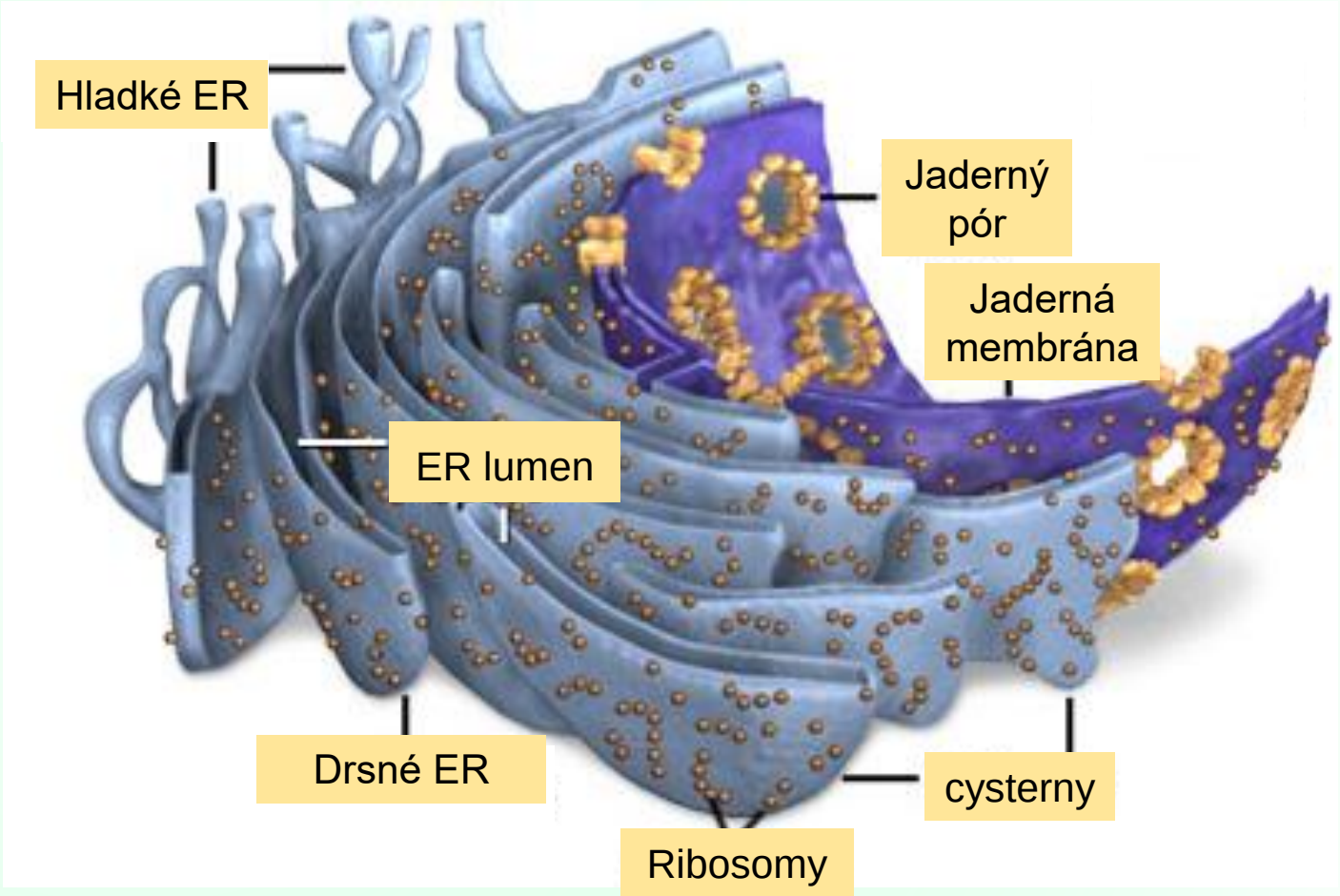


https://www.healthknot.com/cellular_metabolism.html

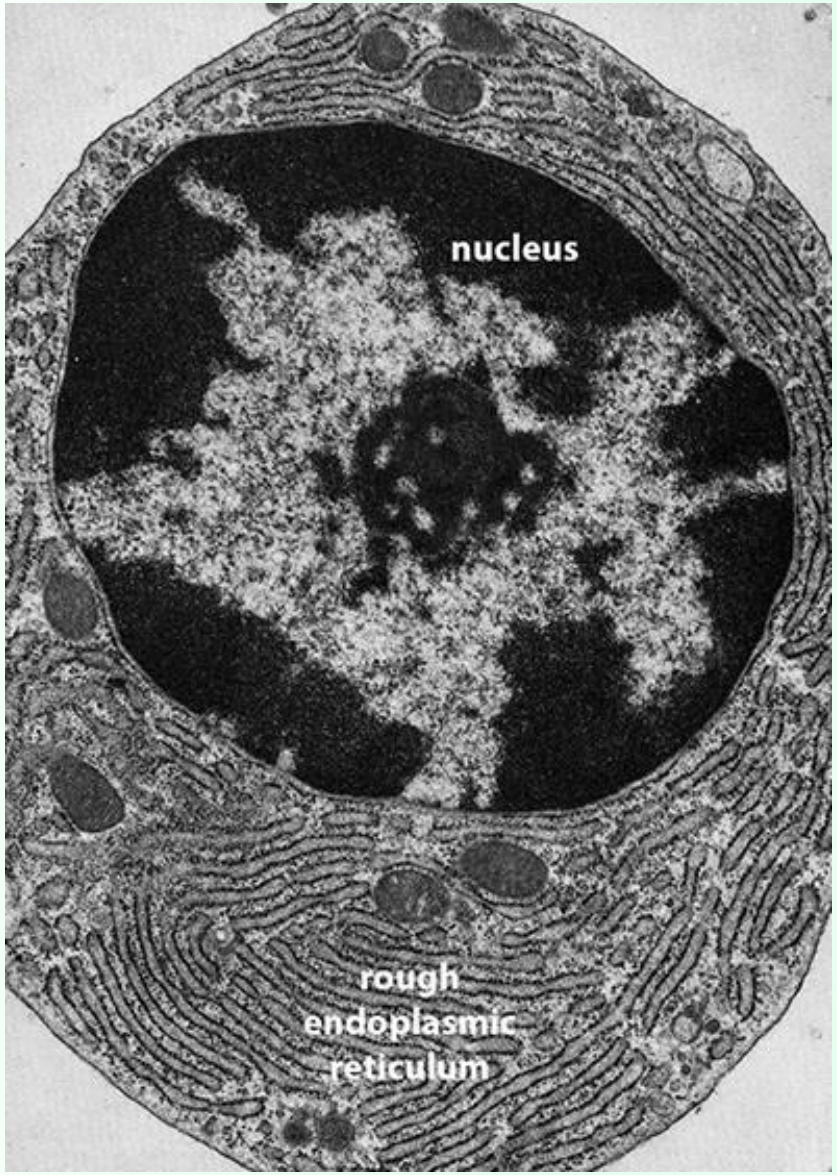
Endoplasmatické retikulum (ER)

- Výrobní linka buňky
- vícekrát stočený membránový list, který vytváří uzavřený vak, **endoplasmatické lumen**
- Spojené s jadernou membránou
- Membrána ER tvoří více jak 50 % membránových struktur v buňce
- Lumen ER zaujímá až 10 % objemu buňky

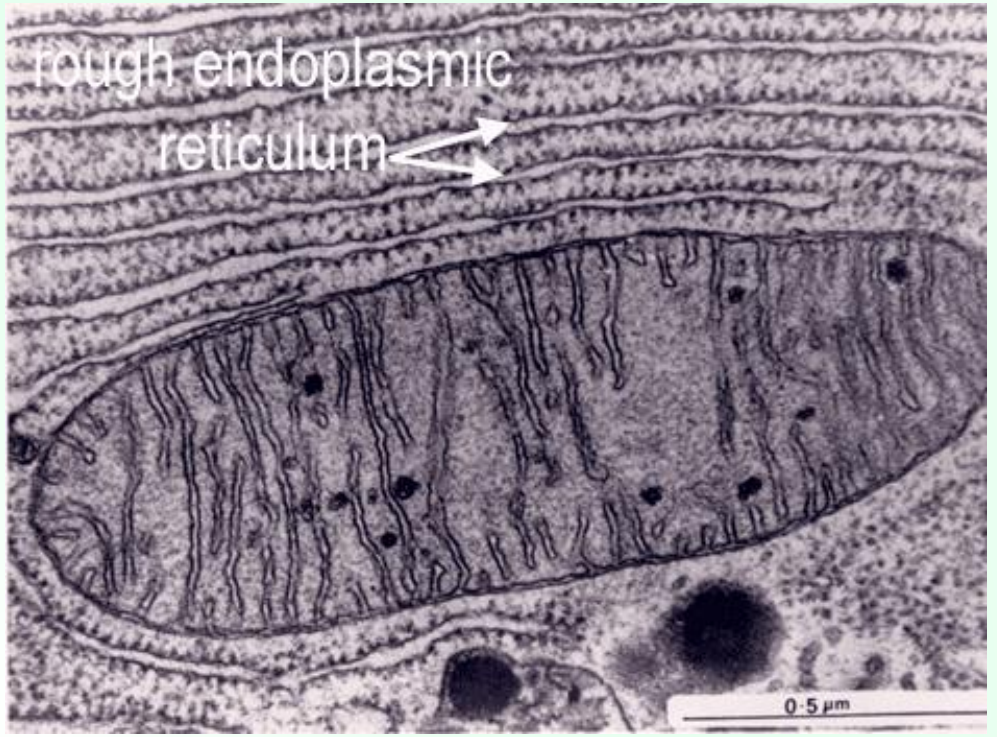
https://micro.magnet.fsu.edu/cells/endoplasmicreticulum/endoplasmicreticulum.html



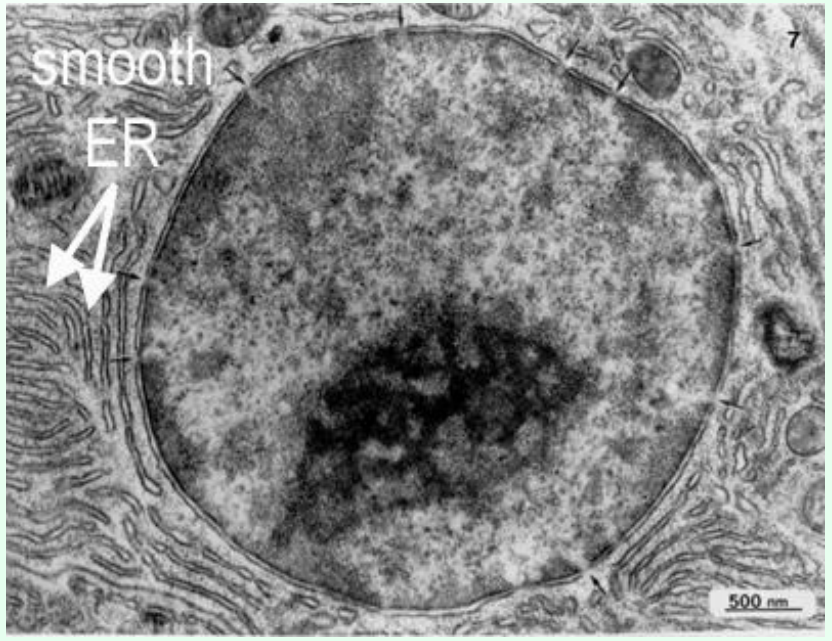
MUNI PHARM



https://www.ncbi.nlm.nih.gov/books/NBK563126/figure/article-28660.image.f1/



https://www.histology.leeds.ac.uk/cell/cell_organelles.php

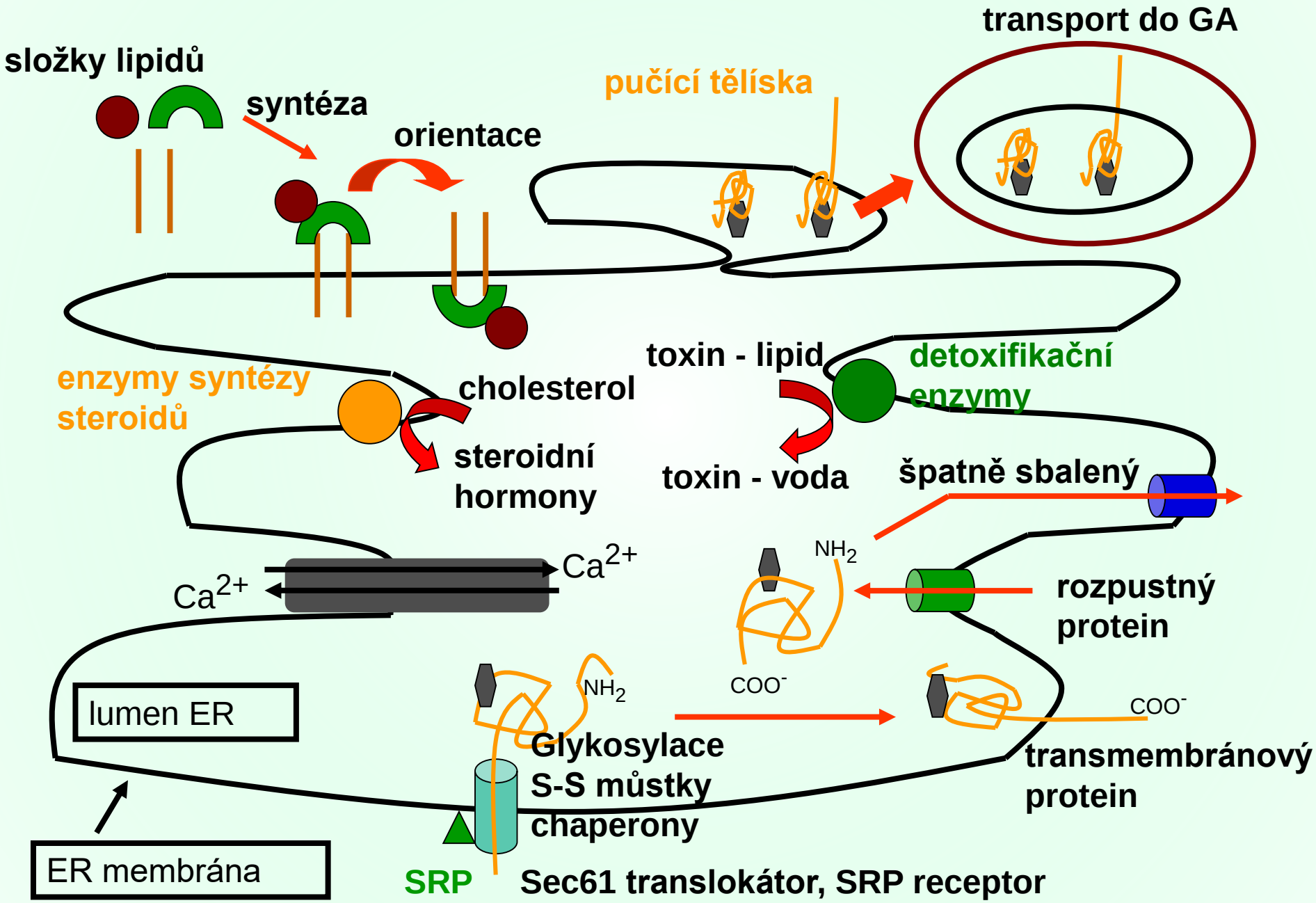


MUNI PHARM

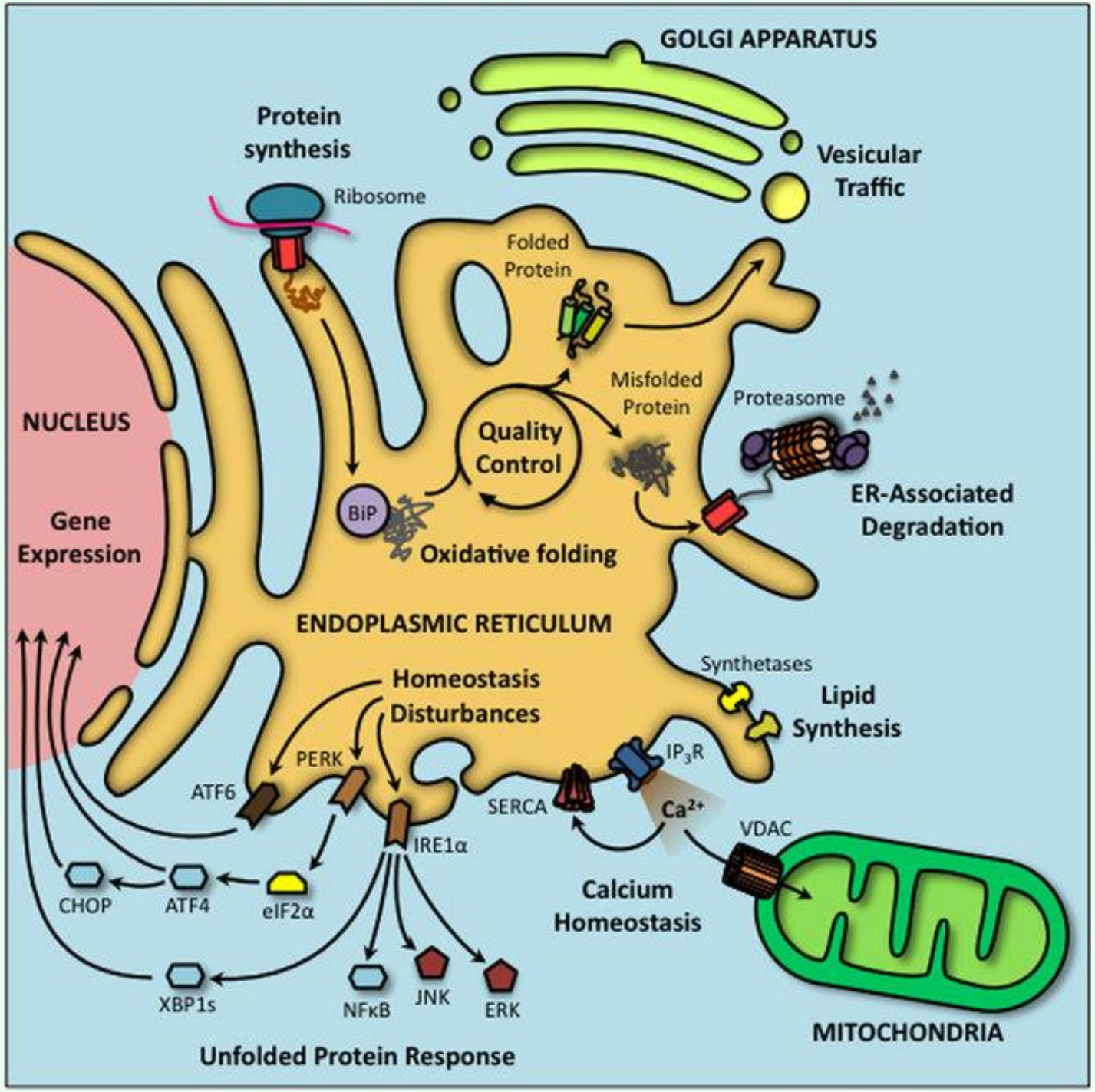
Funkce ER

- **ústřední role v syntéze lipidů, proteinů, steroidů**
- **biosyntéza a metabolizace vlastních látek a xenobiotik**
- usnadňuje vytvoření správné terciární nebo kvartérní struktury proteinů
- transportní systém – distribuce proteinů do cytoplasmy nebo organel
- udržování osmotického tlaku
- **skladování a depozice Ca^{2+} iontů**
- **chemická modifikace proteinů**
  - tvoří se disulfidové můstky oxidací cysteinových párů postranních řetězců
- tvorba glykoproteinů kovalentním napojením krátkého oligosacharidového postranního řetězce – **dokončuje se v GA**
- prekurzor oligosacharidu je napojován O- nebo N-vazbou na molekulu proteinu
- výstup proteinu je kontrolován = nesprávně sbalený protein je zadržen **chaperonem** nebo degradován

Schématické znázornění funkcí ER



MUNI PHARM



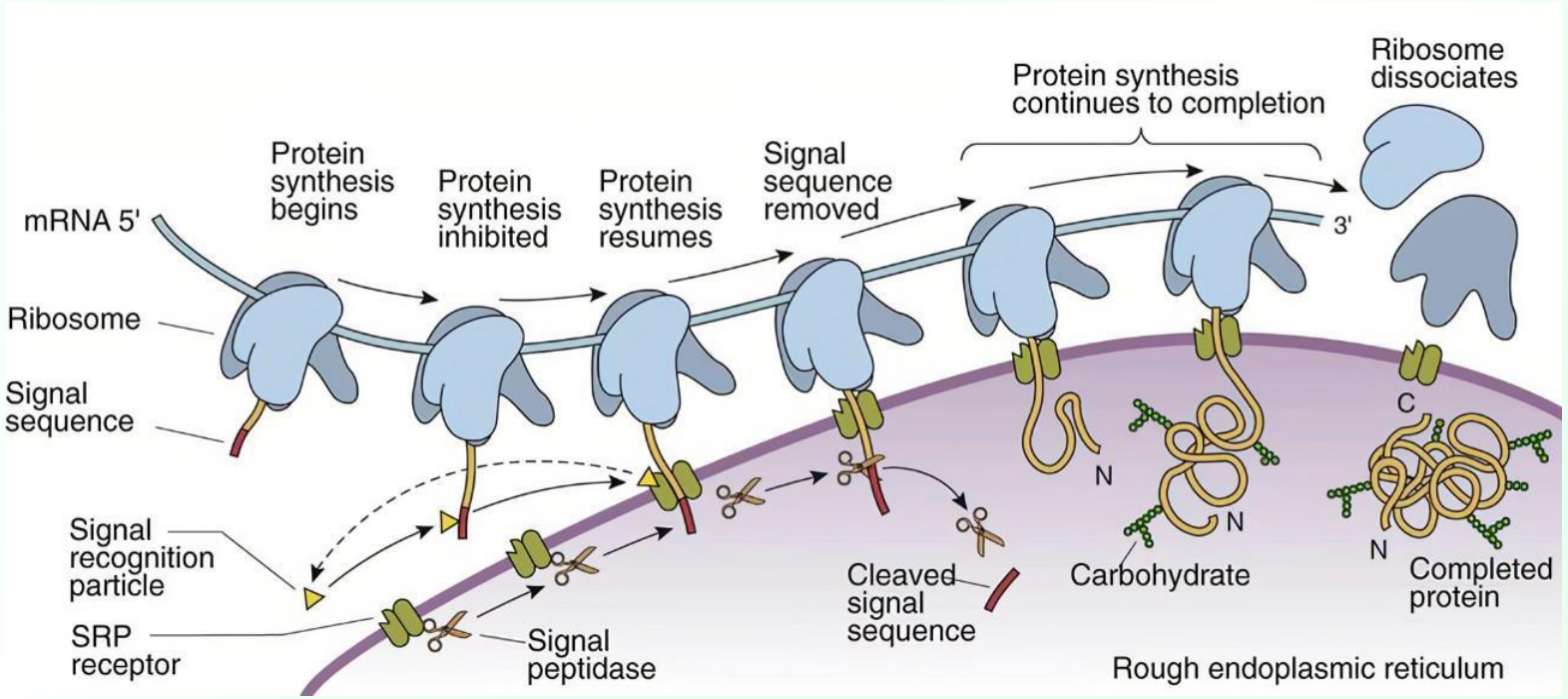
DOI: 10.1016/j.biocel.2011.10.012

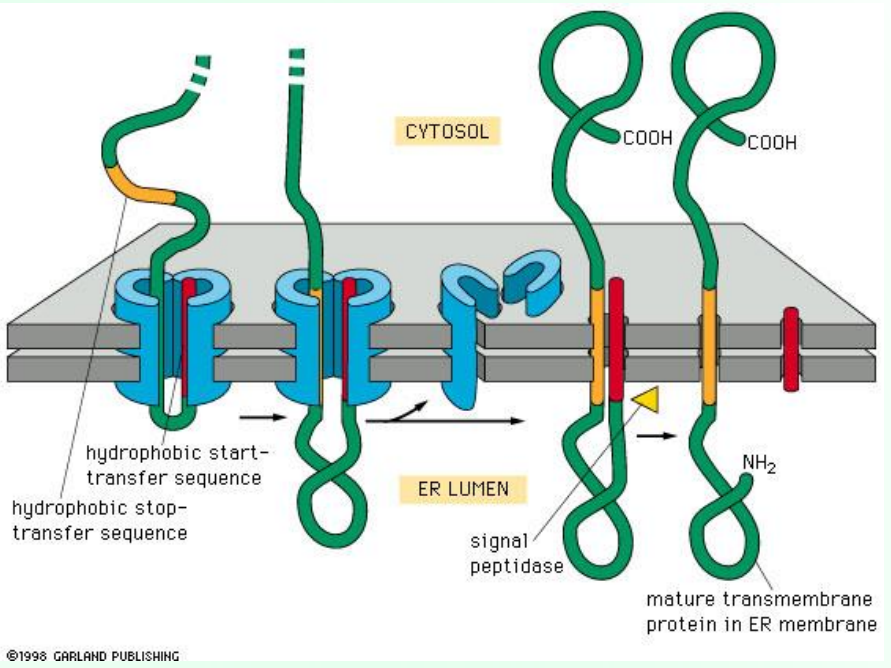
MUNI PHARM

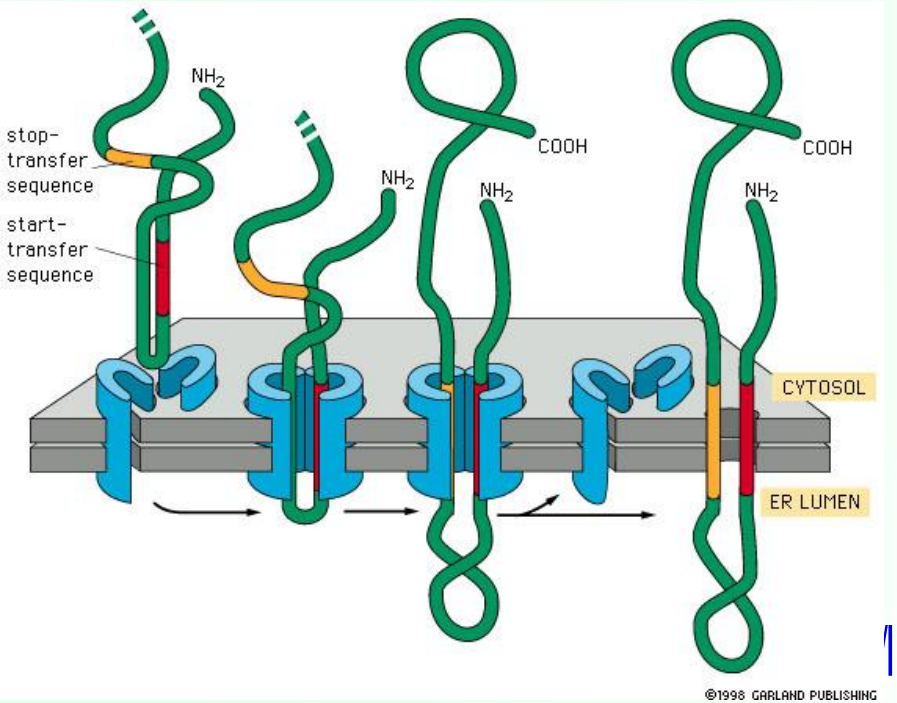
ER – syntéza proteinů

https://www.zoology.ubc.ca/~berger/B200sample/unit_8_protein_processing/er_targeting/lect27.htm

- V ER jsou tvořeny extracelulární proteiny a proteiny vázané na membránu
- Proteosyntéza zažíná v cytoplasmě
- Proteiny jsou tvořeny ribosomy na **drsném ER**
- Post-translační úpravy v ER – **tvorba disulfidických můstků** a **zahájení glykosylace** (ta pokračuje v GA)

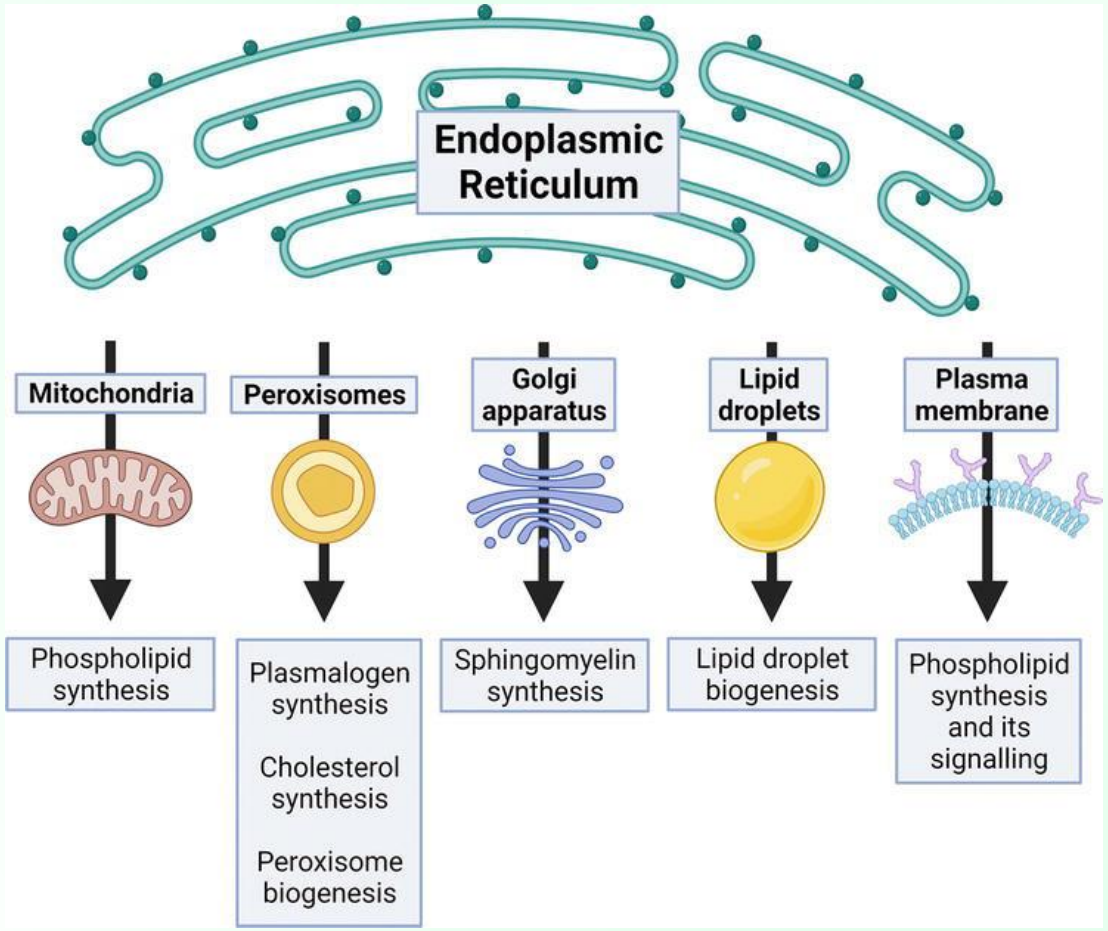


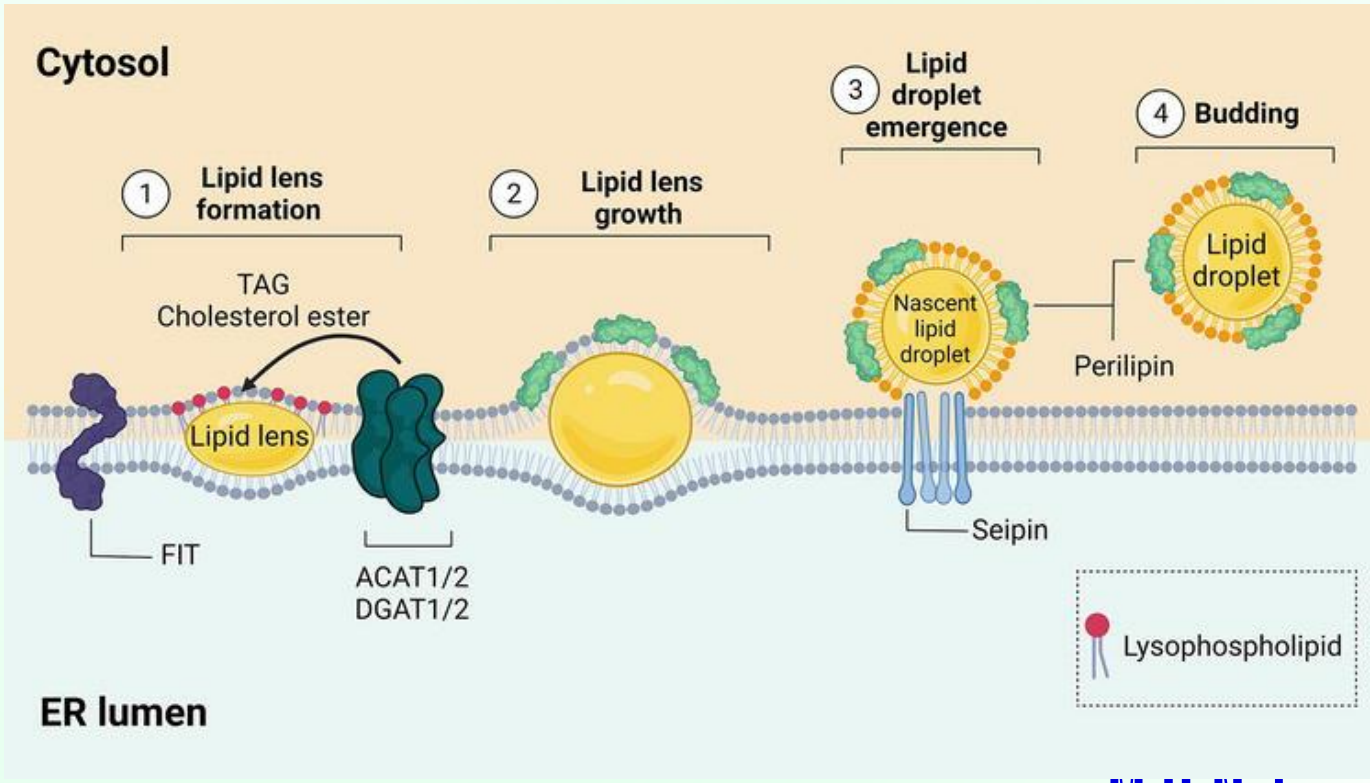




ER – syntéza lipidů

- Lipidy vznikají v hladkém ER ve spolupráci s dalšími organelami
- V ER se vytváří i zásobní lipidové kapky speciálním procesem vychlípením a odškrcením segmentu membrány ER do cytoplasmy





https://www.intechopen.com/online-first/82195

MUNI PHARM

ER – detoxifikace metabolitů a xenobiotik

- Hlavně hladké ER hepatocytů
- Nejdůležitější je **skupina cytochromů P450**
  - Oxidoreduktázy P450 jsou velmi důležité enzymy pro farmakologii známe několik podtypů, podtyp 3A4 a 2C9 metabolizuje většinu léčiv a řadu toxinů a xenobiotik (např na polárnější molekuly pro snadnější vyloučení z těla)
  - P450 se podílí i na metabolismu a syntéze řady důležitých látek, např. **vitamíny, cholesterol, žlučové kyseliny, steroidní hormony,…**

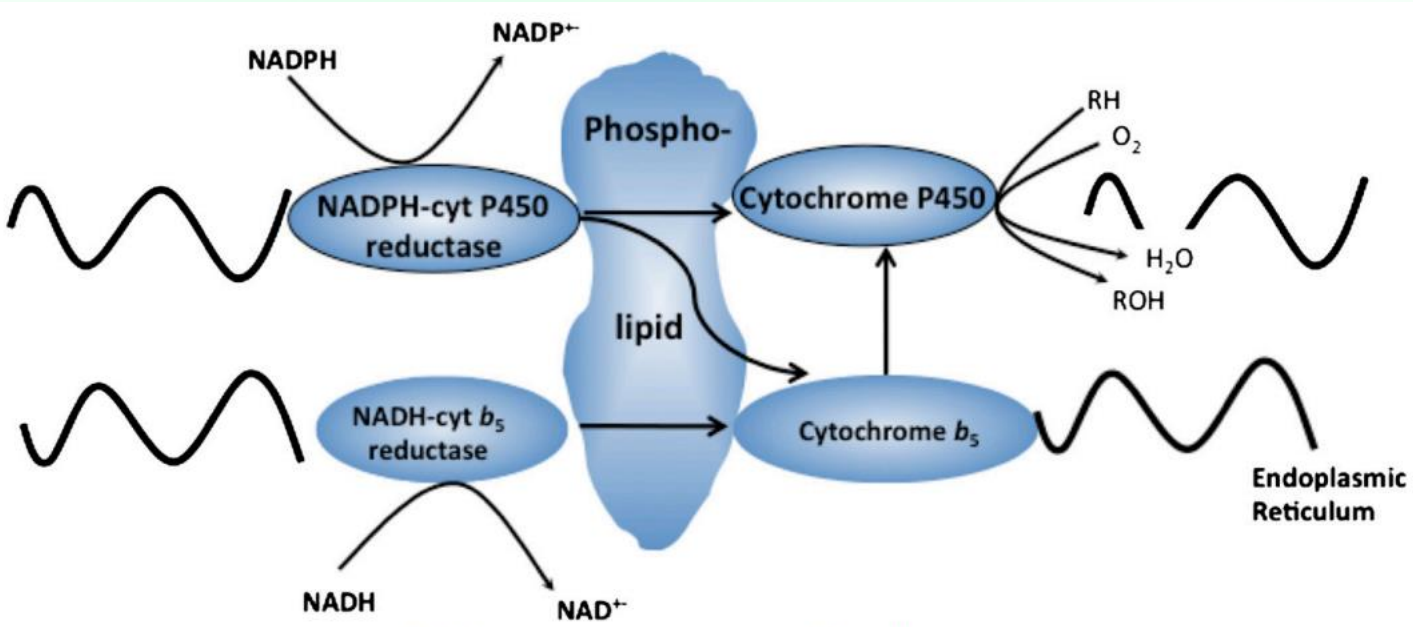
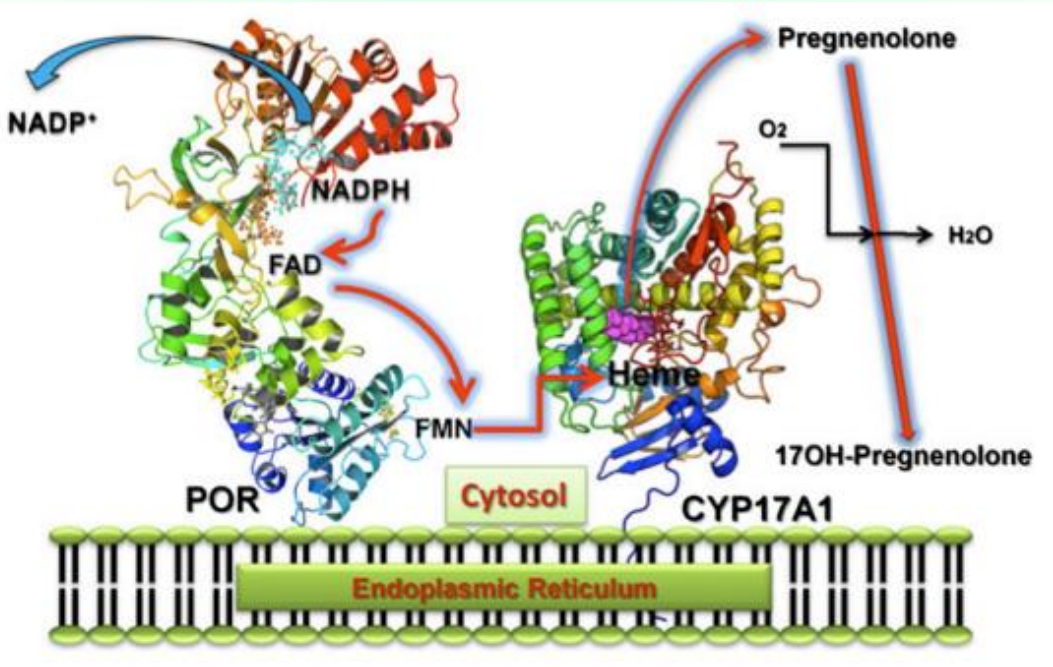


Fig. 3. Electron-transport pathways in the cytochrome P450 system.

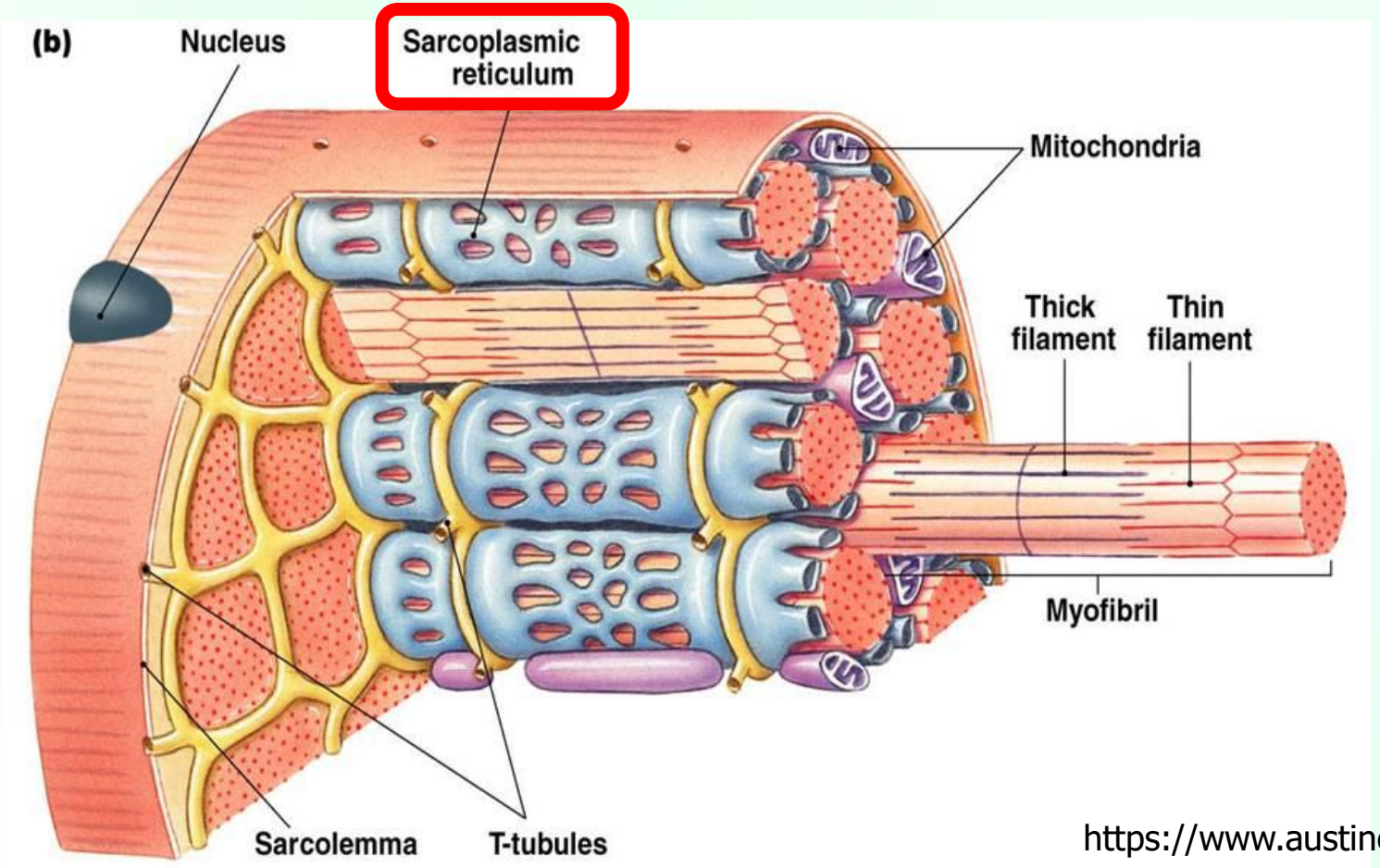


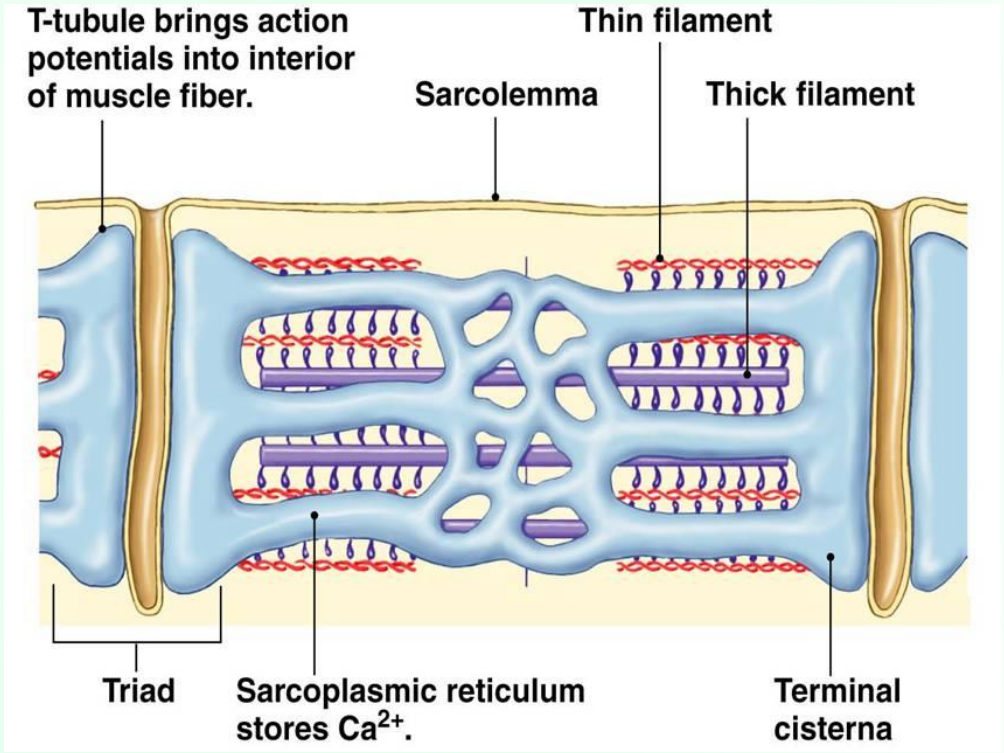
https://doi.org/10.1124/dmd.112.048991

PHARM

ER → Sarkoplasmatické retikulum (SR)

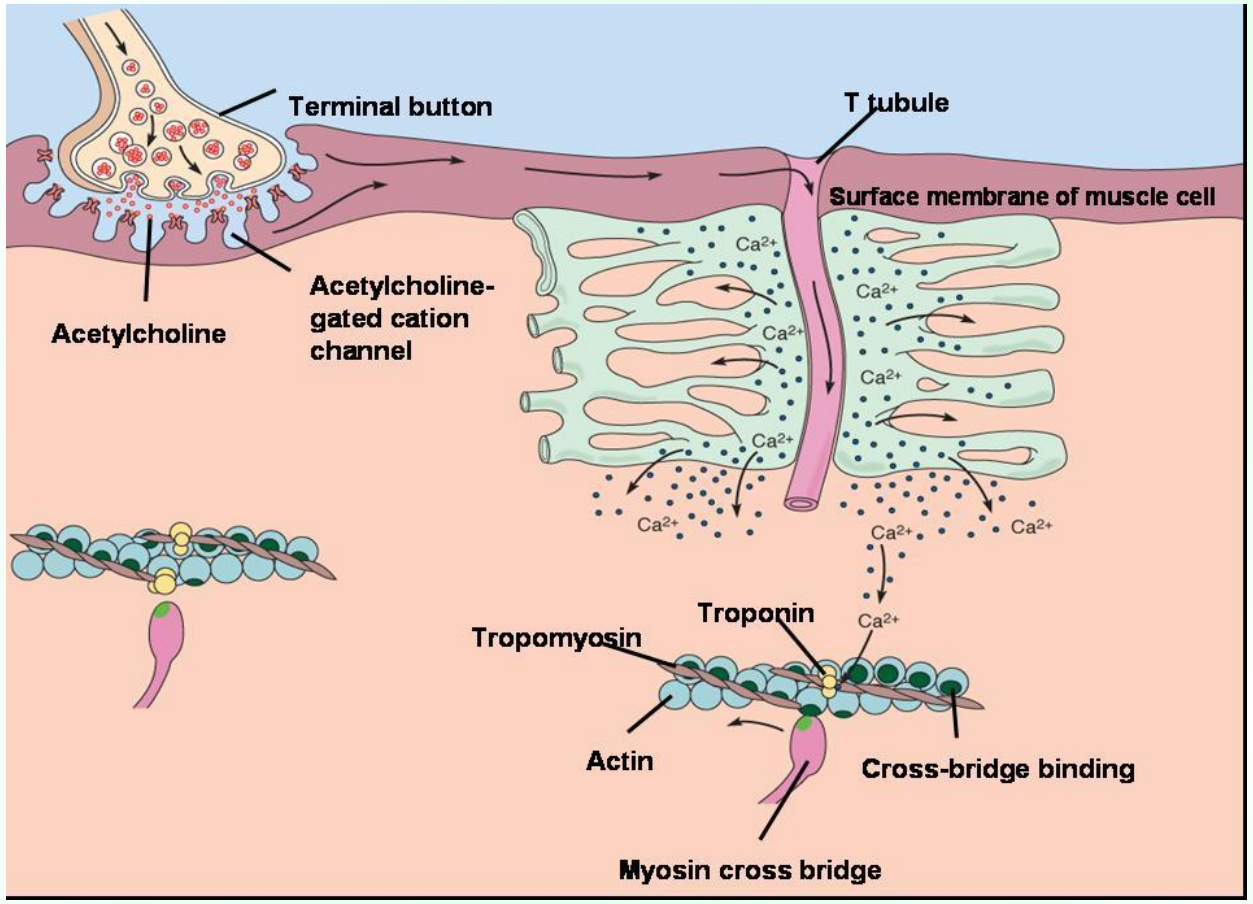
- Sarkoplasmatické retikulum = ER ve svalových buňkách
- SR uvolní Ca^{2+} ionty a zahájí svalový stah

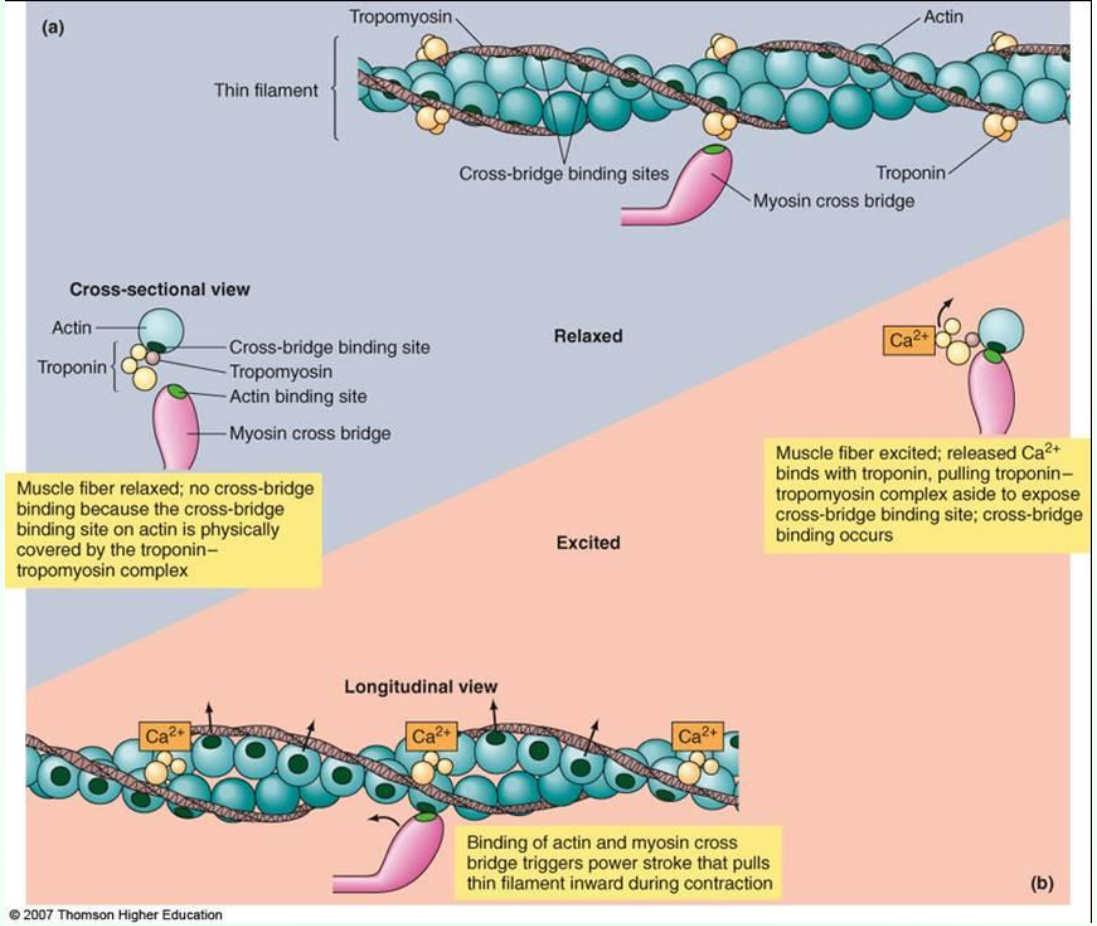


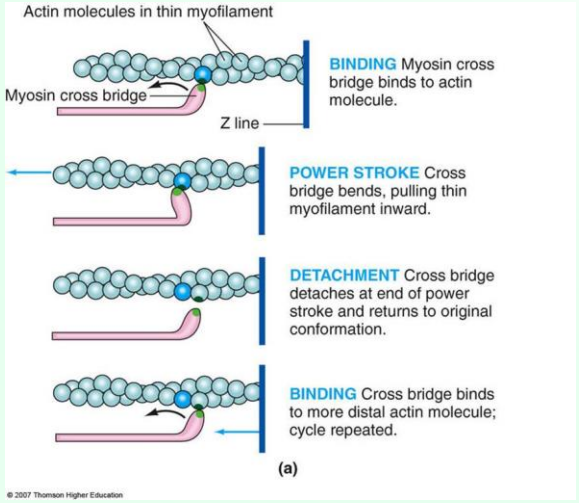


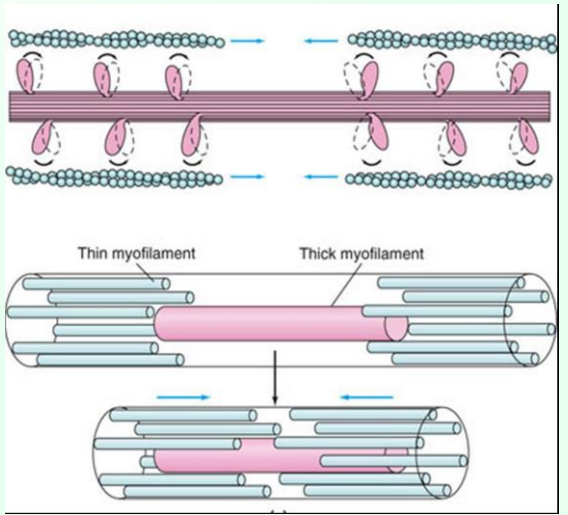
https://www.austincc.edu/apreview/PhysText/Muscle.html

MUNI PHARM







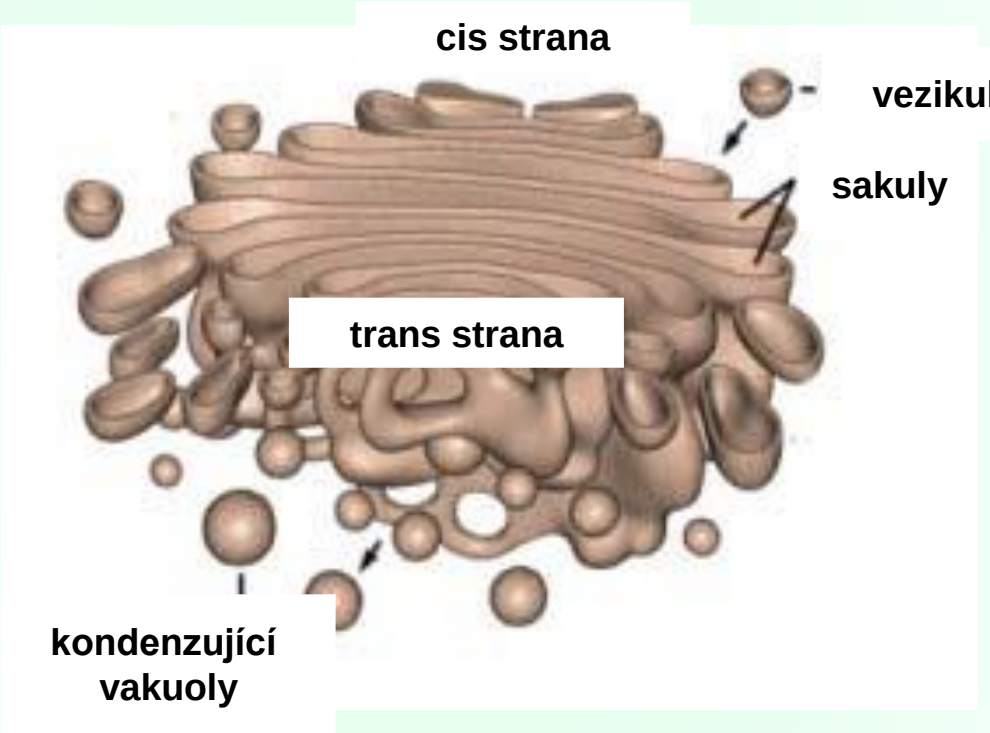


https://www.austincc.edu/apreview/PhysText/Muscle.html

MUNI PHARM

Golgiho aparát (GA) – I.

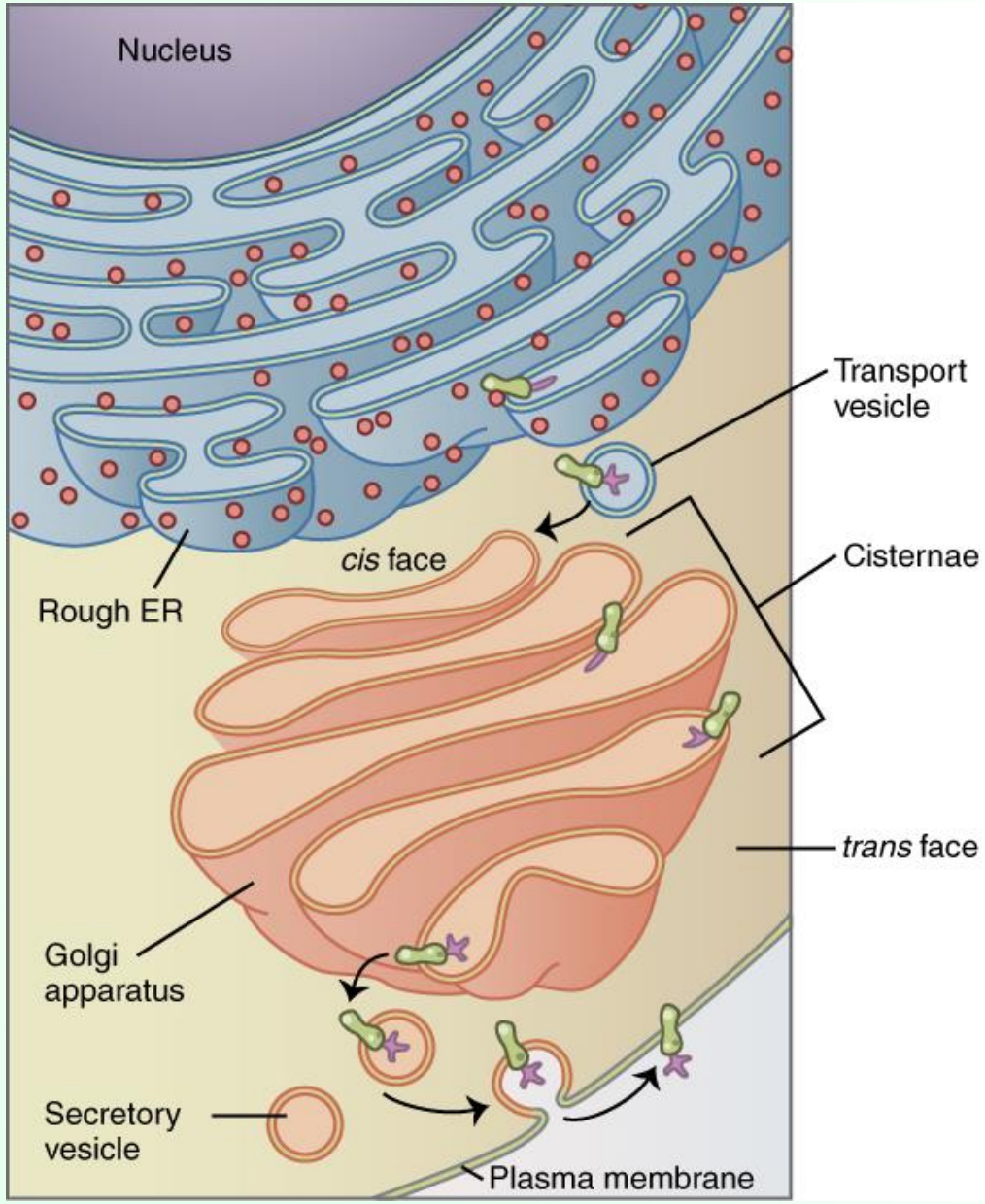
- Komplex tzv. dyktiozómů, shluků cisteren a váčků (vezikulů) (3 až 10 váčků)
- Nacházejí se poblíž jádra a ER
- Sakuly - zploštělé váčky rozšiřující se od centrální části směrem k okraji
- Vezikuly – měchýřky obsahující proteiny vyprodukované v drsném ER, obsah odevzdávají cis-straně GA se kterou splývají
- Kondenzující vakuoly – vezikuly obsahující zpracované proteiny a odškrcující se z trans-strany GA odkud putují k plasmatické membráně kde exocytózou vylučují svůj obsah do extracelulárního prostředí



MUNI PHARM

Golgiho aparát (GA) – II.

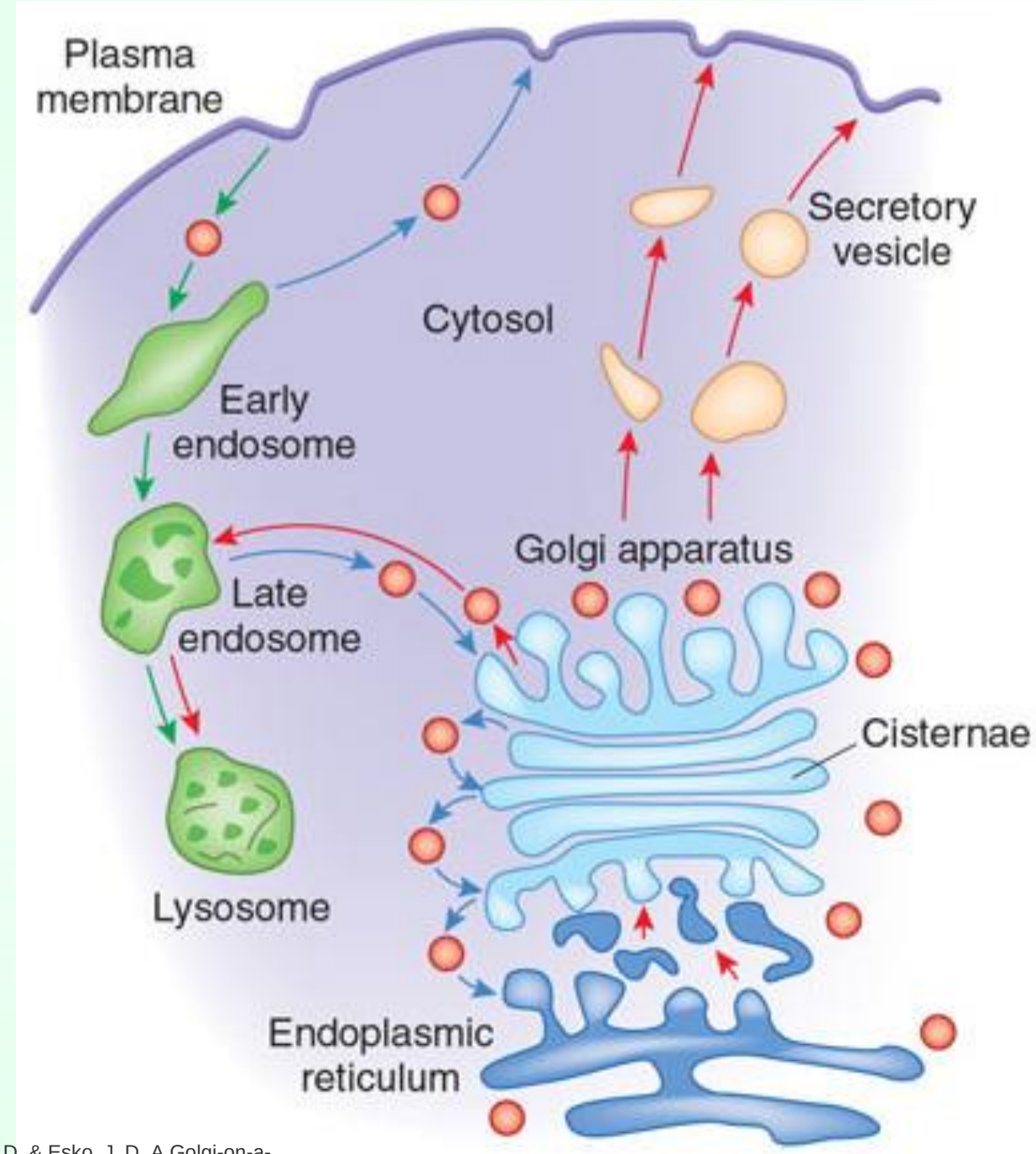
- Dyktiozómy jsou navzájem propojené a zpravidla na straně přivrácené k jádru (**cis strana)** neustále přijímají váčky odštěpené od ER a intenzívně odštěpují váčky naplněné různými buněčnými sekrety **(trans strana)**

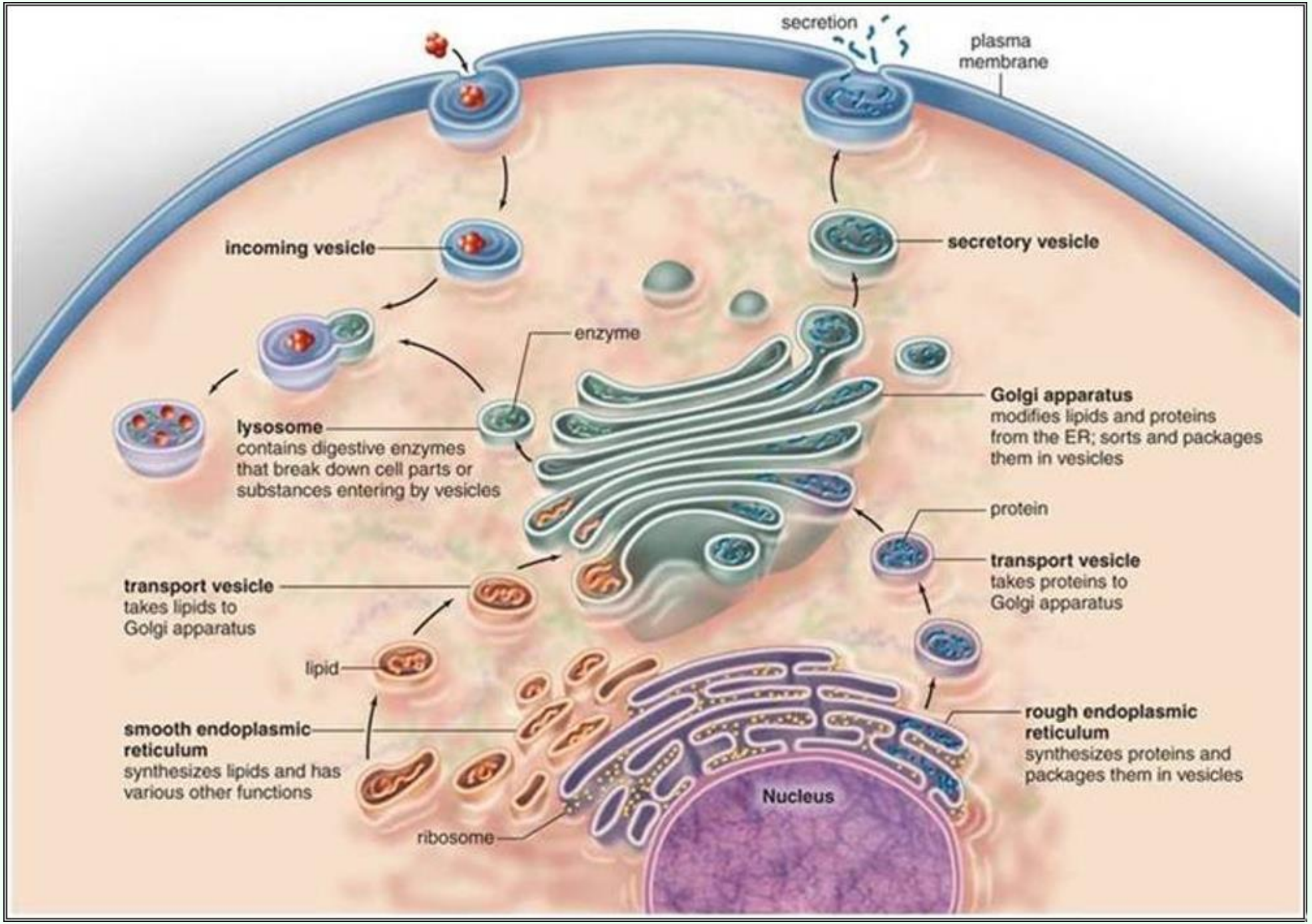


MUNI PHARM

Funkce GA

- Transport a přechovávání látek
- Posttranslační úpravy proteinů
  - Nejčastěji glykosylace, fosforylace, sulfatace, specifická proteolýza
- Syntéza polysacharidů a imunoglobulinů
- Tvorba váčků (sekrečních granul) využívaných při exocytóze
- Vzniká zde materiál pro tvorbu buněčné stěny
- Tvorba a diferenciace lysozómů
- Reparace buněčných povrchů
- Tvorba vakuol



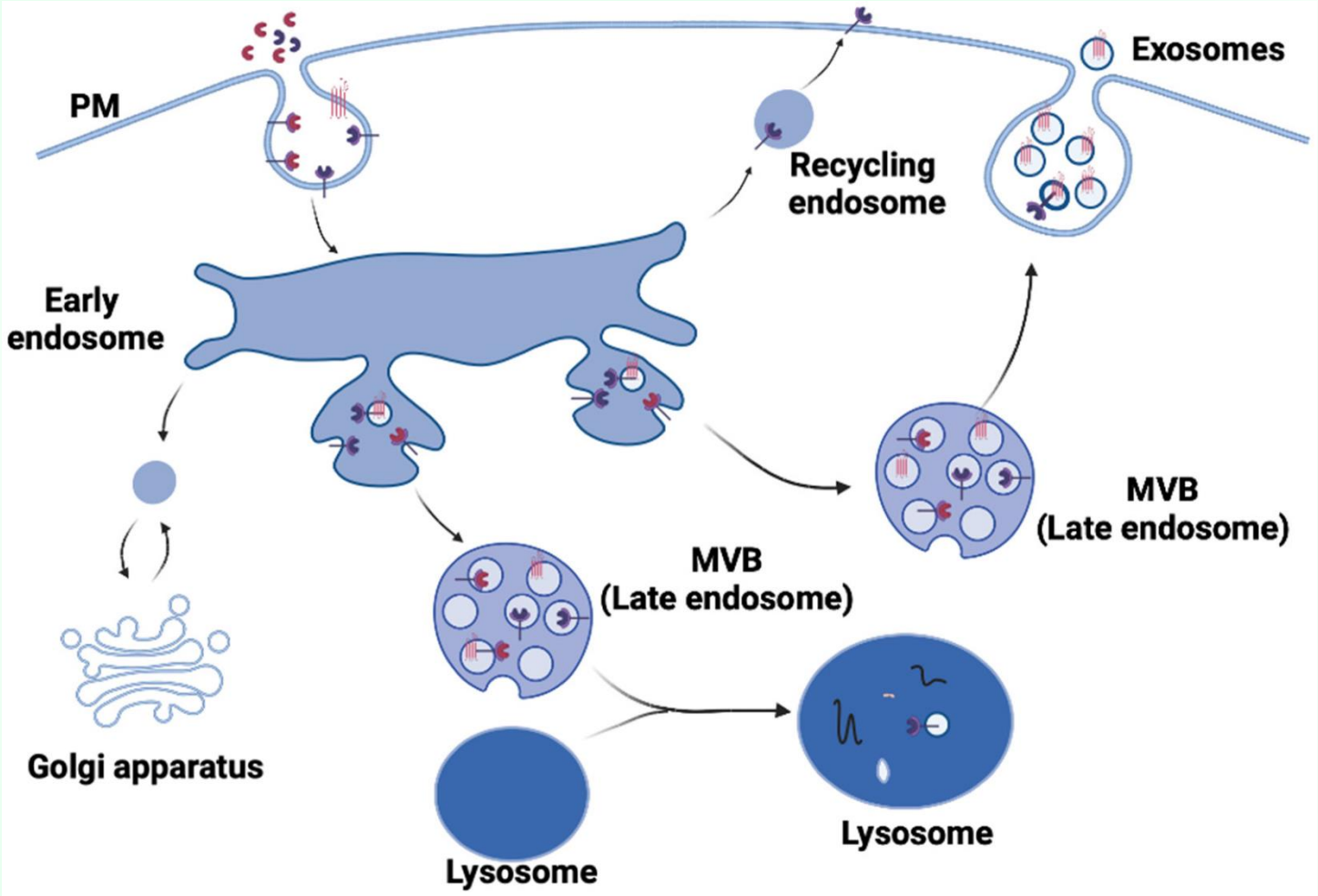


https://doi.org/10.1016/B978-0-444-63772-7.00017-8

MUNI PHARM

Exosomy, endosomy a lysosomy

- Organely/váčky s recyklační funkcí
- **Exosomy** – transportují materiál vně buňku
- **Endosomy** - transportují materiál do buňky
- **Lysosomy** – organely štěpící fagocytovaný obsah



https://doi.org/10.3390/ijms24021337

MUNI PHARM

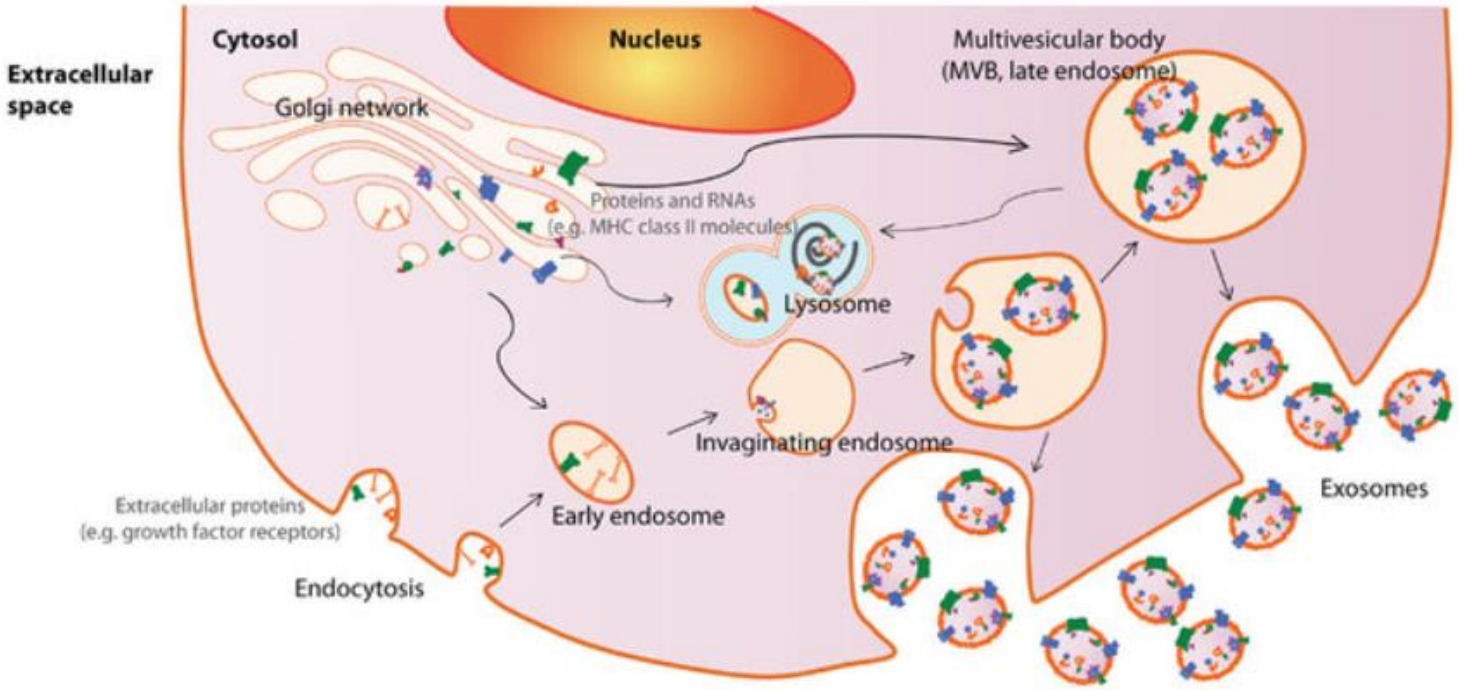


Figure 1: Exosome biogenesis and secretion. Exosomes are released by cells when intracellular organelles called multivesicular bodies (MVBs) fuse with the plasma membrane. MVBs are formed by invaginations of late endosomes, which contained molecules from the Golgi (e.g., MHC class II molecules) or the cell surface (e.g., growth factor receptors). Consequently, exosomes contain cytosolic materials and are enriched in endosome-associated protein markers such as the the Rab proteins, ALIX, TSG101, and MHC class II molecules or endocytic proteins, such as transferrin receptors and clathrins. This figure was modified from Lai et al. (169).

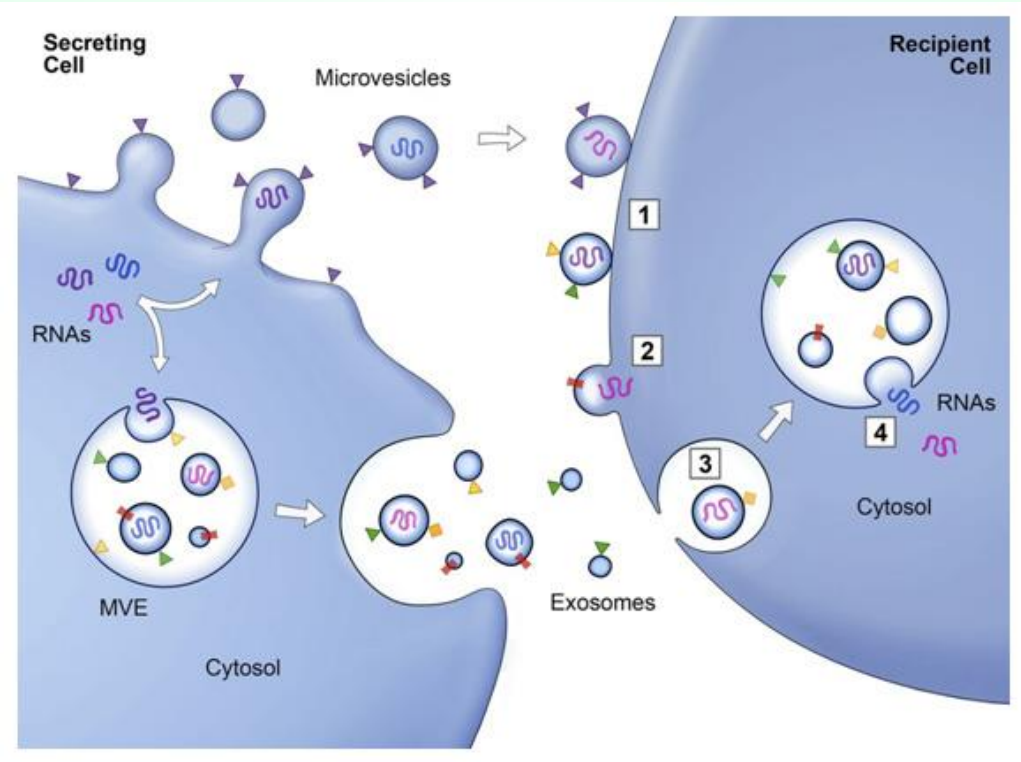
DOI: 10.3389/fimmu.2014.00518

MUNI PHARM

Exosomy – buněční popeláři

- Vezikuly, které pomáhají odstraňovat zplodiny buněčného metabolismu
- Vznikají splynutím buněčné membrány a vnitřních částí buňky

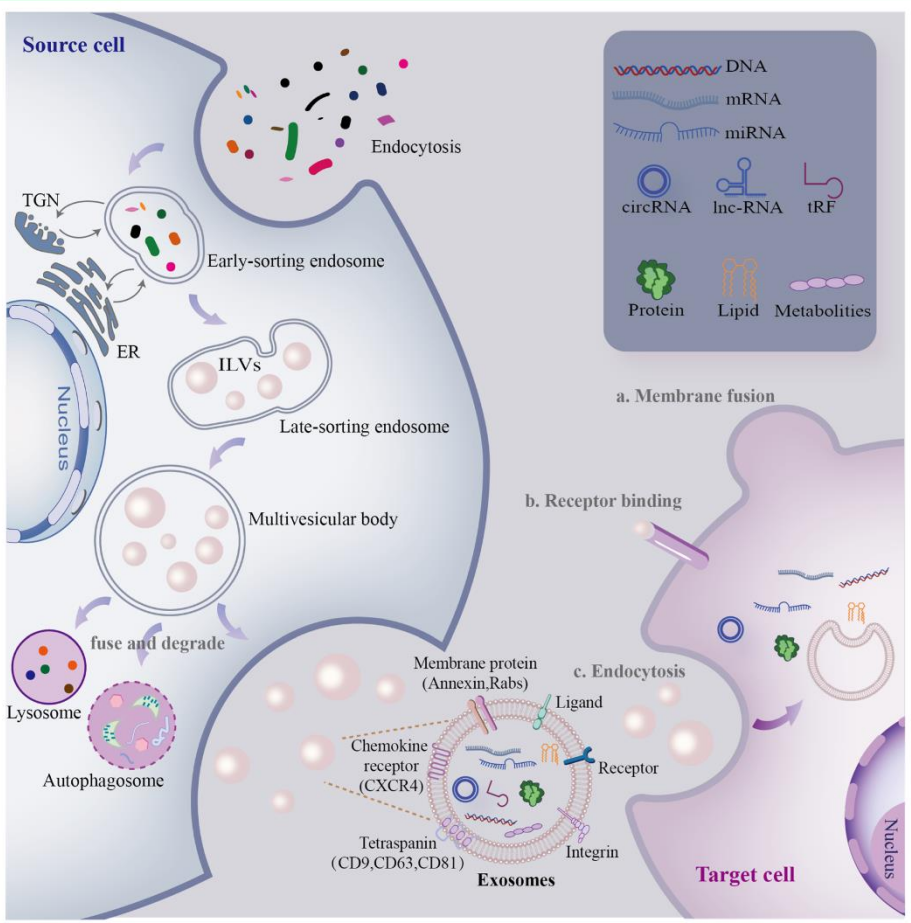
- **<u>Exosomy jsou součástí mezibuněčné komunikace</u>**



MUNI PHARM

Nové funkce exosomů

- Mohou mezi buňkami přenášet **proteiny, nukleové kyseliny, lipidy a metabolity**
- antigen prezentující buňky sdílejí patogeny, které jsou v exozómech zachyceny = zesílení imunitní odpovědi
- některé exozómy např. na svém povrchu vystavují Fas ligand, který po vazbě na Fas receptor (známý také jako „receptor smrti“), iniciuje apoptózu
- mRNA přenášená exozómem může být v cílové buňce přeložena do polypeptidu



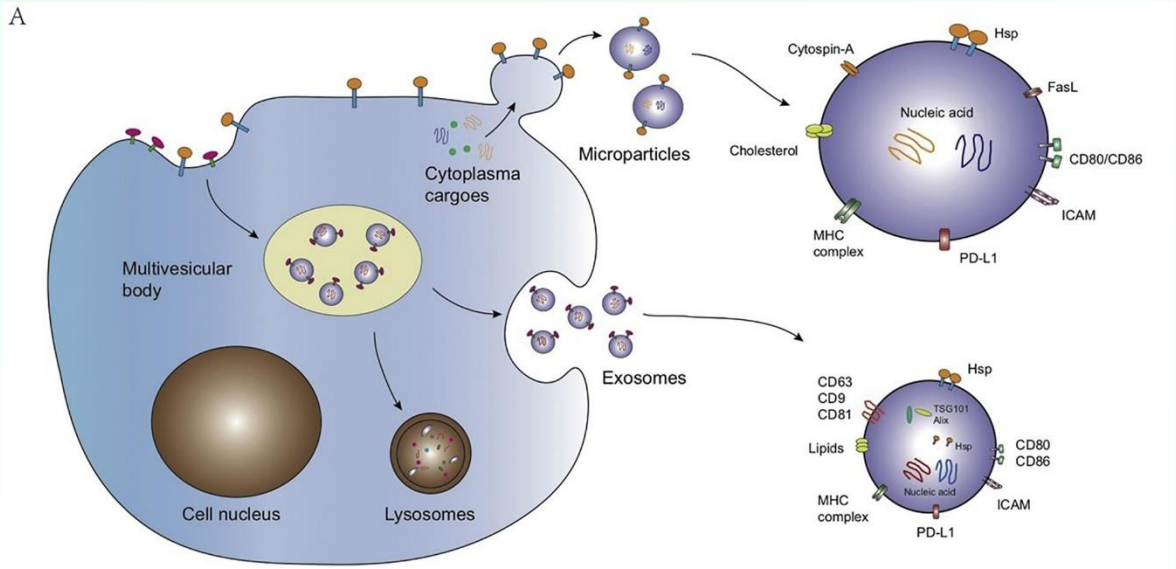
Biogenesis and secretion of exosomes. The secretion of exosomes involves two invaginations of the plasma membrane. Intercellular communication mediated by circulating exosomes occurs through endocytosis, ligand–receptor interaction, and membrane fusion. Components such as proteins, nucleic acids, lipids, and metabolites are delivered by exosomes from the source to target cells [33]. Proteins located in the plasma membrane, including CD63, CD9, CD81, TSG101, and Alix, are commonly used as markers for exosomes [26].

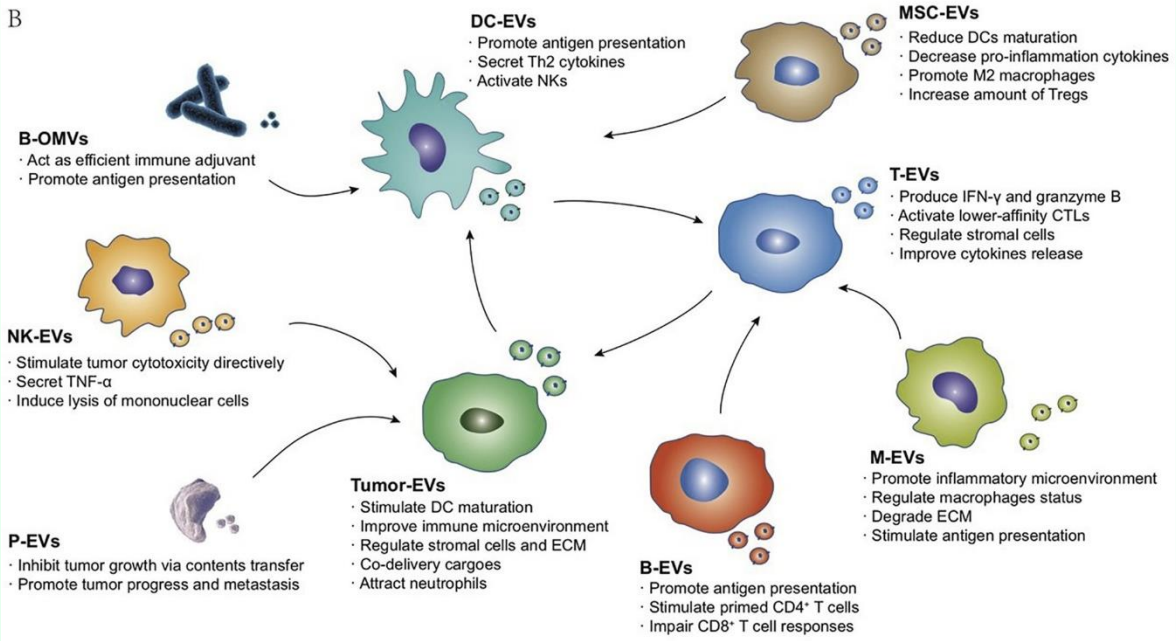
https://www.mdpi.com/2073-4409/12/2/311

MUNI PHARM

Exosomy jako nosiče léčiv pro imunoterapii nádorů

- Extracelulární exosomy a mikročástice imunitních buněk mohou ovlivňovat progresi nádoru





Highlights

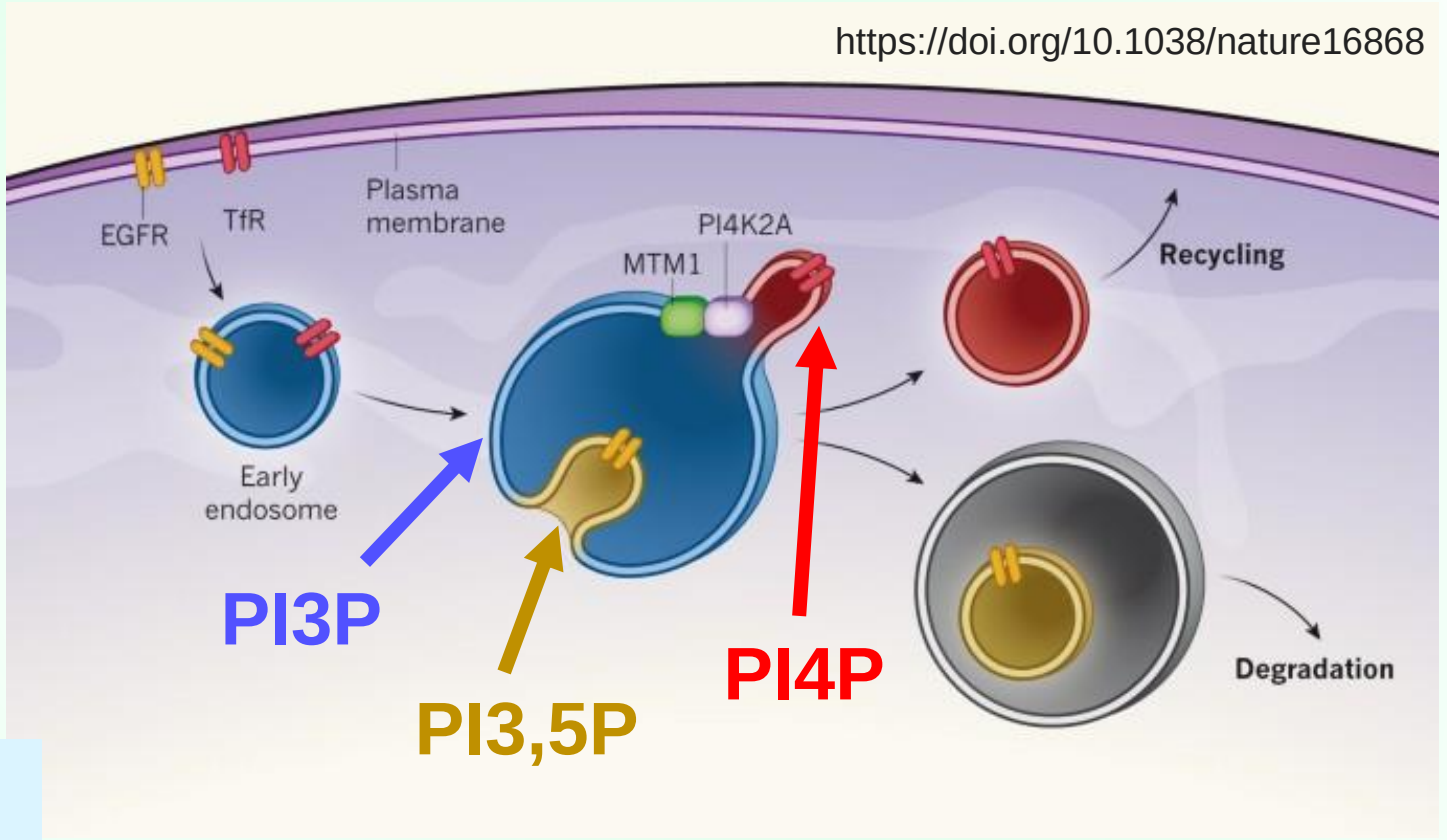
- Extracellular vesicles derived from diverse types of cells possess significant immunomodulation properties.
- Mechanisms of extracellular vesicles regulating tumor immune microenvironment contribute to excellent anti-tumor efficacy.
- Engineering modification of extracellular vesicles is an excellent approach for enhanced therapeutic effects.

https://doi.org/10.1016/j.jconrel.2020.09.028

Recyklace membránových proteinů

- Fosfolipidy plasmatické membrány a membránové proteiny mohou být recyklovány
- V **endosomu** jsou modifikovány fosfolipidy, které slouží jako značky pro recyklaci/degradaci

https://doi.org/10.1038/nature16868



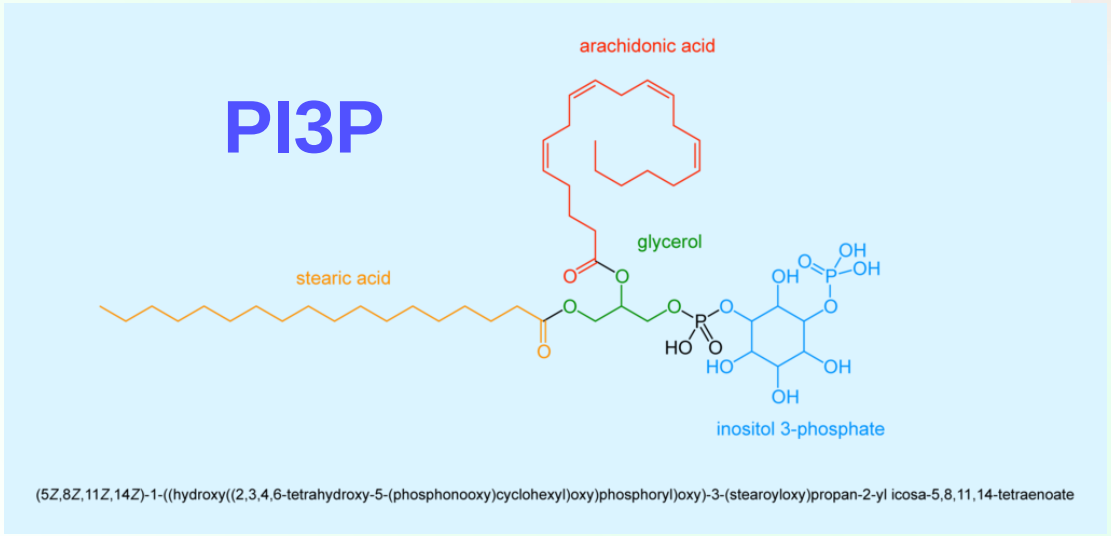
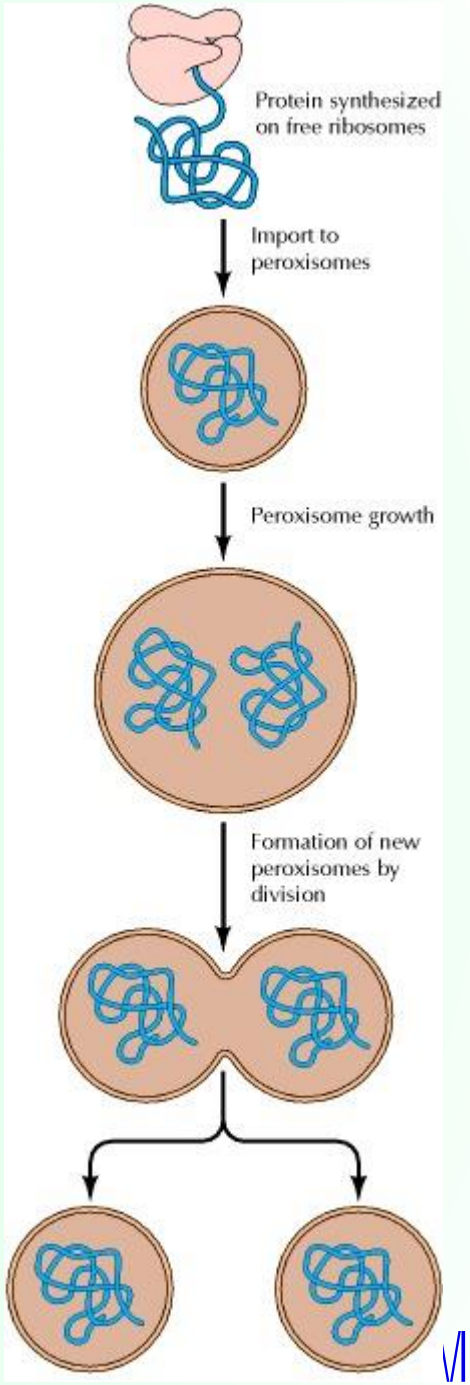


Figure 1 | Phospholipids direct membrane sorting. The proteins epidermal growth factor receptor (EGFR) and transferrin receptor (TfR) are removed from the cell surface in membranous structures called endosomes. The membranes of early endosomes contain PI3P (PI3P-containing membranes are indicated in blue) — a phospholipid of the phosphoinositide family that is tagged with a phosphate group at 'position 3'. As they mature, endosomes are sorted to determine the fate of the proteins they contain. In membrane regions such as those harbouring EGFR, PI3P is converted to $PI(3,5)P_2$ (yellow membranes), marking the region for degradation (the lipids present in the outer membrane of endosomes destined for degradation remain unknown). Ketel *et al.*[1] report that regions destined for recycling, such as those harbouring TfR, are modified by the sequential action of two enzymes. First, MTM1 removes the phosphate group from PI3P, then PI4K2A adds a phosphate group to position 4, generating PI4P (red membranes). The presence of PI4P directs the endosome back to the plasma membrane so that the proteins can be reused.

Peroxisomy

- Jenoduché organely schopné se sami „dělit“
- Proteiny se do peroxisomů dostávají z cytoplasmy, kde je tvoří volné ribosomy
- Funkce:
  - Oxidace různých substrátů → inaktivace toxinů, **beta-oxidace mastných kyselin**
  - Detoxikace kyslíkových radikálů (peroxid vodíku, superoxidy a epoxidy) → **kataláza**
  - Prvních kroky syntézy glycerolipidů či plasmalogenů
  - **Tvorba žlučových kyselin**, dolicholu a **cholesterolu**



https://www.ncbi.nlm.nih.gov/books/NBK9930/