CYTOLOGY

Premed 2018 - JU

◉ Sheet ○ Slides

Number

17

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We talked last time about actin filaments as a component of the cytoskeleton. In this sheet we are going to talk about second component which is:

Microtubules

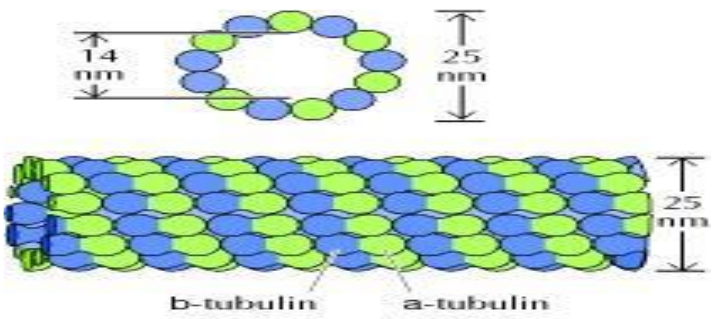
- Second principal component of cytoskeleton.
- They are rigid hollow rods.
- They are dynamic structures that undergo continual assembly and disassembly within the cell.

❖ Functions of microtubules:

1. Cell shape.
2. Cell movement (some forms of cell locomotion).
3. Intracellular transport of organelles.
4. Separation of chromosomes during mitosis (contribute to the end stages of mitosis).

❖ Structure of microtubules:

- As we said microtubules are hollow tubules that are small in size.
- Microtubules are composed of a single type of globular protein called tubulin.
- There are two types of tubulin monomer: α(a)-tubulin, β(b) -tubulin. They bind to each other to form tubulin dimer.
- These dimers are repeated several times, so if we take a cross section through a microtubule there will be alternation between a-tubulin and b-tubulin as shown in the figure below.
- In a circle there are 13 monomers, two of them of the same type meet at the end.
- y-tubulin: concentrated in the centrosome, initiates the microtubule assembly.

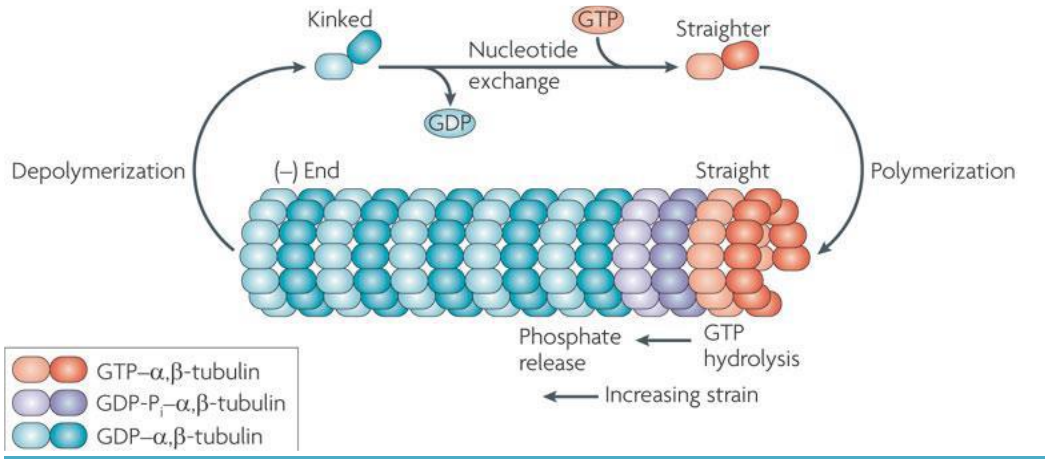


✓ Two differences between actin filaments and microtubules:

- Microtubules are hollow tubes, whereas actin filaments are continuous and condensed structures (there is no hollow inside).
- Microtubules have two types of monomers, whereas actin filaments have one type of monomers (G actin).

❖ Polymerization of tubulin

- It's very similar to the formation of actin filaments, but here we have binding of GDP and GTP to the monomers rather than ATP.
- Tubulin dimers polymerize to form protofilaments (head to tail arrays of tubulin dimers).
- 13 linear protofilaments assemble around a hollow core.
- Whenever the monomers are bonded to GTP, they favor polymerization. Whenever they are bonded to GDP, they favor depolymerization.
- For the depolymerization to occur, there is hydrolysis of GTP to form GDP. For the polymerization to occur, exchange of GDP to GTP happens (which is easier and lower energy-consuming than phosphorylation).
- Binding of monomers to GTP or GDP induces conformational changes. In the presence of GDP, there is weakening of binding affinity, the monomers form kinked structures that will not assemble in a mechanically strong structure. In the presence of GTP, they form straighter structures which bind and assemble in a stronger way.
- So, tubulin molecules are continually lost from the minus end, and replaced by the addition of tubulin molecules bound to GTP to the plus end.



- This indicates that the tubule is polar, having plus end (where the polymerization happens), and minus end (where the depolymerization happens).

- This polarity is an important feature of microtubules because it determines the direction of movement of vesicles and organelles along microtubules.
- Polymerization and depolymerization don't have to occur at the same rate (their length might change, and they can extend and shorthand).
- The difference between polymerization and depolymerization is going to be reflected in the treadmilling property.
- **Treadmilling**: it's the assembly and desassembly of microtubules.

Dynamic instability (Rate of polymerization-depolymerization)

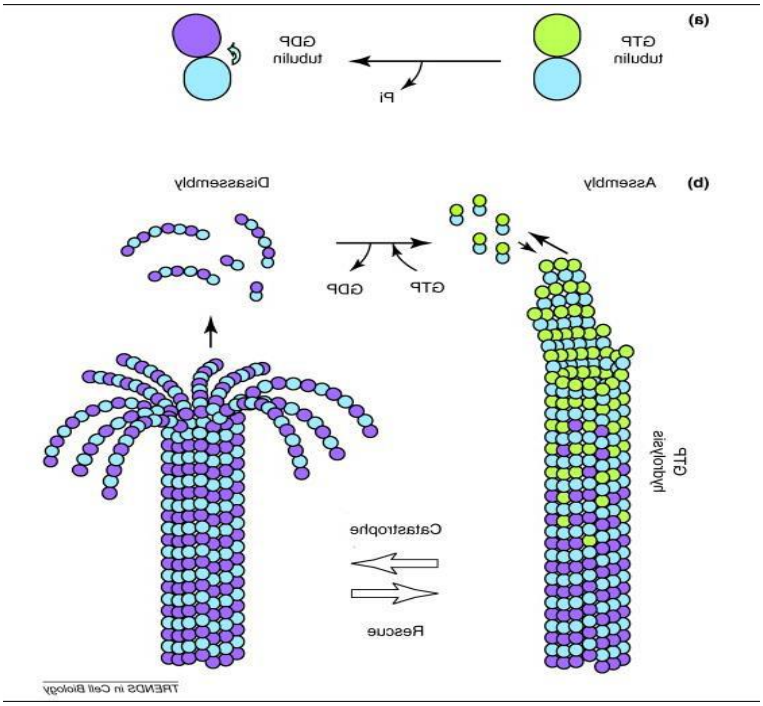
There might be more polymerization in comparison to depolymerization, and vice versa. (alternating cycles between growth and shrinkage).

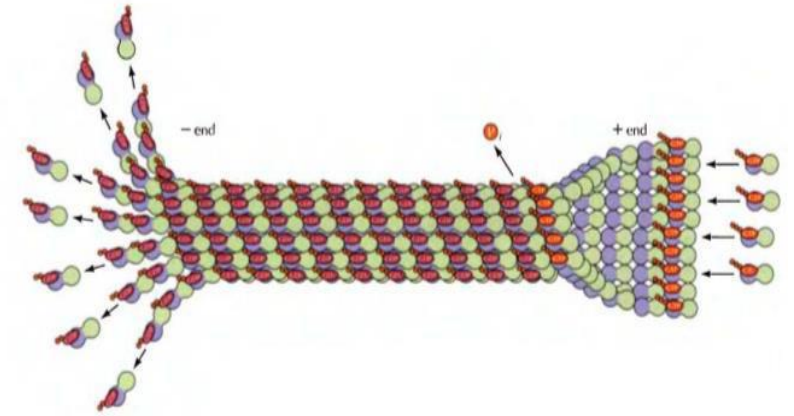
Growth or shrinkage is determined by the rate of tubulin addition relative to the rate of GTP hydrolysis.

In the state of more polymerization (GTP hydrolysis is slower than the addition of GTP-tubulin dimers). ➡ growth / rescue of microtubules.

In the state of more depolymerization (GTP hydrolysed at the plus end before new GTP-tubulin is added)

➡ catastrophe/ shrinkage





To prevent rapid depolymerization, the minus end is anchored to microtubule organizing center or centrosome.

- **Note:** The rate depends on the function of microtubules. For example: They might grow to carry out the separation of chromosomes in muscle cells. Also, they might be in treadmilling (constant length) if vesicles are going to move across them.

❖ Application: drugs that affect microtubule assembly

- If there is inhibition of microtubules assembly, then there is no movement and the cell will not divide.
- Drugs that make this assembly inhibition are used as treatment for cancer.

Examples:

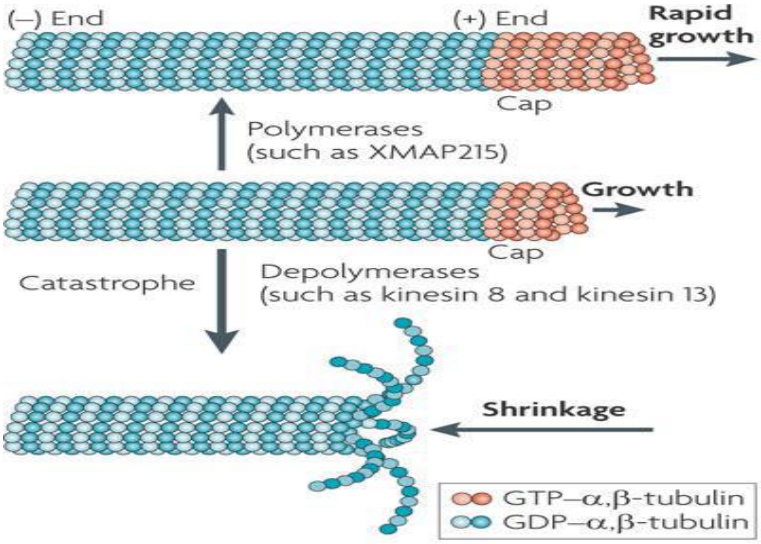
- **Vinblastine** and **vincristine** bind specifically to tubulin and prevent their polymerization to form microtubules resulting in inhibition of rapidly dividing cells.
- **Taxol** stabilizes microtubule and blocks cell division.
- **Colchicine** and **colcemid** bind tubulin, inhibit polymerization, and block mitosis. These are just experimental drugs (they are used for research purposes and not used as treatments).

❖ Regulatory proteins

- As there are different types of actin binding proteins that have different functions in actin filaments, there are also binding proteins for microtubules called **microtubule-associated proteins (MAPs)** such as:

- Polymerases that accelerates growth of at the plus end.
- Depolymerases stimulates shrinkage by accelerating the dissociation of GTP-tubulin from the plus end.
- Clasp, a MAP, prevents disassembly (catastrophe) and promote restarting growth (rescue).

IF IT WAS EASY, EVERYBODY WOULD DO IT!



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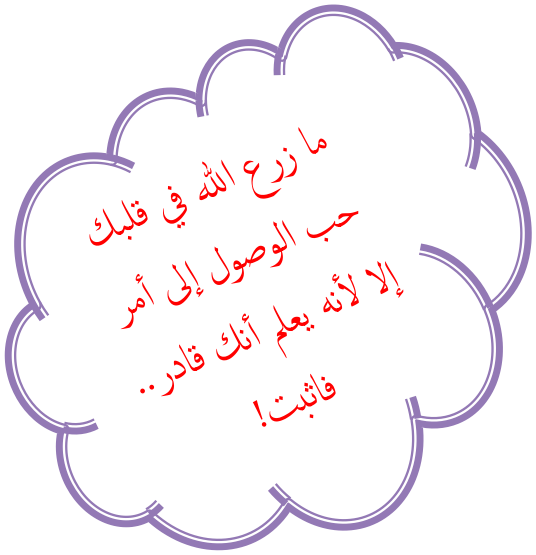
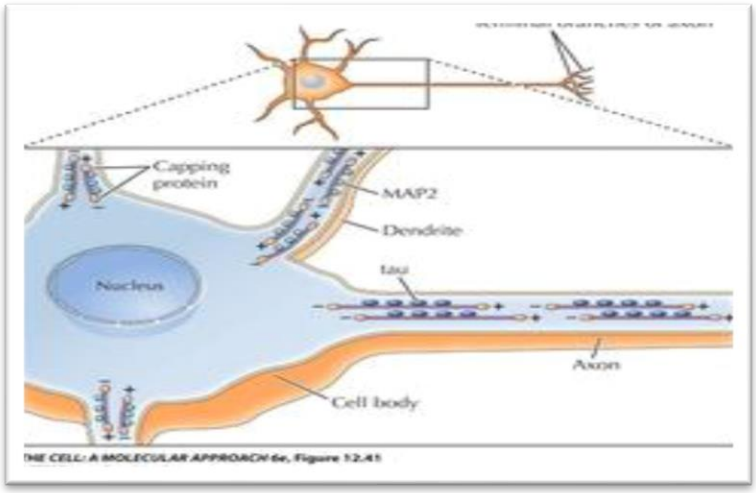
❖ Organization of microtubules within neurons

- An example of a cell is neuron which is composed of cell body, axon, dendrites and there are dendrites (projections) that come out from the cell body.
- **Axon** is long and carries impulses from the cell body to other cells (in forward direction), microtubules are oriented with their plus ends pointing toward the tip of the axon and the minus end toward the cell body.
- **Dendrites** are short and receive impulses from the cell body to other cell, microtubules are oriented in both directions.
- It is needed to transfer the messages from the cell body (where the nucleus and information are located) toward the axon and dendrites.

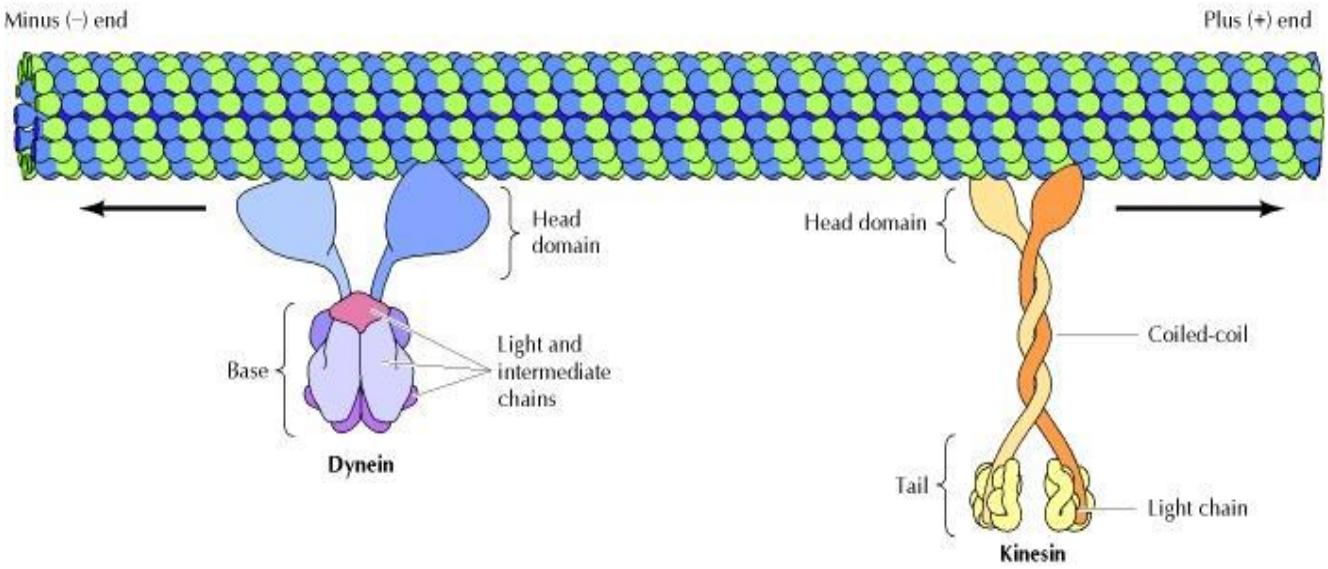




❖ Vesicular transport

- In addition to regulatory proteins, there are motor proteins that bind to the microtubules to perform specific functions. Their binding is temporary (through their movement).
- Motor proteins are used to carry vesicles and organelles along the microtubules to achieve regulation of this movement and to guarantee that these vesicles and organelles will reach the correct destination.
- Examples of motor proteins are kinesin and dynein, which differ in the direction of movement.

- The figure below illustrates the structure of them:



Dynein moves From **plus** end to **minus** end.

The head domain of dynein forms the ATP-binding motor domains that are responsible for movement along microtubules.

The basal portion of dynein is thought to bind to other subcellular structure, such as organelles and vesicles.

In neurons **kinesin** assists in transporting vesicles and organelles toward the end of the axon (From **minus** end to **plus** end).

It gets its energy from hydrolysis of ATP that is bound to the head domain that also binds to microtubule.

The tail portion binds to cell components, such as membrane vesicles and organelles.

Note: The movement of motor proteins requires energy in a form of ATP. Processing of binding, phosphorylation of ADP, hydrolysis of ATP into ADP, will cause conformational changes that may help in the release of vesicles.

- Light chain is the region where the vesicle or organelle is carried.

The role of kinesin and dynein in organelle organization:

1. **Kinesin**
   - kinesin pulls the endoplasmic reticulum toward the cell periphery.
     For example: in the UPR (unfolded protein response) kinesin perform the function of extension of the ER (because it moves from (-) end to (+) end).

- Kinesin positions lysosomes away from the center of the cell.
- Members of kinesin family control the movement of mitochondria.
  For example: after the fission of mitochondria it is used to distribute the high resulted number of mitochondria in the cytosol.

2. **Dynein**
   - Cytoplasmic dynein positions the Golgi apparatus in the center of the cell, (because it moves from (+) end to (-) end).

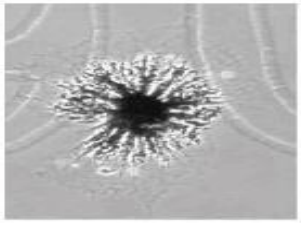
Both kinesin and **dynein** transport selective mRNA molecules in cell.

❖ Stimulated movement

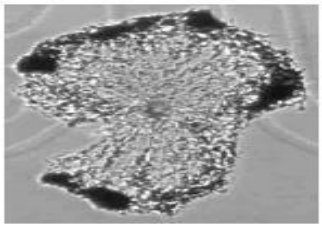
- Organelles often have both types of motors on their surface, allowing cells to adjust their position.
- In the summer, in response to **the presence of light**, the skin gets darker colors, because there is transfer of pigment organelles (**melanosomes**) from **melanocytes** that position these pigments in the center of the cell, toward the **keratinocytes** which are present in the periphery of the cell.
- This transfer is carried out by **kinesin**, this makes sense because when the vesicle is moving toward the periphery of the cell it's moving from (-) end to (+) end, this movement is carried out by kinesin.

- **In the absence of sun light**, the skin gets back its lighter color, because the **melanosomes** return from **keratinocytes** in the periphery toward the **melanocytes** in the center of the cell (from (+) end to (-) end), this transfer is carried out by **dynein**.

- This movement is stimulated by light and not by a chemical substance.



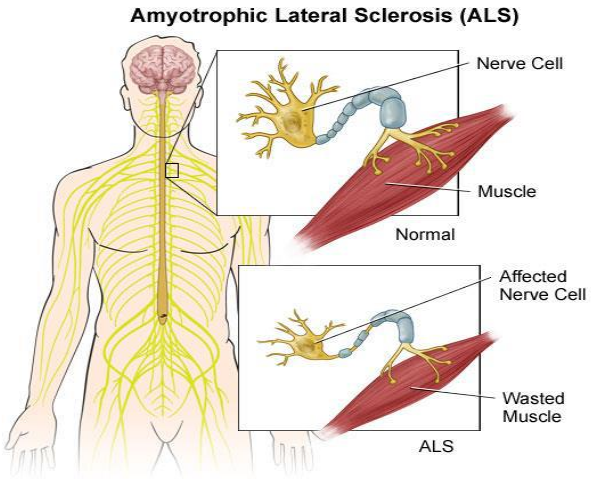
In the absence of light



In the presence of light

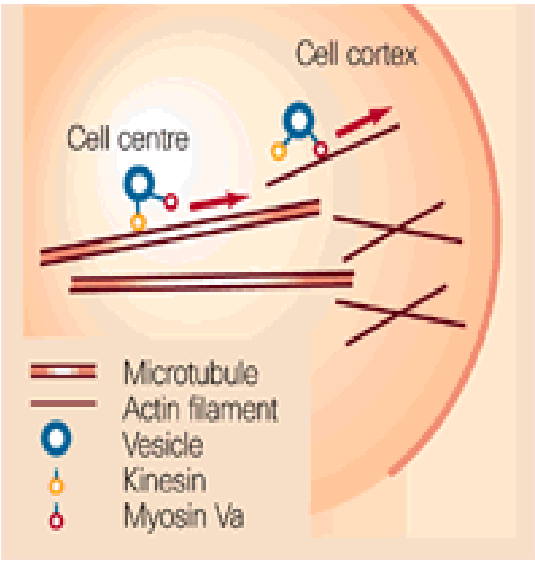
❖ Application: kinesin and diseases

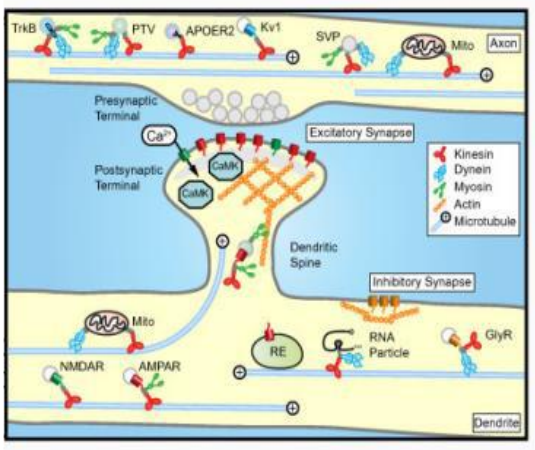
- Different mutations of keratin cause different diseases, mostly these diseases are related to nervous system.
- Mutations in certain kinesin proteins reduce the ability of neurons to move essential organelles from their cell bodies to their axons leading to neurodegeneration, such as Amyotrophic lateral sclerosis (ALS).
- Mutations in kinesins lead to peripheral neuropathies, such as Charcot-Marie-Tooth disease.



❖ Changing horses in midstream

- Once the final destination of motor proteins and the vesicles is very close to the plasma membrane, or there is secretory vesicle that is going to be secreted out of the cell, the motor proteins are going to be changed closely to the plasma membrane, and the cargo is transferred to the other motor protein. This is what is meant by changing of horses.
- After this changing the vesicle might fuse with the plasma membrane
- For example, **kinesin** might be changed to **myosin**.
- Myosin is a protein that is existed underneath the plasma membrane and can act as motor protein in addition to its contribution in muscle contraction.
- Myosin as a motor protein doesn't move across long distances, it transports organelles over shorter distances compared to kinesin and dynein.





- So, as shown in the figure above, Kinesin and myosin transport organelles from the center of the cell toward the periphery, where myosin takes over moving organelles near the plasma membrane.

THANK YOU ALL ❤ GOOD LUCK^_^

فلنقم كلنا للدواء والقلم.. كلنا عطف على من يصارع السقم

ولنواصل المسير نحو غاية أهم.. ونكون حقًا خير أمة بين الأمم

نقضي ساعات طوال نستقي علم العجم.. نستهين كل غال كي نحقق الحلم

إن سئمنا لا نبالي بل نسير للأمام.. إن قمة الجبال تستحق لا جرم