ZOO-302CR:(1.3)CYTOSKELETON

The cell. 1. Cell diversity. Atlas of Plant and Animal Histology
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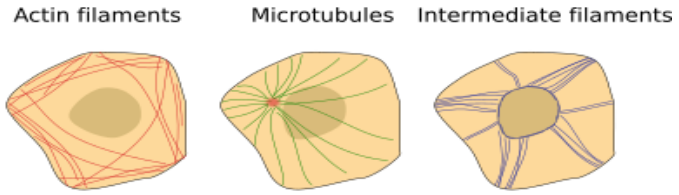
Cytoskeleton is composed of filaments of proteins with a number of functions: cell integrity, motility, organization, division, etcetera.
There are three types of filaments:

- Microfilaments or actin filaments
- Microtubules
- Intermediate filaments

The nucleus and the rest of the organelles are not randomly scattered through the interior of eukaryotic cells. Indeed, there are an internal organizationmainly ruled by several types of proteins arranged in filaments, jointly known as cytoskeleton. These filaments form a dynamic scaffolding distributed through the cytosol, although some of them are found inside the nucleus. Cytoskeleton is particularly important in animal cells because plasma membrane, which basically is a sheet of lipids, would break easily without the anchoring to cytoskeleton filaments. Plant cells, however, are protected by the cell wall. The word cytoskeleton may lead to misunderstand the function of these filaments because they do not only work as a structural scaffold for the cell and organelles, but they are also the"muscles" of the cells. In this regard, cytoskeleton allows cell movement and sets the shape of the cells, determines the internal organization of the organelles, allows the communication between organelles (vesicular traffic), exocytosis and endocytosis, and cell division (both mitosis and meiosis). At the same time, it withstands mechanical loads and cell shape deformations, and determines the cell size of animal cells. Cytoskeleton was invented by eukaryotic cells during evolution, although homologous proteins have been found in prokaryotic cells.



Organization of the three main components of the cytoskeleton in animal cells. Actin filaments are found near the plasma membrane, microtubules are organized radially from the centrosome, and intermediate filaments are anchored to cell junctions and some of them being found inside the nucleus. The general organization of the cytoskeleton may change depending on the cell type and physiological state. In plant cells, the organization of cytoskeleton is completely different than in animal cells.

Cytoskeleton is composed of three types of filaments: actin filaments or

microfilaments, microtubules, and intermediate filaments.Actin filaments, polymers of repeated units of actin protein, are in charge of cell movements, endocytosis, phagocytosis, cytokinesis, and more. They also are part of the molecular machinery needed for muscle contraction, and contribute to form some cell junctions (adherent junctions and tight junctions). They are named as microfilaments because their diameter is lower than those of the other cytoskeleton components. Microtubules, as the name suggests, are tubules made up of dimers of α- and βubulin. Microtubules are needed for the intracellular movement of organelles and vesicles, constitute the skeleton of cilia and flagella, drive the chromosome segregation during cell division, etcetera. Actin filaments and microtubules are used by motor proteins, which are able to carry cargoes using these filaments as rails. Cargoes may be chromosomes, organelles, or macromolecular complexes.Intermediate filaments are responsible for the cell integrity, since they function as intracellular strong cables anchored to cell junctions such as desmosomes and hemidesmosomes. They make possible the adhesion between contiguous cells and cell-extracellular matrix, contributing to the cohesion of tissues. They are specialists in withstand mechanical forces. Unlike the other components of the cytoskeleton, intermediate filaments are polymers that can be made up of different families of proteins, such as keratins, vimentins, laminas, etcectera.

ACTIN FILAMENTS

Actin filaments, also known as microfilaments, are one of the cytoskeleton components.
Actin filaments are made up of actin proteins.
Actin filaments are polarized structures. They have one plus end and one minus end.
Actin associated proteins modulate the organization and polymerization of the actin filaments.
Functions: cell movement, cell shape, vesicular traffic, cytokinesis, they form microvilli, etcetera.

Actin filaments are one of the cytoskeleton components. In animal cells, actin filaments are located close to the plasma membrane arranged in a cortical scaffolding that supports the plasma membrane. In plant and fungal cells, the cell wall protects the plasma membrane so that the distribution of actin filaments in the cytosol is different.

Actin filaments are built by polymerization of actin proteins, which can be found in two isoforms: alpha- and beta-actin. Beta-actin is the most frequent isoform and is found in most of the animal cells. The amino acid sequence of beta-actin is slightly different from alfa-actin, which is abundant in muscle cells. Actin is a very abundant protein in the cytosol, approximately 10 % of the total cytosolic protein content. From the total cytosolic actin protein pool, some are found as part of the actin filaments (which is known as F-actin), and the remaining is free in the cytosol (known as G-protein). The proportion of F-actin and G-actin may change depending on the

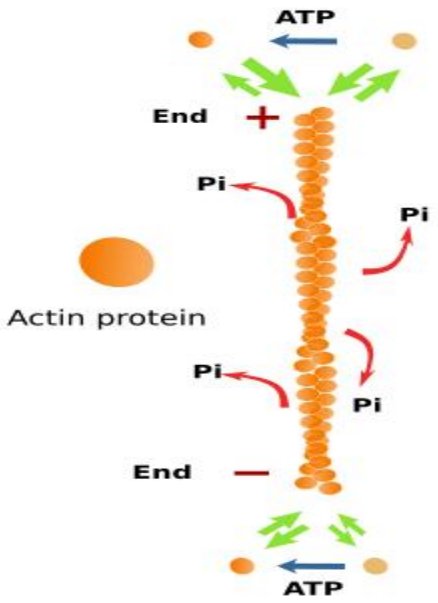
physiological state of the cell, so that the number and length of the actin filaments change by polymerization and depolymerization. Without actin, cells cannot divide, move, do endocytosis, or phagocytosis.

Great deal of knowledge about actin filament function has been provided by pathogens. Pathogen manipulation and eukaryotic cell mutants have helped to uncover many of the functional aspects of actin filaments.

Common organization of actin filaments in eukaryotic cells in culture.

Structure

Actin filaments are 7 μm in thickness. This is lower than the thickness of the other cytoskeleton filaments, microtubules and intermediate filaments. That is why actin filaments are also known as microfilaments. Every actin filament has a minus end and a plus end, which means that they are polarized filaments. This is because of the ordered disposition of the actin proteins in the filament, they are assembled keeping the same orientation. In the plus end, the polymerization, adding new actin proteins, is more frequent than depolymerization, whereas in the minus end depolymerization is more frequent. The increase and decrease in the microfilament length is by polymerization and depolymerization, respectively. In the cell, these changes are happening all the time, as well as nucleation and complete depolymerization of microfilaments. Actin filaments are the most dynamic component of the cytoskeleton. However, the concentration of free actin proteins in the cytosol is not enough to spontaneously assembling of actin filaments. Thus, the formation of new microfilaments is driven by protein complexes such as Arp2/3 and formins. Arp2/3 proteins work as nucleationsites for new microfilaments, whereas formins stabilize transient spontaneous associations of actin proteins, boosting the formation and elongation rate of microfilaments. This control of microfilament formation and elongation is very useful for the cell because new microfilaments are formed when and where they are needed.



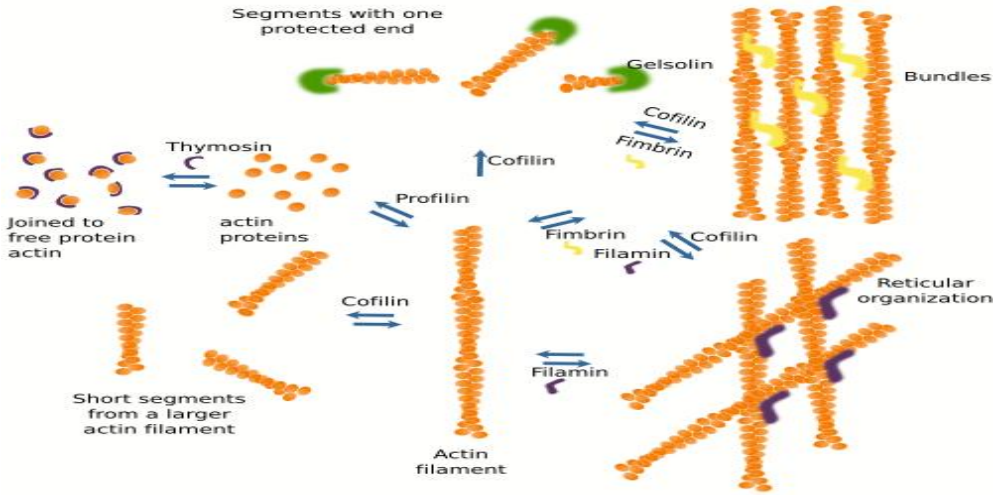
An actin filament is depicted. It is showing the helicoidal arrangement of actin proteins. Microfilaments are polarized structures with two ends (minus and plus ends), which show different polymerization and depolymerization rates. Free ATP-actin proteins are prone to join to the microfilament by polymerization. After some time of being part of the filament, the ATP will be hydrolysed to yield ADP-actin proteins. The ADP-actin form constitutes most of the filament. (Modified from Pollard and Earnshaw, 2007).

Actin filaments are more abundant, shorter, and more flexible than microtubules (see next page). One of the more salient features of the actin filaments is that they are highly adaptable: are formed and removed easily, and are associated between each other in many ways to form 3D scaffolds. This versatility relies on more than 100 different modulator proteins or actin associated proteins. These proteins influence the filament polymerization and depolymerization rates, nucleation of new filaments, destruction of existing filaments, as well as 3D organization. Actually, there is no naked actin filaments or free actin proteins in the cytosol, but they are always linked to some associated protein.

Proteins associated to actin filaments can be divided in different categories. A) Affecting polymerization. Some proteins, such as profilin, join free actin (G-actin) and boost actin filament polymerization. Other proteins, such as thymosin, join free actin proteins and hamper the polymerization process by preventing the spontaneous polymerization of actin filaments. B) There are modulator proteins, such as fimbrin and alfa-actinin, which make cross-bridges between actin filaments to form bundles of actin filaments, whereas other proteins make possible the arrangement of actin filaments in reticular structures. C) Some actin binding proteins, such as cofilin, katanin, and gelsolin, break and reorganize the actin filaments. D) There are also proteins that are intermediaries between actin filaments and other proteins. For example,

tropomyosin mediates interaction between actin filament and myosin in the muscle cells. E) Some proteins are in charge of anchoring actin filaments to other cellular structures like membranes and other components of the cytoskeleton.

There are additional elements that affect the action of actin associated proteins on the behavior of actin filaments, such as calcium concentration, activity of Rho-GTPases, presence of lipids, and higher or lower gen expression of their genes. There are also drugs that influence the polymerization of actin filaments. For example, cytochalasin inhibit polymerization, whereas phalloidin inhibit depolymerization.



Polymerization and depolymerization of actin filaments are under the control of many actin associated proteins. In this image, several organizations of actin filaments are depicted, as well as the actin associated proteins that influence these arrangements. (Modified from Pollar and Earnshaw, 2007).

Functions.

Cell movement. Cells do not swim, they crawl through the tissues, as do, for example, the embryonic cells during development, amoeba when moving around, lymphocytes when heading toward damage tissues, and the growth cone of neurons when searching for their targets. For cell movement, several steps are needed: production and extension of cytoplasmic protrusions, adhesion of these protrusions to some elements of the environment, and drag the rest of the cell toward these anchoring points. The cellular protrusions are known as podia, lamellipodia when they are sheet-like, filopodia when they are thin and long, and lobopodia when they are thick and tubular. When cells are treated with cytochalasin, a polymerization inhibitor of actin filaments, protrusions disappear and cells stop moving. This indicates that actin has a prominent role in protrusions formation. Actually, it is known that it is the actin polymerization what pushes plasma membrane outward and forms the protrusions. Nucleation of actin filaments by Arp 2/3 is very important during the lamellipodia formation. When these protrusions make physical contact with an extracellular

element, either extracellular matrix molecules or other cell, adhesion proteins located in the plasma membrane establish anchoring points. Once the cell makes an adhesion contact, intracellular actin filaments, together with the motor protein myosin, help to move all the intracellular content toward the anchoring points.

Intracelular movement. Organelles are moved through the cytoplasm individually, and also in groups when the cellular shape is changed. Actin filaments, together with myosin motor proteins, help with the organelle movements. This role is very important in plant cellswhere most of the internal movements of organelles are carry out by actin filaments, whereas microtubules are the main responsible for these movements in animal cells. Myosin motor proteins walk along the actin filaments propelled by the energy of ATP. There are two main types of myosin: I and II. Myosin I protein contains a globular structure, known as head, that binds to actin filaments, and a tail that selects the cargo to be transported. By means of conformational changes, the head is able to move along the actin filament, dragging the cargo. Myosin I is found in most of the eukaryotic cells and may transport some organelles, but it can also produce deformations of the cellular periphery, such as protrusions.

Myosin II is a family of proteins mainly found in muscle cells, although it is also present in other type of cells. This protein has two heads, with motor activity by using ATP, and a tail. Myosin II usually appears in couples linked by their tail. In muscle cells, many myosin II molecules are joined together to form the myosin filaments, known as thick filaments, where every myosin II protein is oriented with the head toward one of the ends of the filament and the tail toward the middle part of the filament. Thus, there are tails forming the compact part of the filament and heads protruding at the surface. In this way, those actin filaments in contact with a myosin filament are always dragged toward the middle part of the myosin filament. This process is the molecular mechanism for muscle contraction and animal movement. In the smooth muscle, the interaction between actin filaments and myosin filaments is mediated by phosphorylation of myosin heads. In this way, all the process of dragging actin filaments by myosin is slower because kinases are needed.

Sometimes, actin filaments are able to move organelles in a weird way: a short actin filament becomes attached to an organelle by one of its ends and the polymerization (elongation) of this filament pushes the organelle through the cytosol.

Endocytosis and phagocytosis.In animal cells, actin filaments are usually located close to the plasma membrane, in the so-called cellular cortex or periphery, although they are also found in inner places of the cell. The peripheral localization is suitable for participating in endocytosis and phagocytosis. Formation of vesicles in the plasma membrane is not accomplished if the actin filaments are inhibited. Furthermore, the cellular protrusions, needed during phagocytosis to engulf particles, depend on the actin filaments polymerization.

Cytokinesis. The final constriction of the cytoplasm during cell division is

produced by a ring of actin filaments that, helped by myosin motor proteins, gets progressively smaller in diameter until the complete separation of the cytoplasm of the two new cells. This process is mediated by type II myosin.

Membrane domains. Actin filaments may influence the lateral movement of proteins of the plasma membrane by acting as physical barriers, like fences, on the cytosolic face of the plasma membrane. In this way, actin filaments are able to delimitate areas where the movement of the proteins are confined, and hamper long lateral movements by diffusion.

Microvilli. Microvilli are filiform expansions of apical part of some cells, particularly abundant in epithelial cells, where they increase the surface of the plasma membrane (more than 30 %). For example, they can be found in the epithelium of the gut and in the proximal tube of the nephron. Every of these little expansions or microvillus are 1 to 2 µm height and around 0.1 µm thick. They contain several dozens of actin filaments oriented parallel to the longitudinal axis of the microvillus. These filaments are interconnected by proteins like myosin, fimbrin, and vilin, and together form a strong scaffold. Furthermore, thanks to other intermediary proteins, the actin filaments are anchored to the plasma membrane. At the base of microvilli, in the peripheral cytoplasm, there is a net of proteins known as terminal web, which is composed of actin filaments, spectrin, myosin II and tropomyosin. The terminal web connects the actin filament of every microvillus between each other and stabilizes the whole set of microvilli.

M I C R O T U B U L E S

Microtubules are a component of the cytoskeleton, made up of many dimers of α- and β- tubulin proteins.

Microtubules are polarized filaments where polymerization and depolymerization of the microtubule alternatively occur, process known as dynamic instability.

Microtubules are mainly nucleated by protein complexes known as γ-tubulin rings.

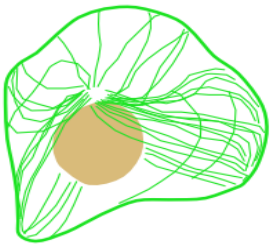
In the animal cells, γ-tubulin rings are located in the pericentriolar material of the centrosome. In plant, they can be found at different locations of the cell.

Microtubules are involved in a number of cellular functions such as intracellular organization of the cytoplasm and the cell division. These jobs are done with the help of motor proteins: dyneins and kinesins.

Cilia and flagella have microtubules for structural support and movement (helped by motor

proteins).

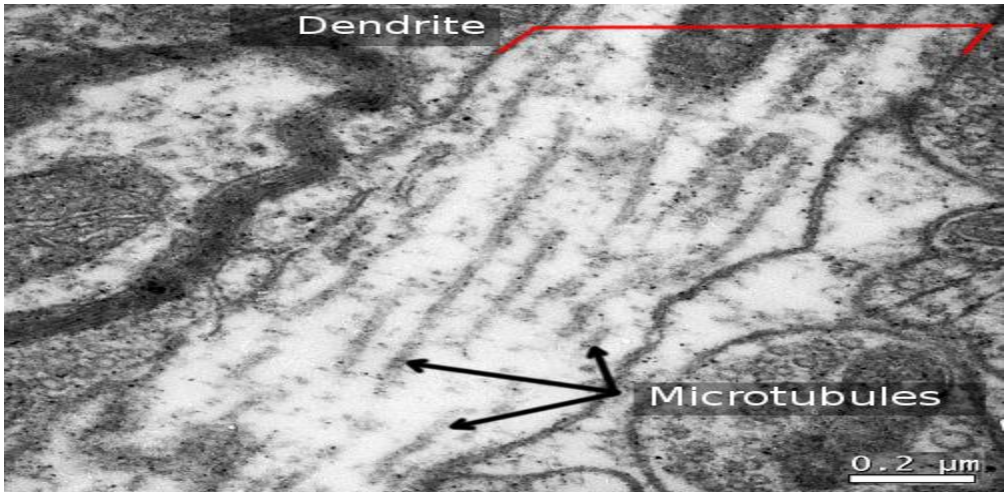
Microtubules are a component of the cytoskeleton involved in the organization of the eukaryotic cell cytoplasm. They carry out many functions, such as the spatial organization of organelles, work as tracks for vesicular trafficking, are needed for cell division since they form the mitotic spindle, help with the cell movement, and are the skeleton of cilia and flagella.



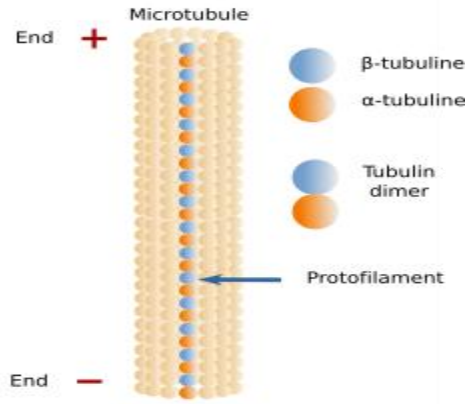
Organization of microtubules in an animal cell in culture.

Structure

Microtubules are long and relatively stiff tubules. Their wall is made up of many dimers of globular proteins: α- and β-tubulin, which are lined up in long rows known as protofilaments. Within a protofilament, there is no chemical bonds between adjoining tubulin dimers. A microtubule is usually composed of 13 protofilaments. α- and β-tubulin pairs are oriented in the same way, so that there is always α-tubulin in one end of the protofilament and β-tubulin in the other. Thus, microtubules are polarized structures. The end formed by α-tubulin is known as minus end, and that formed by β-tubulin is known as plus end. Microtubules are dynamic structures, which means that there is a continuous gain and lost of tubulin dimers, i.e. polymerization and depolymerization, respectively. New tubulin dimers are mainly added to the plus end, where the growth of the microtubule usually happens, although depolymerization also occurs. In the minus end, depolymerization prevails over polymerization. In this way, microtubules growth occurs at plus end, whereas shrinkage occurs at the minus end. That is why the minus end is usually protected against lost of tubulin dimers. However, plus end is very dynamic, and polymerization-depolymerization alternancecommonly happens, sometimes so intense that the microtubule may disappear by a complete depolymerization.



Transmission electron microscopy image showing microtubules inside a dendrite of a neuron. Microtubules are oriented parallel to the long axis of the dendrite.

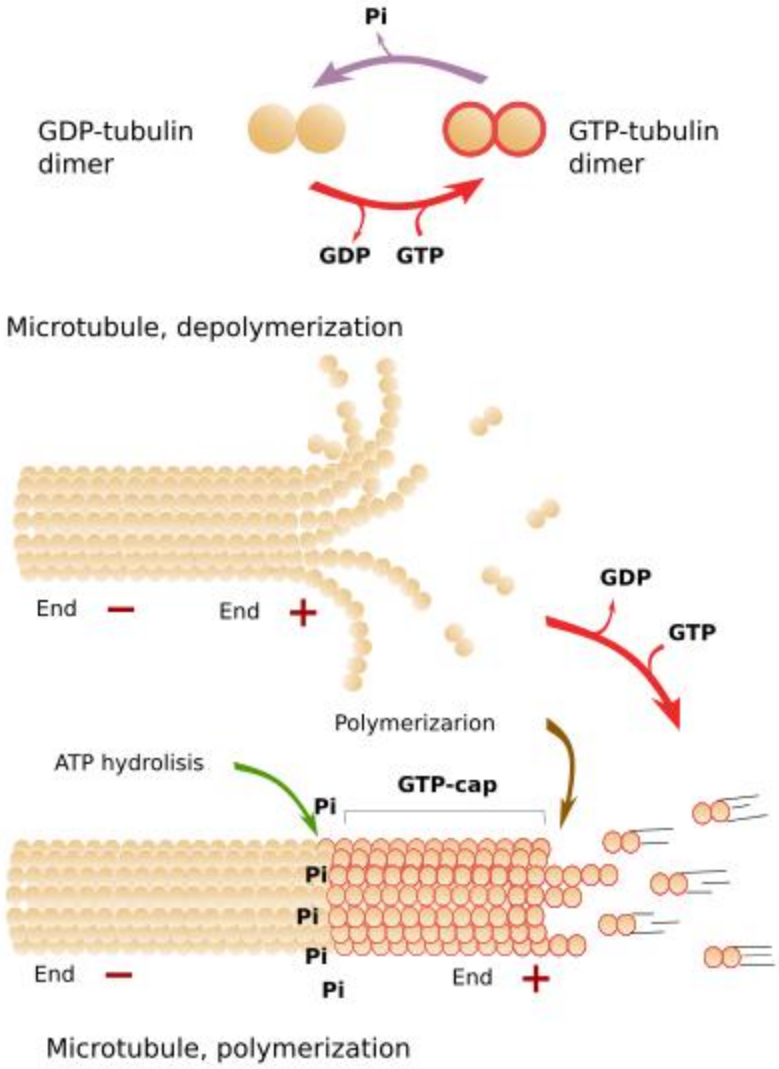


Organization of the tubulin dimers inside one protofilament. Note that α-tubulin is oriented to the minus end, whereas β-tubulin is the plus end.

Microtubules undergo a continuous polymerization and depolymerization, mainly happening in the plus end. In fibroblasts, half of the available tubulin is free in the cytosol, and the other half are microtubules. This situation is quite different from that of the intermediate filaments, where most of the proteins are in the filaments. In microtubules, there is a continuous interchange of tubulin dimers between the microtubules and the cytosol, which becomes important when cell has to change the spatial arrangement of microtubules.

Dynamic instability

Once a microtubule has been nucleated, the growing in length is by addition of new tubulin dimers to the plus end. The growth is stopped from time to time, and growth periods are alternated with shrinkage periods. The depolymerization is sometime so fast that the complete microtubule may disappear. But, it is most frequent the restarting of a new polymerization period. This alternance happens in most of the plus ends of cytosolic microtubules, and it is known as dynamic instability. How is the molecular process?



In this image, GTP- and GDP-tubulin dimers are depicted. In the cytosol, GDP-tubulin dimers are transformed in GTP-tubulin dimers, whereas the opposite process occurs in the so-called hydrolysis zone of the microtubule wall. A microtubule shrinks when GDP-tubulin dimers are part of the plus end (there is no GTP cap), whereas it grows when GTP-tubulin dimers constitute the plus end (there is GTP cap).

Free tubulin dimers have a GTP molecule linked to the β-tubulin. Sometime after the joining of tubulin dimer to the plus end of a microtubule, GTP is hydrolyzed to ADP and inorganic phosphate (Pi). However, the hydrolysis is not inmediate. If the rate of adding tubulin dimers to the plus end is faster than the hydrolysis rate, there will be always a group of tubulin dimers with GTP in the plus end, which is known as GTP-cap. GTP-cap stabilizes the plus end of the microtubule and boosts the polymerization. The addition, polymerization, of new tubulin dimers depends on many aspects and may be different in different parts of the cytosol, where the plus end may be located. If the addition rate is low, the hydrolysis rate may overcomes the polymerization speed. This means that there are ADP-tubulin dimers at

the plus end, which form non so stable protofilaments. In this situation, depolymerization starts, and ADP-tubulin dimers are released to the cytosol. In the cytosol, ADP-tubulin dimers are quickly phosphorylated to GTP-tubulin dimers, which are ready to join to a microtubule plus end. If the polymerizaation rate increases, the GTP-cap will be formed again and elongation of the microtubule restarts.

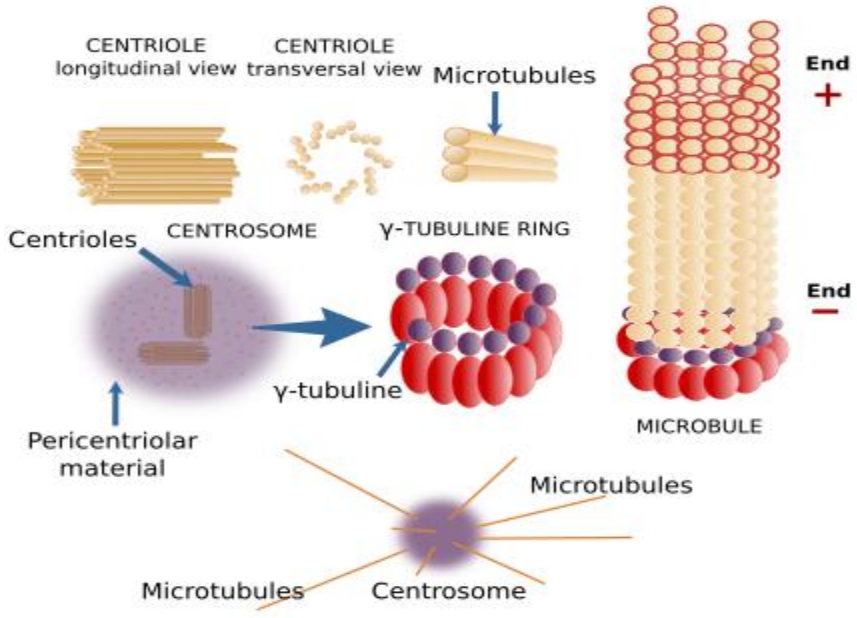
MAPs

As occurs with other cytoskeleton filaments, there are microtubules associated proteins(MAPs). They regulate the polymerization and depolymerization, stability, as well as 3D organization of the cellular scaffold of microtubules. MAPs usually interact with the microtubule plus end, affecting the dynamic stability, either by boosting growth or depolymerization. For example, XMAP215 and EB proteins favour the polymerization by stabilizing tubulin dimers in the microtubule plus end. Katanin develops a more drastic action because it breaks the microtubules down into pieces, which are quickly depolymerized or may function as seeds for new microtubules. MAPs also allow microtubules to interact with other cellular elements such as organelles or cytosolic molecules. Some substances that affect the polymerization or depolymerization of microtubules have been used as medicine drugs. For example, colchicine inhibit microtubule growth, whereas taxol strongly attach to microtubules avoiding depolymerization.

MTOCs

The concentration of cytosolic tubulin dimers is not high enough to spontaneously polymerizes and form new microtubules. In the cell, there are structures known as microtubule organizing centers (MTOCs) where microtubule are nucleated. The minus end of the new microtubules are anchored at MTOCs, whereas the plus end grows microtubules through the cytosol. Rings of γ-tubulin, located at the MOTCs, are molecular complexes where new microbules nucleate. Other proteins, such as TPX2 and XMAP125 also contribute to form new microtubules, either alone or cooperating with γ-tubulin rings.

Centrosome is the major MTOC in animal cells. It is the main responsible for the number, localization and spatial organization of microtubules in the cytoplasm. In most of the animal cells, during G1 and G0 phases of the cell cycle, there is one centrosome per cell located close to the nucleus. Although one centrosome is commonly found in most of the animal cells, there are others like megakaryocytes containing multiple centrosomes, whereas muscle fibers lack centrosomes, and neurons show non radial microtubule organization. Centrosome is made up of two components: a couple of orthogonally oriented centrioles and a surrounding pericentriolar material, which is mostly proteins. Every centriole is a cylindrical structure with a wall made up of 9 triplets of microtubules. A typical centriole is 0,5 µm in length and 0,2 µm in diameter.



In animal cells, centrosome is the main responsible for the microtubule scaffold organization. Centrosome contains a couple of orthogonally arranged centrioles surrounded by the pericentriolar material. γ-tubulin rings, which nucleate microtubules, are located in the pericentriolar material.

There are many γ-tubulin molecules in the pericentriolar material organized as rings, known as γ-tubulin rings. Centrioles, however, do not participate in the formation of microtubules nor in the spatial orientation, except the distal and subdistal appendages, which are structures attached to centrioles that can nucleate microtubules. The function of centrioles is still a mystery. For example, plant cells lack centrioles, and they can segregate chromosomes and divide in two new cells, and organize their microtubules without any problem. Centrioles are similar to basal bodies, structures located in the basal part of cilia and flagella. Basal bodies are capable of nucleating microtubules to form the skeleton of cilia and flagella. In lab conditions, spontaneous polymerization of microtubules can be done when γ-tubulin is present, and the concentration of α- and β-tubulin dimers is high enough. But such conentrations are hardly found in the cytosol.

Centrosome, besides being a microtubule nucleator, is also important during the cell cyclebecause it contains many proteins involved in the progress of the cell cycle and in the organization of the mitotic spindle. For example, duplication of centrosomes before mitosis is essential to produce two "healthy" new cells. In this way, centrosome has been proposed as the cause of different types of cancer since many tumor cells have supernumerarycentrosomes that may produce multipolar mitotic spindles and unequal distribution of chromosomes (aneuploidy).

There are other cellular places where microtubules can be nucleated. For example, chromosomes during mitosis, cisterns of Golgi apparatus, basal bodies of cilia and

flagella, and some new nucleation points sometimes depend on other microtubule. Blepharoplasts(also MTOCs) are molecular complexes of plant cells, occasionally found in animal cells, which are able to nucleate microtubules, and sometimes give rise to centrioles and centrosomes. Plant cells lack centrioles and do not form typical centrosomes, but they have γ-tubulin rings throught the cytoplasm or associated to the nuclear envelope, so that they mainly nucleate microtubules in the cytoplasm periphery and on the nuclear envelope. In plant cells, the mitotic spindle is made up of microtubles nucleated on the chromosomes. In any case, γ-tubulin rings are needed. In yeasts, the main MTOC is known as polar body, which is inserted in the nuclear envelope (the mitotic spindle is intranuclear).

Function

Organization and movement of organelles. Microtubules are classified in two types: stable microtubules, located in cilia and flagella, and dynamic microtubules, located in the cytosol. Cytosolic microtubules, besides their role in the mitotic spindle formation and chromosome segregation, are also involved in the internal movement of organelles such as mitochondria, lysosomes, pigment inclusions, lipid drops, etcetera. They are also needed for vesicular trafficking. When cells in culture are observed at light microscopy, organelles show an alternation between quick movement and quiet periods. This behavior, known as saltatory movement, occurs when organelles are moving along the microtubules.

Microtubules are rather passive structures since they do not interact directly with organelles. The movement of organelles along the microtubules is produced by the activity of proteins known as motor proteins. There are two families of motor proteins: kinesins and dyneins. Both can "walk" along the external surface of microtubule walls. Kinesins go toward the plus end, whereas dyneins go toward the minus end. Their molecular structure has two globular domains and a tail domain. The globular domains bind ATP, generate the movement, and interact directly with the microtubule, whereas the tail selects and binds the cargoes (mainly organelles). ATP hydrolysis in the globular part leads to tridimensional molecular changes that allow the movement of the protein along the microtubule, dragging the cargo. Besides moving cargoes through the cytoplasm, motor proteins are also involved in the shape and localization of some organelles such as the Golgi complex and endoplasmic reticulum. Addition of colchicine depolymerizes the microtubular system of the cell, and both organelles collapse and divide in small vesicles scattered through the cytoplasm. When colchicine is removed and microtubule repolymerization occurs, both organelles get again the typical shape and cellular localization. These experiments indicate that there are proteins in the membranes of these organelles that are recognized by motor proteins.

Cilia and flagella are cellular structures protruding from the cell surface, contain microtubules, and are delimited by plasma membrane. Cells use cilia and flagella to move the surrounding liquid. They are also sensory structures. Cilia are shorter than flagella, are more numerous, and their movements propel the liquid parallel to the cell surface. Flagella

move the surrounding liquid perpendicular to the cell surface.

Cilia and flagella are complex structures made up of more than 250 different proteins. Both have a central structure of microtubules known as axoneme, surrounded by the plasma membrane. Axoneme is formed by 9 outer pairs of microtubules, plus a central pair of microtubules. This organization is written down as 9x2+2. Microtubules of the axoneme grow from the microtubules of the basal body. Basal body have 9 triplets of microtubules (i.e. 9x3+0). The axoneme organization is strengthened by a scaffold of proteins. The outer pairs of microtubules of the axoneme are connected between each other by nexin proteins, whereas protein spokes connect the outer pairs with the central pair. The motor protein dynein is located between the outer pairs. Dynein is involved in the movement of cilia and flagella. The movement is a consequence of the sliding of one outer pair over another adjacent one, which forces the bending of the axoneme.

Some type of cilia are known as primary cilia. Primary cilia cannot move, are scarce, and sometimes appear alone in the cells. At least one cilium is present in most of the animal cells studied so far. Primary cilia bear in their membranes many receptors and ionic channels, so that a sensory role has been suggested. Nowadays, both primary and moving cilia are thought to develop a sensory function since both of them have receptors in their membranes.

INTERMEDIATE FILAMENTS

Intermediate filaments are one of the components of the cytoskeleton providing mechanical strenght. They are usually anchored to the cell adhesion complexes.

Intermediate filaments are distributed through the cytoplasm, and are also a component of the nuclear envelope.

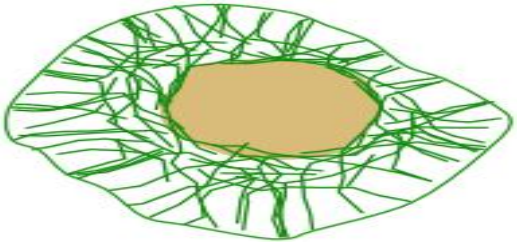
Intermediate filaments are made up of proteins with three molecular domains: two globular domains and one central straight domain.

There are several types of intermediate filaments, such as keratin.

Intermediate filaments are a primary component of the cytoskeleton. They withstand mechanical stress, mainly stretching. This role is clear in animal cells. In plant cells, however, counteracting mechanical forces is carried out by the cell wall. Intermediate filament proteins have been found in plant cells, but their function is not fully understood.

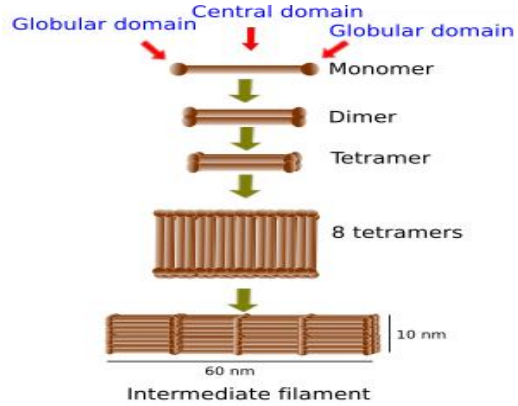
The diameter of intermediate filaments is 10 to 12 nm, between 7-8 nm of actin filaments and 25 nm of microtubules. That is why the name intermediate. Intermediate filaments are found in the animal cells, but also in plant and fungi (not like long filaments since they have cell wall). Intermediate filaments form a net that spreads from the nuclear envelope to the plasma membrane. They are usually anchored to adhesion cell complexes such as desmosomes, hemidesmosomes and focal adhesions. They are also found inside the nucleus

as nuclear lamina, a component of the nuclear envelope. Intermediate filaments are abundant in those cells under heavy mechanical stress, such as nerves, muscle cells, and epithelial cells.



Distribution of intermediate filaments in an animal cell in culture.

In humans, there are 70 genes coding for proteins that, after polymerization, become intermediate filaments. These proteins contain a globular domain in the C terminus end, another one in the N-terminus end, and, between them, a large central domain containing about 310-350 amino acids. The central domain shows an α-helix structure, which is responsible for the association of these proteins to form dimers. Two dimers are laterally associated to form tetramers, and tetramers join to form a sheet of eight tetramers. This sheet rolls over itself (coiled structure of about 10 nm in diameter) and gets aligned with other three to form a basic unit (around 60 nm in lenght), so that several basic units join by their ends to form intermediate filaments like long ropes. The different types of intermediate filaments show proteins with similar central domains, both in size and amino acid sequence. However, the globular domains show differences in amino acid composition and in shape. Globular domains are responsible for the interaction with other cellular proteins.



Assembling of monomers to form intermediate filaments.

Intermediate filaments are flexible and resistant, two features to withstand mechanical stress. It is estimated that they can be stretched about 250 to 350 % of the resting length, because the monomers may slide over the others. On the

contrary, microtubules and actin filaments are quite stiff. Besides resistance, intermediate filaments are involved in other cell functions. For example, they are proposed as anchoring structures for molecules involved in signaling. Furthermore, intermediate filaments interact with some organelles as mitochondria, Golgi complex, and lysosomes, so they may influence their functions.

Although intermediate filaments are stableduring longer times than microtubules and actin filaments, they can be depolymerized and polymerized again under some circumstances like during cell movement, cell division, and when mechanical forces on cells change the direction.

Intermediate filaments are divided in three families: a) keratin filaments in the epithelial cells, b) vimentin and other related filaments in connective tissue cells, muscle cells and neurons, and c) neurofilaments in neurons. The keratin family is the most diverse, so that different epithelia express different keratin filaments. There are also different types of keratin in the hair, feathers, and nails. Furthermore, keratin filaments are made up of different combinations of keratin monomers.

Keratin filaments in the epithelium are usually anchored to desmosomes and hemidesomes. Epidermolysis bullosa simplex is a pathology caused by gene mutation affecting the keratin filaments. It results in blistering lesions on the skin and mucosal layers due to the weak strength of the skin against mechanical stress, because cells are not strongly attached between each other. This is one of the 75 human pathologies associated to intermediate filaments. There are also myopathies, amyotrophic lateral sclerosis, Parkinson disease, eye cataracts, etcetera.