CYTOSKELETON

CYTOSKELETON which consists of a network of protein filaments extending throughout the cytoplasm of all eukaryotic cells. The cytoskeleton provides a structural framework for the cell, serving as a scaffold that determines cell shape, the positions of organelles, and the general organization of the cytoplasm. In addition to playing this structural role, the cytoskeleton is responsible for cell movements. These include not only the movements of entire cells, but also the internal transport of organelles and other structures (such as mitotic chromosomes) through the cytoplasm. Importantly, the cytoskeleton is much less rigid and permanent than its name implies. Rather, it is a dynamic structure that is continually reorganized as cells move and change shape—for example, during cell division.

The cytoskeleton is composed of three principal types of protein filaments: actin filaments, intermediate filaments, and microtubules, which are held together and linked to subcellular organelles and the plasma membrane by a variety of accessory proteins

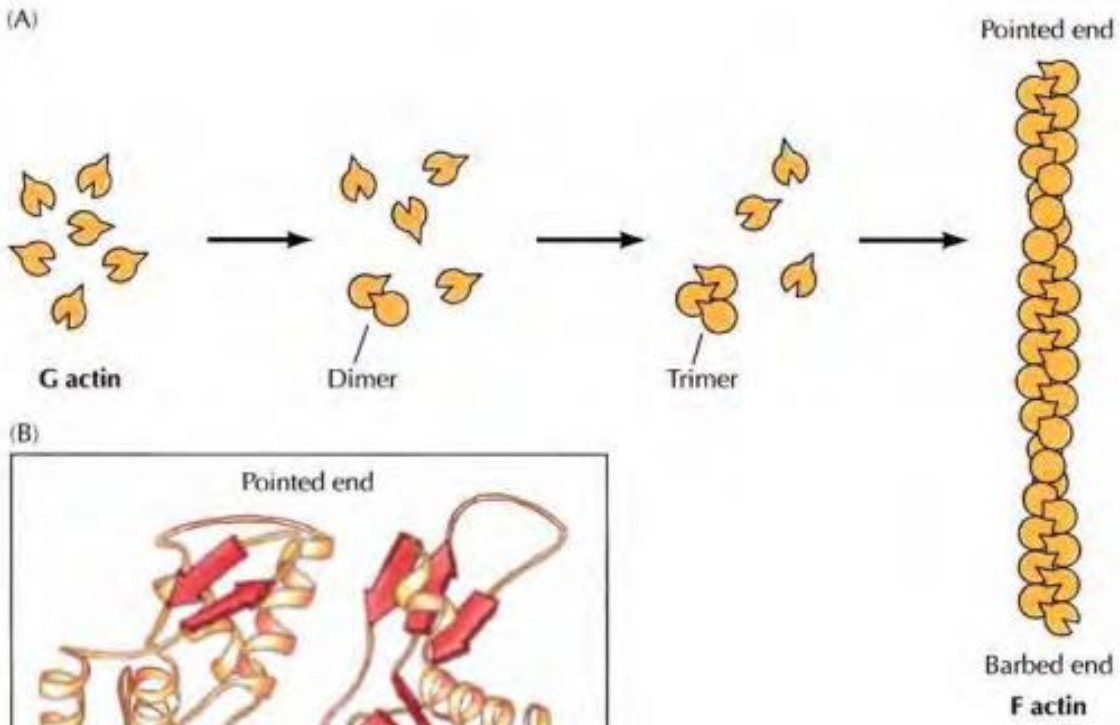
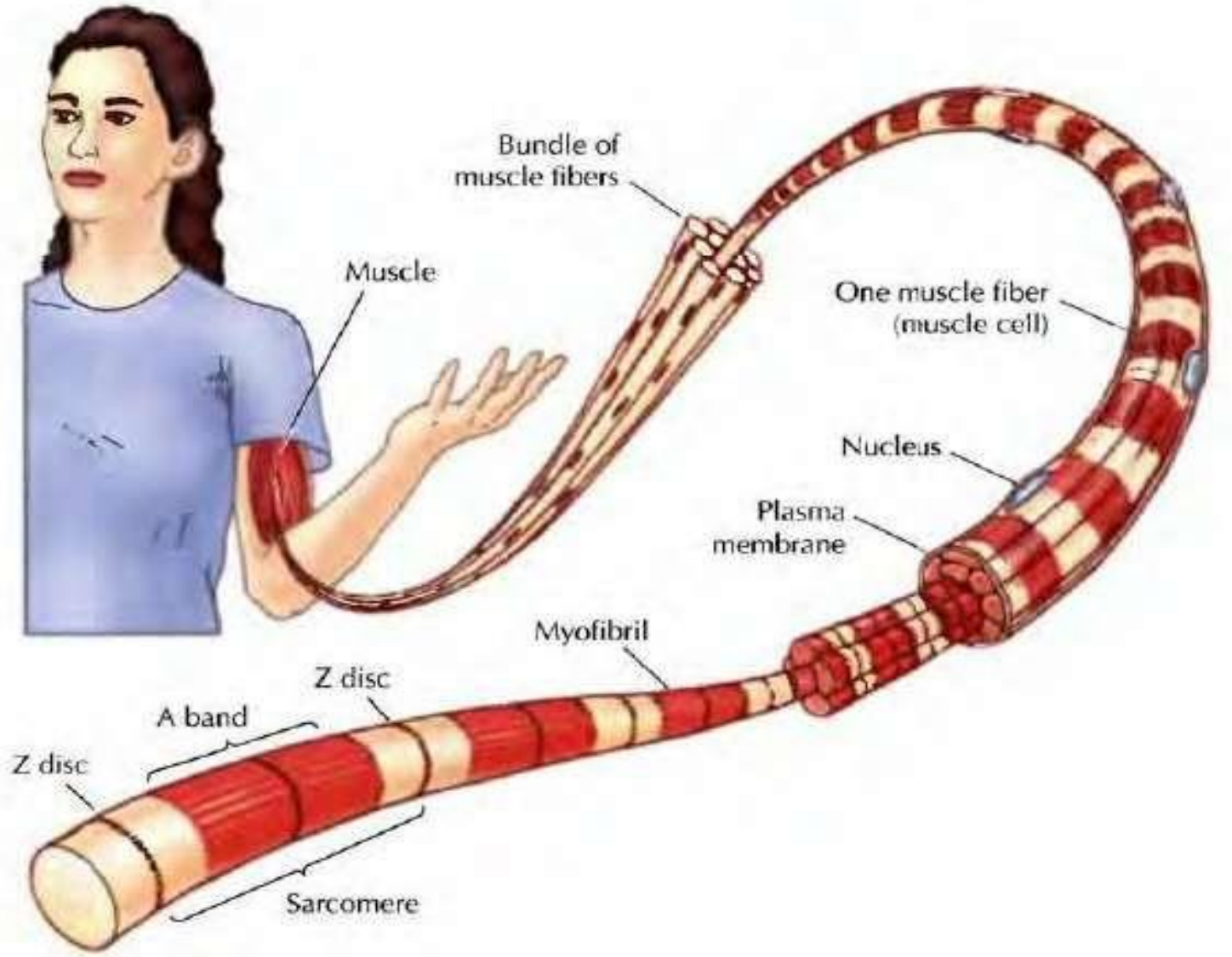


FIGURE 12.2 Assembly and structure of actin filaments (A) Actin monomers (G actin) polymerize to form actin filaments (F actin). The first step is the formation of dimers and trimers, which then grow by the addition of monomers to both ends. (B) Structure of an actin monomer. (C) Space-filling model of F actin. Fourteen actin monomers are represented in different colors. (C, based on data from Chen et al., 2002. *J. Struct. Biol.* 138: 92.)

Muscle Contraction

- Skeletal muscles are bundles of muscle fibers
- Most of the cytoplasm consists of myofibrils, which are cylindrical bundles of two types of filaments: thick filaments of myosin (about 15 run in diameter) and thin filaments of actin (about 7 nm in diameter).
- Each myofibril is organized as a chain of contractile units called sarcomeres, which are responsible for the striated appearance of skeletal and cardiac muscle.

Structure of muscle cells



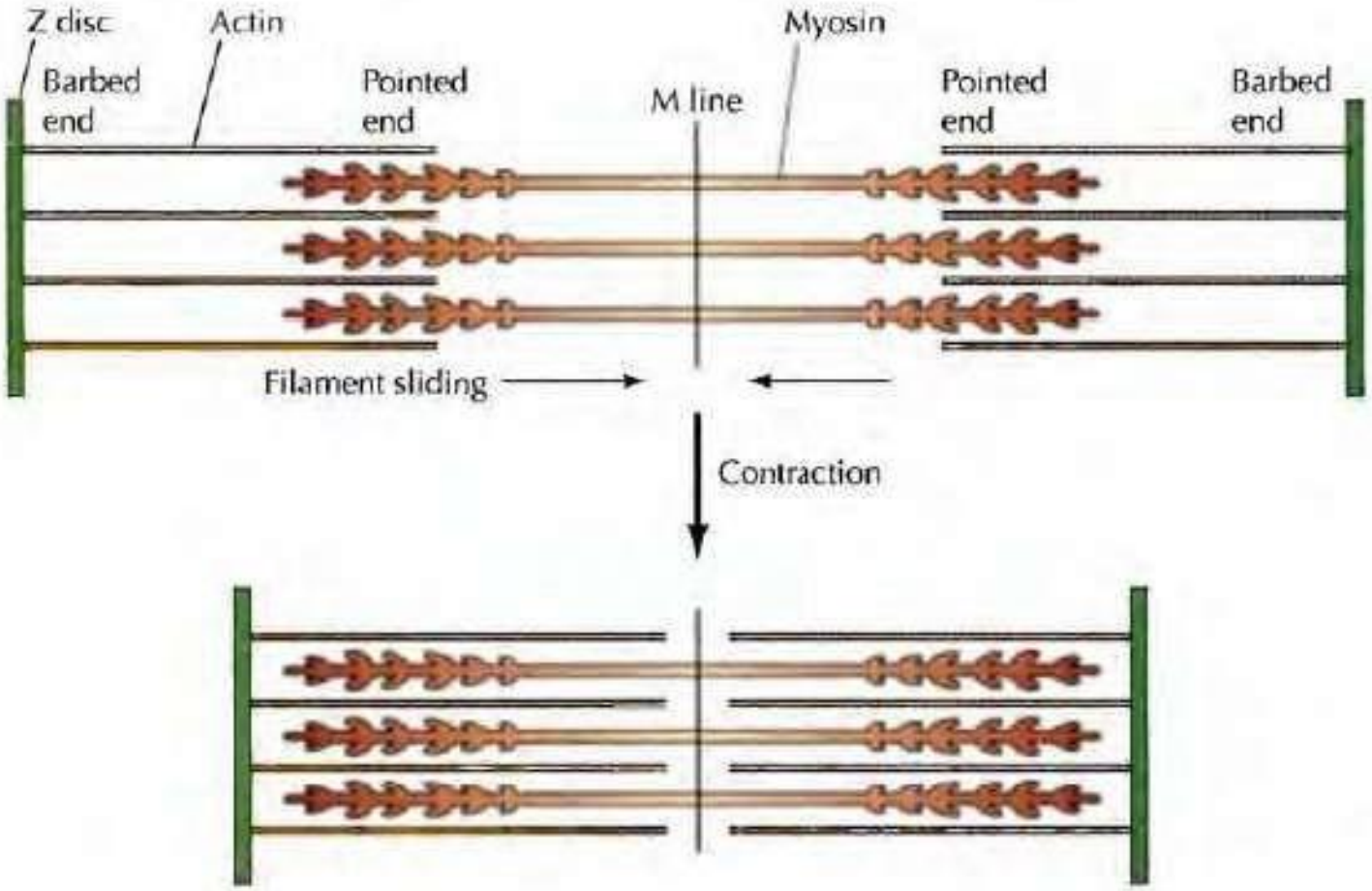
Sarcomere

- The ends of each sarcomere are defined by the Z disc.
- Within each sarcomere, dark bands (called A bands because they are anisotropic when viewed with polarized light) alternate with light bands (called I bands for isotropic).
- The I bands contain only thin (actin) filaments, whereas the A bands contain thick (myosin) filaments.
- The myosin and actin filaments overlap in peripheral regions of the A band, whereas a middle region (called the H zone) contains only myosin.

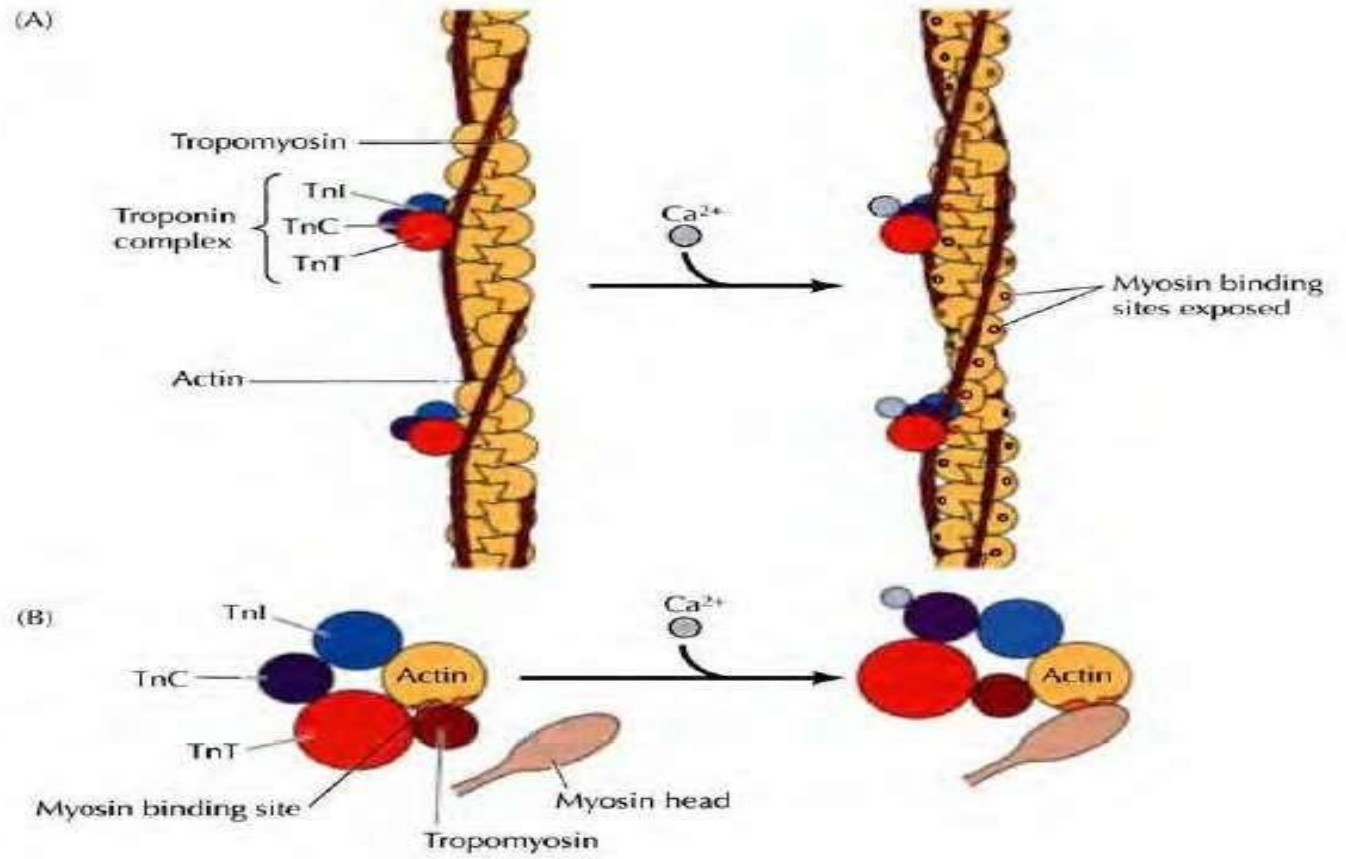
Muscle contraction

- The basis for understanding muscle contraction is the sliding filament model, first proposed in 1954 both by Andrew Huxley and Ralph Niedergerke and by Hugh Huxley and Jean Hanson
- During muscle contraction each sarcomere shortens, bringing the Z discs closer together.
- There is no change in the width of the A band, but both the I bands and the H zone almost completely disappear.
- These changes are explained by the actin and myosin filaments sliding past one another so that the actin filaments move into the A band and H zone.
- Muscle contraction thus results from an interaction between the actin and myosin filaments that generates their movement relative to one another.
- The molecular basis for this interaction is the binding of myosin to actin filaments, allowing myosin (motor protein convert chemical energy to mechanical) to function as a motor that drives filament sliding.

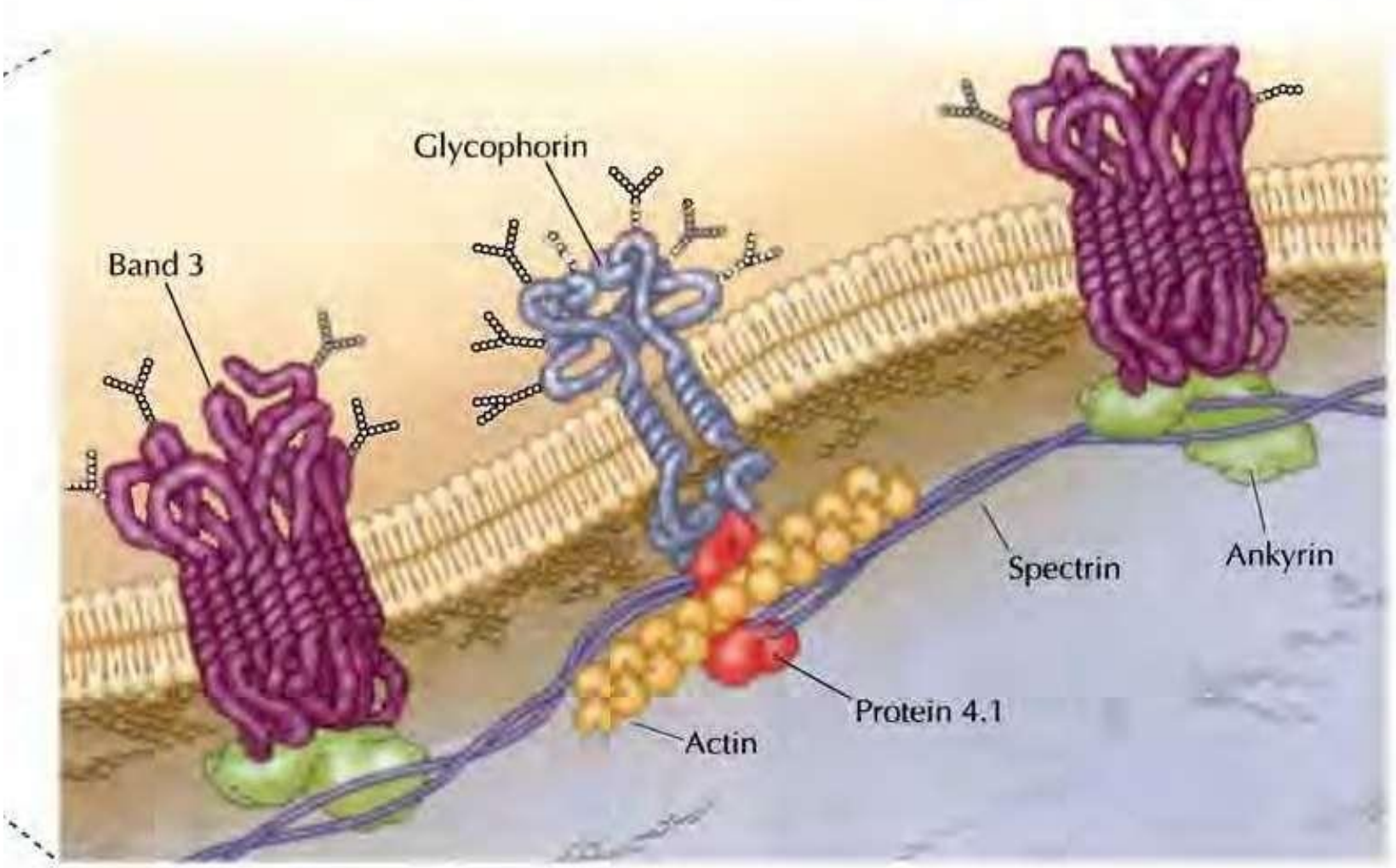
Sliding filament model (sarcomere)



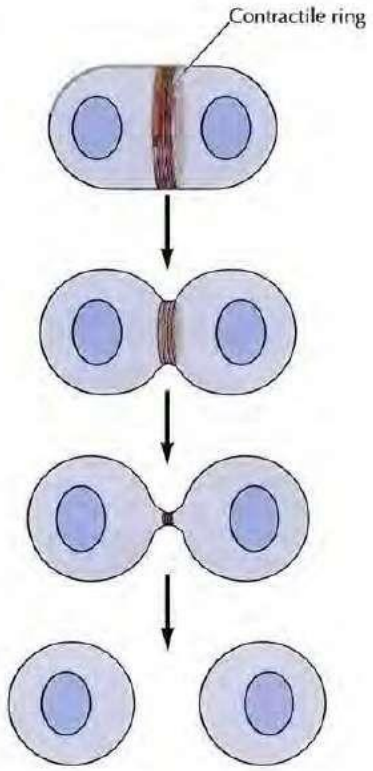
Association of tropomyosin and troponins with actin filaments

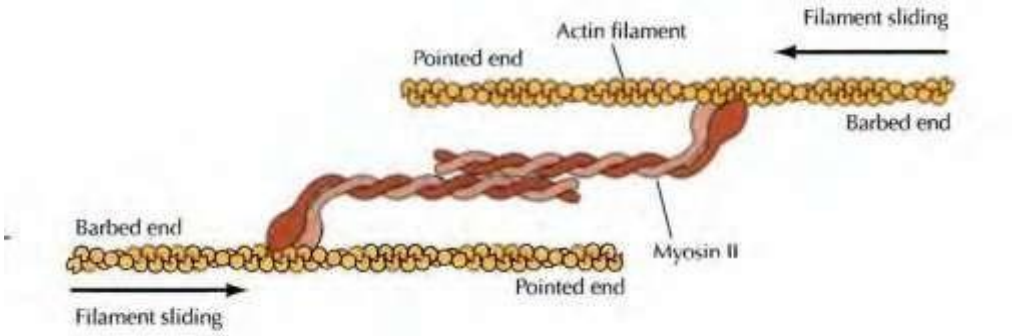


Association of the erythrocyte cortical cytoskeleton with the plasma membrane



Non muscular myosin and actin leads to cytokinesis





Contractile assemblies in nonmuscle cells

- The most dramatic example of actin-myosin contraction in nonmuscle cells, is provided by cytokinesis

- Toward the end of mitosis in yeast and animal cells, a contractile ring consisting of actin filaments and myosin assembles just underneath the plasma membrane.

- Its contraction pulls the plasma membrane progressively inward, constricting the center of the cell and pinching it in two. Interestingly, the thickness of the contractile ring remains constant as it contracts, implying that actin filaments disassemble as contraction proceeds.

- The ring then disperses completely following cell division

- In nonmuscle cells and in smooth muscle, however, contraction is regulated primarily by phosphorylation of one of the myosin light chains called the regulatory light chain

Formation of Protrusions and Cell Movement

- The movement of cells across a surface represents a basic form of cell locomotion employed by a wide variety of different kinds of cells.

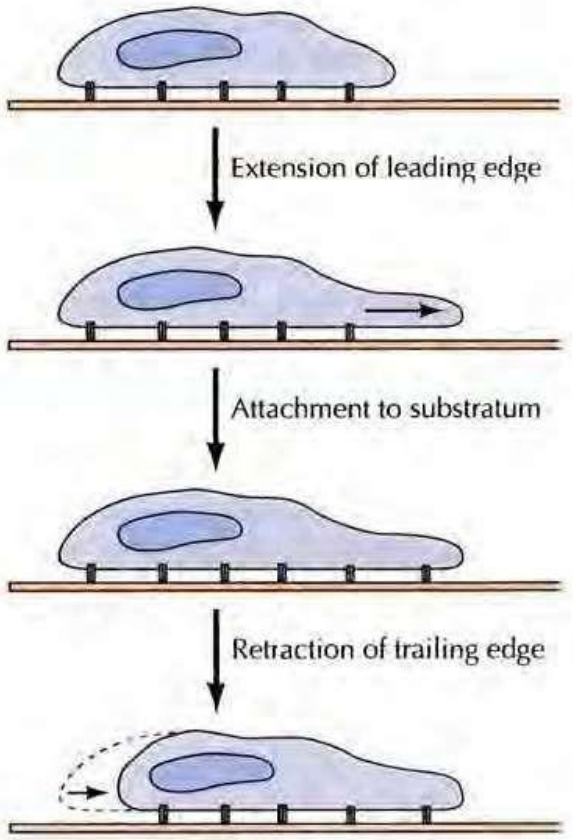
Examples includes:

- ✓ The crawling of amoebas
- ✓ The migration of embryonic cells during development
- ✓ The invasion of tissues by white blood cells to fight infection
- ✓ The migration of cells involved in wound healing
- ✓ The spread of cancer

- All of these movements are based on local specializations and extensions of the plasma membrane driven by the dynamic properties of the actin cytoskeleton.

Cell movement or extension involves a coordinated cycle of movements

- First, cells must develop an initial polarity via specialization of the plasma membrane or the cell cortex.
-
- Second, protrusions such as pseudopodia, lamellipodia, or filopodia must be extended to establish a leading edge of the cell. These extensions must then attach to the substrahtm across which the cell is moving.
- Finally, during cell migration the trailing edge of the cell must dissociate from the substratum and retract into the cell body.



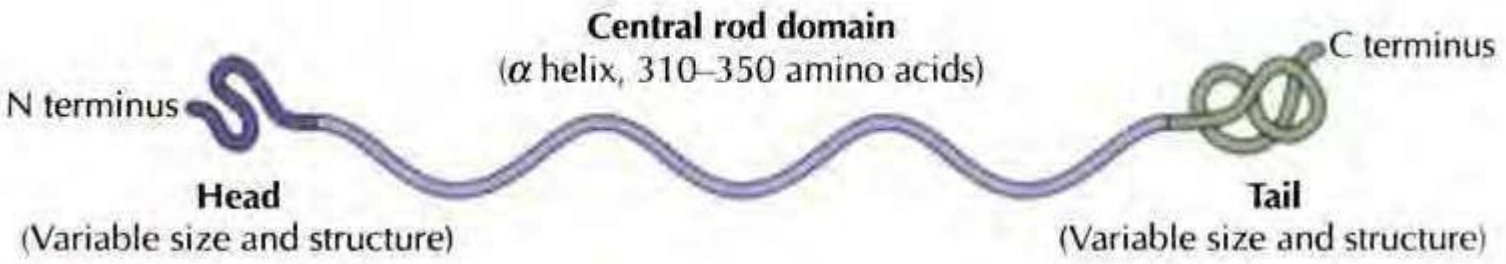
Intermediate Filaments

- Intermediate filaments have diameters between 8 and 11 nm
- Not involved in cell movements instead, play a structural role by providing mechanical strength to cells
- Intermediate filaments are apolar
- Intermediate filaments are composed of a variety of proteins that are expressed in different types of cells
- More than 65 different intermediate filament proteins have been identified
- These proteins are classified into six groups based on similarities between their amino acid sequences

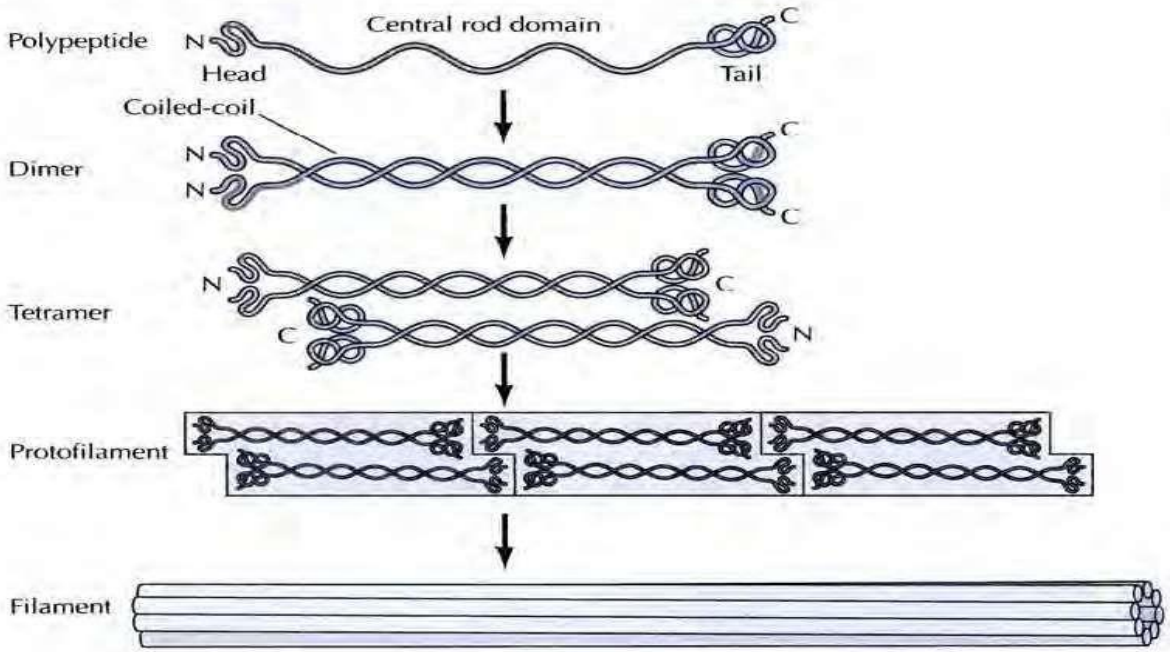
Classes of intermediate filament and their functions

Class	IF Protein	Molecular Mass (kDa)	Tissue	
I	Acidic cytokeratins	40–56.5	Epithelial cells	Mechanical strength
II	Basic cytokeratins	53–67	Epithelial cells	Mechanical strength
III	Vimentin	54	Fibroblasts; cells of mesenchymal origin; lens of eye	Maintenance of cell shape
III	Desmin	53–54	Muscle cells, especially smooth muscle	Structural support for contractile machinery
III	GFA protein	50	Glial cells and astrocytes	Maintenance of cell shape
IV	Neurofilament proteins		Central and peripheral nerves	Axon strength; determines axon size
	NF-L (major)	62		
	NF-M (minor)	102		
	NF-H (minor)	110		
V	Nuclear lamins		All cell types	Form a nuclear scaffold to give shape to nucleus
	Lamin A	70		
	Lamin B	67		
	Lamin C	60		
VI	Nestin	240	Neuronal stem cells	Unknown

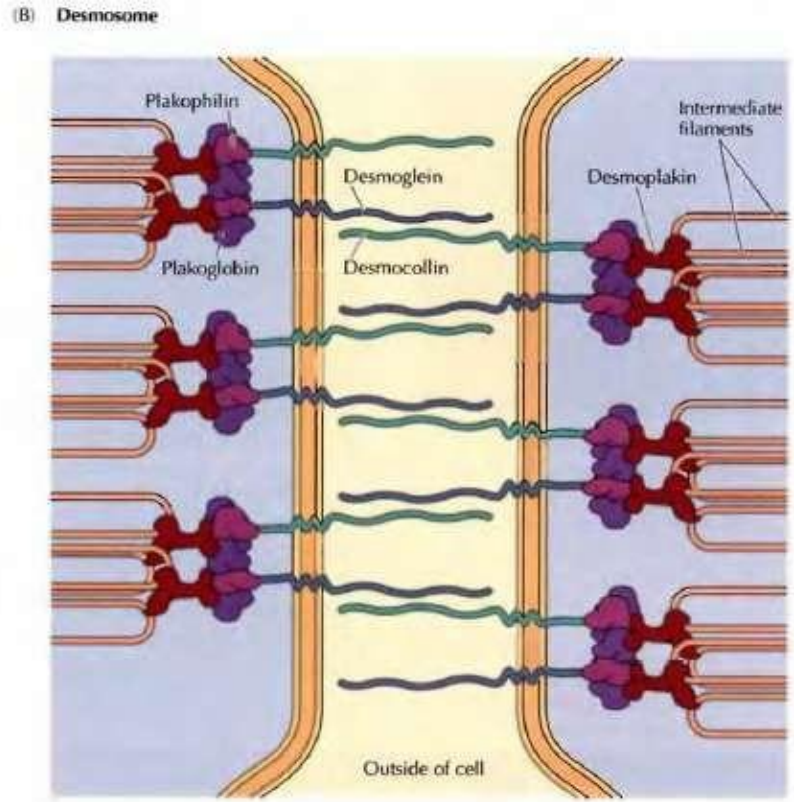
Structure of Intermediate Filaments

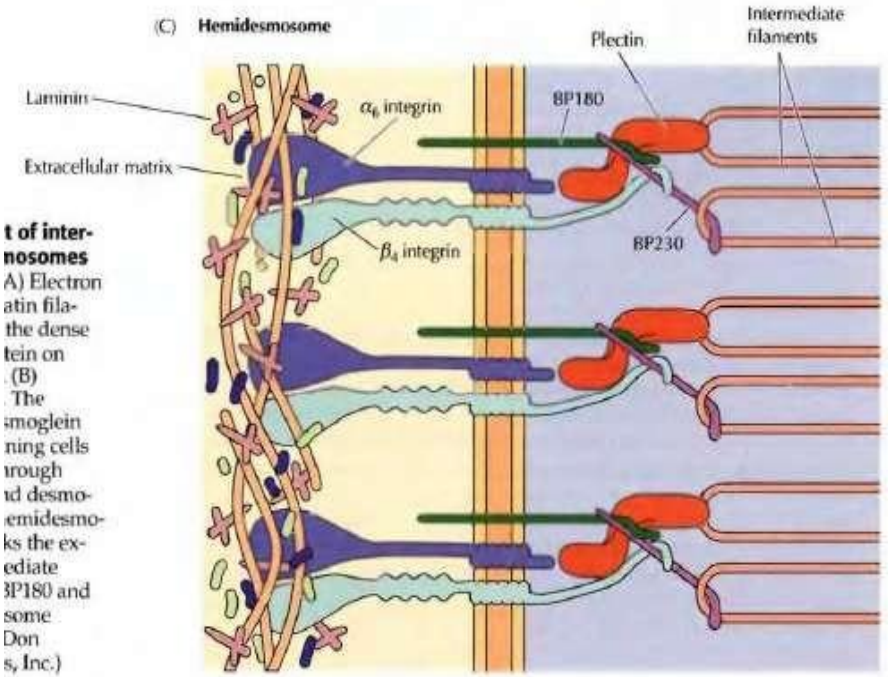


Assembly of intermediate filament



Attachment of intermediate filaments to desmosomes and hemidesmosomes





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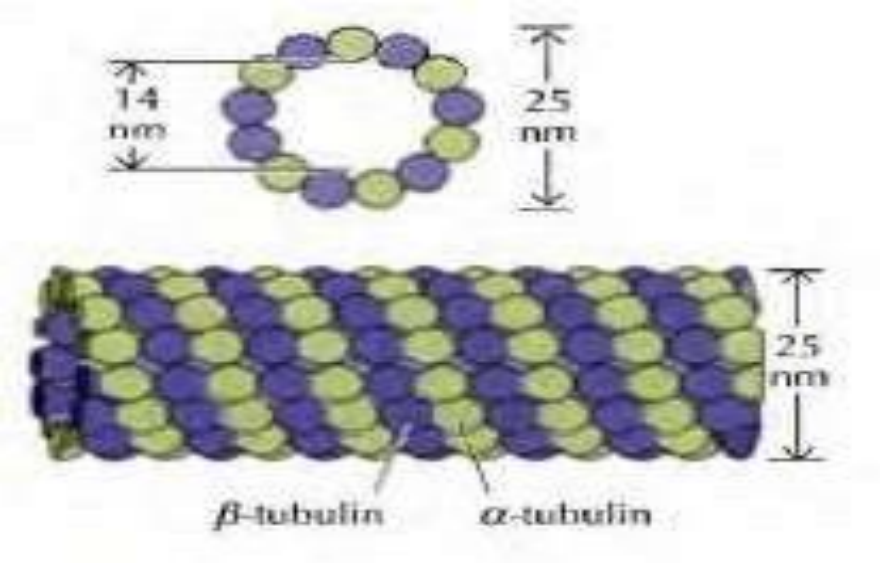
Microtubules

- Microtubules are hollow, relatively rigid, tubular structures
- Components of mitotic spindle of dividing cells and the core of cilia and flagella
- An outer diameter of 24 nm and inner 14 nm
- wall of a microtubule is composed of globular proteins tubulin
- They are the dynamic structure



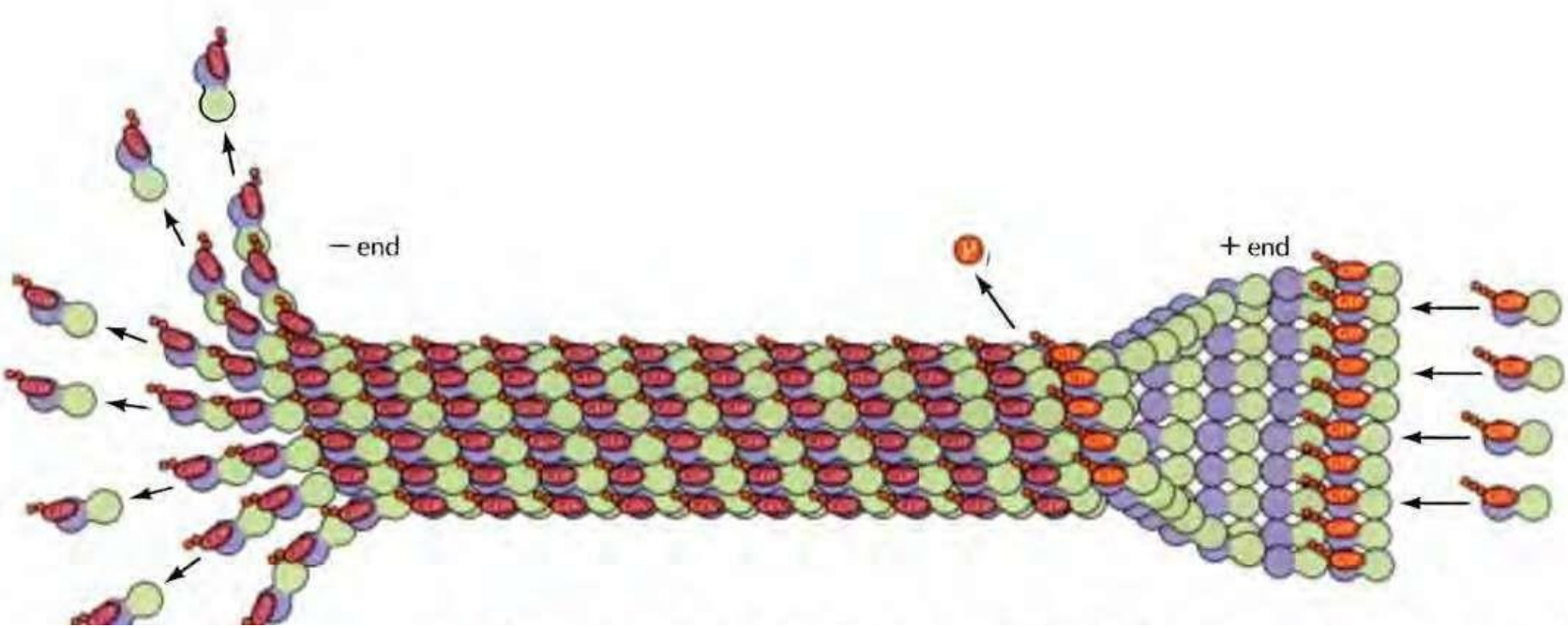
Structure

- Building block of microtubule is tublin dimer of alpha and beta tublin
- A third type of tubulin y-tubulin is concentrated in the centrosome where it plays a critical role in initiating microtubule assembly
- Tublin dimer polymerize to form microtubule
- Tubulin protein are arranged in longitudinal rows, forms protofilaments, that are aligned parallel to the long axis of the tubule
- Microtubules are seen to consist of 13 protofilaments aligned side by side in a circular pattern within the wall
- Noncovalent interactions between adjacent protofilaments
- Tubulin polymerization can be studied *in vitro*
- Microtubules like actin filaments) are polar structures with two distinct ends: a fast-growing plus end and a slow growing minus end.
- This polarity is an important consideration in determining the direction of movement along microtubules

Structure and assembly

- The tubulin dimers are organized in a linear array along the length of each protofilament
- The protofilament is asymmetric, with an a-tubulin at one end and β -tubulin at the other end
- All of the protofilaments of a microtubule have the same polarity
- One end of a microtubule is known as the *plus end* and is terminated by a row of β -tubulin subunits
- The opposite end is the *minus end* and is terminated by a row of β - tubulin subunits.
- The structural polarity of microtubules is an important factor in the growth of these structures and their ability to participate in directed mechanical activities.

Treadmilling and the role of GTP in microtubule polymerization



Treadmilling of microtubule

- Like actin fi laments, microtubules undergo treadmilling a dynamic behavior in which tubulin molecules bound to GDP are continually lost from the minus end and replaced by the addition of tubulin molecules bound to GTP to the plus end of the same microtubule.
- The minus ends grow less rapidly than the plus ends of microtubules.
- This difference in growth rate is reflected in a difference in the critical concentration for addition of tubulin dimers to the two ends of the microtubule.
- Tubulin dimers with GTP bound to β -tubulin associate with the rapidly growing plus ends in a flat sheet, which then zips up into the mature microtubule just behind the region of growth.
- Shortly after polymerization the GTP bound to β tubulin is hydrolyzed to GDP, and since GDP-bound tubulin is less s table in the microtubule, the dimers at the minus end begin to peel off.
- Treadmilling takes place at tubulin dimer concentrations intermediate between the critical concentrations for the plus and minus ends.
- Under these conditions there is a net dissociation of dimers (bound to GOP) from the minus end, balanced by the addition of dimers (bound to GTP) to the plus end.

Cilia and flagella

- Cilia and flagella are microtubule-based projections of the plasma membrane that are responsible for movement of a variety of eukaryotic cells

- Eukaryotic cilia and flagella are very similar structures

- The minus ends of the microtubules of cilia and flagella are anchored in a basal body, which is similar in structure to a centriole

- Basal bodies thus serve to initiate the growth of axonemal microtubules as well as anchoring cilia and flagella
- to the surface of the cell.

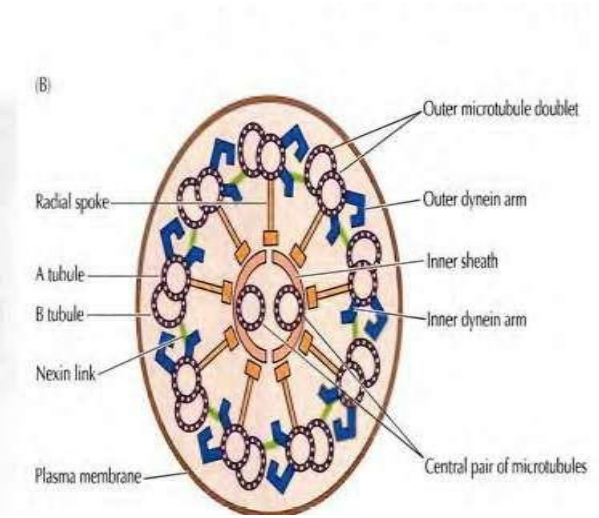
Structure of the axoneme of cilia and flagella

- The fundamental structure of both cilia and flagella is the axoneme which is composed of microtubules and their associa ted proteins

- The microtubules are arranged in a characteristic "9 + 2" pattern in which a central pair of microtubules is surrounded by nine outer microtubule doublets.

- The two fused microtubules of each outer doublet are distinct: One (called the A tubule) is a complete microtubule consisting of 13 protofilaments; the other (the B tubule) is incomplete, containing only 10 or 11 protofilaments fused to the A tubule.

- The outer microtubule doublets are:



- connected to the central pair by radial spokes and to each other by links of a protein ca lled nexin.

- In addition, two arms of dynein are attached to each A tubule, and it is the motor activity of these axonemal dyneins that drives the beating of cilia and flagella.

Movement of microtubules in cilia and flagella

- The bases of dynein arms are attached to A tubules, and dynein head groups interact with the B tubules of adjacent doublets.
- Movement of the dynein head groups in the minus end direction (toward the base of the cilium) then causes the A tubule of one doublet to slide toward the base of the adjacent B tubule.
- Because both microtubule doublets are connected by nexin links, this sliding movement forces them to bend and form the basis of beatin movement

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