بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Cytology & Molecular Biology | Lecture 8

Intermediate Filaments

Written by : DST

Reviewed by : Tuqa Al-Soud

The third cytoskeletal structure exist in cells :

Intermediate filaments

What are they?

- Intermediate filaments have a diameter that is intermediate between actin filaments and microtubules.

Thinnest **Thickest**

- Functions:
  - They provide mechanical strength to cells and tissues.

➢ **They are the real skeleton to cell if we want to compare them to actin filaments and microtubules.**

  - They provide a scaffold **3D structure** that integrates the components of the cytoskeleton

➢ **means that they connect microtubules to actin filaments.**

  - They organize the internal structure of the cell.

➢ **particularly the nucleus ,so they maintain the overall structure for cell and nucleus.**

*Recall : actin filaments and microtubules support cell structure and shape but they are dynamic, meaning that the cell shape changes with external factors or stimulants (molecules that induce the cell to move or secrete certain products) .

- Intermediate filaments are less dynamic so they are a bit more rigid in the way they connect with each other.

Types of IFs

﴿ إِنَّ اللَّهَ يُحِبُّ الْمُتَوَكِّلِينَ ﴾

- They are composed of a variety of proteins, which are classified into 5 groups based on similarities between their amino acid sequences.

Each one of the 5 diff types either has its own chemical characteristic or functional characteristic, and unique cell distribution .

  - Types I and II are expressed in epithelial cells which synthesize at least one type I (acidic) and one type II (neutral/basic) **keratin**.
    - Hard keratins are found in hair and nails.

➢ **Hair is somewhat hard, nails are harder since nails have more disulfide bonds.**

*** Recall : keratins are Important structural proteins (exists in hair or nails) they become harder if there are More disulfide bonds exist within IFs.**

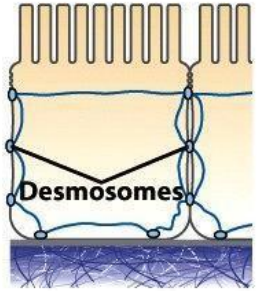
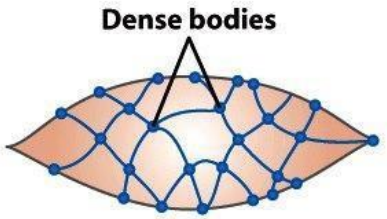
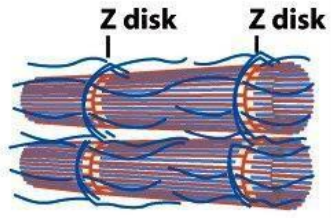
    - Soft keratins exist in the cytoplasm of epithelial cells.

- Type III:
  - Vimentin exist in fibroblasts, smooth muscle cells, and white blood cells.
  - Desmin is specifically expressed in muscle cells.
- Type IV: neurofilaments (NF) found in the axons of motor neurons.
- Type V: nuclear lamins, components of the nuclear envelope.

↳ **Like lamin a (they maintain the shape and structure of the nucleus)**

Types of IFs

TABLE 18-1 The Major Classes of Intermediate Filaments in Mammals

CLASS	PROTEIN	DISTRIBUTION	PROPOSED FUNCTION	
I	Acidic keratins	Epithelial cells	Tissue strength and integrity	 Epithelial cell
II	Basic keratins	Epithelial cells		
III	Desmin, GFAP, vimentin	Muscle, glial cells, mesenchymal cells	Sarcomere organization, integrity	 Smooth muscle  Skeletal muscle
IV	Neurofilaments (NFL, NFM, and NFH)	Neurons	Axon organization	 Axon
V	Lamins	Nucleus	Nuclear structure and organization	 Nucleus

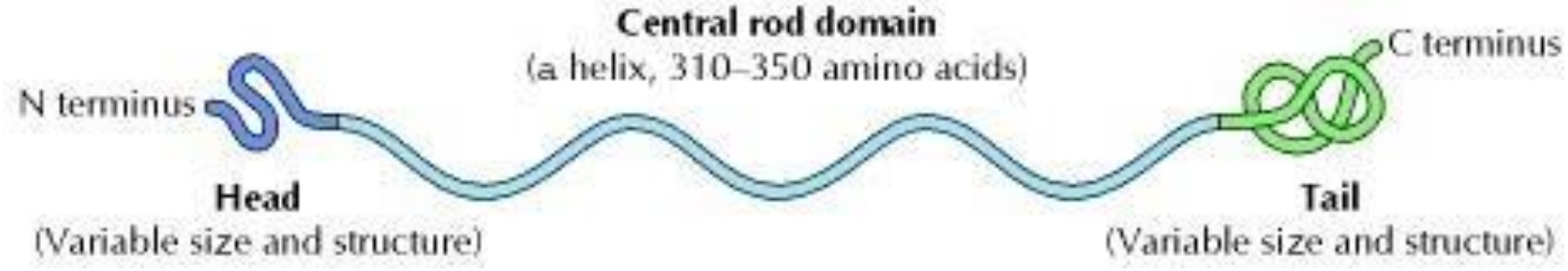
Structure of Ifs

- **Basic structure: helical polypeptide chain.**

- A central α-helical rod domain for filament assembly
- Amino- and carboxy-terminal domains that vary in size, sequence, and secondary structure among the different intermediate filament proteins and that determine the specific functions of the different intermediate filament proteins.

- **At the ends there are 3D structures, domain at C term and another ant N term, those domains are globular.**

Rod domain that exist in the center



Assembly of IFs

No polarity

*Recall : actin filaments and microtubule have:
- ✓ Plus end : keeps growing
- ✓ Minus end : keeps depolymerzing

Intermediate filament proteins contain central α-helical rod domains and N-terminal head and C-terminal tail domains.

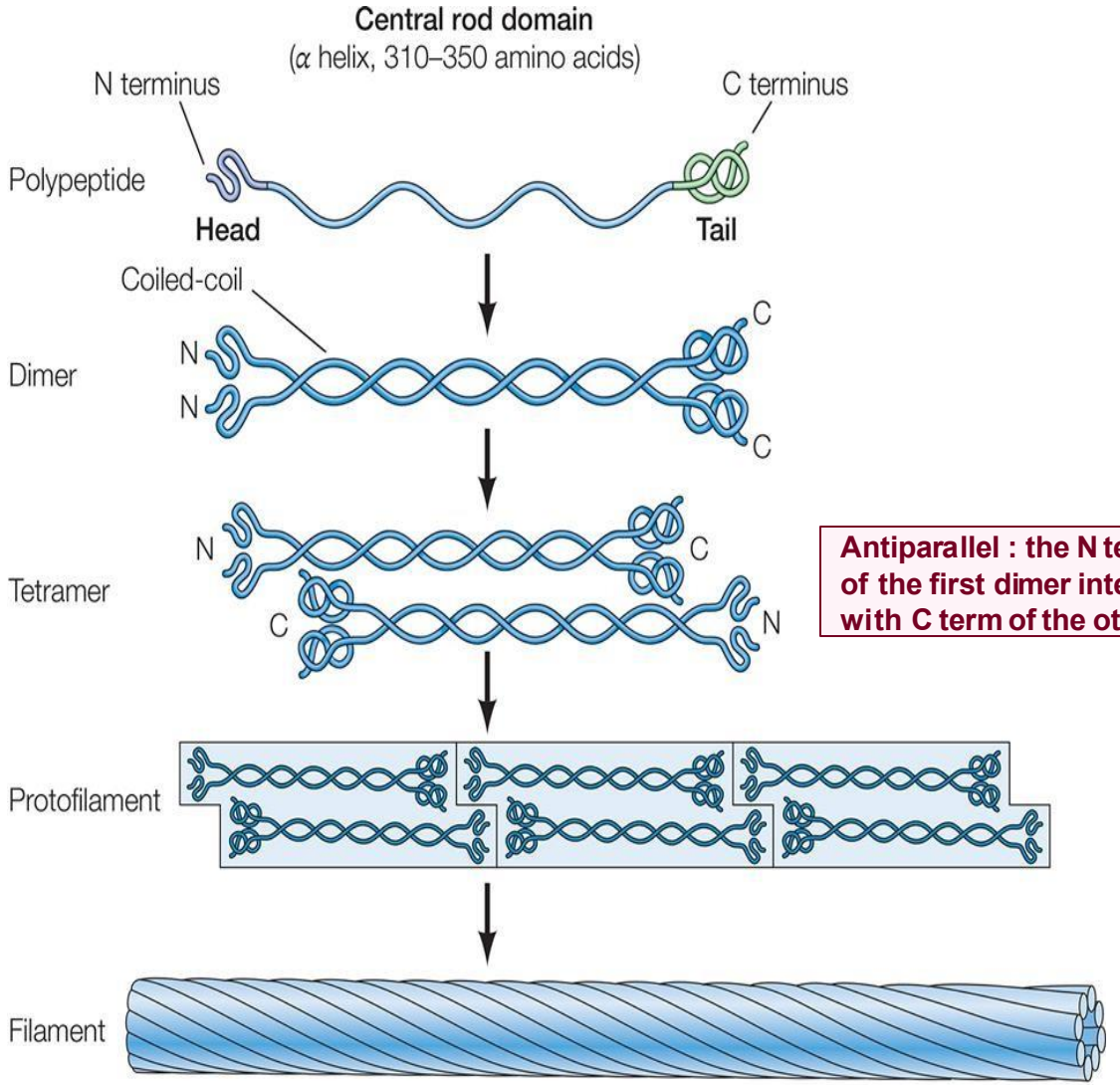
The central rod domains of two polypeptides wind around each other in a coiled-coil structure to form dimers.

Diners then associate in a staggered anti- parallel fashion to form tetramers

- Although they are anti-parallel, they aren't exactly on top of each other (a bit sliding on each other).

Tetramers associate end to form protofilaments and laterally to form filaments.

Each filament contains approximately eight protofilaments wound around each other in a ropelike structure.



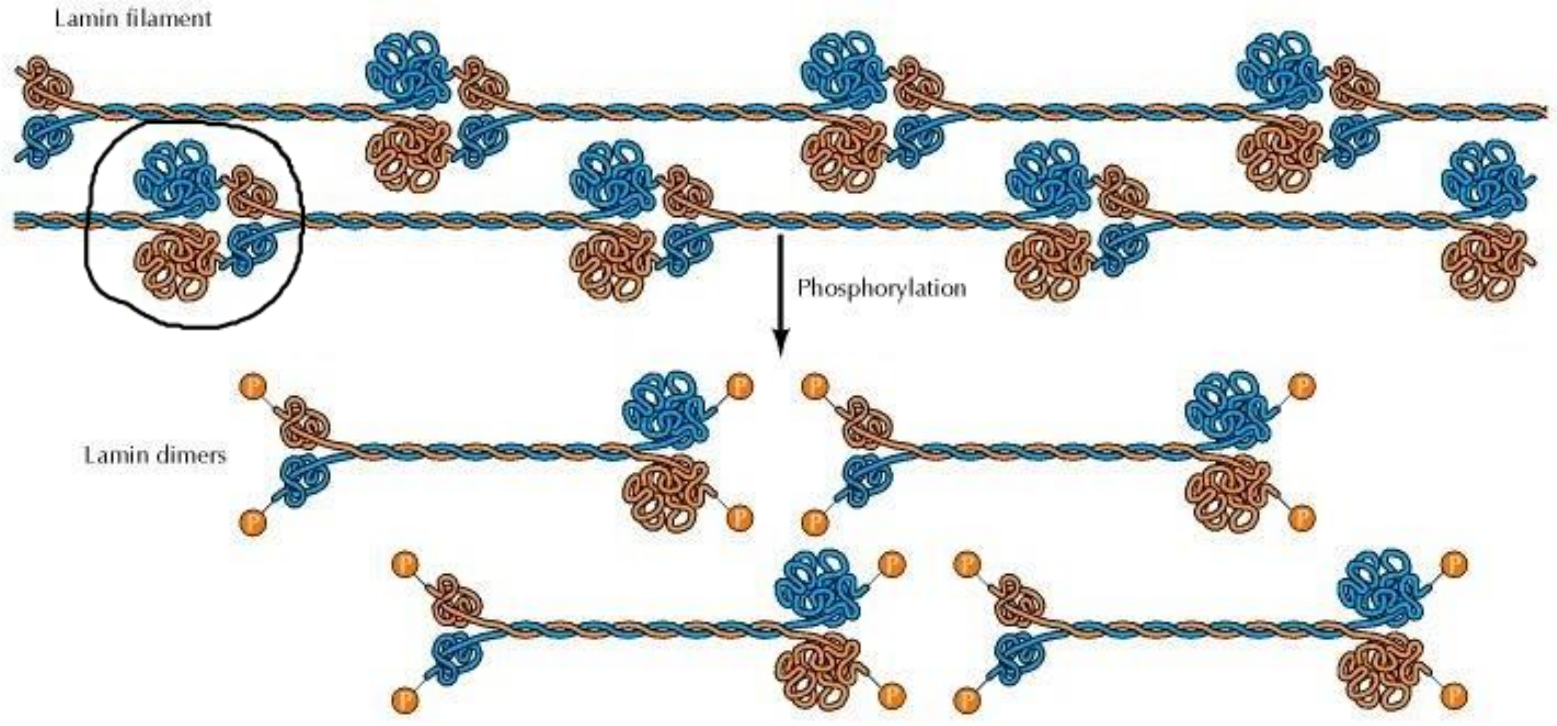
Antiparallel : the N term of the first dimer interact with C term of the other.

Relative to actins and microtubules

- More stable
- Not dynamic
- Not regulated by GTP, but regulated by phosphorylation
  - When nuclear lamins and vimentins are phosphorylated, they are disassembled.

➢ **Phosphorylation results in dissociation of filaments and protofilaments.**

➢ **Phosphorylation occurs at the globular head groups or tail groups that exist at both ends.**



Intracellular Organization of IFs

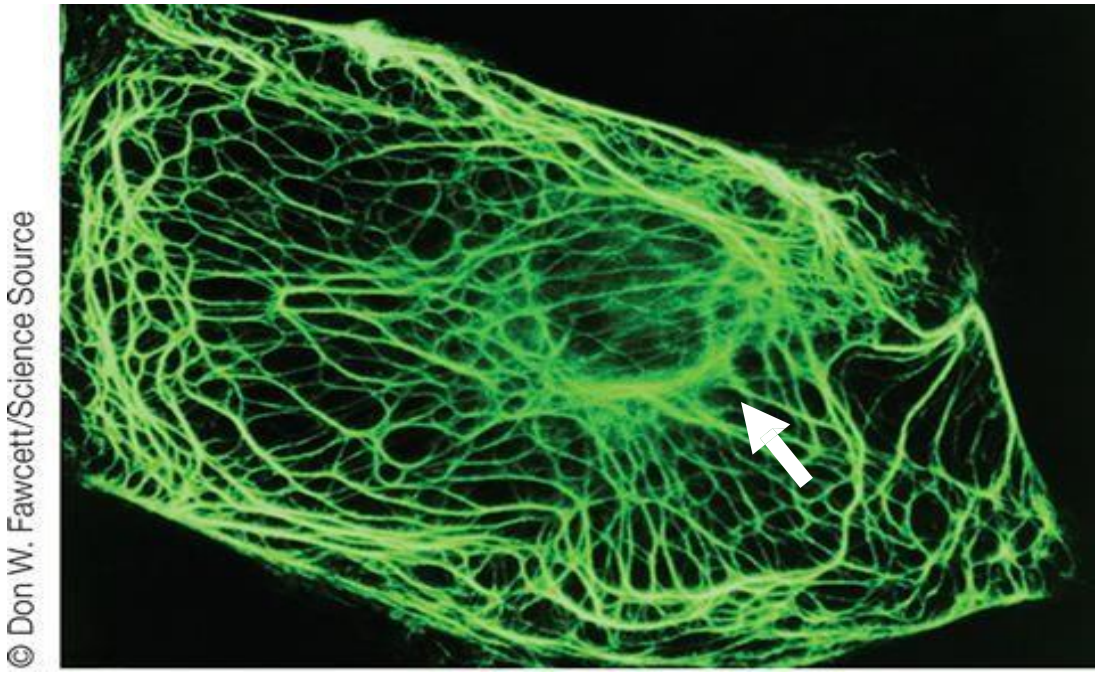
Intermediate Filaments play a major role in intracelluler organization particularly in Nucleus , Muscle cells , Neurons , Epithelial cells.

Intracellular Organization of IFs (*The nucleus)*

- **Intermediate Filaments exist all over the cell , particularly , they are concentrated around the nucleus , so they support it.**

- Both keratin and vimentin filaments attach to the nuclear envelope to position and anchor the nucleus within the cell.

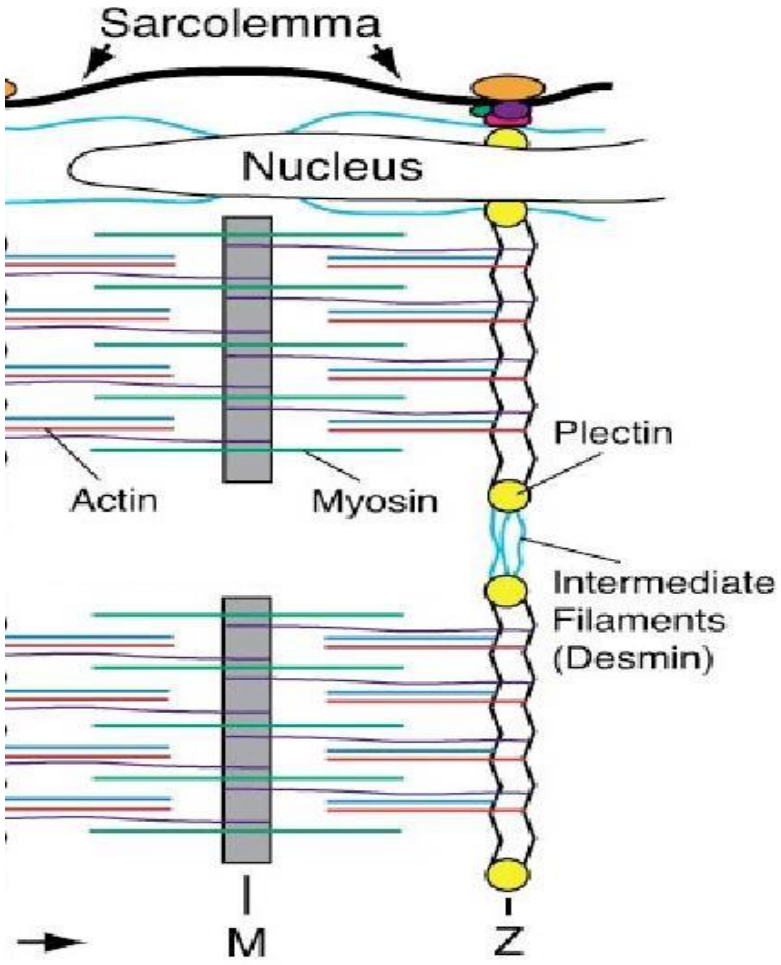
- **If these INTERMEDIATE FILAMENTS are mutated , they affect the activity of genes (gene expression) resulting in an abnormal gene activity as well as some diseases like Marie-Charcot-Tooth disease. (IFs ARE REALLY IMPORTANT !)**



Intracellular Organization of IFs (*Muscle cells)*

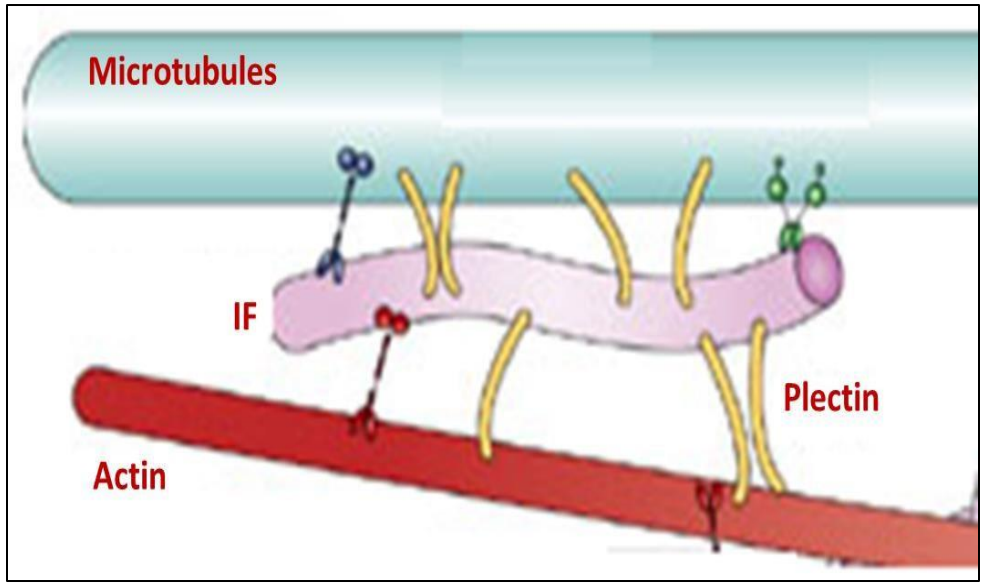
- The IF desmin **(type III intermediate filaments in muscle cells)** connects the actin filaments in muscle cells to one another and to the plasma membrane , thereby linking the actions of individual contractile elements.

➢ **<u>INTERMEDIATE FILAMENTS</u> play a major role in organizing actin filaments inside muscle cells (connect them to each other) , as a result , they regulate muscle contraction.**

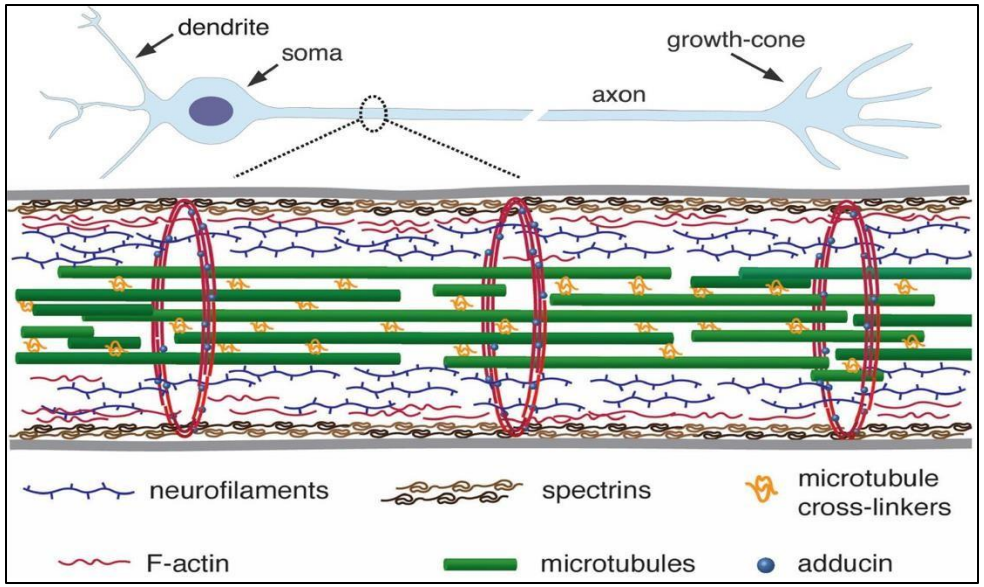


Intracellular Organization of IFs (*Neurons)*

- Neurofilaments in axons of mature neurons bridge actin filaments and microtubules stabilizing them and increasing the mechanical stability of the cell.



➢ **INTERMEDIATE FILAMENTS in neurons connect MICROTUBULES to the ACTIN MICROFILAMENTS , so they support them.**



➢ **This is an overview of the axon , AFs exist near the plasma membrane. MTs are those thick , green filaments. IFs exist in the middle connecting MTs to Afs providing mechanical stability & support for the axon and the neuron overall.**

Intracellular Organization of IFs (*Epithelial cells)*

➢ **There are specialized structures in epithelial cells like focal adhesions , adherens junctions or desmosomes.**

- The intermediate filaments provide mechanical stability to the tissue at desmosomes and hemidesmosomes

➢ **Desmosomes and hemodesmosomes are specialized structures exist in the plasma membrane of epithelial cells). They support the whole tissue by cell-cell or cell-matrix interactions .**

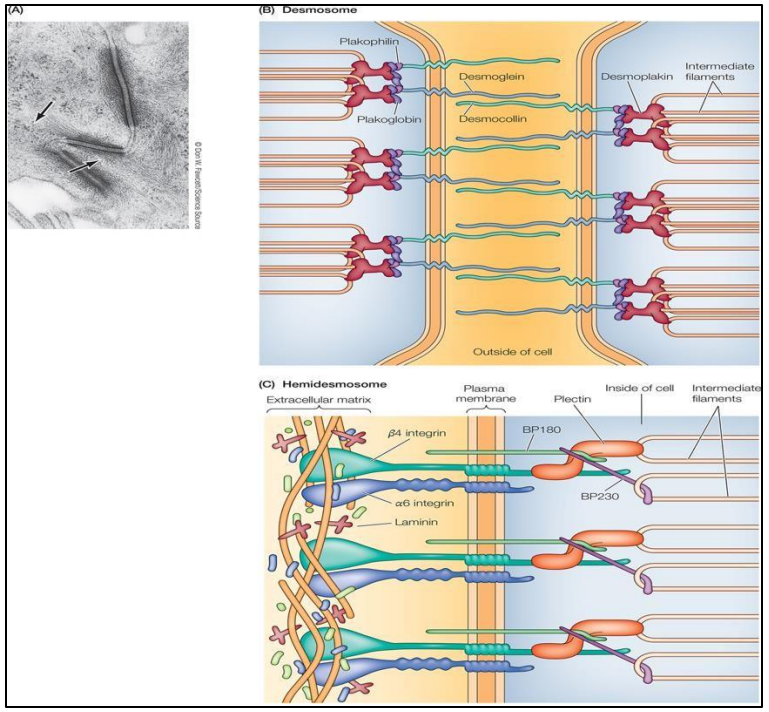
- **Desmosomes** : Junctions between cells connected to each other via cadherin-like transmembrane proteins and intermediate-binding proteins (similar to adherens junctions).

- **Hemidesmosomes** : Junctions linking intermediate filaments to the extracellular matrix via integrins (transmembrane receptors) and intermediate filament-binding proteins (like focal adhesions).

❖ TO BE CONTINUED

Desmosomes

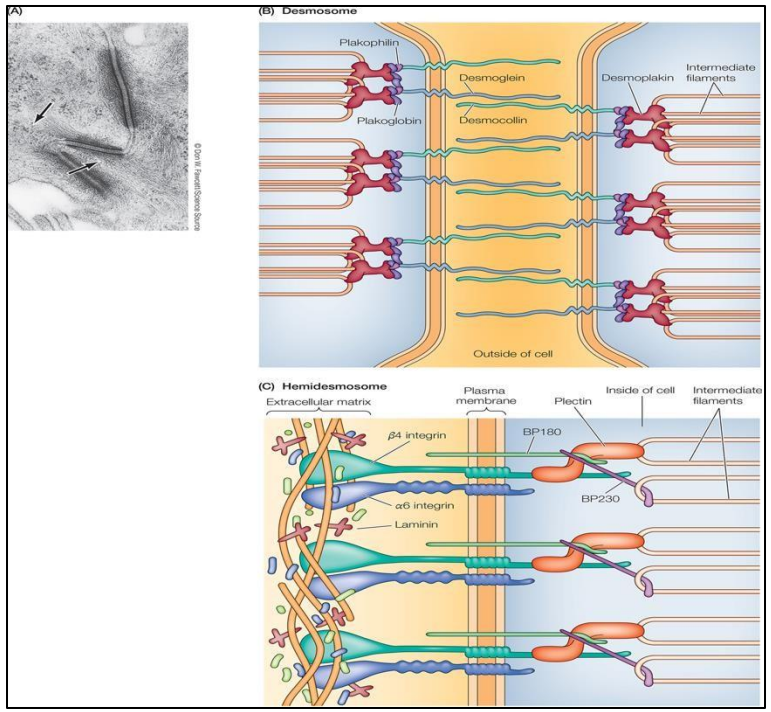
Cell-cell contacts



- In desmosomes we have interaction between receptors (transmembrane proteins like Catherine-like transmembrane proteins) of both cells , they contact each other.
- These proteins interact with intracelluar proteins (IFs binding proteins) which interact with IFs .
- They are similar to adherens junctions where we have the cadherins interact with actin filaments via catenins.

Hemidesmosomes

Cell-substratum contacts



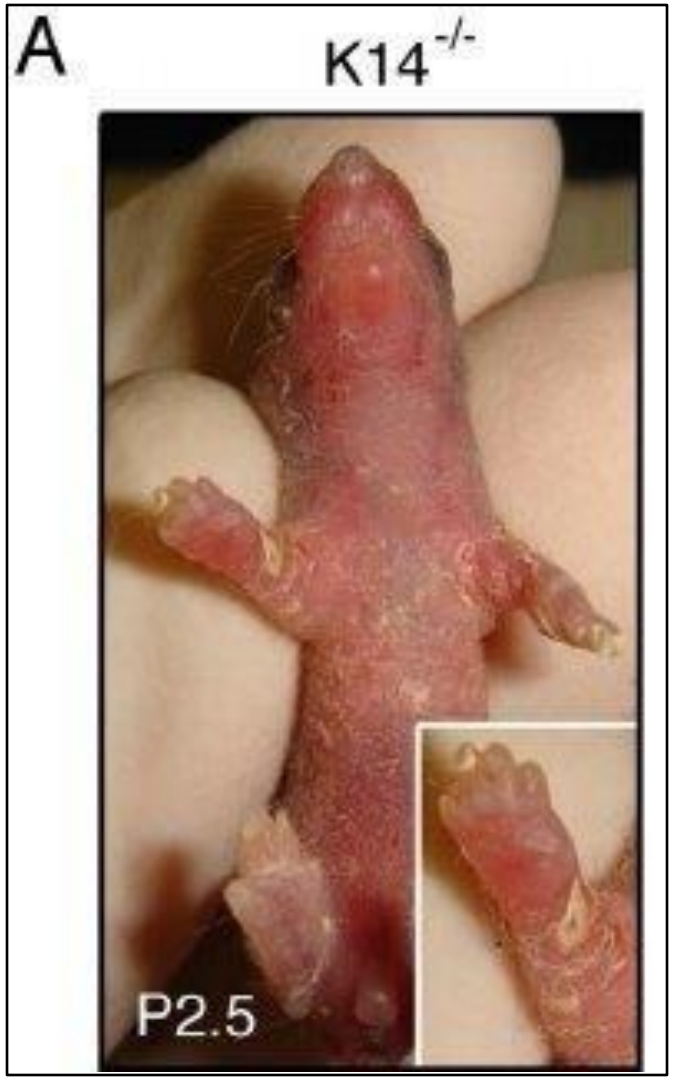
- In hemidesmosomes we have interaction between transmembrane receptors on the cell surface (integrins) , which react with IFs inside the cell via specialized proteins on one side , and with matrix proteins on the other side , so we have indirect connection between IFs inside and the matrix proteins outside. So , anything happens outside the cell can be sends inside the cell by changing the structure of the IFs (like focal adhesions)

IFs and diseases

- It appears that the primary role of intermediate filaments is to strengthen the cytoskeleton of cells in the tissues of multicellular organisms.

➢ **In one famous experiment , one of the intermediate filaments was mutated in mice . That resulted in development of blisters (حبوب/ بثور) of injuries in the skin of the mice. The skin became vulnerable , susceptible to injury and mechanically sensitive to pressure , stress or abrasions(احتكاك / خدش)**

Transgenic mice expressing mutated keratins suffer from severe skin abnormalities (blisters due to epidermal cell lysis following mild mechanical trauma).

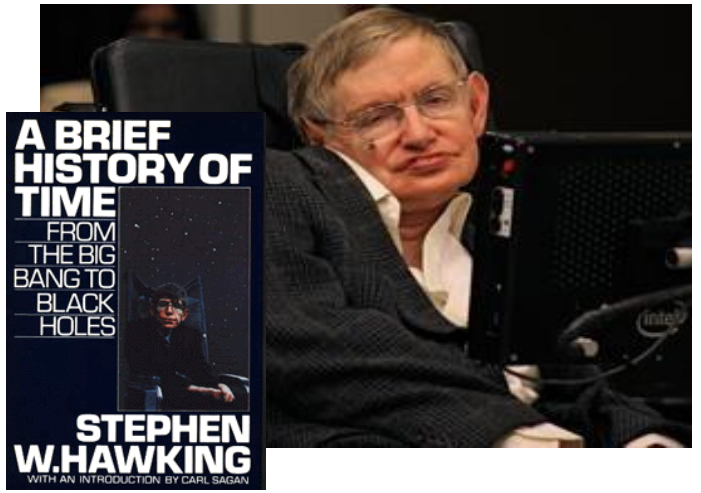


Human diseases

- Human epidermolysis bullosa simplex is caused by keratin gene mutations that interfere with the normal assembly of keratin filaments.

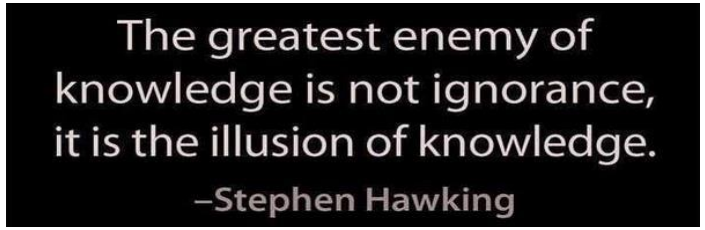
➢ **This condition is caused by a defective keratin (mutation in keratin genes) and that results in defective skin that is susceptible or vulnerable. It becomes injured quite easily because it is not stable or strong.**

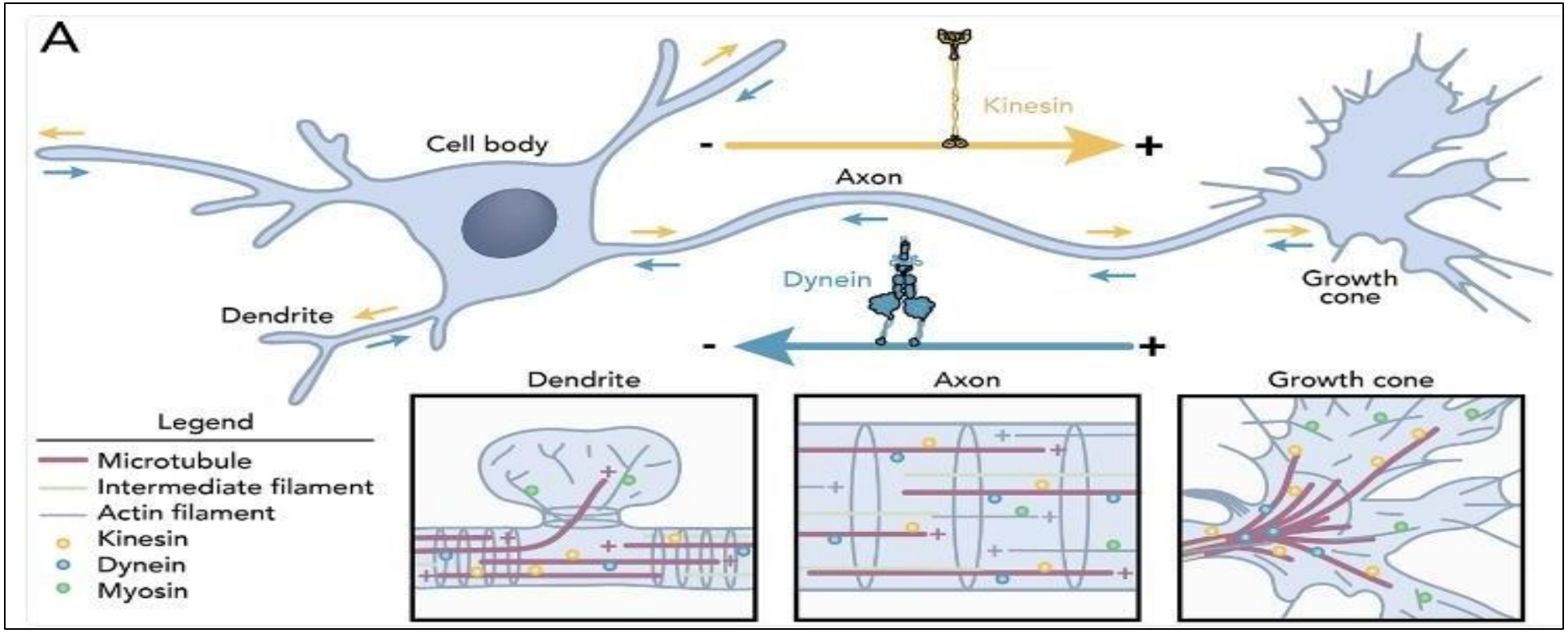
- Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease is characterized by the accumulation and abnormal assembly of neurofilaments.



➢ **This condition can be caused by different factors like mutations in lamin A (the IFs nuclear skeleton protein) OR because of abnormalities in microtubule motor protein (kinesin). ALSO, it can be caused by defective neurofilaments.**

➢ **The most famous person affected by ALS is STEPHEN W.HAWKING , the writer of "A BRIEF HISTORY OF TIME" book.**





Exp Neurol. 2022 September ; 355: 114143. doi:10.1016/j.expneurol.2022.114143.

Multiple roles for the cytoskeleton in ALS

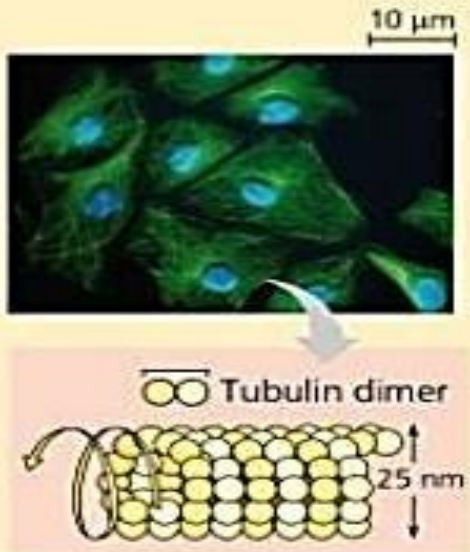
Xinbei Liu[a], Jessica L. Henty-Ridilla[a,b,*]

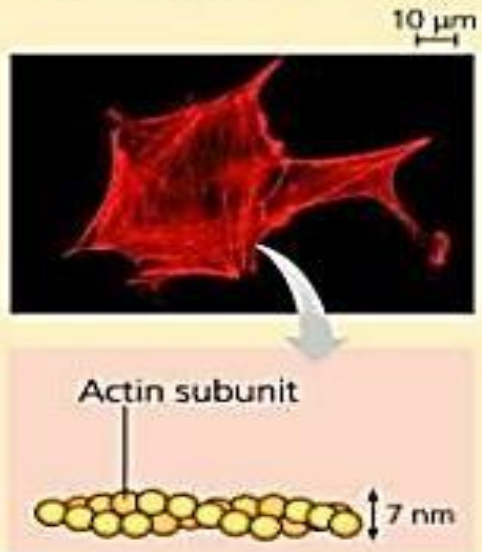
- This figure takes about ALS and the significance of the cytoskeletal protein in ALS (Defective KERATIN , Defective ACTIN BINDING PROTEINS , Defective MICROTUBULE MOTOR PROTEINS) all can cause ALS .
- That shows how this cytoskeletal systems are connected to each other and how the three of them are important in the biology of nerve cells and the normal physiology of the CNS .

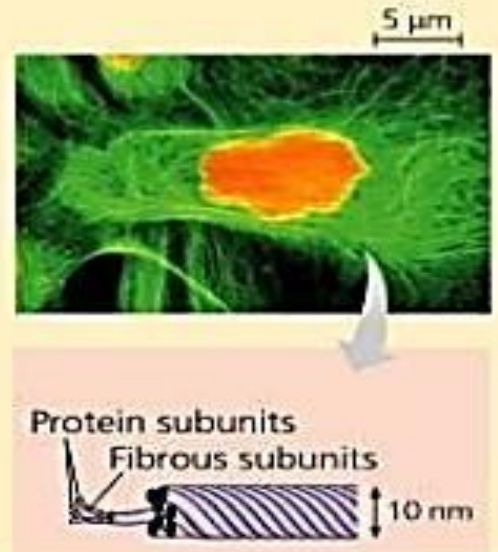
اَلْحَمْدُ لِلّٰه

Table 7.2 The Structure and Function of the Cytoskeleton

Property	Microtubules	Microfilaments (Actin Filaments)	Intermediate Filaments
Structure	Hollow tubes; wall consists of 13 columns of tubulin molecules	Two intertwined strands of actin	Fibrous proteins supercoiled into thicker cables
Diameter	25 nm with 15-nm lumen	7 nm	8–12 nm
Protein subunits	Tubulin, consisting of α-tubulin and β-tubulin	Actin	One of several different proteins of the keratin family, depending on cell type
Main functions	Maintenance of cell shape (compression-resisting "girders") Cell motility (as in cilia or flagella) Chromosome movements in cell division Organelle movements	Maintenance of cell shape (tension-bearing elements) Changes in cell shape Muscle contraction Cytoplasmic streaming Cell motility (as in pseudopodia) Cell division (cleavage furrow formation)	Maintenance of cell shape (tension-bearing elements) Anchorage of nucleus and certain other organelles Formation of nuclear lamina







Additional Resources:

رسالة من الفريق العلمي:

﴿ يَا زَكَرِيَّا إِنَّا نُبَشِّرُكَ ﴾

وَهَنَ عَظْمُهُ،
وَاشْتَعَلَ رَأْسُهُ شَيْبًا،
وَكَانَتِ امْرَأَتُهُ عَاقِرًا،
لَكِنَّهُ كَانَ يَعْرِفُ أَنَّ الأَسْبَابَ تَحْكُمُ النَّاسَ،
وَلَا تَحْكُمُ اللَّهَ جَلَّ فِي عُلَاه.

فَرَفَعَ يَدَيْهِ وَدَعَا: ﴿ فَهَبْ لِي مِن لَّدُنكَ وَلِيًّا ﴾
فَجَاءَتْهُ الِاسْتِجَابَةُ: ﴿ يَا زَكَرِيَّا إِنَّا نُبَشِّرُكَ بِغُلَامٍ ﴾

مَنْ عَلَّقَ قَلْبَهُ بِالأَسْبَابِ، تَرَكَهُ اللَّهُ إِلَيْهَا!
وَمَنْ عَلَّقَ قَلْبَهُ بِاللَّهِ، هَيَّأَ لَهُ الأَسْبَابَ!

من كتاب رسائل من القرآن - أدهم الشرقاوي

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			