

YTOLOGY

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Sheet

Slides

Number

18

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Intermediate filaments

Intermediate filaments (IFs)

- ✓ Their diameter is intermediate between those of actin filaments and microtubule.
- ✓ They provide mechanical strength to cells and tissues.
- ✓ They provide a scaffold for localization of cellular processes
- ✓ Not involved directly in cell movement.
- ✓ They are composed of a variety of proteins, which are classified into 5 groups based on similarities between their amino acid sequences.

-IF are intermediate in size and in connecting microtubules to actin filaments

* we cannot connect them directly, they must be connected by IF

-Their function:

1) They contribute to the shape as they extend as a network through the cytosol (they start next to the nucleus and extend toward the plasma membrane).

2) Localization of cellular processes

-They act *as a scaffold*: a place where certain proteins and molecules with specific functions are collected together in order to prepare for a specific process.

-They are not involved in cell movement:

The movement of the cell is done by **actin filaments** and the internal movement of vesicles and organelles *are* done by **the microtubules**.

Types of IFs Proteins

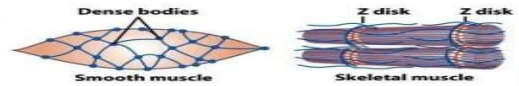
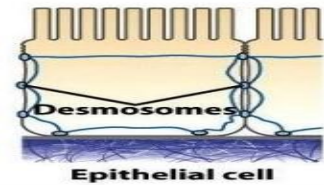
Types I and II are expressed in epithelial cells

Each cell type synthesizes at least one type I (acidic) and one type II (neutral/basic) keratin.

- **Hard** keratins are used for production of structures such as hair, nails, and horns.
- **Soft** keratins are abundant in the cytoplasm of epithelial cells.

Type III:

- Vimentin is found in fibroblasts, smooth muscle cells, and white blood cells.
- Desmin is specifically expressed in muscle cells.



SOME NOTES

-Depending **on the monomer proteins** they are classified into **5 types**.

*The monomers in different types of **IF** are going to form **dimers**.

***Type I** and **Type II** are composed of keratin and found **in epithelial cells**.

They are going to form Hetrodimers (**2 different types of keratin**) one **acidic** and one (**basic or neutral**).

-keratins are either **hard or soft** depending on their location in the epithelial cells.

***Type III** is generally found in the **connective tissue**.

It can be found in fibroblasts, smooth muscle cells, and white blood cells (like Vimentin) Another example is Desmin, which can be found in the muscle tissue.

-Fibroblast:

A cell that is spindle in shape, its function is to lay down fibers found in different types of tissues (not specialized to a specific tissue).

*when having a deep wound or burn, instead of replacement of the damaged tissue by the specialized cells the fibroblasts **produce fibers that lead to a scar**.

But in the case of a superficial wound everything returns to normal because of the *correct wound healing*.



*Type IV:

The importance of* the presence of **NF in *the axons*:

The axon is long and contain microtubules, although the **MT** are longer in structure than **IF** but they need some support (mechanical support and some protection)

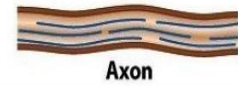
*Type V:

we have different types of lamins (lamin1,2...)

Types of IFs Proteins

Type IV: neurofilament (NF) found in mature neurons and the axons of motor neurons.

Nestin in stem cells



Type V: nuclear lamins, components of the nuclear envelope.



Stem cells are cells that can differentiate into several other types of cells

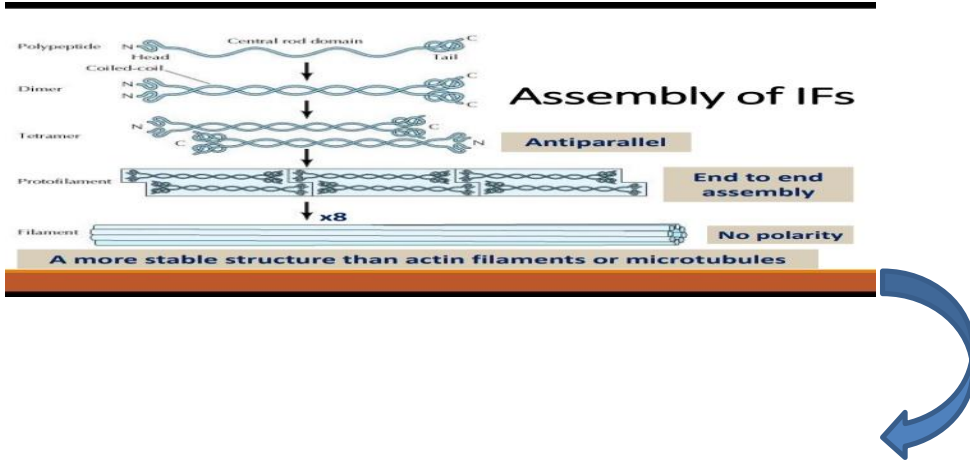
*The general and common structure of IF proteins:

Structure of IFs



A central α -helical rod domain for **filament assembly**

Flanking amino- and carboxy-terminal domains that vary among the different intermediate filament proteins in **size, sequence, and secondary structure** that determine **the specific functions of the different intermediate filament proteins**.



-Two polypeptides coil to form a dimer (either heterodimer or homodimer depending on the **type of the IF**) they coil head to head and tail to tail.

-The dimer will interact with another dimer to form tetramer (N-terminus of the first dimer is close to C terminus of the second dimer, i.e they interact head to tail & tail to head (**antiparallel**) to provide better structure in term of mechanical strength and allow compaction.

-then this tetramer is going to bind end to end to assemble a protofilament (at each end of the protofilament we have 2 head and 2 tails, and this indicate that there is no polarity in the IF).

-then **8** of the protofilament are going to organize next to each other to form the final structure of the IF.

-so far, the IF differs that they **do not** have polarity and they **do not** bind to **GTP or ATP**, yet they are dynamic structures.

*some notes



*Keratin form heterodimers.

*Type III forms either:

(homodimers) e.g., vimentin.

(heterodimers) e.g., vimentin + desmin.

Interaction of IF types

- ✓ Keratin filaments are always assembled from heterodimers containing one type I and one type II polypeptide.
- ✓ The type III proteins can assemble into filaments containing only a single polypeptide (e.g., vimentin) or consisting of two different type III proteins (e.g., vimentin plus desmin).
- ✓ The type III proteins do not form copolymers with the keratins.
- ✓ α -internexin, a type IV protein, can assemble into filaments by itself, but the NFs copolymerize to form heteropolymers.
- ✓ Phosphorylation affects the assembly and disassembly of IFs.

*An example of NF is alpha internexin that form a homodimer, but after making the protofilament it possible to connect it to different polymers forming heteropolymers.

The disassembly is going to be regulated by the phosphorylation of the protein by **the kinase enzyme.**

The **heads** and the **tails** are **phosphorylated.**

The **phosphate groups** have negative charges and they are going to repulse each other leading to disassembly of the filament.

And **the size of the phosphate groups** will **contribute** in separating them from each other.

They will disassemble at the end to be in a **stable state**

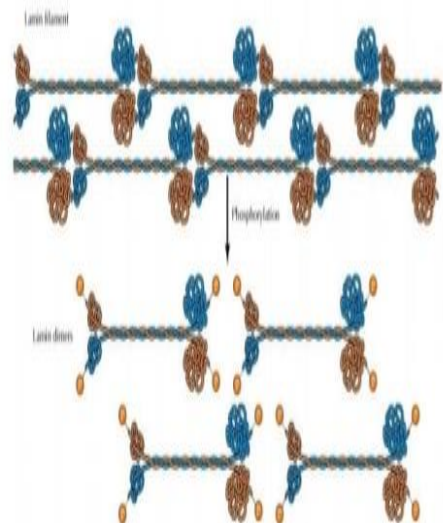
IFs versus actins and microtubules

More stable

More dynamic within cells

Not regulated by GTP, but regulated by phosphorylation

When nuclear lamins and vimentins are phosphorylated, they disassemble.

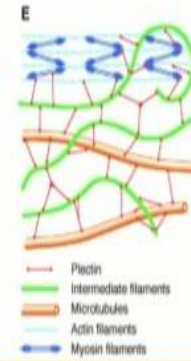


Intracellular Organization of IFs

IFs form an elaborate network in the cytoplasm extending from a ring surrounding the nucleus to plasma membrane

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

IFs can associate not only with the plasma membrane but also with the actin filaments and microtubules.



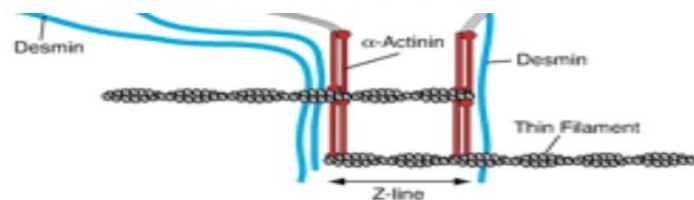
IFs provide a scaffold that integrates the components of the cytoskeleton and organizes the internal structure of the cell.

*connecting microtubules to actin filaments is going to be through the

IF are not going to be connected directly to the microtubules ..., AF, they need a connector protein

Desmin IFs in muscles

Desmin connects the actin filaments in muscle cells to one another and to the plasma membrane, thereby linking the actions of individual contractile elements.



Desmin mutations cause muscle defects such as early onset cardiomyopathy

the contractile unit (actin + **myosin**) must be held strongly because the contraction and relaxation of muscles involve a lot of forces, so we must have a mechanical stability of the structure, so the actin filaments must be hold in place ... **how**??

-The actin bundles are cross-linked by alpha actinin. They are also bound together by IF made of Desmin.

*If a person **has a mutation in Desmin** the structure of the contractile unit will be **weak**, so he will suffer **from early onset cardiomyopathy**.

AN EXAMPLE

**The death of a player while playing a sport like football
Because of heart failure.**

**This player undergoes a high stress and activity, so his heart
must make a double effort (the number of heartbeats will be
much higher than normal)**

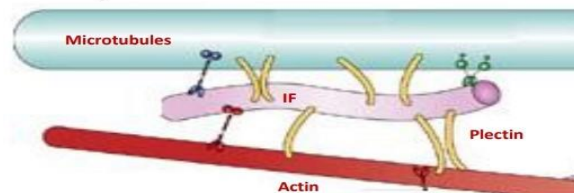
**He challenges his heart with an effort that cannot be exerted
by his heart → lead to failure in heart → may
lead to death**

Neurofilaments in neurons

➤ Neurofilaments in mature neurons are anchored to actin filaments and microtubules by neuronal members of the plakin family.

➤ Neurofilaments provide mechanical support and stabilize the cytoskeleton in the long, thin axons of nerve cells.

Plectin connects IFs to other cytoskeletal elements



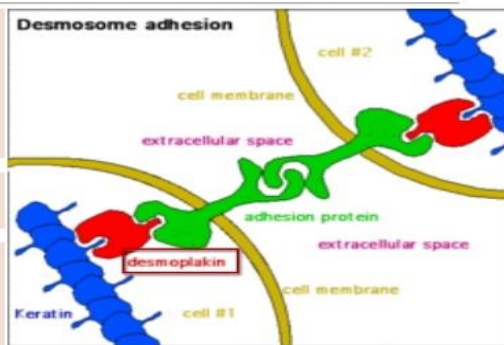
Plectin bridges microtubules to actin filaments and stabilizing them and increasing the mechanical stability of the cell.

Cellular Junctions: Desmosomes

The keratin filaments of epithelial cells are tightly anchored to the plasma membrane at two areas of specialized cell contacts, desmosomes and hemidesmosomes

Desmosomes anchor IFs to regions of cell-cell contacts

Keratin filaments anchored to both sides of desmosomes serve as a mechanical link, thereby providing mechanical stability to the entire tissue.



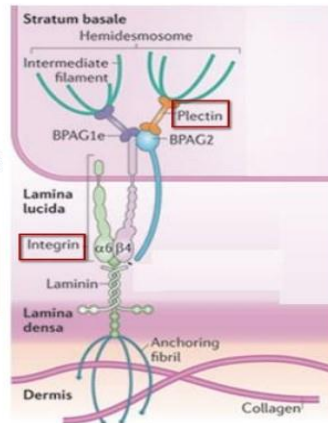
HEMIDESOSOMES

*Hemidesmosome junction connects the cell to the extra cellular matrix so I have half of the components

***so, we have the membrane proteins (integrin) connected through the connected protein (plectin) to the IFs.

Hemidesmosomes

Hemidesmosomes anchor IFs to regions of cell-substratum contacts



APPLICATION : IFs and diseases

* Previously it was thought that the IFs are not important and if a mutation occurs in them, it will not cause any affect .

*an experiment was done to show the importance of the IFs:

-caused a mutation in a keratin gene and this gene is inserted into a plasmid (a circular DNA molecule) structure.

-then the plasmid is injected into a fertilized egg (zygote). This plasmid may as well have other genes that induce and help its insertion into the genomic DNA then the mutated gene will be expressed .

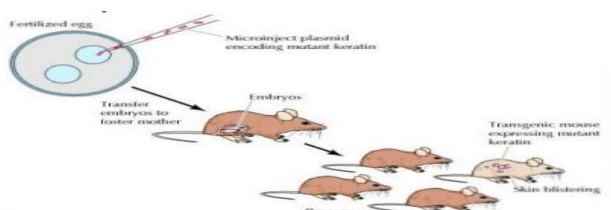
-the zygote is transferred and implanted into a mouse uterus.

-the result : some embryos are affected with the mutated keratin .

***why having skin abnormalities ?**

Because there is a problem in the keratin that present in the skin so any small trauma will cause blisters (a bubble filled with liquid) this blisters will pop causing exposure of the layers under the skin to

bacteria and viruses leading to infections .



IFs and Human diseases

Human epidermolysis bullosa simplex is caused by keratin gene mutations that interfere with the normal assembly of keratin filaments causing skin blisters after minor trauma.

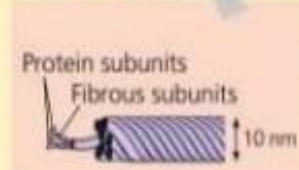
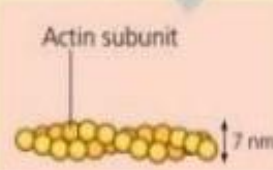
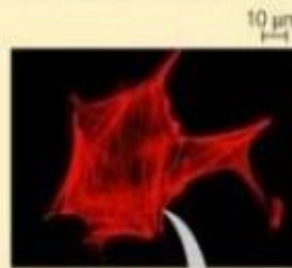
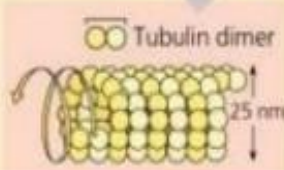
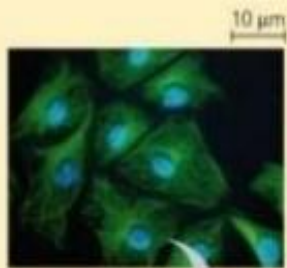


Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease is characterized by the accumulation and abnormal assembly of neurofilaments.



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



لا تنهزم يوم الصعاب ولا
تهن هي غيمة صيف عابرة

