CYTOLOGY

Premed 2018 - JU

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Number

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In this chapter, we covered the following topics:

1)What is the cytoskeleton.

2)What is the actin filaments structure and function.

3)Formation of actin filament.

4)Actin-binding protein.

5)Types of actin filaments.

6)Actin fibers in the cell

7) Spectrin as a structural component of cortical cytoskeleton.

8) Actin filaments-plasma membrane interaction (specifically with the spectrin-actin network)

Now we are going to talk about **other types of connecting proteins that connect the cell cortex (actin filaments) to the cell membrane:**

-The type of the connecting molecule depending on the cell type.

-They act as linkers between the filaments and the cell membrane (the same as spectrin).

Examples:

1) **The ERM** proteins (protein 4.1-related) link actin filaments to the plasma membranes of *different kinds of cells*.

2) **Filamin** (spectrin-related) links actin filaments with the plasma membrane of *blood platelets*.

3) **Dystrophin** (spectrin-related proteins) links actin filaments to transmembrane proteins of *the muscle cell plasma* membrane and the latter link the cytoskeleton to the extracellular matrix.

- This maintains cell stability during muscle contraction.

Dystrophin and muscular dystrophies

-The dystrophin protein could face inherited genetic mutations during development.

-Depending on the different types of mutations that are going to be present in dystrophin protein, we are going to have different phenotypes for the same disease (different degrees of the same disease).

-Mutations in the gene cause two types of muscular dystrophy, **Duchenne's** (severe) and **Becker's** (moderate).

-X-linked inherited diseases.

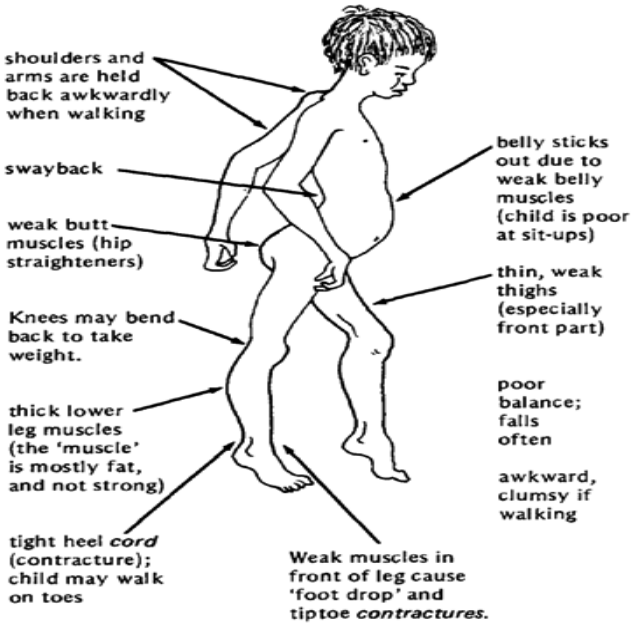
-Progressive degeneration of skeletal muscle.

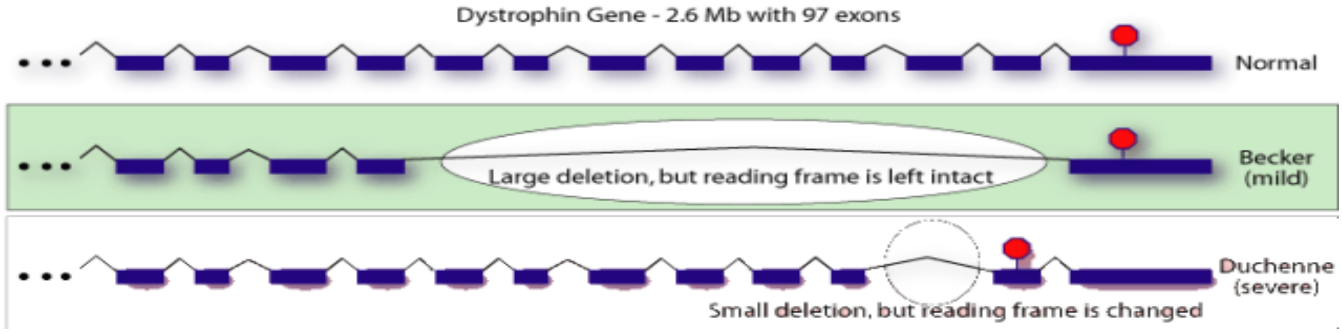
-Patients with Duchenne's muscular dystrophy usually die in their teens or early twenties.

- Look at the picture below, we notice that the patient loses a big part of the dystrophin gene in Beker's type and has a small deletion with a frameshift in Duchenne's type.

Why Duchenne's is more severe?

*The deleted small part could be an uncompleted codon which leads to a change in all codons and a completely different polypeptide chain.

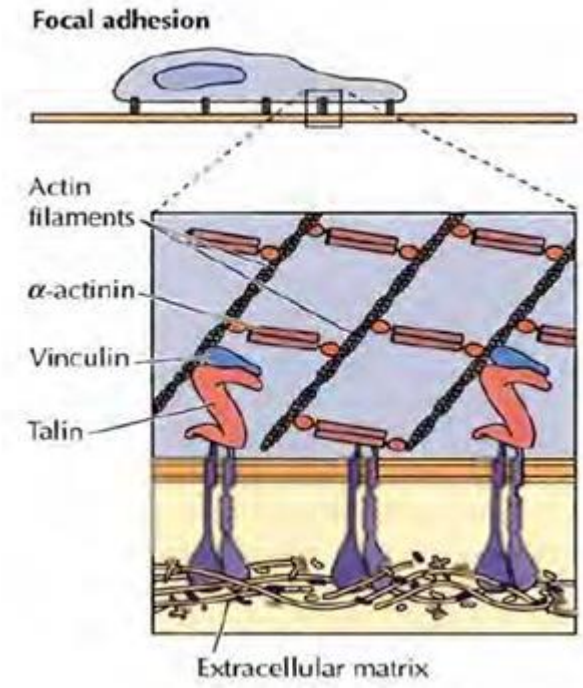




Focal adhesion

***Another role in which the actin filaments are involved is **the formation of focal adhesion**.

* Specialized regions that serve as attachment sites for bundles of actin filaments (stress fibers) that anchor the cytoskeleton (and cells) to areas of cell contact or to extracellular matrix via the binding of transmembrane proteins (called **integrins** form different types of dimers) to the extracellular matrix.



* The two dimers are usually not similar integrins.

Hint: integrins ⟶ البروتينات اللي بتلزّق ^^

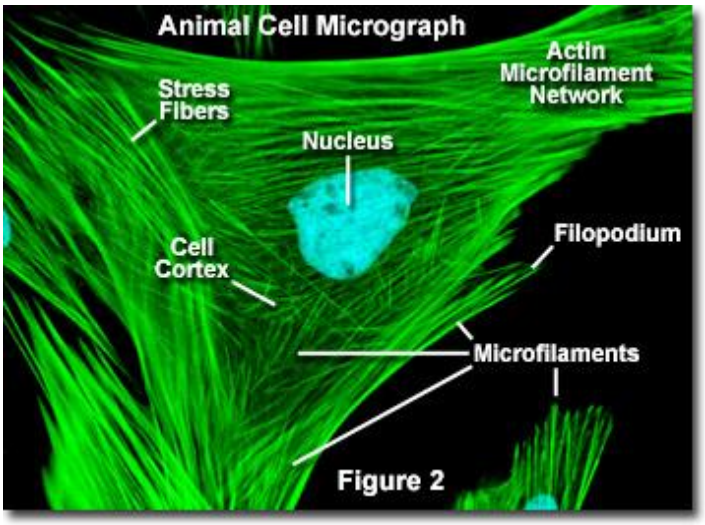
⟶ they are present in the plasma membrane as integral membrane proteins. Also , they are mostly involved in the attachment of cells together and formation of different types of adhesions in between the cells.

The integrins are going to interact with the actin filaments with the cell cortex indirectly by other proteins which are talin and vinculin in this case.
Then the extracellular side of the integrins is going to bind components of the extracellular matrix or with another integrin in another cell (adjacent cell).

Stress fibers are contractile bundles of actin filament that form under stress conditions.

The stress fibers are crosslinked by α-actinin.

* These associations, are mediated by several proteins, including talin and vinculin.



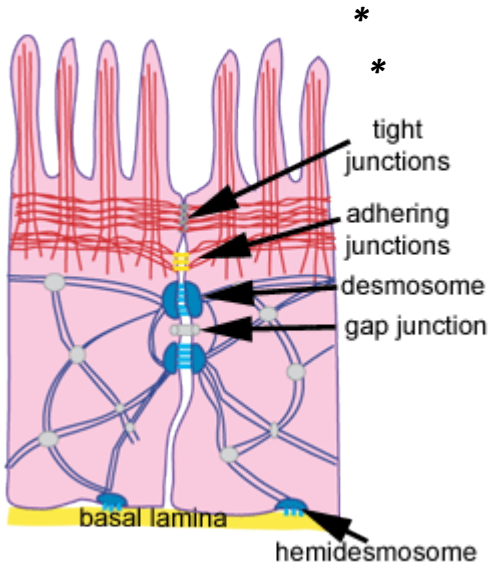
Adherence junctions

* A type of connections (adhesions) between different cells (OR between cells and extracellular matrix) , specifically between epithelial cells (compact and connecting cells).

* Regions of **cell-cell contact** to which actin cytoskeleton is anchored.

Found specifically in epithelial cell.

They form a continuous belt like structure (**adhesion belt**) around each cell in which an underlying contractile bundle of actin filaments is linked to the plasma membrane.

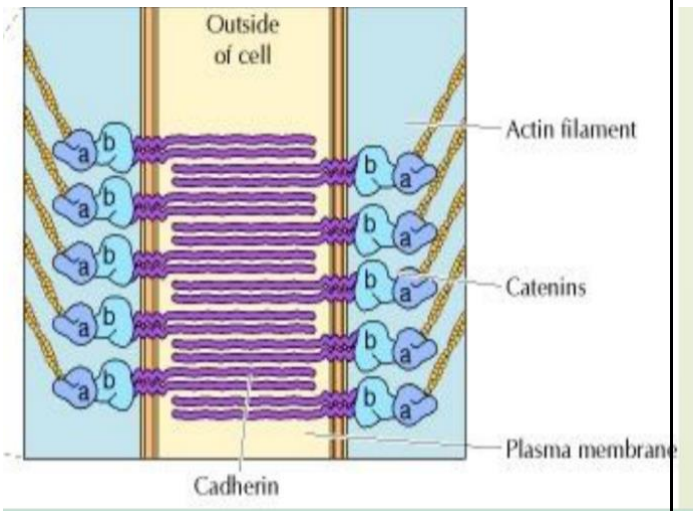


* Contact between cells is mediated by cadherins transmembrane proteins that form a complex with cytoplasmic proteins called catenins, which associate with actin filaments.

* a ⟶ actin.

* b ⟶ cadherin (membrane protein).

*In adherens junctions ⟶ Different molecules (here a & b) ⟶ Different sizes ⟶ Different spaces between cells (Small molecules ⟶ more tight ,and vice versa).

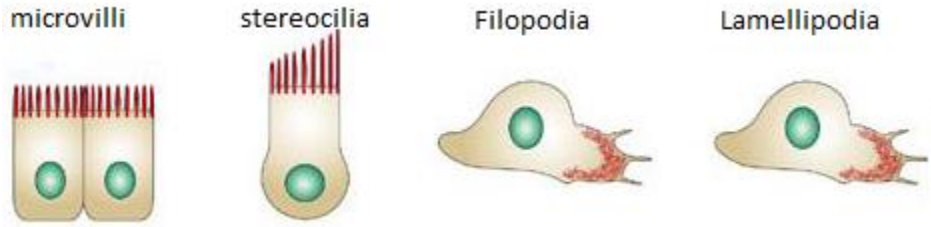


protrusions of the cell surface

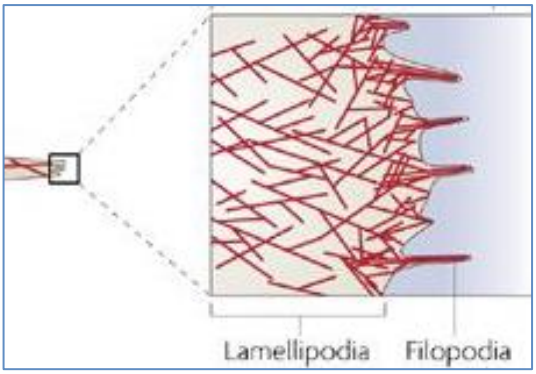
-The surfaces of cells have a variety of protrusions or extensions that **<u>are involved</u>** in: [1]cell movement,[2]phagocytosis, or [3]specialized functions, such as absorption of nutrients.

-Most of these cell surface extensions are based on **actin filaments**, organized into either [1]relatively permanent or [2]rapidly rearranging bundles or networks.

-Types of protrusions:



REMEMBER
lamellipodia: large protrusions of moving cell, and filopodia: protrusions of the protrusions (i.e. small projections that come out of lamellipodia)



-As example these cells, which lining trachea and bronchi (parts of the respiratory system), have cilia to collect microbes that enter our body during the process of inhalation.

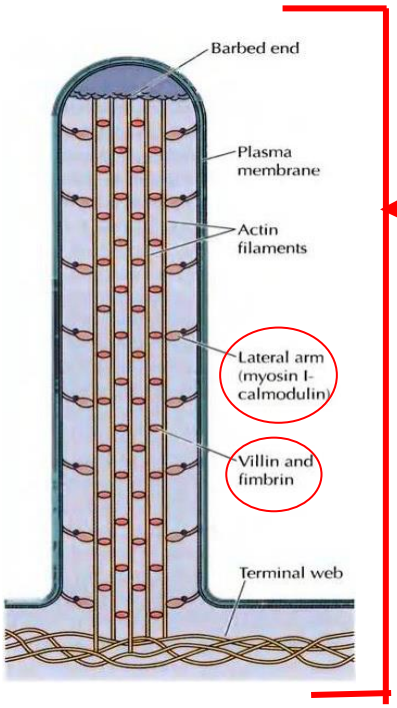
-Microvilli can be found in the apical surface of intestinal cells.

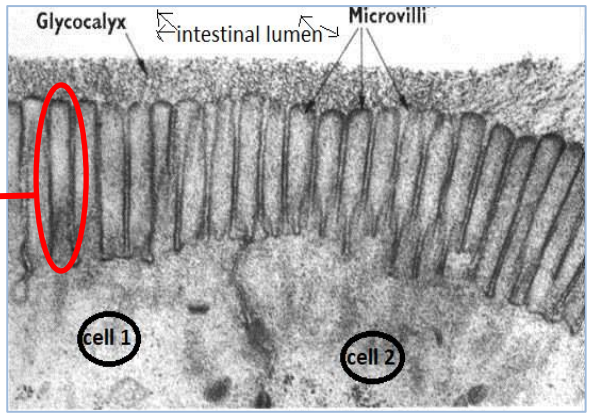
Microvilli

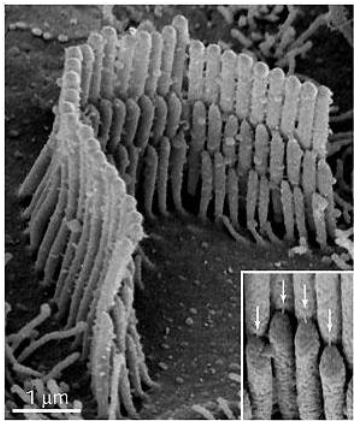
- It is fingerlike extensions of the plasma membrane (of the apical surface) that are particularly abundant on the surfaces of cells involved in absorption, such as the epithelial cells lining the intestine.

-How they increase the exposed surface area available for absorption? They form a layer on the apical surface (called a **brush border**).

- Microvilli form bundles inside them, to make this small and thin structure stand at this strong way, it need mechanical supports, so actin filaments have to rigid (even more rigid than the once present in muscle cells) by [1]making them close to each other (decrease the spaces between them by using cross linker proteins that are **<u>smaller</u>** in size than a-protein to make actin filaments very close to each other) [2]anchorage these bundles to the membrane by connecter protein.







*<u>**20-30**</u> closely packed parallel bundles

*Filament bundles are linked <u>**by villin (major) and fimbrin (cross-linker proteins).**</u>

*Attachment <u>to plasma membrane</u> is mediated <u>**by calmodulin and myosin I**</u> to assist in movement, (the mainly contact is through myosin I)

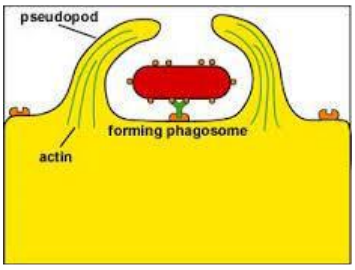
*Filaments are linked <u>to the cortex at the base</u> via a spectrin-rich region

Stereocilia

-specialized forms of <u>microvilli</u> on the surface of only limited number of cells like <u>auditory hair cells</u>, are responsible for hearing by detecting sound vibrations.

-make sure that since they are form of microvilli they have actin filaments, they have the same structure

Other protrusions



* The cell must have abundant amount of actin in order to get the force for making these protrusions.

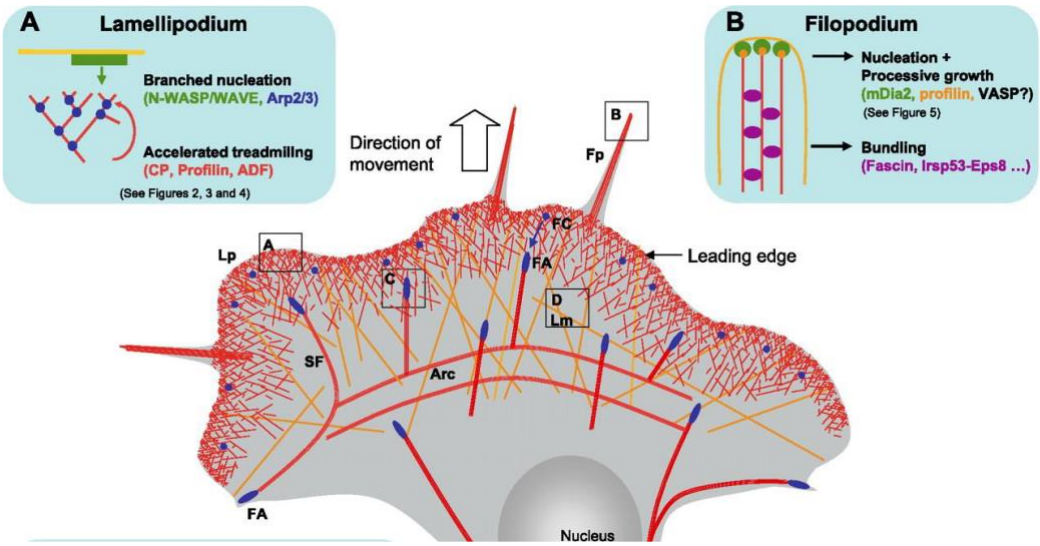
* There is much more polymerization and formation of actin filaments right underneath the membrane that protruding.

1) Pseudopodia: extensions of moderate width responsible for phagocytosis

2) Lamellipodia: broad, sheet-like networks of actin leading edge of moving fibroblasts

3) Filopodia: thin projections extending from lamellipodia

Cell migration



-Lamellipodia and Filopodia are projections extend from **certain region of the membrane** when the cell moving <u>(so when the cell is moving not all regions of the membrane is going to form Filopodia and lamellipodia)</u> , as well as , underneath this region there is high amount of actin filaments helping to push the membrane according to the direction of movement.

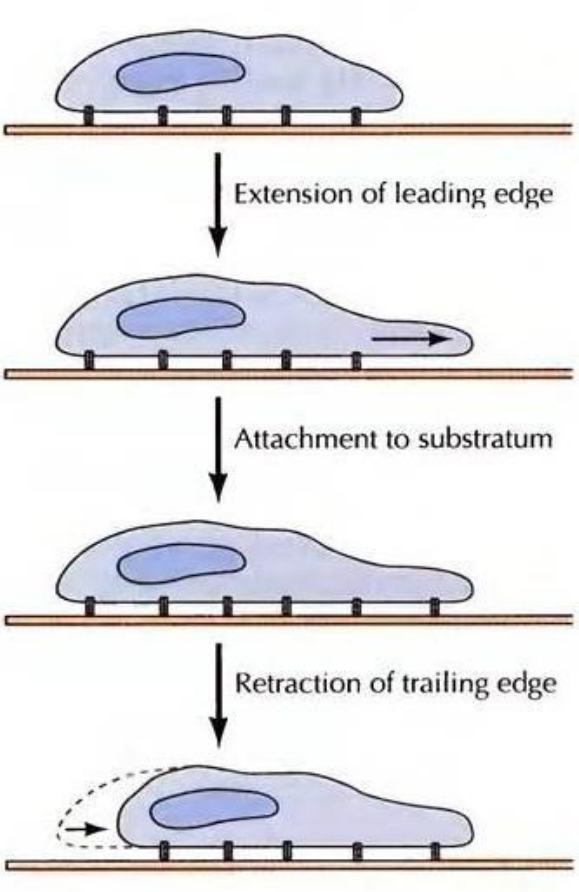
-movement process:

1) Develop polarity via specialization of the plasma membrane or the cell cortex according to where the cell is located.

2) Extend protrusions (lamellipodia, filopodia, pseudopodia) at the leading edge via the force of branching and polymerization of actin filaments.

3) Attach to substratum (e.g. **focal adhesions**) <u>(so it doesn't retraction)</u>

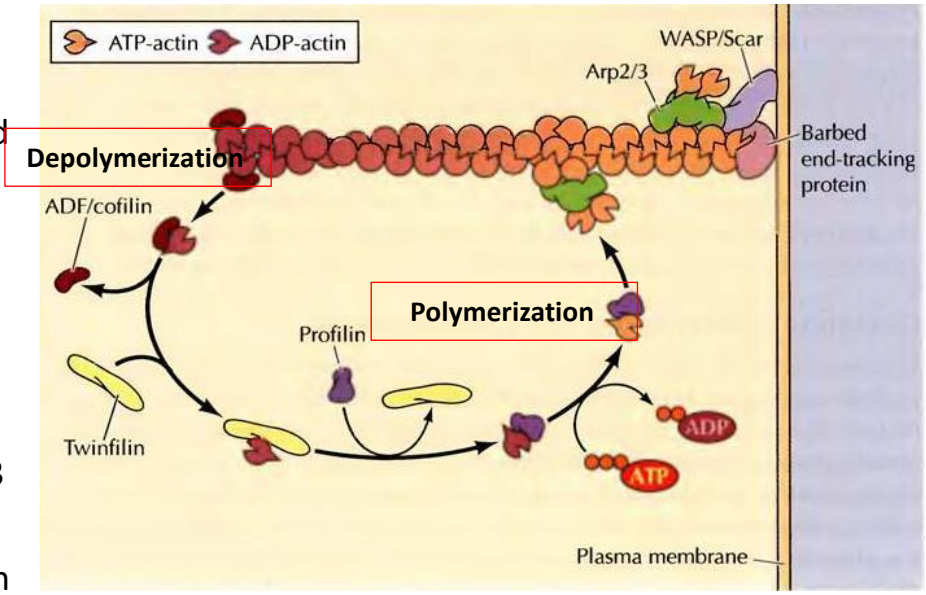
4) The trailing edge dissociates from substratum and retract into the cell body by breaking down the **focal adhesions** (because of the <u>mechanical stress</u> in the trailing edge which will appear)



Mainly focal adhesion is the type of adhesion involved in cell movement by forming (in the leading edge) and deforming (in the trailing edge)

Dynamics of actin filament at the leading edge

-Certain signals lead to the **recruitment** of [1]Arp2/3, [2]WASP/Scar, and [3]barbed-end tracking proteins to the leading edge, to do polymerization of actin filaments to push the membrane.



- WASP/Scar **activates** Arp2/3 initiating filament branching to provide more force to push against the membrane.

- At the pointed end, ADP-actin is disassembled by ADF-cofilin.

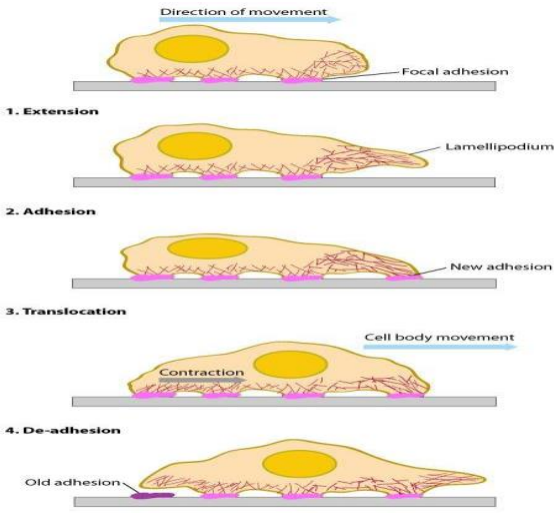
- ADP-actin monomers are carried to leading edge by **twinfilin and reactivated by profilin.**

modification of focal adhesions

- Cell-substratum attachment is **initiated** via transporting actin-bundling proteins and focal adhesion proteins (e.g., vinculin and talin) to the leading edge in connection with integrins.

- At trailing end, focal adhesions are broken down.

Note: This is true for slow moving cells like fibroblasts and epithelial cells, but rapidly moving cells like macrophages form diffuse contacts with the substratum whose composition is unknown.



قيل لابن المبارك : الى متى تطلب العلم ؟

فقال : لعل الكلمة التي تنفعني لم أكتبها بعد.