Lecture 18 Integrating cells into tissues I

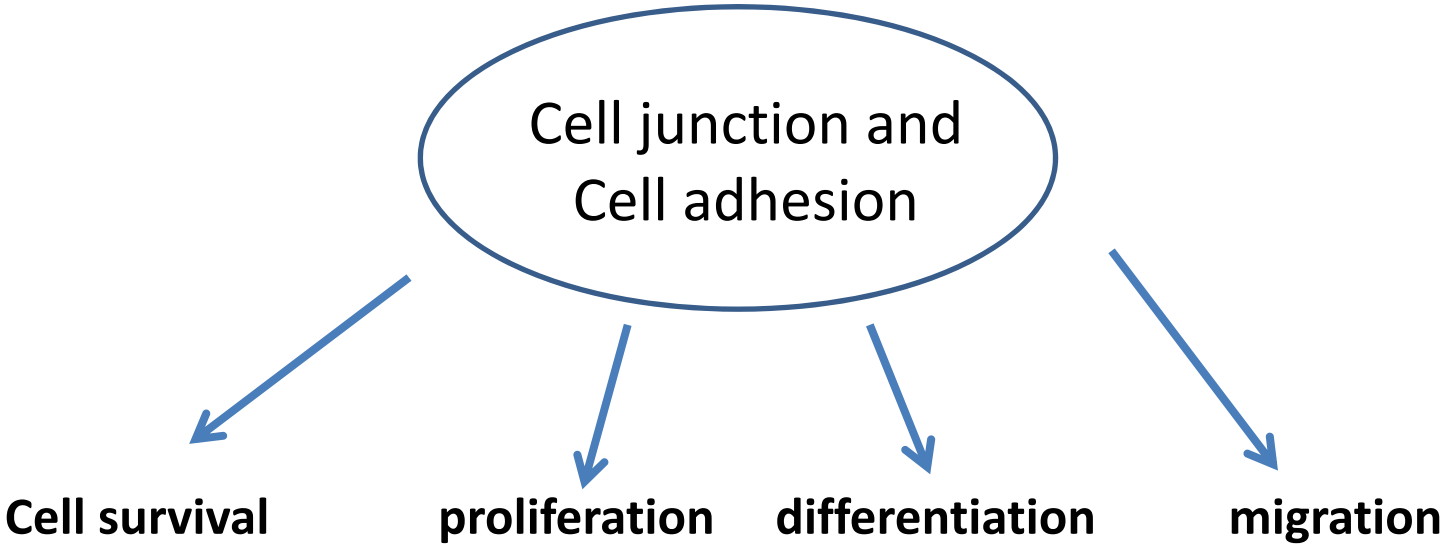
Outline

I. Cell-cell and cell-ECM (**e**xtra **c**ellular **m**atrix) junction and adhesion - an overview
II. Cadherins and cell- cell adhesion
III. Integrins in cell-ECM adhesion

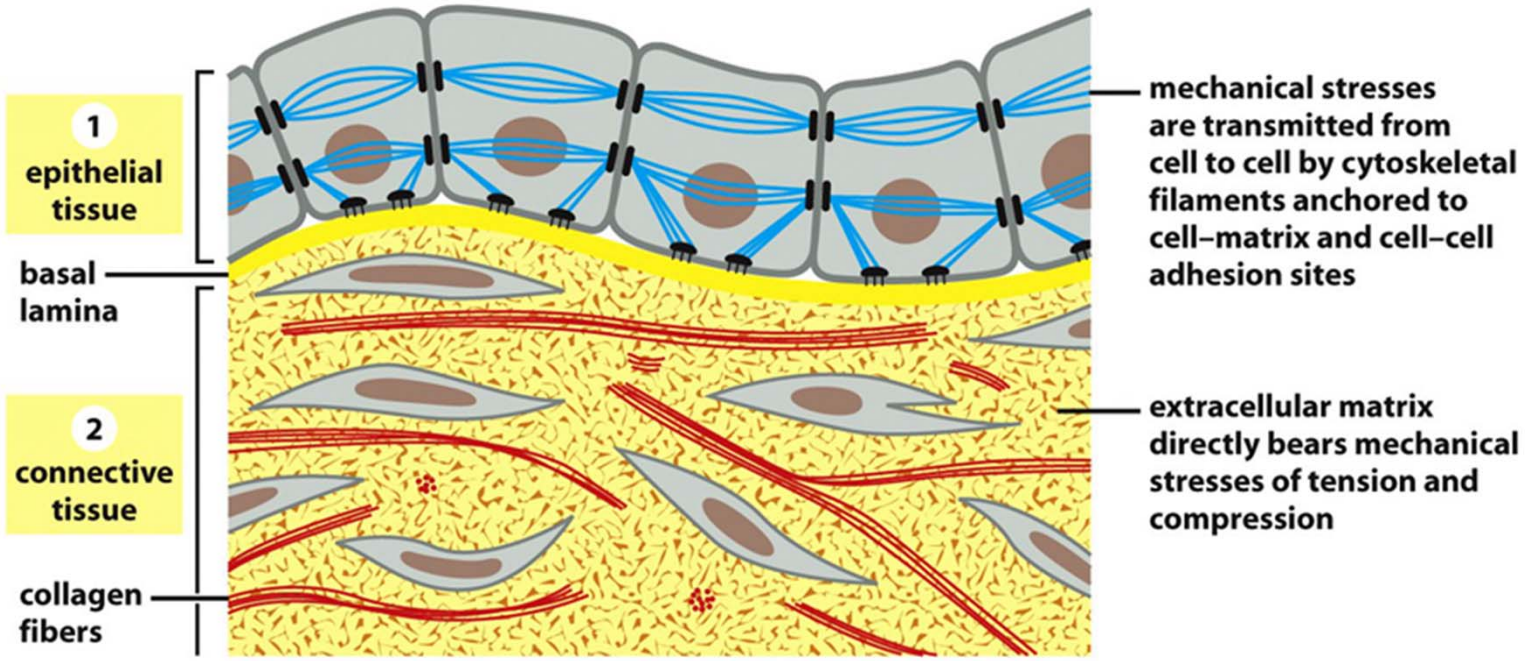
I. Cell junction and adhesion are very important for multicellular organisms

Allow cells to aggregate into distinct tissues

Bidirectional communication between interior and exterior of cells



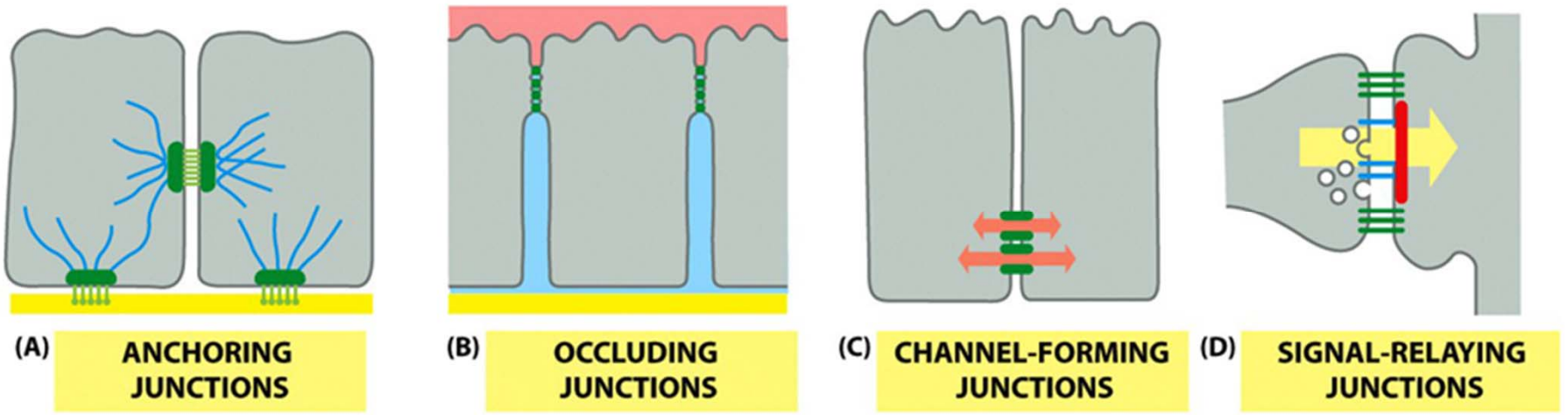
Epithelial and connective tissues:
two ways in which animal cells are bound together



- **Epithelial tissue (lining sheets)**:
  cell-cell junctions, cytoskeleton of the cell transmits mechanical stresses (from cell **to** cell via cell-cell adhesion sites <u>and</u> **to** the **basal matrix**)
- **Connective tissue (e.g. bones & tendon)** : Cell-ECM adhesions
  (**It is the matrix -rather than the cells-** that **bears most of the mechanical stress** to which the tissue is subjected)

The four major types of junctions

1. **Anchoring** junctions
2. **Occluding** junctions
3. **Channel-forming** junctions
4. **Signal relaying** junctions



Functional classification of cell junctions

ANCHORING JUNCTIONS

Actin filament attachment sites

1. cell–cell junctions (adherens junctions)
2. cell–matrix junctions (actin-linked cell–matrix adhesions)

Intermediate filament attachment sites

1. cell–cell junctions (desmosomes)
2. cell–matrix junctions (hemidesmosomes)

OCCLUDING JUNCTIONS

1. tight junctions (in vertebrates)
2. septate junctions (in invertebrates)

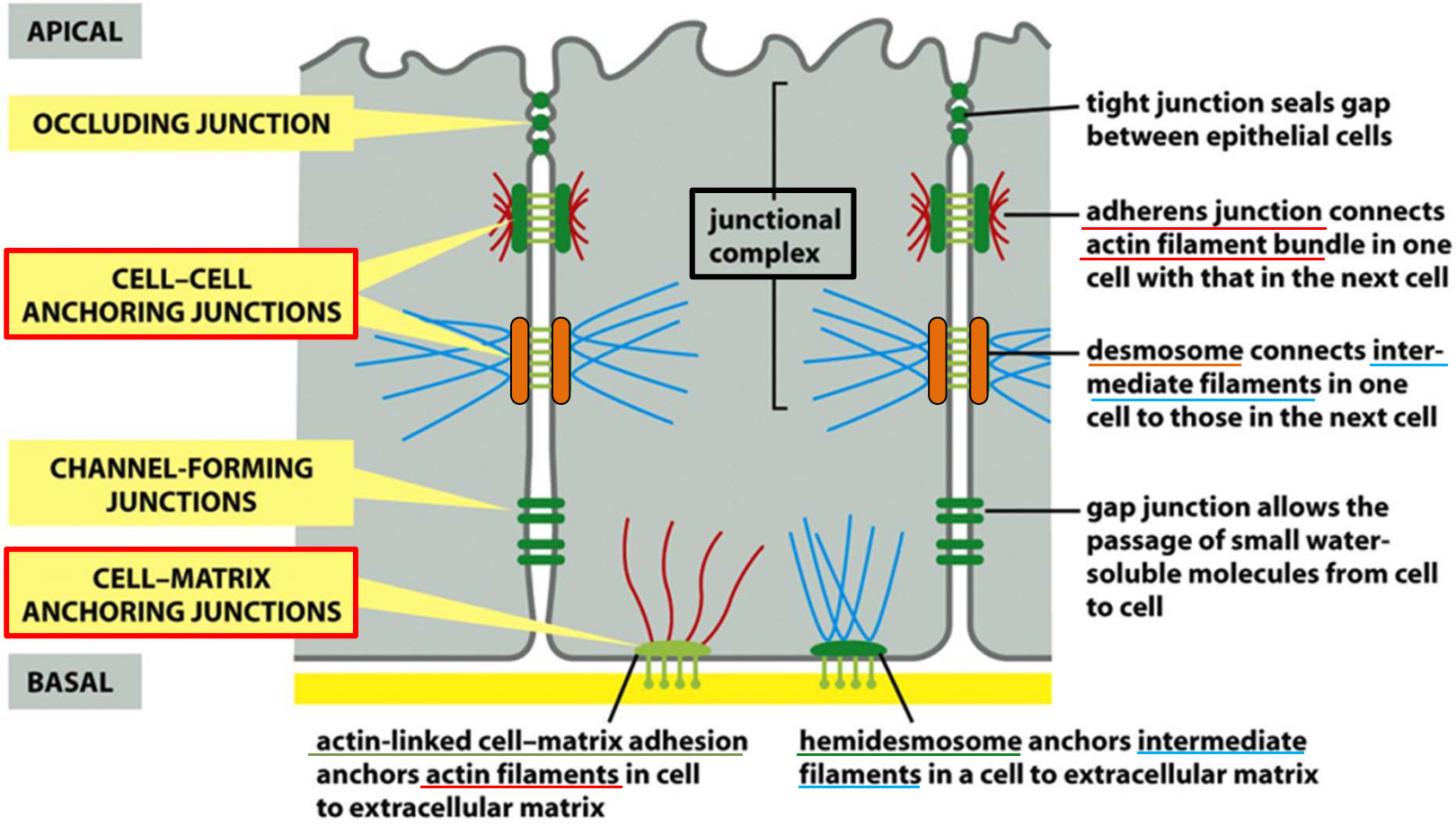
CHANNEL-FORMING JUNCTIONS

1. gap junctions (in animals)
2. plasmodesmata (in plants)

SIGNAL-RELAYING JUNCTIONS

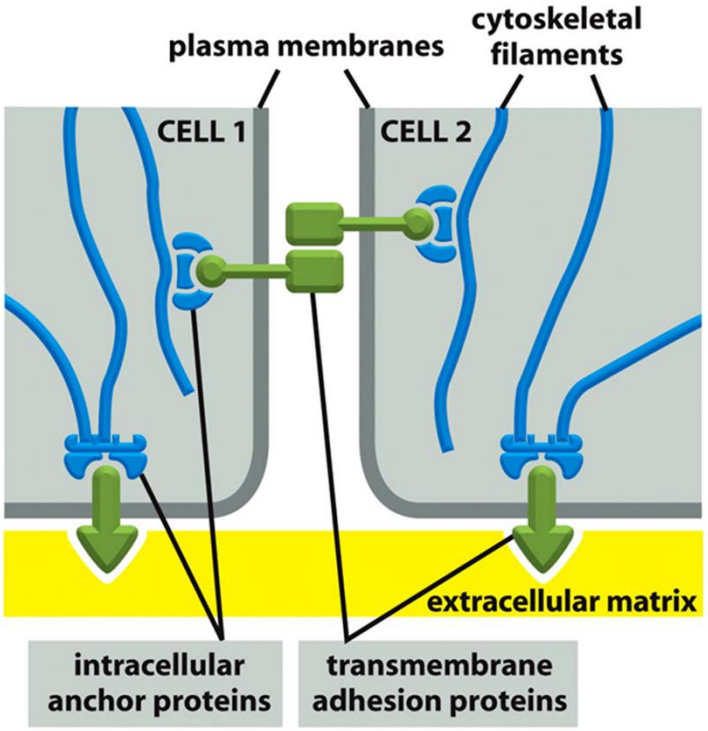
1. chemical synapses (in the nervous system)
2. immunological synapses (in the immune system)
3. transmembrane ligand–receptor cell–cell signaling contacts (Delta-Notch, ephrin-Eph, etc.). Anchoring, occluding, and channel-forming junctions can all have signaling functions in addition to their structural roles

Summary of the cell junctions



Transmembrane adhesion proteins mediate anchoring junctions

With one end, **transmembrane adhesion proteins linking to** the **cytoskeleton <u>inside</u>** the cell via **anchor proteins** <u>and</u> the other end **linking to** other **structures outside**.



- **Cadherins**: cell-**cell** attachment (link actin filaments or intermediate filaments)
- **Integrins**: cell-**matrix** attachment (link actin filaments or intermediate filaments

Protein-protein interactions in anchoring junctions

Table 19–2 Anchoring Junctions

JUNCTION	TRANSMEMBRANE ADHESION PROTEIN	EXTRACELLULAR LIGAND	INTRACELLULAR CYTOSKELETAL ATTACHMENT	INTRACELLULAR ANCHOR PROTEINS
Cell–Cell				
adherens junction	cadherin (classical cadherin)	cadherin in neighboring cell	actin filaments	α-catenin, β-catenin, plakoglobin (γ-catenin), p120-catenin, vinculin, α-actinin
desmosome	cadherin (desmoglein, desmocollin)	desmoglein and desmocollin in neighboring cell	intermediate filaments	plakoglobin (γ-catenin), plakophilin, desmoplakin
Cell–Matrix				
actin-linked cell–matrix adhesion	integrin	extracellular matrix proteins	actin filaments	talin, vinculin, α-actinin, filamin, paxillin, focal adhesion kinase (FAK)
hemidesmosome	integrin α6β4, type XVII collagen (BP180)	extracellular matrix proteins	intermediate filaments	plectin, dystonin (BP230)

II. Cadherins and cell-cell adhesion and cadherin-based anchoring junctions

1. **Cadherin** protein family
2. **Homophilic** binding of cadherins
3. **Adherens** junctions
4. **Desmosome** junctions
5. **Specialized adhesion mechanisms**:
    - **Selectins** mediate Ca^{2+}-**de**pendent blood cells adhesion
    - **Adhesive immunoglobulin** (Ig) proteins mediate Ca^{2+}-**in**dependent adhesion

1. the cadherin protein family

- Name is derived from ***Ca^{2+}*** and ***adherin***, meaning **Ca^{2+}-dependent adhering**
- Dissociation of cells from tissue needs EDTA/trypsin;
  (EDTA chelates the Ca^{2+} to ***deactivate*** the cadherin-cadherin interaction)
- Classical cadherins and non-classical cadherins,
  over 180 family members in humans.
- **Plants**, **fungi**, **bacteria** and **archaea** have **no cadherins**

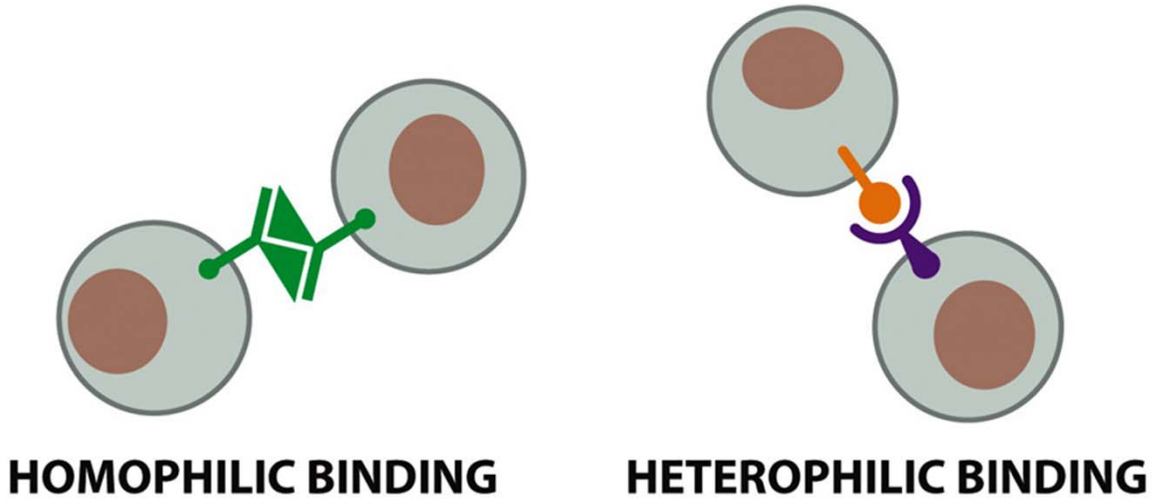
The cadherin superfamily

NAME	MAIN LOCATION	JUNCTION ASSOCIATION	PHENOTYPE WHEN INACTIVATED IN MICE
Classical cadherins			
E-cadherin	many epithelia	adherens junctions	death at blastocyst stage; embryos fail to undergo compaction
N-cadherin	neurons, heart, skeletal muscle, lens, and fibroblasts	adherens junctions and chemical synapses	embryos die from heart defects
P-cadherin	placenta, epidermis, breast epithelium	adherens junctions	abnormal mammary gland development
VE-cadherin	endothelial cells	adherens junctions	abnormal vascular development (apoptosis of endothelial cells)
Nonclassical cadherins			
Desmocollin	skin	desmosomes	blistering of skin
Desmoglein	skin	desmosomes	blistering skin disease due to loss of keratinocyte cell–cell adhesion
T-cadherin	neurons, muscle, heart	none	unknown
Cadherin 23	inner ear, other epithelia	links between stereocilia in sensory hair cells	deafness
Fat (in *Drosophila*)	epithelia and central nervous system	signal-relaying junction (planar cell polarity)	enlarged imaginal discs and tumors; disrupted planar cell polarity
Fat1 (in mammals)	various epithelia and central nervous system	slit diaphragm in kidney glomerulus and other cell junctions	loss of slit diaphragm; malformation of forebrain and eye
α, β, and γ-Protocadherins	neurons	chemical synapses and nonsynaptic membranes	neuronal degeneration
Flamingo	sensory and some other epithelia	cell–cell junctions	disrupted planar cell polarity; neural tube defects

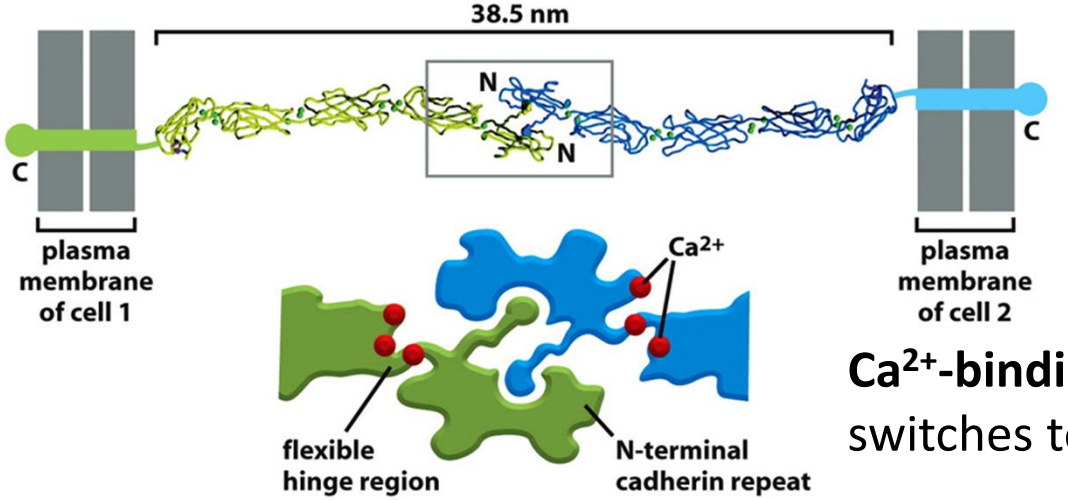
2. Homophilic adhesion of cadherins

Homophilic adhesion:

- the **same type of cadherin** binds to the **same type of cadherin**
- ensures linkage of the **same type of filaments** across cell borders
- ensures linkage of the **same type of cells and make sure** that **different types of cells remain separated** (see below…)

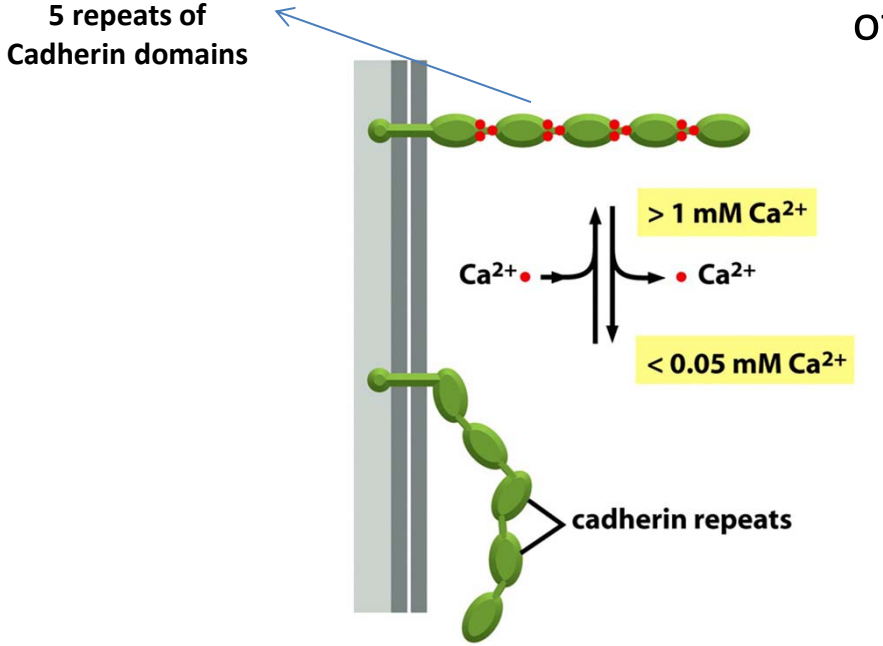


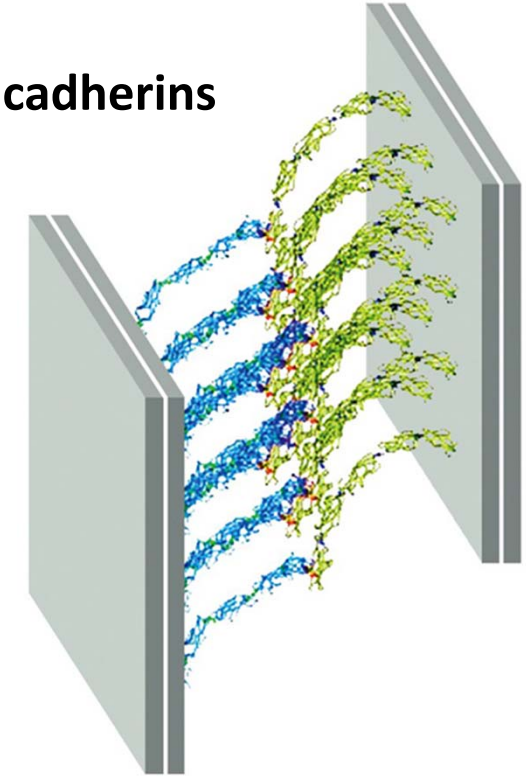
Mechanisms for cadherin function



Ca^{2+}-binding by cadherins switches to an **extended configuration…**

…allowing **binding to cadherins** of a neighboring cell.

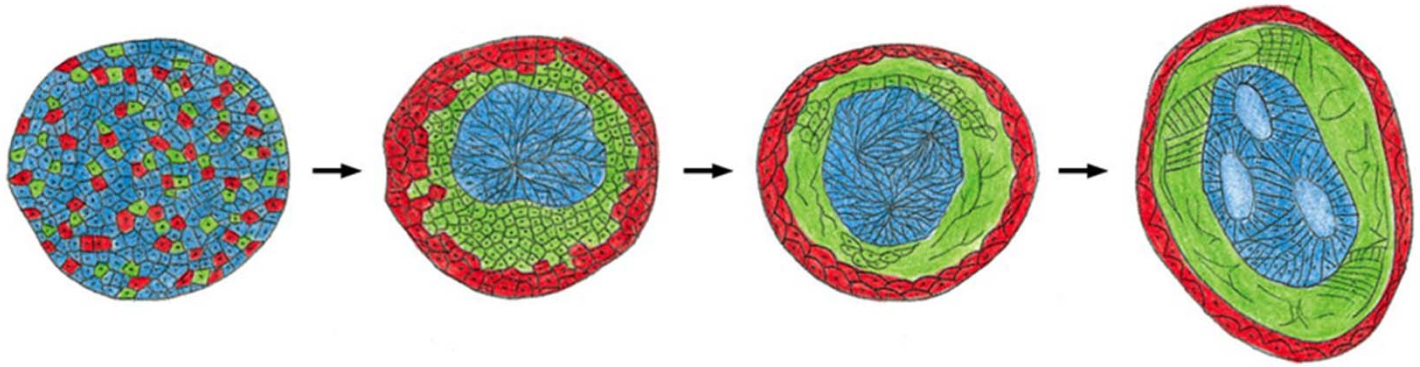




Cadherins control selective assortment/recognition of cells

<u>Classical experiment (1950s)</u>:

- **disaggregation** and **reaggregation** of an **early amphibian embryo *in vitro.***
- **The embryo consisting of mesoderm cells, neural plate cells and epidermal cells has been disaggregated and then reaggregated in a random mixture**



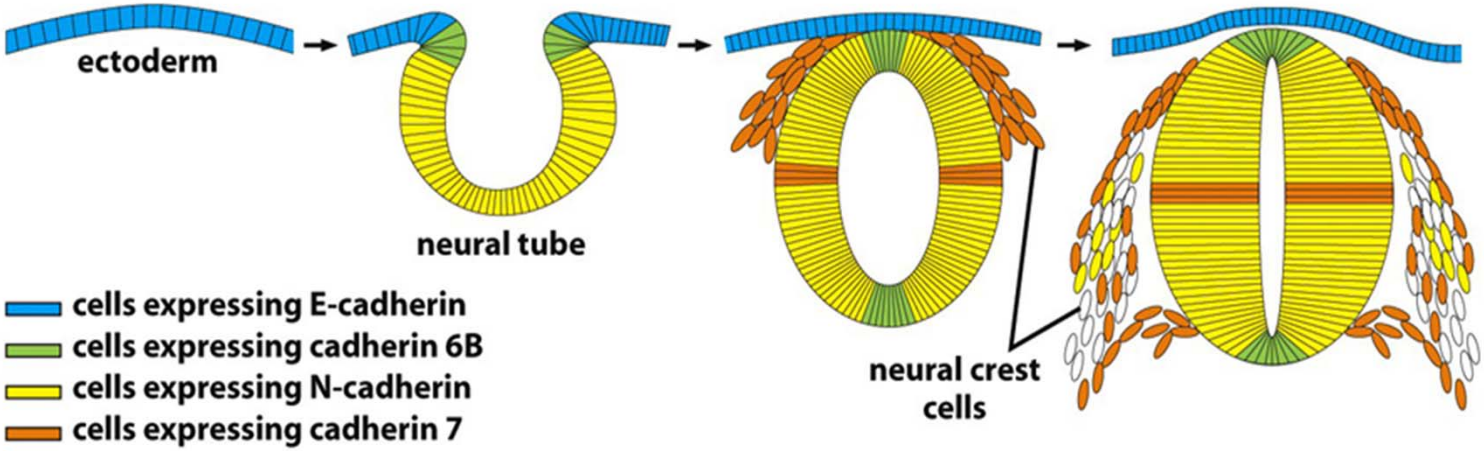
disaggregated embryo (randomized arrangement of different cell types)

"self"-arrangement reminiscent of a <u>normal</u> embryo with a "**neural tube**" **internally**, **epidermis externally**, and **mesoderm in between**

Cadherins control selective assortment/recognition of cells

During embryonic development: **cells expressing** the **same cadherins group together**

The **appearance** and **disappearance** of **specific cadherins** correlate with steps in embryonic development where cells **regroup** and **change their contacts** to **create new tissue structures**.



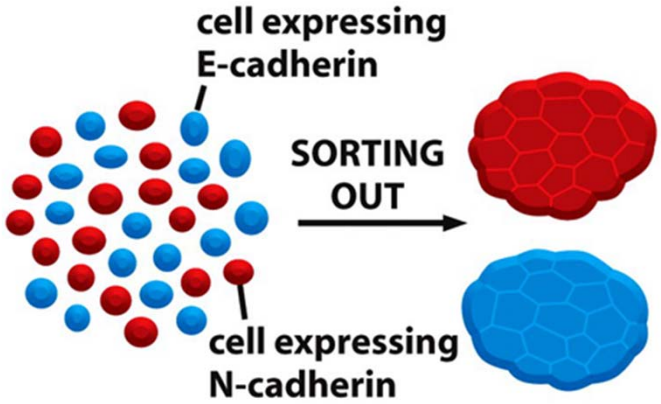
In the vertebrate (here: chick) embryo changes in cadherin expression are seen when the neural tube forms and pinches off from the overlying ectoderm:

- **neural tube cells lose E-cadherin** and **acquire other cadherins** (**N-cadherin**), while the **cells in the overlying ectoderm continue to express E-cadherin.**
- **Neural crest cells** express **cadherin 7**, **allowing detachment/migration** away from the neutral tube but **keeps holding them** together.
- For **ganglion formation**, cells **switch back to N-cadherin expression**.

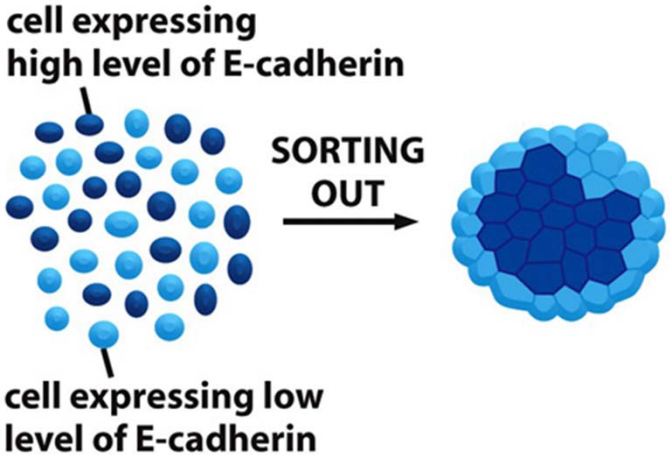
Cadherin-dependent cell sorting by overexpression of different cadherins

Mixed populations of cells expressing **<u>either</u> different cadherins** (**E**-cadherin/**N**-cadherin) **or even different levels of the same cadherin** sort out from each other

Cells expressing **E-cadherin** sort out from cells expressing **N-cadherin**

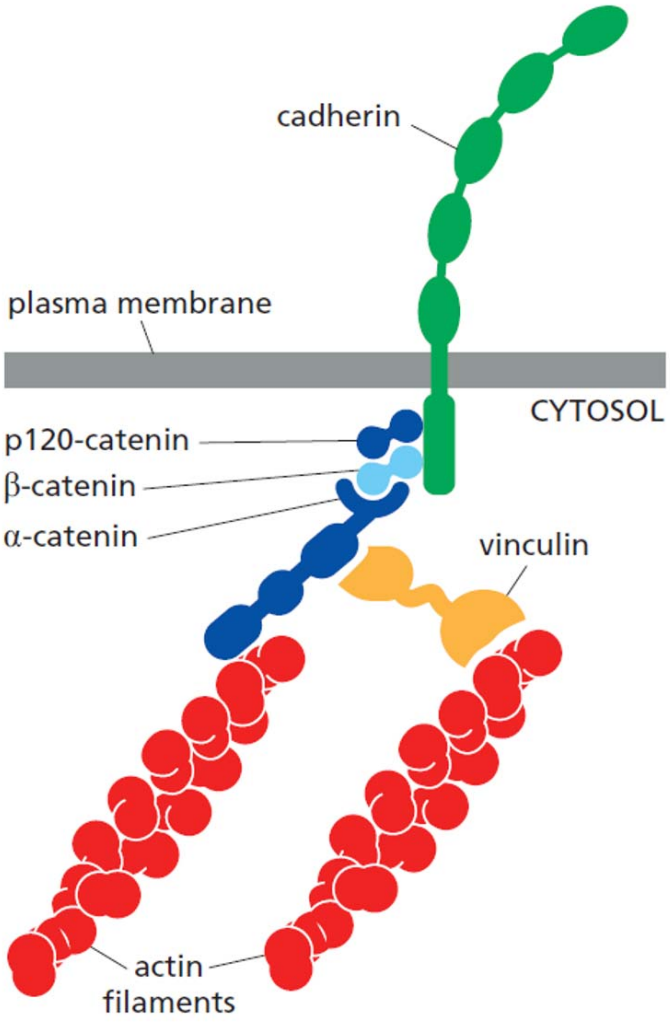


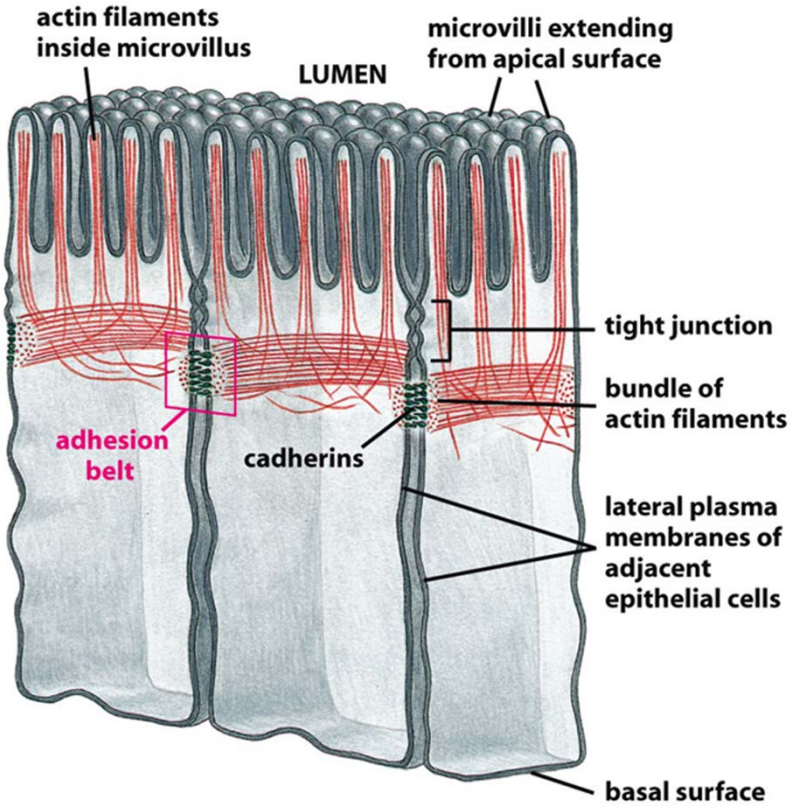
Cells expressing **different levels** of **E-cadherin** sort out from each other



Qualitative and quantitative differences in the expression of cadherins play a role in the organization of tissues

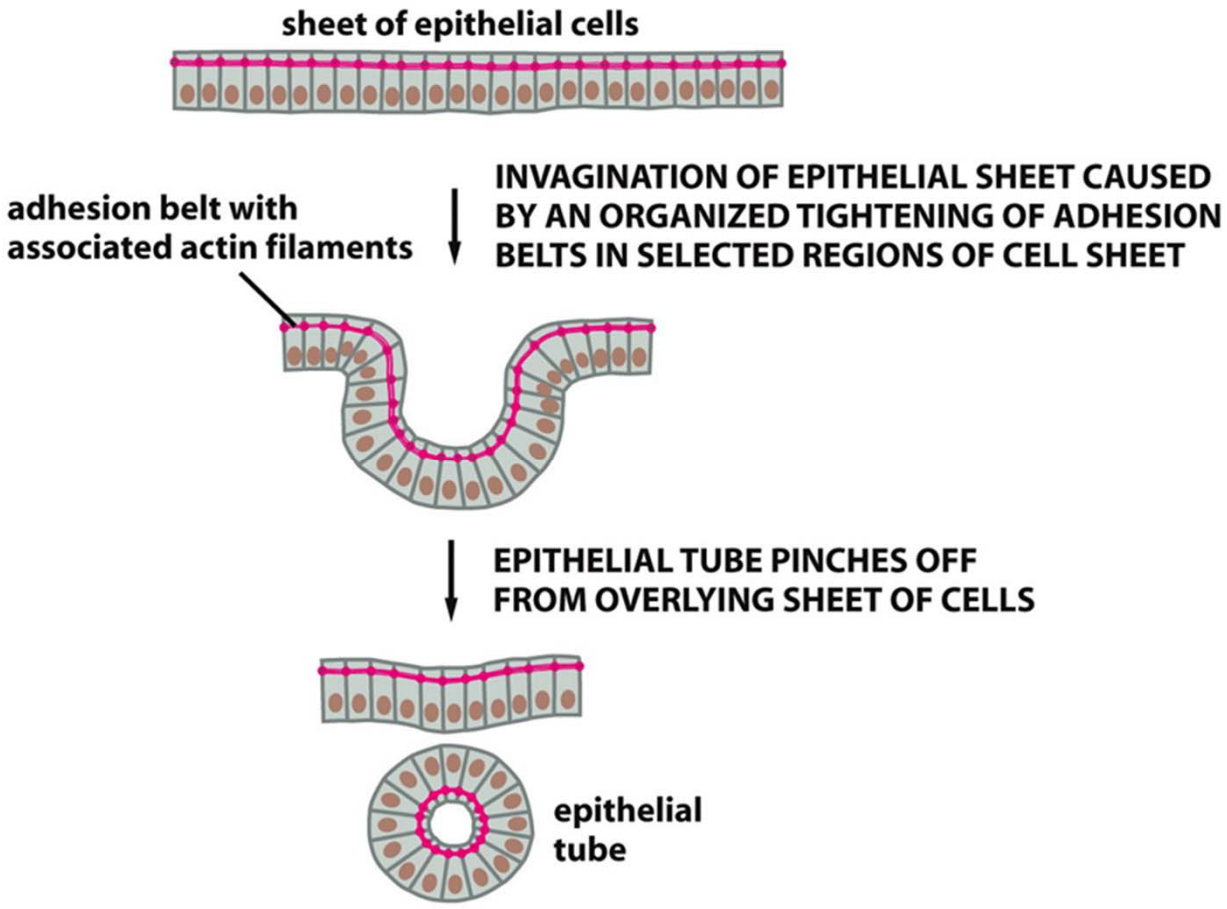
3. **β-Catenin <u>links</u> classical cadherins to the actin cytoskeleton**
in adherens junctions between adjacent epithelial cells





Tissue remodeling depends on the coordination of **actin-mediated contraction** with cell–cell adhesion

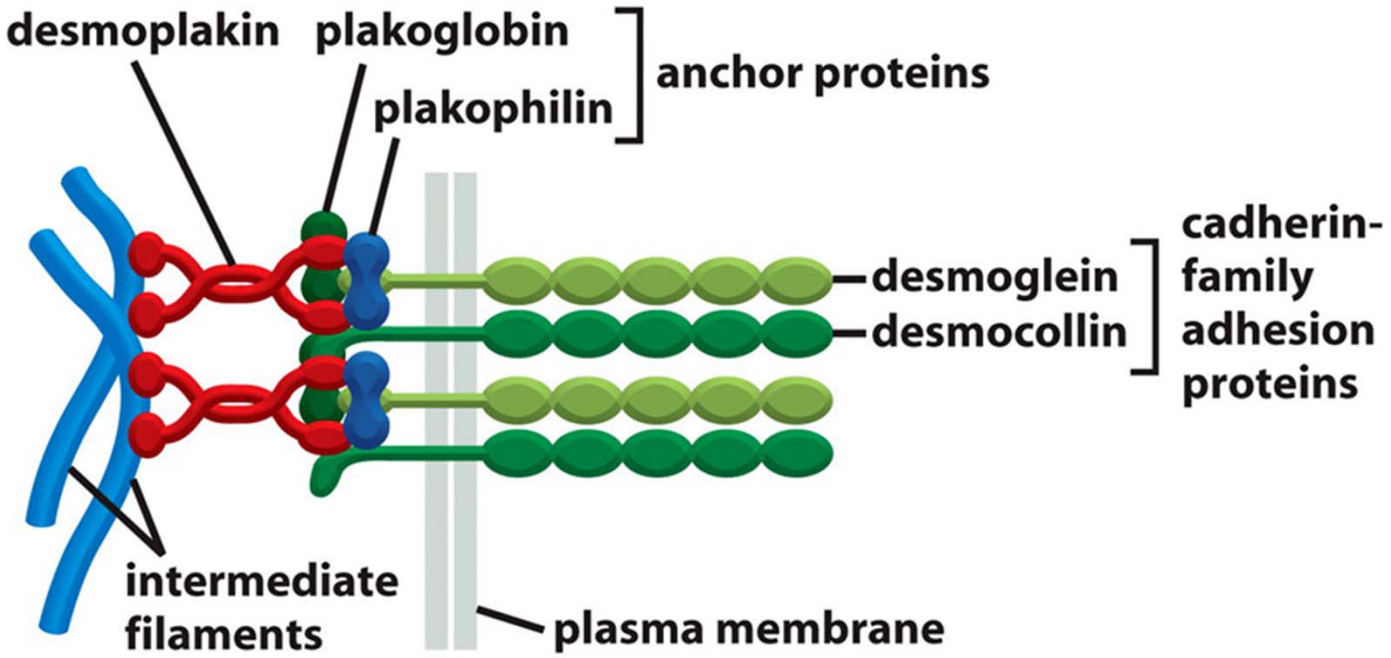
Myosin motors can cause contraction on the adhesion belt to form epithelial tube



4. Desmosome junctions

- Desmosomes are **structurally similar** to adherens junctions
- In Desmosomes, **cadherins** link to **intermediate filaments**
  (in adherens junctions, cadherins link to actin filaments)
- Desmosomes give cells mechanical strength
- Desmosomes are particularly plentiful in tissues that are subject to mechanical stress (heart muscle, epithelium)
- Desmosomes are not found in *Drosophila*

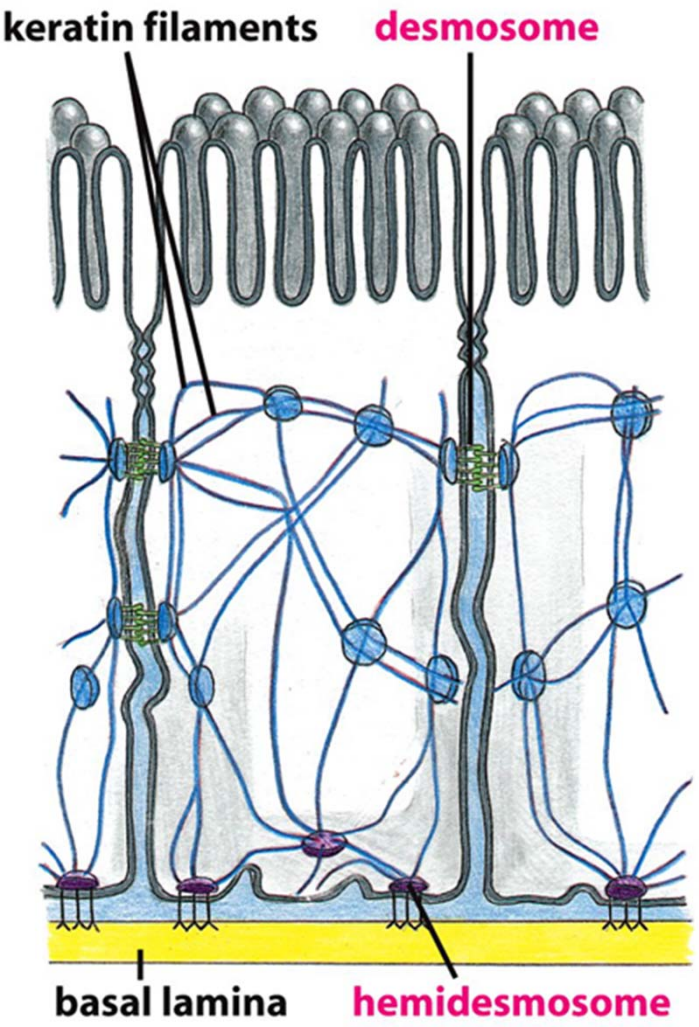
Structure and mechanism of desmosome junctions



Desmoglein and **desmocollin** are **nonclassical cadherins**.

- Their cytoplasmic tails bind ***plakoglobin*** **(γ-catenin)** and ***plakophilin*** (a distant relative of p120-catenin), which in turn bind to ***desmoplakin*****.**
- **Desmoplakin** binds to the **sides of intermediate filaments**, thereby tying the desmosome to these filaments.

Desmosome, hemidesmosome and intermediate filament network



5. Specialized adhesion mechanisms:
1) **Selectins** mediate **cell-cell adhesion** in the blood stream

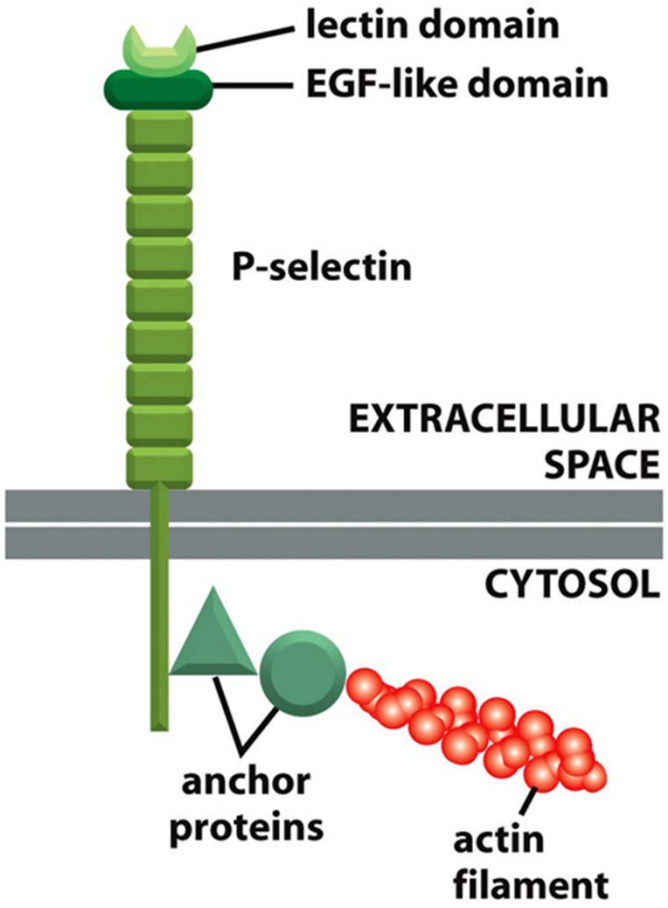
- **Selectins** are **cell-surface carbohydrate-binding proteins** (lectins)
- **Ca^{2+}-dependent** adhesion mechanism
- Mediate **transient adhesions** in the blood stream
- **Bind to lectins** on other cell-surface proteins
- At least 3 types:

  L-selectin: on white blood cells (**l**eucocytes)

  P-selectin: on **p**latelets and endothelial cells

  E-selectin: on activated **e**ndothelial cells

The structure and functions for selectins



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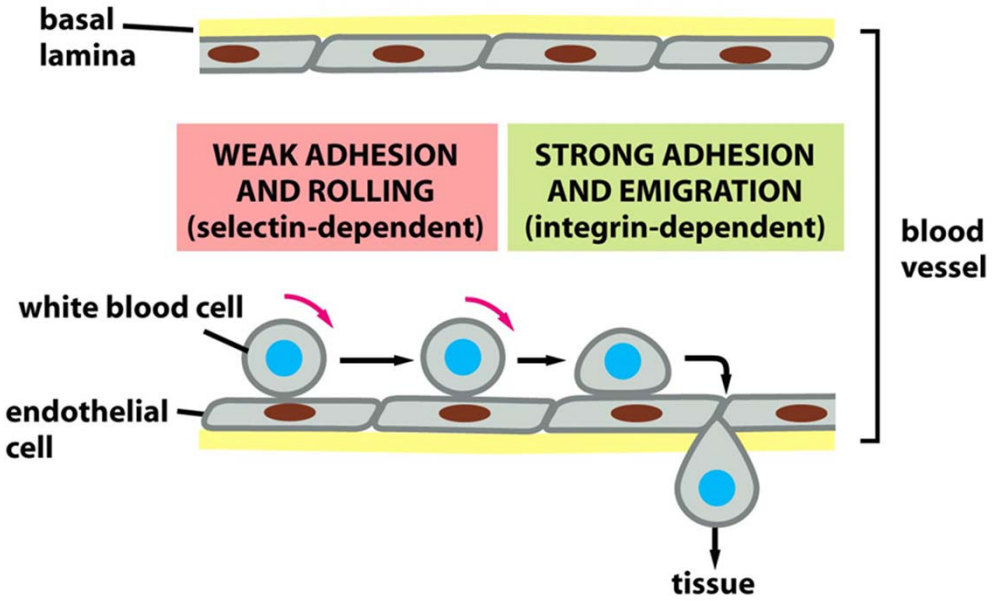


Selectins binding is weak, they collaborate with **integrin** to cause **migration of white blood cells** from the blood stream **into** tissues.

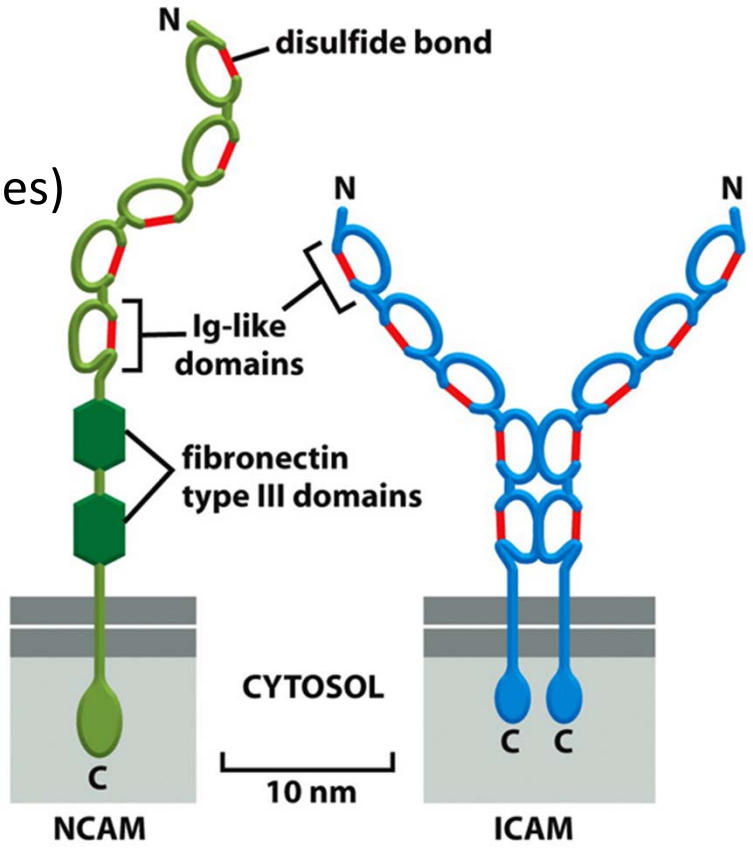
5. Specialized adhesion mechanisms:
2) Immunoglobulin superfamily members

- **Ca^{2+} -independent**
- Heavy glycosylation, multiple disulfide bonds
- Bind to integrin
- several major proteins:

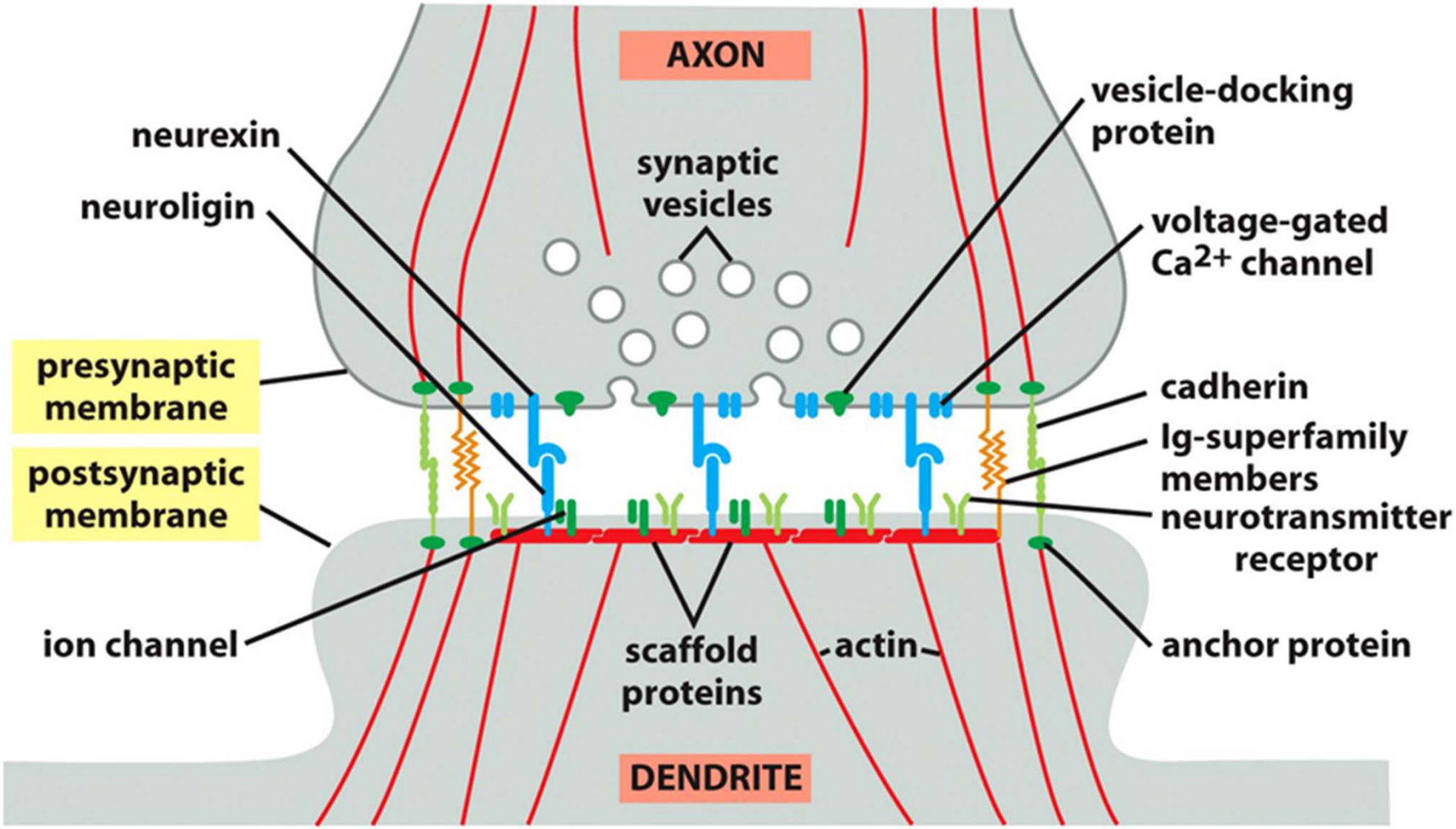
  ICAMs (**i**ntercellular **c**ell **a**dhesion **m**olecules)

  VCAMs (**v**ascular **c**ell **a**dhesion **m**olecules)

  NCAM (**n**eural **c**ell **a**dhesion **m**olecules)



Many types of adhesion molecules act together to create a synapse



III. Integrins mediate cell–matrix adhesion

- **Integrins** are **transmembrane proteins** composed of **α-** and **β- subunits**
- **Bind** to extracellular matrix proteins, they are matrix receptors).
- Play important role in **regulating** cellular function
- Play important role in **bidirectional signaling** between the cell and the matrix (from the cell to the matrix **and** from the matrix to the cell)
- **Defects** in integrins signaling **cause many genetic diseases**

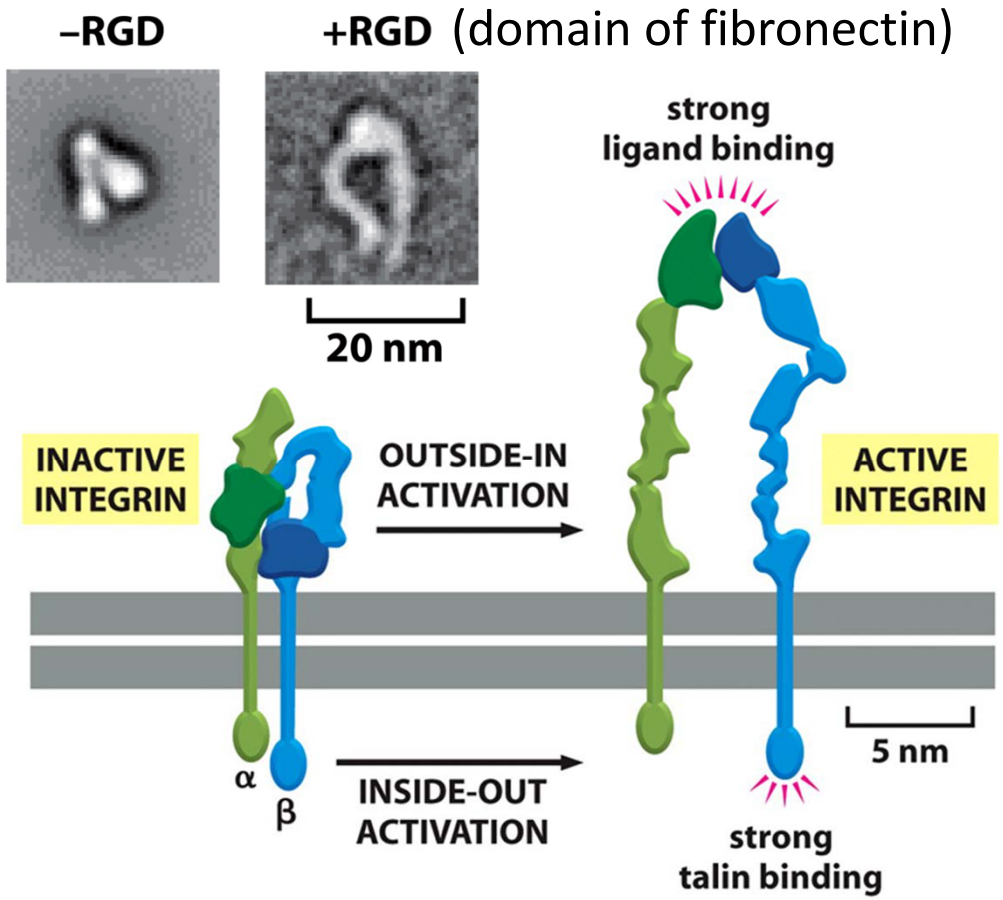
Table 19–4 Some Types of Integrins

INTEGRIN	LIGAND*	DISTRIBUTION	PHENOTYPE WHEN α SUBINUT IS MUTATED	PHENOTYPE WHEN β SUBUNIT IS MUTATED
α5β1	fibronectin	ubiquitous	death of embryo; defects in blood vessels, somites, neural crest	early death of embryo (at implantation)
α6β1	laminin	ubiquitous	severe skin blistering; defects in other epithelia also	early death of embryo (at implantation)
α7β1	laminin	muscle	muscular dystrophy; defective myotendinous junctions	early death of embryo (at implantation)
αLβ2 (LFA1)	Ig superfamily counterreceptors (ICAM)	white blood cells	impaired recruitment of leucocytes	leucocyte adhesion deficiency (LAD) impaired inflammatory responses; recurrent life-threatening infections
αIIbβ3	fibrinogen	platelets	bleeding; no platelet aggregation (Glanzmann's disease)	bleeding; no platelet aggregation (Glanzmann's disease); mild osteopetrosis
α6β4	laminin	hemidesmosomes in epithelia	severe skin blistering; defects in other epithelia also	severe skin blistering; defects in other epithelia also

*Not all ligands are listed.

Integrin activation can result from both: **inside-out** and **outside-in** mechanisms

Integrins can switch between an active and an inactive conformation

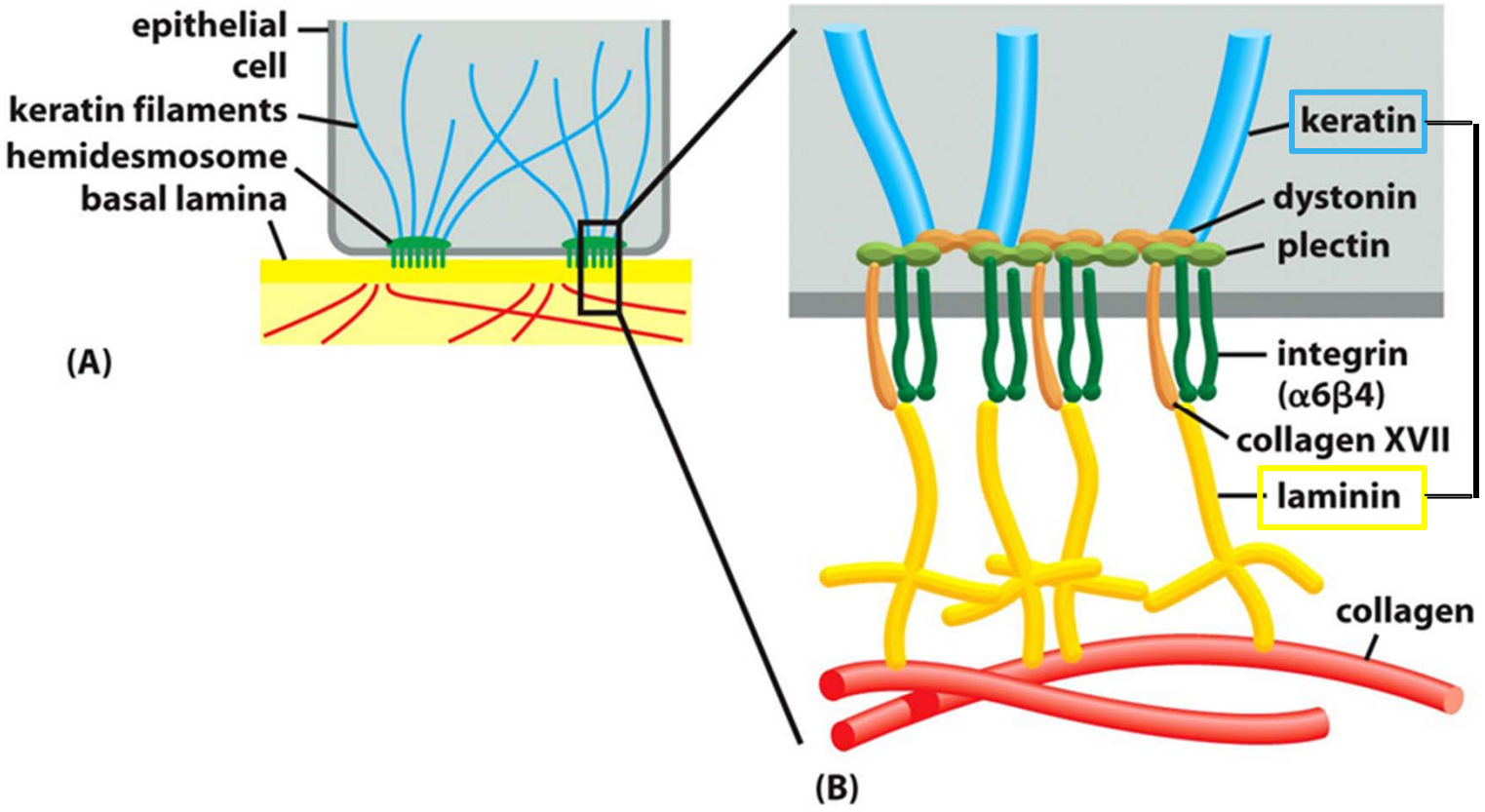


- Switching from inactive to active states is a major conformational change that simultaneously exposes the external and internal ligand-binding sites at the ends of the integrin molecule.
- External matrix binding and internal cytoskeleton linkages are thereby coupled.

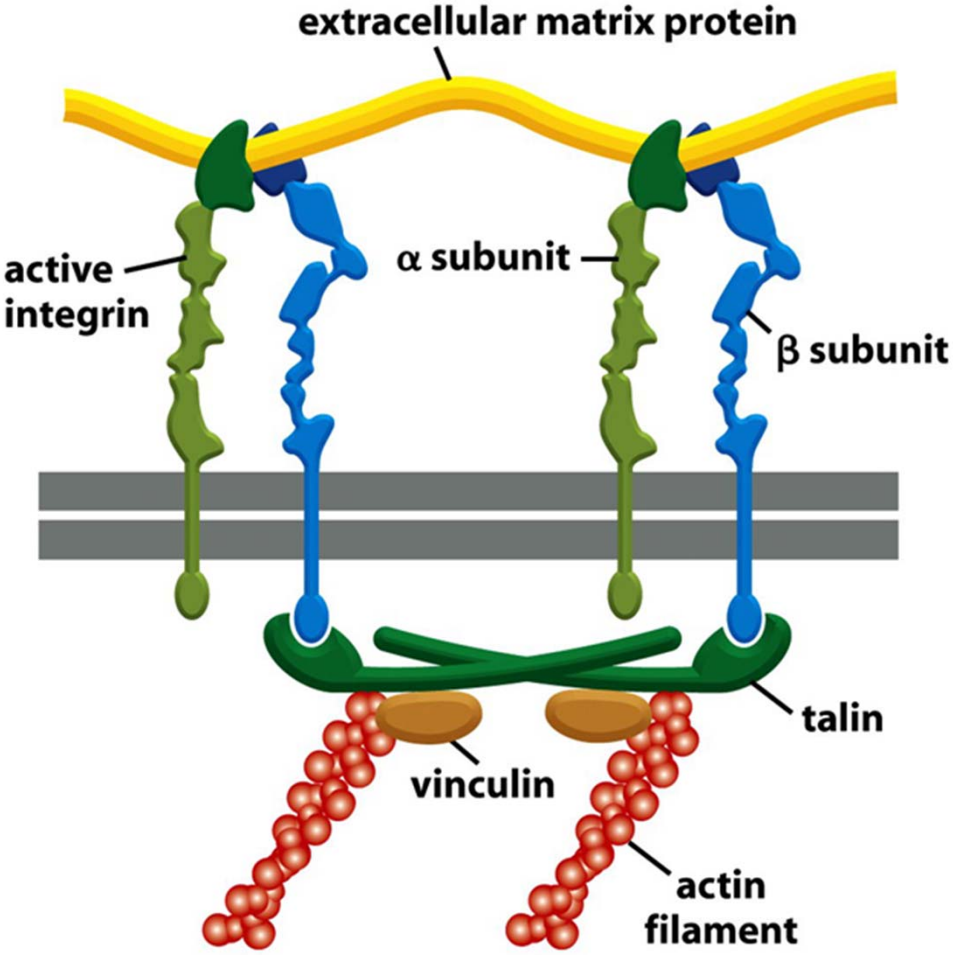
1. **Outside-in activation**: extracellular ligand binding
2. **Inside-out:** strong talin binding in response to intracellular signaling molecules such as PIP2, etc.

Integrins in hemidesmosomes

Hemidesmosomes **spot-weld epithelial cells to the basal lamina**
by **<u>linking</u> laminin** outside the cell **<u>to</u> keratin filaments** inside of the cell



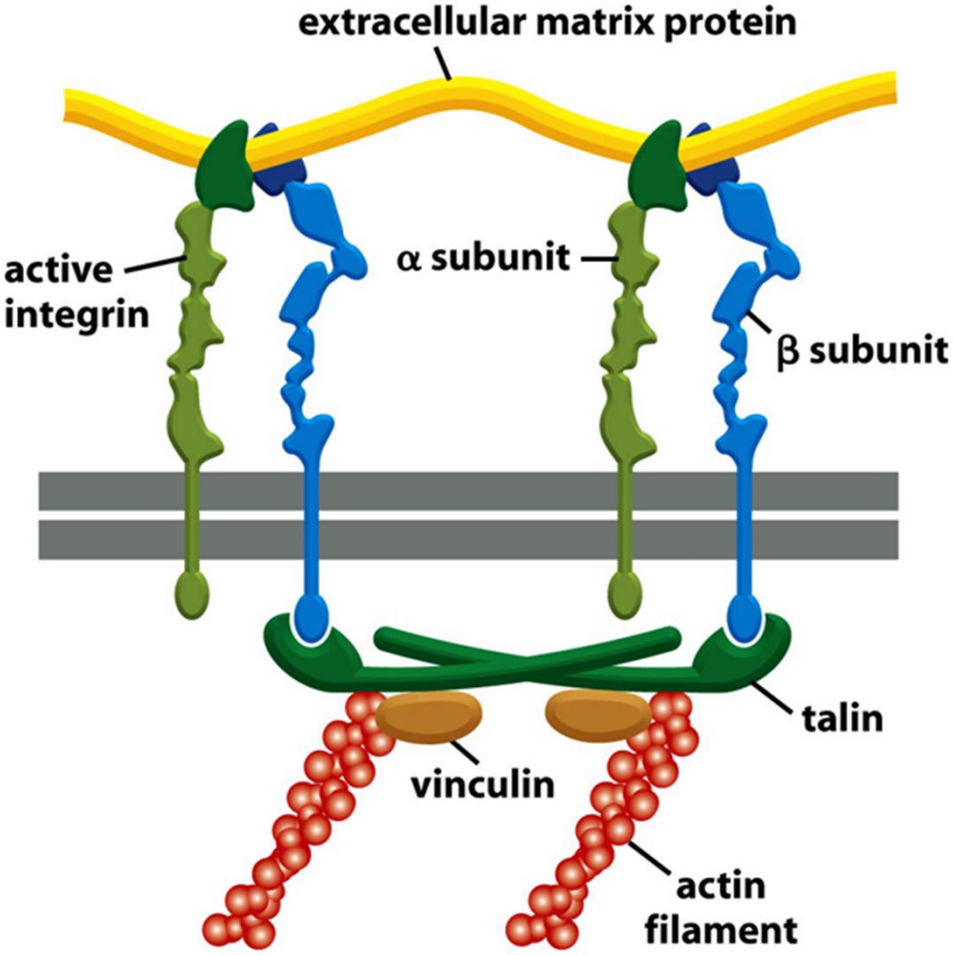
Integrins link extracellular matrix to the intracellular actin cytoskeleton



Arangement:

- The N-terminal heads of the integrin chains attach directly to an extracellular matrix protein such as fibronectin
- C-terminal intracellular tail of the integrin β subunit binds to adaptor proteins that interact with actin.
- Talin is an adaptor, which contains a string of multiple domains for binding actin and other proteins, such as vinculin (helps reinforcing/and regulating actin linkage.
- One end of talin binds to a specific site on the integrin β subunit cytoplasmic tail; other regulatory proteins, e.g. kindlin, bind at another site on the tail.

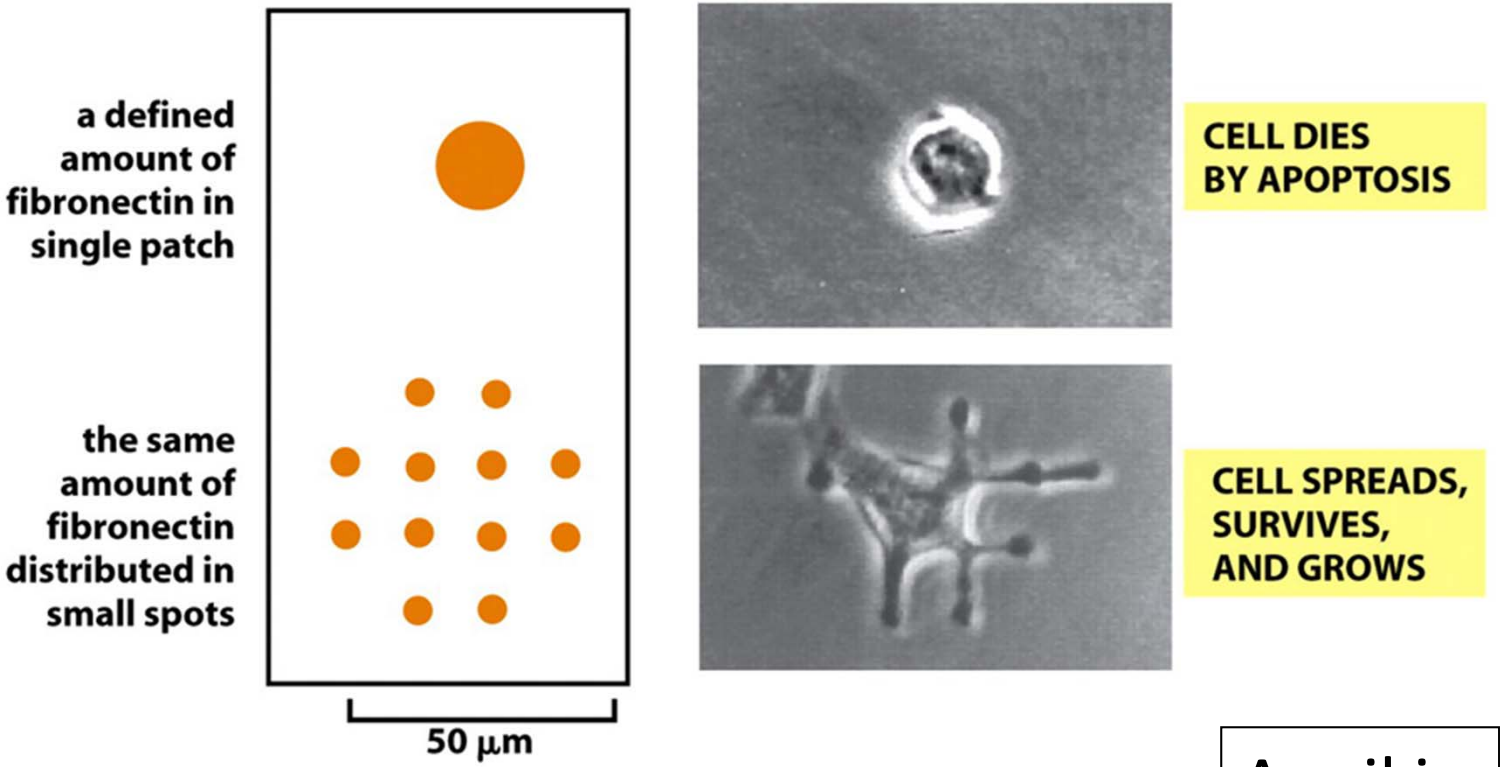
Integrins link extracellular matrix to the intracellular actin cytoskeleton



<u>Function principle:</u>

- **Tension applied to an integrin** can cause it to tighten its grip on intracellular and extracellular structures
- **Loss of tension** can loosen its hold, so that molecular signaling complexes fall apart on either side of the membrane.
- This way, integrins serve **<u>not only</u>** to **<u>transmit</u> mechanical and molecular signals**, but **also to convert** one type of signal into the other.

Integrin signaling controls cell proliferation and survival



Anoikis

Cells without attachment will die by apoptosis
Cells with attachment and activated integrin signaling survive and proliferate.