

# Cell and Molecular Biology

**Ninth Edition**

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## Chapter 7

Interactions Between Cells and  
Their Environment

# 7.1 | Overview of Extracellular Interactions (1 of 2)

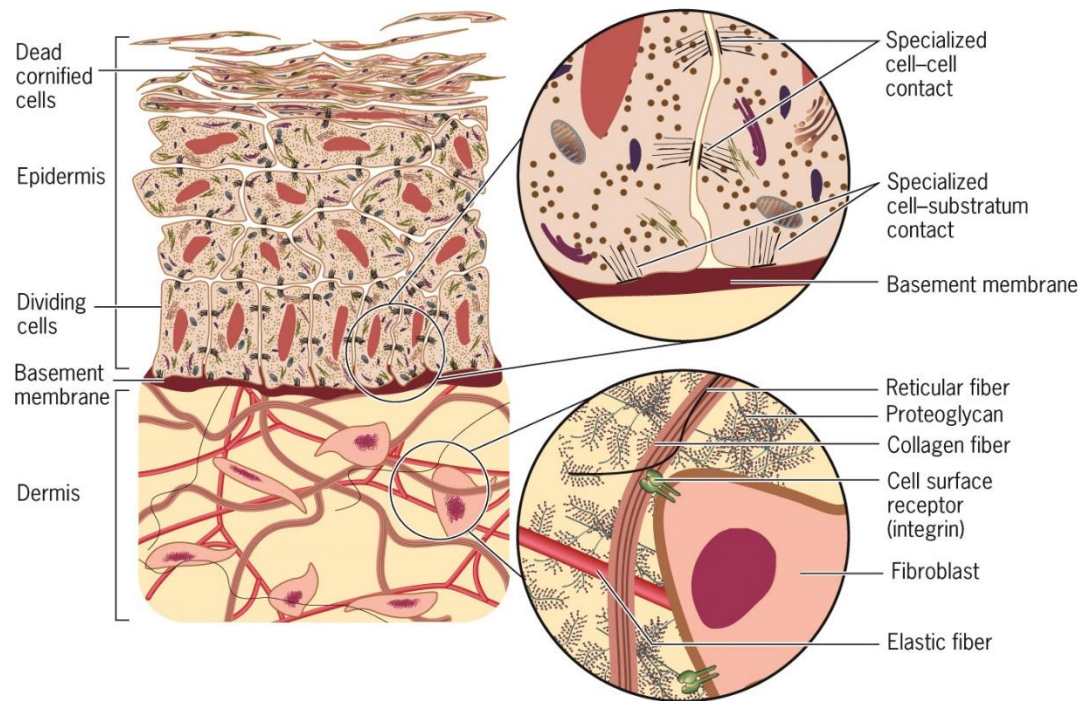
- Materials present outside the plasma membrane play an important role in the life of a cell.
- Most cells in a multicellular plant or animal are organized into clearly defined tissues.
- There are many diverse activities that are regulated by this.

Extra cellular matrix → plasma membran → Cytoskeleton

انشطة داخل  
الخلية تتظم من  
طريق EXH

# 7.1 | Overview of Extracellular Interactions (2 of 2)

- Cells interact with their extracellular environment
- The epidermis has closely packed cells of epithelial tissue  
 بشرية خلايا طلائية  
 له يكون مترابطة ومضغوطة بشكل كبير وقوي
- The dermis is a type of connective tissue  
 طبقة الادمة نسيج حناني
- Fibroblasts of the dermis have receptors that mediate interactions and transmit message.  
 نوع خلايا توصيل الرسائل



An overview of how cells are organized into tissues and how they interact with one another and with their extracellular environment.

# 7.1 | The Extracellular Matrix (1 of 3)

Carbohydrate projections form part of the **glycocalyx** on the outer surface of the plasma membrane.

→ Sugar Coat

Membrane تغلف  
Plasma membrane تغطي

Roles of the glycocalyx

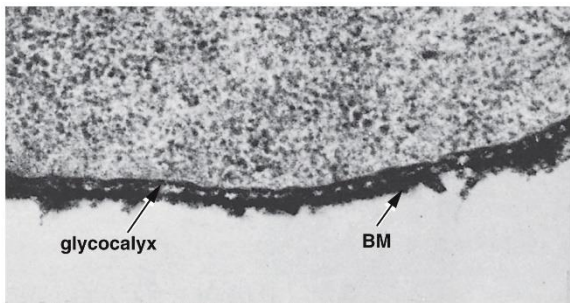
- Mediator of cell-cell and cell-substratum interactions
- Mechanical protection
- Barrier to molecular movement
- Regulatory factor binding site

تنظيم

مكان لارتباط عوامل التنظيم  
(اعطاء الاشارة)

Basal surface of ectodermal cell, early chick embryo

خارجية حلية



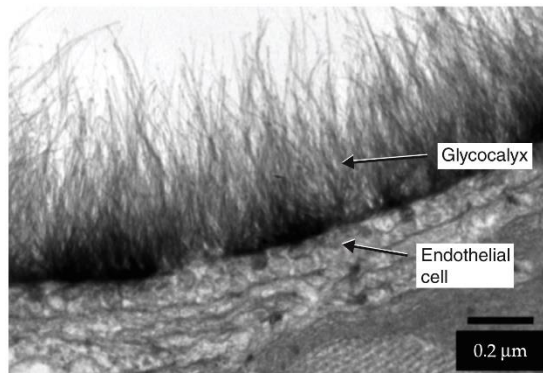
Source: From A. Martinez-Palermo, *Int. Rev. Cytol.* 29:64, 1970. © 1970, with permission from Elsevier.

0.5 μm

EM: endothelial glycocalyx in a coronary capillary

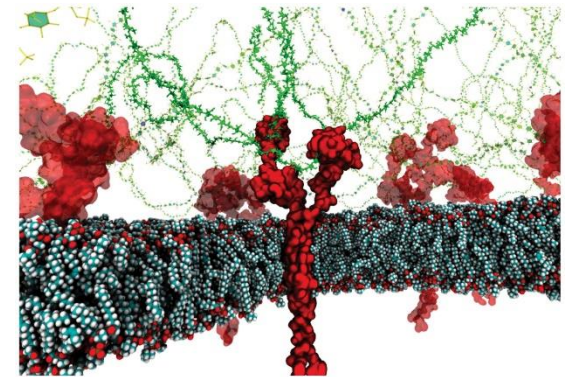
بطانة

دموية شعيرات



Source: By courtesy of B.M. van den Berg, The Eindhoven Laboratory for vascular medicine, Division of Nephrology, Liden University Medical Center, Liden, the Netherlands.

Molecular model of the glycocalyx



Source: Courtesy of Igor Pivkin et al., Università della Svizzera Italiana, Biophys. Journal 106(1):232-234, 2014, with permission from Elsevier.

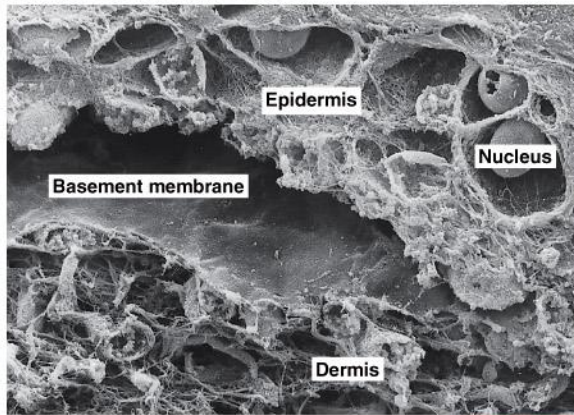
# 7.1 | The Extracellular Matrix (2 of 3)

→ Mech. Support  
Barrier

- One of the best defined extracellular matrices (ECM) is the basement membrane that surrounds muscles that nerves and fat cells.
- Underlies the epidermis of the skin, the digestive and respiratory tract and the lining of blood vessels.

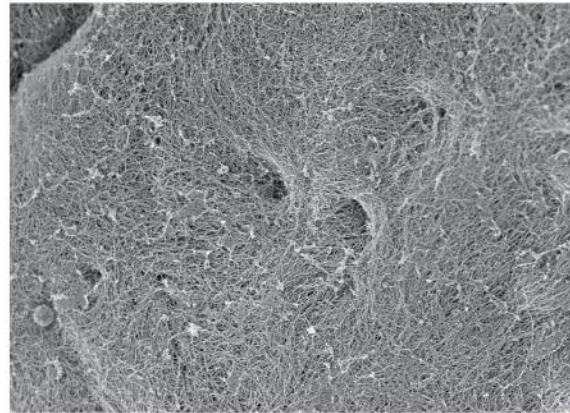
بشرة  
بطانة  
الدعوية  
الأوعية

Source: Courtesy of Karen Holbrook

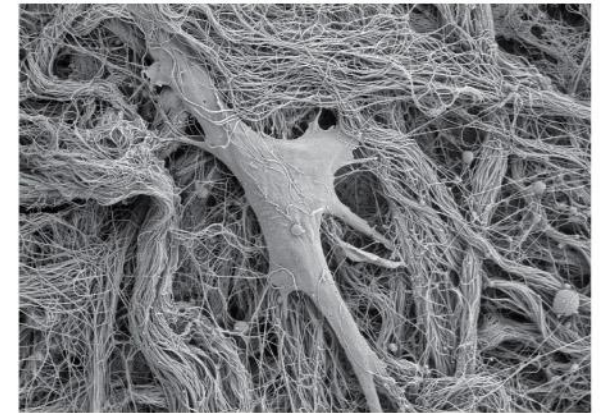


10 μm

Source: Reprinted from Stoitzner, P., Pfaller, K. Stössel, H. A Close-Up View of Migrating Langerhans Cells in the Skin. *Journal of Investigative Dermatology* 118: 117–125, 2002, with permission from Elsevier.



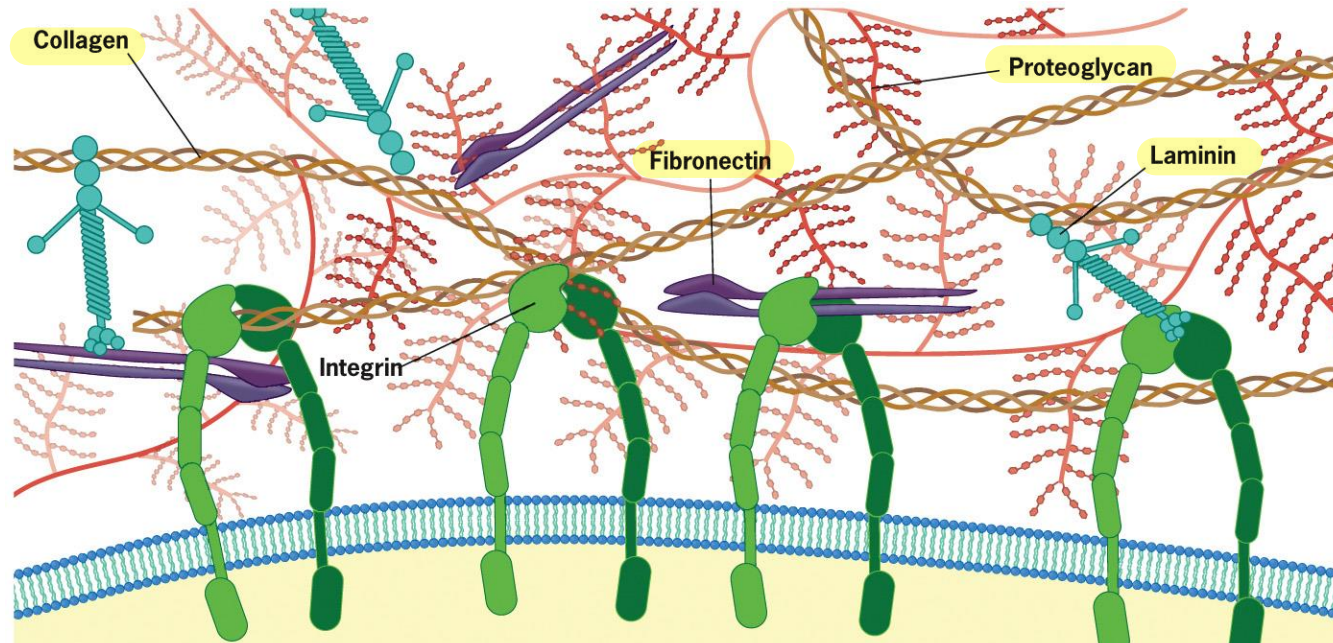
Source: Reprinted from Stoitzner, P., Pfaller, K. Stössel, H. A Close-Up View of Migrating Langerhans Cells in the Skin. *Journal of Investigative Dermatology* 118: 117–125, 2002, with permission from Elsevier.



Scanning electron micrographs of human skin

# 7.1 | The Extracellular Matrix (3 of 3)

- The ECM may take diverse forms in different tissues and organisms ECM بتأخذ أشكال واحجام مختلفة
- Most proteins inside cells are **globular**.
- These proteins are secreted into the extracellular space. هذه البروتينات تصنع وتفرز خارج الخلية تصنع في ER



Organized network of extracellular materials outside plasma membrane, provides support and determines shape and activity of cell.

# 7.1 | Components of the Extracellular Matrix (1 of 7)

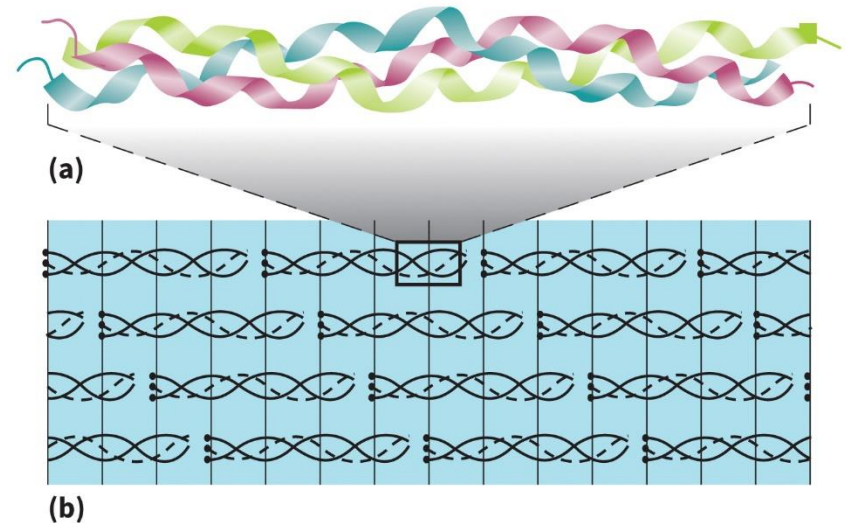
Collagen → Fibrous

## Collagen

- **Collagen molecule: triple helix of three helical alpha chains**
- Collagens comprise **a family of fibrous glycoproteins** present only in the ECM.
- Collagen **is the single most abundant protein in the human body.**
- Collagen is produced by fibroblasts, smooth muscle and epithelial cells.
- **28 fiber types, often mixed in ECM**

كُلُّ عُنْدِي أَنْوَاعٍ مُخْتَلِفَةٍ مِنْهُ مَوْشَرِّطٌ كَلِمَةً مَعَ بَعْضٍ فِي عَمَلِهِ  
حَسَبَ نَوْعِ الْإِطْلَاقِ وَحَاجَتِهَا بِتَقْسِيمِ

each tissue has a unique mixture

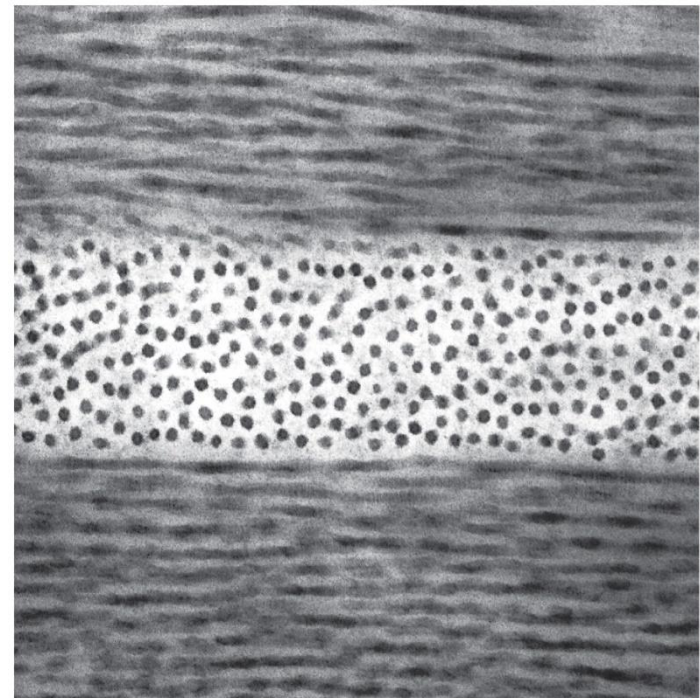


Collagen I molecules become aligned in staggered rows

# 7.1 | Components of the Extracellular Matrix (2 of 7)

## Collagen

- Collagen provides the insoluble framework that determines many of the mechanical properties of the matrix.
- Tissue properties can often be correlated with the 3D organization of its collagen (e.g., tendons, cornea).



Source: Reprinted from Nigel J. Fullwood, *Structure* 12:169, 2004, Fig. 1; 2004, with permission from Elsevier.

200 nm

**Corneal stroma:** layers of collagen fibrils of uniform diameter and spacing arranged at right angles

Collagen: (Found in animal cell)

Family of protein (Fibrous glycoproteins)

(I, II, III, ... 28)

Fibrillar protein

كل ما قبل الرشم كل ما كان هذا البروتين أقوى مثلاً (1) يوجد في العظام

how it's produce

$\alpha$  Chain

x3 chain

ProCollagen

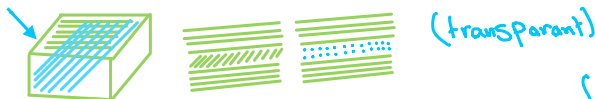
Collagen

Function:

- 1) the most abundant protein
- 2) high tensile strength
- 3) provide the Insoluble Framework that determines Mechanical properties of the matrix
- 4) Tissue properties Can often be Correlated with the 3D organization of its Collagen

كـهـ مـضـائـفـ الـانـسـجـةـ المـخـتـلـفـةـ تـعـضـدـ بـسـكـلـ كـيـمـ مـعـ (الـتـنـظـيـمـ تـلـفـيـ الـابـطـا)

Cornea (قرنية العين)



(transparent)

كـهـادـ الـتـنـظـيـمـ بـهـيـمـ الطـريـقـةـ الـلـلـكـولـاجـينـ خـلـيـفـهاـ تـبـيـرـ سـتـفاـة (transparent + strength)

Tendons (الأوتار)

3d shape + determines mechanical properties



(high tensile strength)

where

It's produce by

- 1- Fibroblasts
- 2- Smooth muscle
- 3- epithelial cell

then it's secretes out the cell to ECM so they present only in ECM

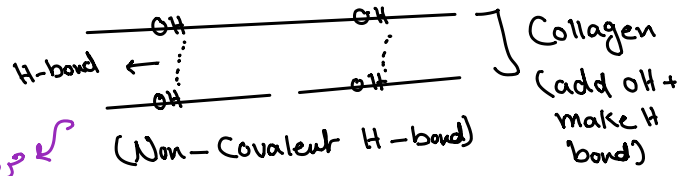
by what

but they are synthesized by (ER + glycosylation)

5

Something that the Collagen need it is Vitamin C

Vitamin C (Ascorbic Acid)



قوة

Not the Same as (Covalent cross link)

↑ age ↑ cross link  
كـخـيـرـ مـرنـةـ لـذـلـكـ يـتـكـرـ العـظـمـ بـرـعـةـ + الـاسـنـان

→ How does collagen determine tissue properties?

✓ 3D organization of collagen:

- In the cornea (القرنية), collagen fibers are arranged perpendicularly, which allows transparency
- In tendons (الأوتار), collagen is arranged in a way that provides high strength and stability

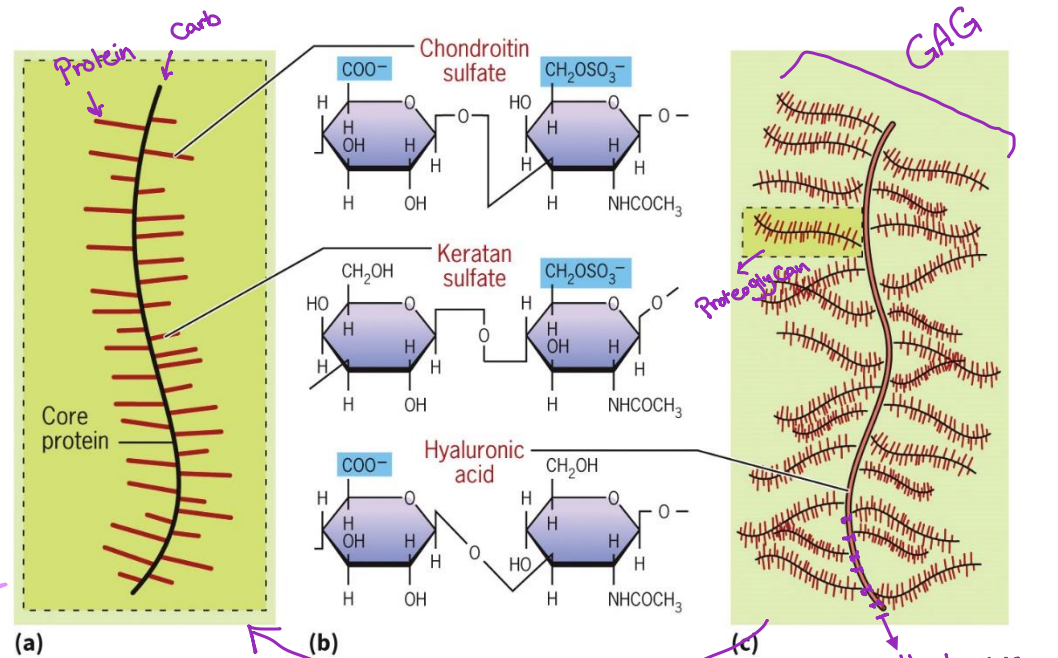
▪ Mutations in genes encoding type II collagen alter the properties of cartilage tissue, causing dwarfism, skeletal deformities

# 7.1 | Components of the Extracellular Matrix

(3 of 7) (Ground Substance) 1) glycoprotein + Proteoglycans + (GAG) glycosaminoglycans

## Proteoglycans → Carbs عليه بروتين

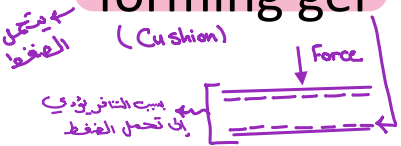
- **Proteoglycans** – protein-polysaccharide complex, with a core protein attached to glycosaminoglycans (GAGs).
- Have a repeating disaccharide structure, -A-B-A-B-, where A and B represent two different sugars.
- Common in basement membranes, attract water, forming gel



Schematic representations of a single proteoglycan, repeating disaccharide structure of GAGs, and linkage to hyaluronic acid to form a giant complex

اربع طين في مخلقة

→ have alot of (-) End So attract (مع + ماء) تربط الطين الى جيل + موجود في الغضاريف



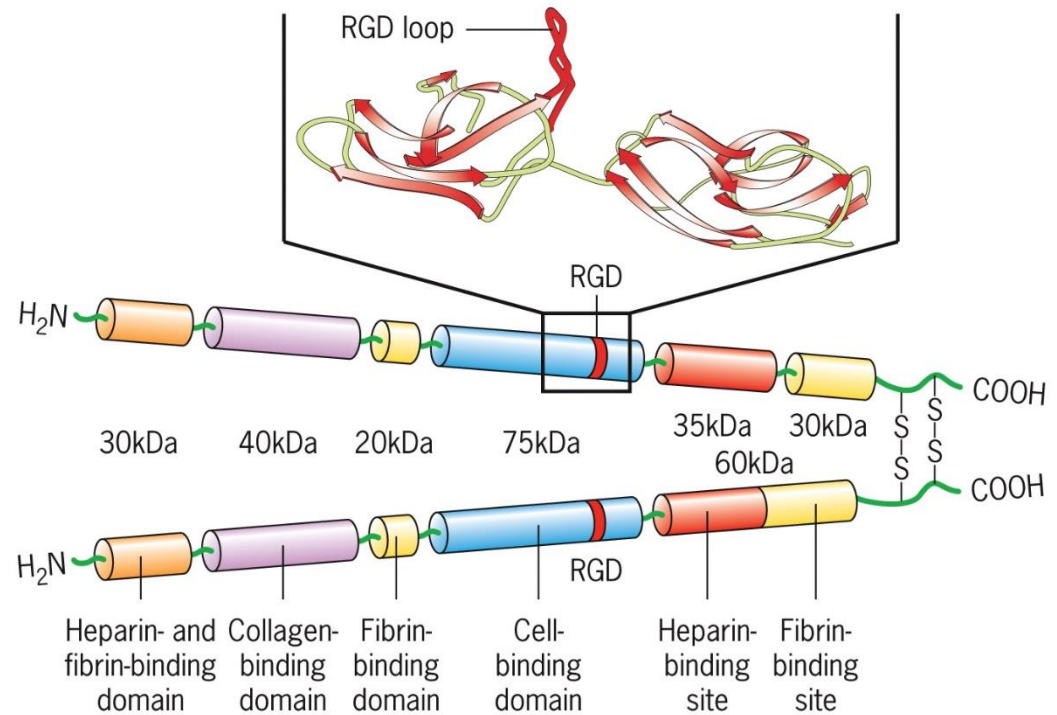
# 7.1 | Components of the Extracellular Matrix

(4 of 7)

Type of glycoprotein:   
 → bind Integrant Protein with ECM   
 → Binding + Interaction

## 1) Fibronectin

- Fibronectin consists of a linear array of 30 Fn domains to give a modular construction
- Fn-type domains are found in blood clotting factors and receptors.   
 (المدم، نختن، عوامل)
- Bind to numerous ECM components   
 (معدید)
- Bind to cell surface receptors (RGD) → Integrin protein



Human fibronectin molecule consists of two similar polypeptides joined by disulfide bonds.

# 7.1 | Components of the Extracellular Matrix (5 of 7)

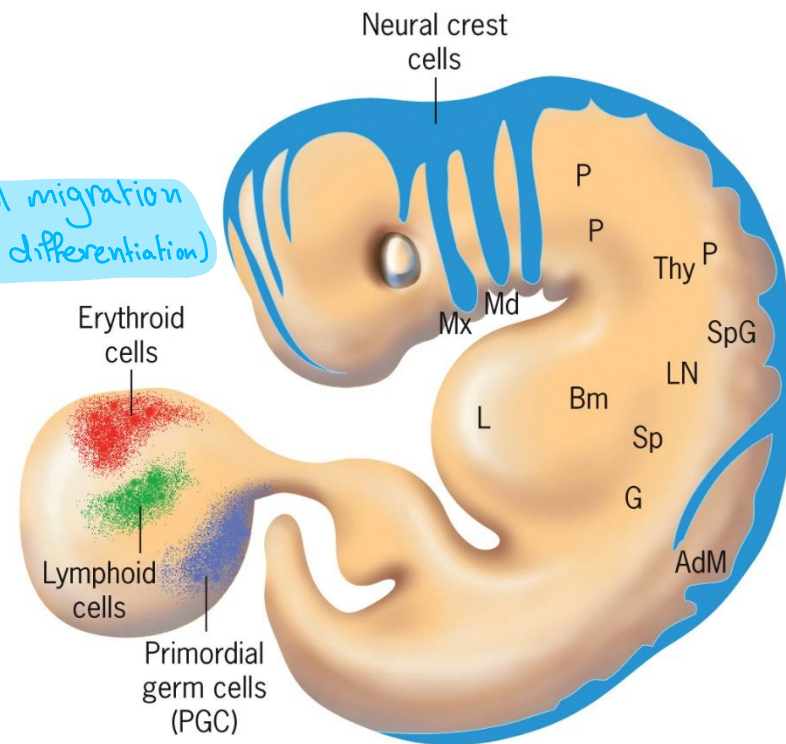
## Fibronectin

- Fibronectin and other extracellular proteins have important roles during embryonic development.

(Cell migration + Cell differentiation)

- Development is characterized by waves of cell migration.

يتميز التطور بهجرات متتالية (تسمى موجات) لأنه لا يخص مرة واحدة بل على مراحل عدة وهي منظمة جداً



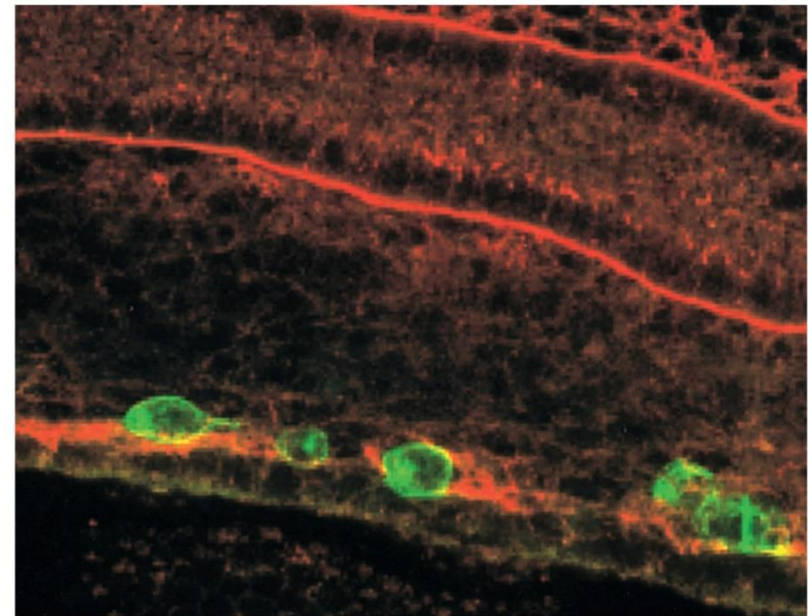
Source: A. A. Moscona & R. E. Hausman, *Cell and Tissue Interactions*, J. W. Lash & M. M. Burger (Eds.), Raven Press, 1977 ISBN: 0890041806.

A summary of some of the cellular traffic occurring during mammalian development

# 7.1 | Components of the Extracellular Matrix (7 of 7)

## 2) Laminin

- Family of at least 15 extracellular glycoproteins.
- Laminin has three polypeptide chains linked by disulfide bonds  
*So it's a covalent bond*
- They can greatly influence a cell's potential for migration, growth, and differentiation.  
*تعلم (العجزة)*
- Role in development of neuronal outgrowth  
*هو أساسي لنمو الأعصاب وتمدها، لأنه يوفر الطريق الذي يتمشي عليه الخلايا العصبية وهي عم تنمو*
- Strengthen basement membrane  
*له هو المكون الأساسي الـ لربط كل المكونات والانسجة مع بعض*



Source: © 1997 Martin J. Garcia-Castro et al. Originally published in *The Journal of Cell Biology* <https://doi.org/10.1083/jcb.138.2.471>.

20  $\mu$ m

Primordial germ cells (green) migrating along a tract of laminin (red) from the dorsal mesentery to the developing gonad.

# 7.1 | Dynamic Properties of the Extracellular Matrix

- ECM can exhibit dynamic properties both in space and time
- Spatially, ECM fibrils can stretch several times their normal length
- Matrix metalloproteinases degrade ECM materials *It contain Zinc which is Important to his activity*
- The physiological roles of MMPs are thought to be involved in tissue remodeling, embryonic cell migration, wound healing, and the formation of blood vessels
- Abnormal expression of MMPs linked to a variety of diseases

Examples:

- ✓ Wound healing: ECM is broken down and rebuilt to repair tissue
- ✓ Angiogenesis (blood vessel formation): cells must degrade ECM to form new vessels

# Dynamic Properties of the Extracellular Matrix

ECM degradation is accomplished by a family of zinc-containing enzymes called **matrix metalloproteinases** (MMPs) secreted into the extracellular space or anchored to the plasma membrane.

As a group, MMPs can digest nearly all of the diverse ECM components, although individual family members are limited as to the types of extracellular molecules they can attack.

كل نوع من هذه البروتينات MMPs يتكون متخصص لنوع معين من الجزيئات التي يفسد يهاجمها أو يحطمها

The physiological roles of MMPs are thought to be involved in tissue remodeling, embryonic cell migration, wound healing, and the formation of blood vessels.

التئام الجروح

Inappropriate MMP activity has been implicated in arthritis, tooth and gum disease, formation of blood clots and heart attack, and tumor progression.

غير مناسب

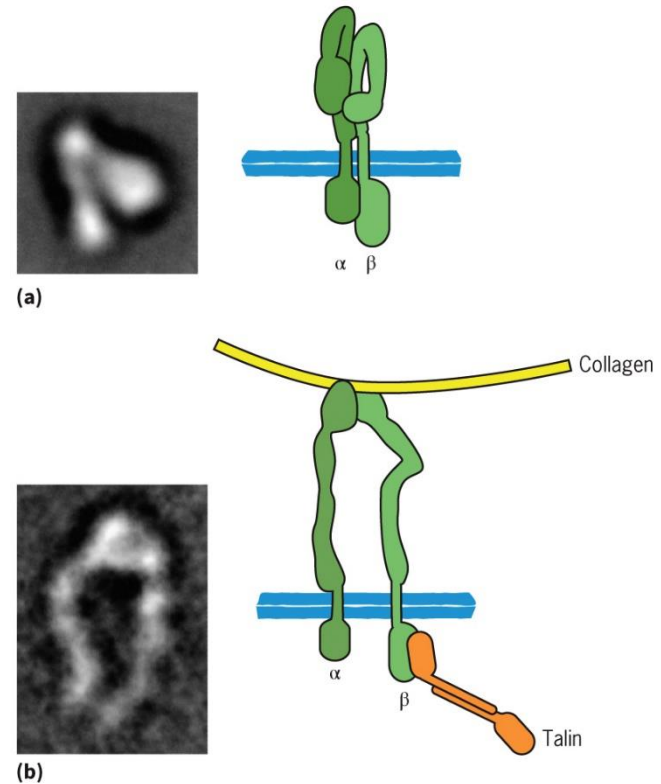
استخلت

الإصابة من التي تستب إذا مثل يشتغل

# 7.3 | Interactions of Cells with Extracellular Materials (1 of 4)

## Integrins

- Family of membrane proteins unique to animals.
- Composed of two membrane-spanning polypeptide chains, an  $\alpha$  chain and a  $\beta$  chain. → with non-covalent bond
- The <sup>تنين</sup> bent <sup>شكل</sup> conformation of integrin corresponds to its inactive state, Integrins with a bound ligand are found in an upright conformation.
- The transmembrane domains of the two subunits are in close proximity. ← تكون المظلمات العابرة للغشاء في تقارب وثيق



EMs and ribbon drawings of the extracellular domains of an integrin ( $\alpha_v\beta_3$ ) in the “bent”/inactive and “upright”/active conformation. Changes driven by divalent metal ions.

Source: Electron micrographs from Junichi Takagi et al., *Cell* 110:601, 2002, with permission from Elsevier.

# 7.3 | Interactions of Cells with Extracellular Materials (2 of 4)

## Integrins

- Integrins have two major activities: adhesion of cells to their substratum (or to other cells) and transmission of signals between the external environment and the cell interior.
- Outside-in signals can induce a conformational change in talin. → the name of the protein (Inside the cell)
- Cytoplasmic protein kinases (e.g. FAK and Src) can be activated to phosphorylate other proteins. Outside-in signals transmitted by integrins can influence differentiation, motility, growth, and cell survival.
- Most malignant cells are capable of growing in liquid suspension. (adhesion) معلق (adhesion)
- Normal cells can only grow and divide if they are cultured on a solid substratum.

- Integrins have a globular extracellular head and legs extending through the membrane.
- Each subunit crosses the membrane as a **single helix** and ends with a short cytoplasmic domain.
- X-ray structure revealed that integrin is bent at the "knees" , not upright.
  - \* This bend positions the head close to the plasma membrane surface.
- Most cells possess a variety of different integrins; conversely, most integrins are present on a variety of different cell types.

بعد ارتباط ال ligand بال Integrin  
 يبدأ رأس خنثي Clustering (تجمع) ال Integrin  
 مع بعض عتاد يصير خنثي المنضوق اقوى وارتباط اقوى  
 دارسك اشارة قوية للداخل

- Integrins have been implicated in **two major types of activities**:
  - Adhesion** of cells to their substratum (or to other cells).
  - Transmission** of signals between the external environment and the cell interior.

### Outside-In Signaling

#### 1. Initiation (Binding)

Begins when the extracellular domain of an integrin binds to a ligand such as:

fibronectin ,collagen

#### 2. Conformational Change

This binding induces a conformational change at the cytoplasmic end of the integrin, especially in the: B subunit

#### 3. Intracellular Effects

The change at the cytoplasmic end leads to: altered interactions between integrin and cytoplasmic proteins modification of their activity

#### 4. Key Example (Talin & Actin)

Outside-in signals can:

induce a conformational change in talin initiate a cascade of events leading to actin filament polymerization in the cytoskeleton

#### 5. Activation of Kinases

Integrin binding to an extracellular ligand can activate:

protein kinases such as: FAK ,Src

These kinases: phosphorylate other proteins trigger a chain reaction

#### 6. Signal Transmission to the Nucleus

In some cases:

the signaling cascade reaches the nucleus leading to activation of specific genes

#### 7. Effects of Outside-In Signaling on Cell Behavior

It influences: differentiation ,motility ,growth,survival

#### 8. Example: Effect on Cell Survival

#### Normal Cells:

Require:

attachment to a solid substratum

If placed in suspension: they die

#### Malignant Cells:

Can: grow even when suspended in a liquid medium

#### Activation mechanism:

\* **In the inactive state**, the two transmembrane subunits are close together and held by noncovalent interactions.

\* The protein talin causes separation of the subunits and activates integrin.

\* This conformational change allows ligand binding.

\* Increased activation is associated with clustering of integrins on the cell surface

\* This process is **called inside-out signaling**.

ص ٣٣  
مذكرة  
Sheet ٣٣

## المرحلة الأولى: التنشيط من الداخل للخارج (Inside-out signaling)

هذه المرحلة هي "قرار الخلية" بالالتصاق.

- البداية: الخلية ترسل إشارة داخلية تنشط بروتين **التالين (Talin)** الموجود في السيتوبلازم.
- الآلية: يرتبط التالين بالذيل السيتوبلازمي للوحدة الفرعية  $\beta$ .
- التغيير الشكلي: هذا الارتباط "يفصل" الأرجل ( $\alpha$  Units &  $\beta$ ) عن بعضها، مما يحول الإترجين من الشكل المنحني الخامل (**Bent/Inactive**) إلى الشكل القائم النشط (**Upright/Active**).
- الهدف: زيادة قدرة الإترجين على الارتباط بالليكاندات (Ligands) في الخارج.

## المرحلة الثانية: الارتباط والالتصاق (Adhesion)

- الارتباط: يمسك رأس الإترجين بـ "الليكاند" (مثل الكولاجين أو الفيبرونيكتين) الموجود في المادة خارج الخلية (ECM).
- التجمع (**Clustering**): بمجرد الارتباط، تتجمع جزيئات الإترجين معاً على سطح الغشاء لتقوية الالتصاق.

## المرحلة الثالثة: إرسال الإشارات من الخارج للداخل (Outside-in signaling)

هذه المرحلة هي "استجابة الخلية" للمعلومات الخارجية.

- الآلية: ارتباط الليكاند يغير شكل الذيل السيتوبلازمي للإترجين (تحديداً  $\beta$ ).
- نقل الإشارة: هذا التغيير يحفز سلسلة من الأحداث داخل الخلية:
- 1. بلمرة خيوط الأكتين (**Actin filaments**) في الهيكل الخلوي.
- 2. تنشيط بروتينات كينيز (**Protein kinases**) مثل **FAK** و **Src**.
- 3. هذه الكينيزات تبدأ تفاعلاً متسلسلاً (Chain reaction) يصل أحياناً إلى النواة لتنشيط جينات معينة.

## المرحلة الرابعة: التأثير النهائي (Biological Outcomes)

ماذا تستفيد الخلية من كل هذا؟ الإشارات المنقولة عبر الإترجين تتحكم في:

1. التمايز (**Differentiation**): تحديد تخصص الخلية.
2. الحركة (**Motility**): قدرة الخلية على الانتقال.
3. النمو (**Growth**): تحفيز الانقسام.
4. البقاء (**Survival**): وهذه أهم نقطة في صورتك الجديدة.

## ! قاعدة "الارتباط من أجل الحياة" (Life-saving signals)

هنا نلاحظ الفرق الجوهرى بين الخلايا الطبيعية والسرطانية:

- الخلايا الطبيعية (**Normal cells**): تحتاج للالتصاق بسطح صلب (**Solid substratum**) لتعيش.
- إذا وضعت في سائل (**Suspension**)، تموت؛ لأن الإترجينات لا تجد ما ترتبط به، فلا ترسل "إشارات البقاء" (**Life-saving signals**) للداخل.

## • الخلايا السرطانية (**Malignant cells**):

- خبيثة لأنها لا تعتمد على ارتباط الإترجين لتعيش.
- تستطيع النمو والانقسام حتى وهي عائمة في السائل، لأنها ترسل إشارات البقاء من داخلها دون الحاجة لليكاند خارجي.

## ملخص للدراسة (احفظه عندك):

- تالين ← فصل  $\alpha$  و  $\beta$  ← شكل قائم ← جاهز للارتباط: **Inside-out**.
- إشارات للنواة ← **FAK/Src** تنشيط ← **Clustering** ليكاند ← تجمع: **Outside-in**.

### 1. في حالة "من الداخل للخارج" (**Inside-out**)

- الترتيب: (إشارة داخلية → التالين يرتبط بالذيل → الإترجين يفتح ويصبح مستقيماً).
- هنا التالين هو "البادئ": هو الذي "دفع" الأرجل لتنفصل. بدونها، يبقى الإترجين منحنيًا وخاملاً.

### 2. في حالة "من الخارج للداخل" (**Outside-in**)

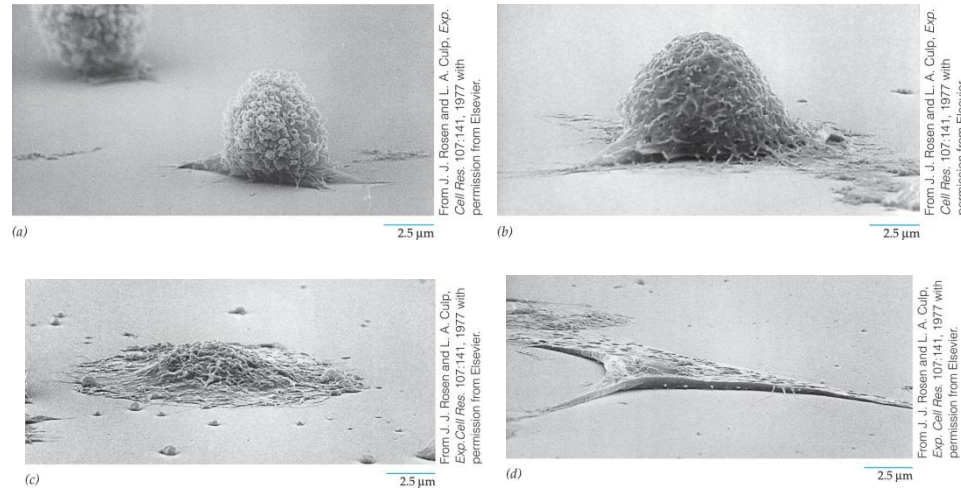
- الترتيب: (الليكاند يرتبط من الخارج → تتجمع الإترجينات (**Clustering**) → التالين يرتبط بالذيل ليربطه بالهيكل الخلوي).
- هنا التالين هو "المثبت": بعد أن يمسك الليكاند بالإترجين، يحتاج الإترجين لشيء يثبته بقوة من الداخل لكي يستطيع نقل "هزة" الإشارة. فيقوم التالين بالارتباط بالذيل ليعمل كجسر يربط الإترجين بخيوط الأكتين (**Actin filaments**).
- كيف نميز بينهما؟
- الأمر يعتمد على "حالة الإترجين" قبل وصول التالين:
- إذا كان الإترجين منحنيًا (**Bent**): يأتي التالين ليفتحه (**Inside-out**).
- إذا كان الإترجين مرتبطًا بليكاند (**Bound**): يأتي التالين (أو يزيد ارتباطه) ليرسخ الاتصال وينقل الإشارة الميكانيكية للداخل (**Outside-in**).

# 11.6 | Anchoring Cells to Their Substratum

Since it is easier to study the cell interactions with a culture dish than with an ECM inside an animal, in vitro experiments have been instrumental in understanding cell-matrix interactions.

At first, the cell has a rounded morphology, but once the cell makes contact with the substratum, it sends out projections that form increasingly stable attachments.

Over time, the cell flattens and spreads itself out on the substratum.



## Steps in the process of cell spreading.

ولكن بمجرد أن تلامس الخلية الركيزة (السطح)، فإنها ترسل نتوءات (بروزات) تشكل روابط مستقرة بشكل متزايد. "

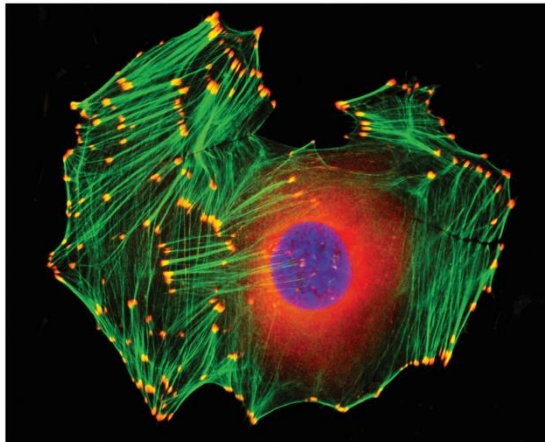
يتم مسطح السطح الذي عليه سوف تزرع خلايا بجوار  
 باد ECM لذلك الخلية يتمسك فيهم + بالاصم الخلية هي الي

ببني الـ ECM وبتفرزه للخارج (المفانة هي وسيلة حياة ارحوم) ← البناء عند الحياة

# 7.3 | Interactions of Cells with Extracellular Materials (3 of 4)

## Focal Adhesions

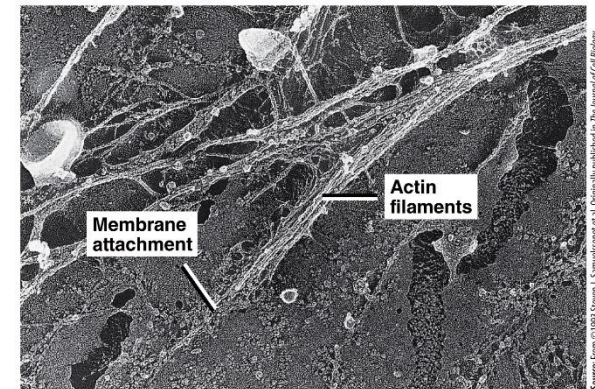
- Cultured cells are anchored to the surface of the dish only at scattered, discrete sites, called focal adhesions.
- Focal adhesions play a key role in cell locomotion.
- Focal adhesions are dynamic structures.



Source: From Molecular expressions.com at Florida State University

**Cultured cell:** actin filaments (gray-green), integrins (red); sites of focal adhesions

Amphibian cell processed for quick-freeze, deep-etch analysis



Source: From © 1993 Steven J. Szymanski et al. Originally published in *The Journal of Cell Biology* <http://dx.doi.org/10.1083/jcb.112.2.485>

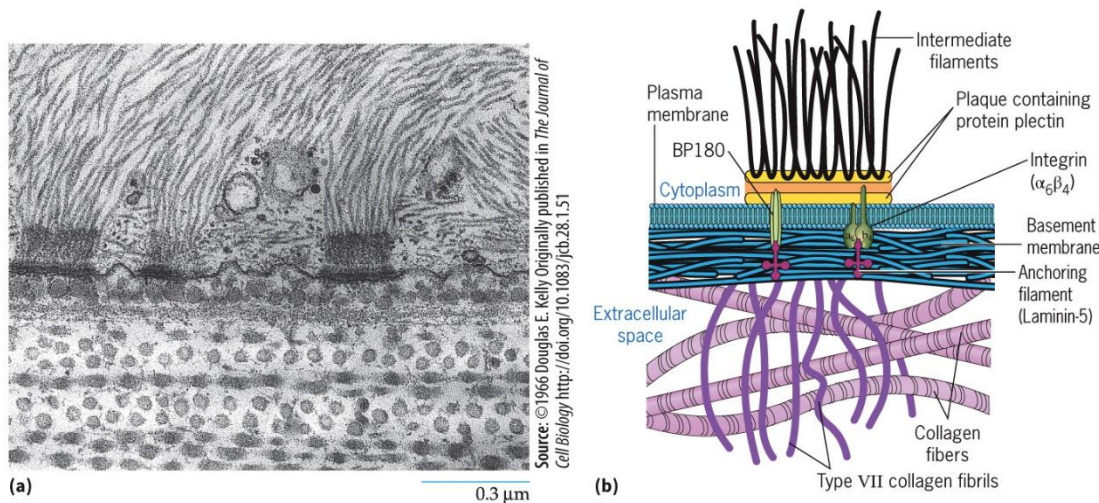
2.5 μm



# 7.3 | Interactions of Cells with Extracellular Materials (4 of 4)

## Hemidesmosomes

- Cell-matrix attachment in vivo is seen at the basal surface of epithelial cells, anchored to the underlying basement membrane.
- Hemidesmosomes contain a dense cytoplasmic plaque with keratin filaments.
- Keratin filaments are linked to the ECM by integrins.



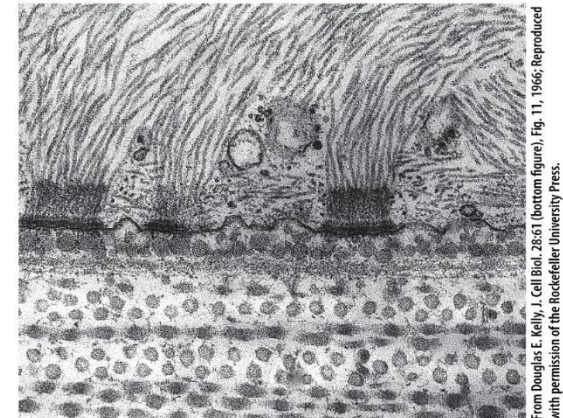
Hemidesmosomes: EM and schematic diagram.

# Hemidesmosomes

In the autoimmune disease **bullous pemphigoid**, antibodies are made towards proteins present in these adhesive structures.

These auto-antibodies cause the epidermal layer to lose attachment to the underlying basement membrane and result in severe skin blistering.

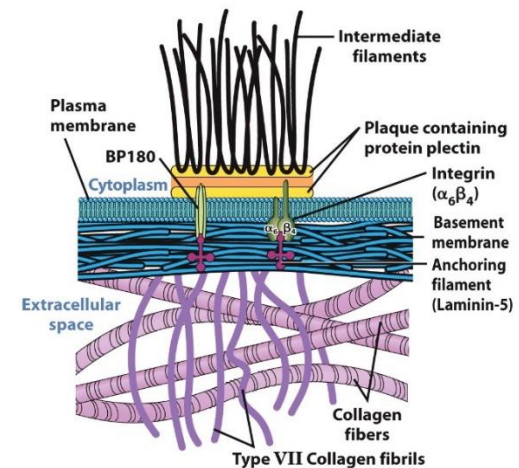
**Epidermolysis bullosa** results from genetic alterations in hemidesmosomal proteins, including the  $\alpha 6$  or  $\beta 4$  integrin subunit, collagen VII, or laminin-5.



From Douglas E. Kelly, J. Cell Biol. 28:61 (bottom figure), Fig. 11, 1966; Reproduced with permission of the Rockefeller University Press.

0.3 μm

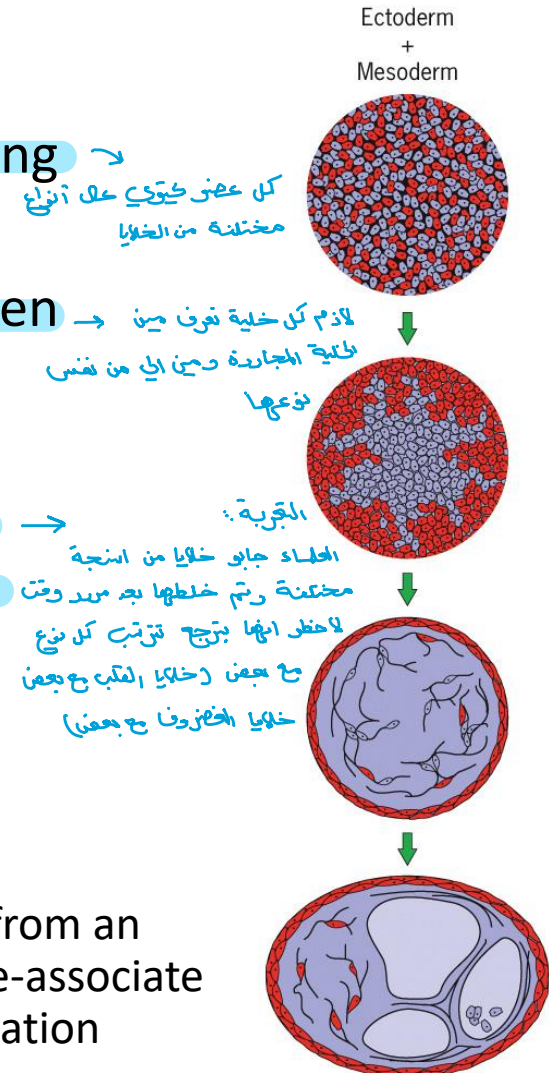
## Hemidesmosomes: EM and schematic diagram.



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# 7.4 | Interactions of Cells with Other Cells (1 of 2)

- Organs have a complex architecture involving a variety of different cell types.
- Dependent on *selective* interactions between cells of the same type, as well as between cells of different types.
- Experiments demonstrated that separated cells would redistribute themselves so that each cell adhered only to cells of the same type



Ectoderm and mesoderm from an early amphibian embryo re-associate after initial random dissociation

Source: P. L. Townes, J. Holtfreter, *Journal of Experimental Zoology* 128:53, 1955.

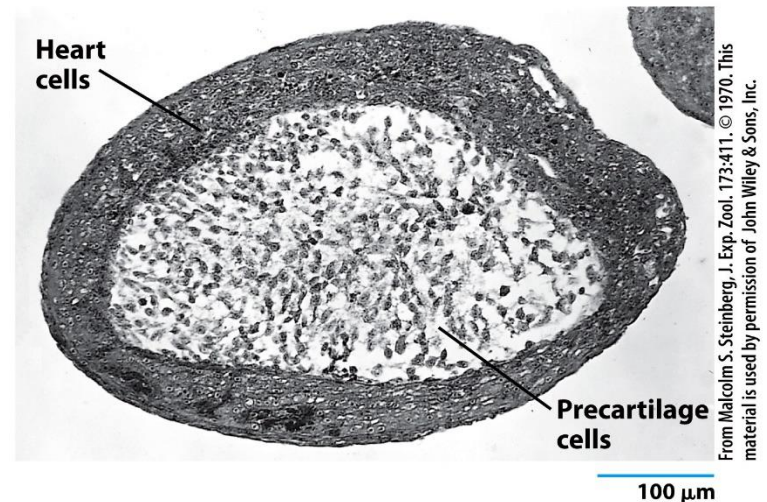
# Interactions of Cells with Other Cells

Over time, cells would redistribute themselves so that each cell adhered only to cells of the same type.

الانضال

Once segregated, cells would differentiate into many of the structures they would have formed within an intact embryo.

Four distinct families of integral membrane proteins play a major role in mediating cell–cell adhesion: (1) **selectins** (2) certain members of the **immunoglobulin superfamily (IgSF)**, (3) certain members of the **integrin** family, and (4) **cadherins**.

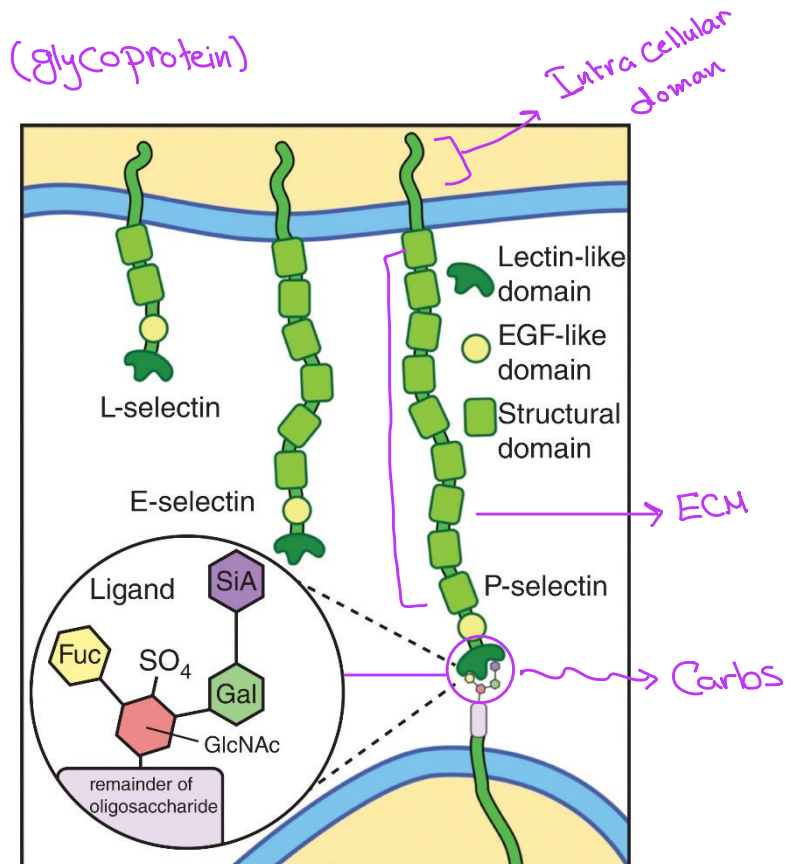


Light micrograph: mixed pre-cartilage cells from a chick limb and chick heart ventricle cells re-sort based on cell type

# 7.4 | Interactions of Cells with Other Cells (2 of 2)

## Selectins (glycoprotein)

- Selectins are a family of membrane glycoproteins that bind to specific oligosaccharides.
- “Lectin,” is a term for a compound that binds to specific carbohydrate groups.
- Selectins have a small cytoplasmic segment, a single membrane-spanning domain, and a large extracellular portion.



Schematic of the three selectins and their CHO ligand

# Selectins

inflammation response  $\leftrightarrow$  blood wall

Selectins are a family of membrane glycoproteins that bind to specific oligosaccharides on the surfaces of neighboring cells.

“Lectin,” is a term for a compound that binds to specific carbohydrate groups.

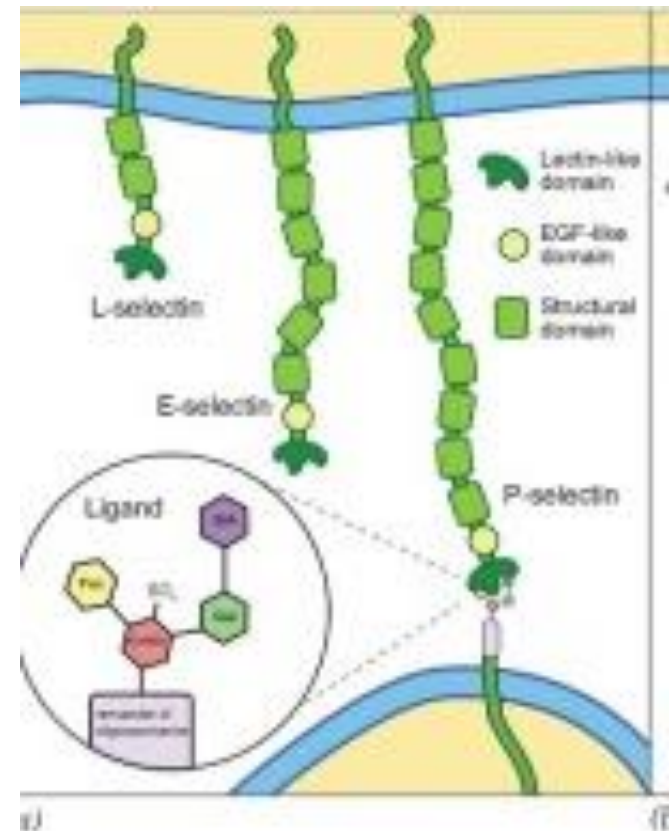
Selectins have a small cytoplasmic segment, a single membrane-spanning domain, and a large extracellular portion.

Three cell-specific selectin types:

*E-selectin*, endothelial cells;

*P-selectin*, platelets and endothelial cells;

*L-selectin*, leukocytes (white blood cells).



Schematic of the three selectins and their ligand

# Selectins

في بعضهم يتاجر البعض الآخر

Binding of selectins to their carbohydrate ligands requires **calcium**.

As a group, selectins mediate transient interactions between circulating leukocytes and vessel walls at sites of inflammation and clotting.

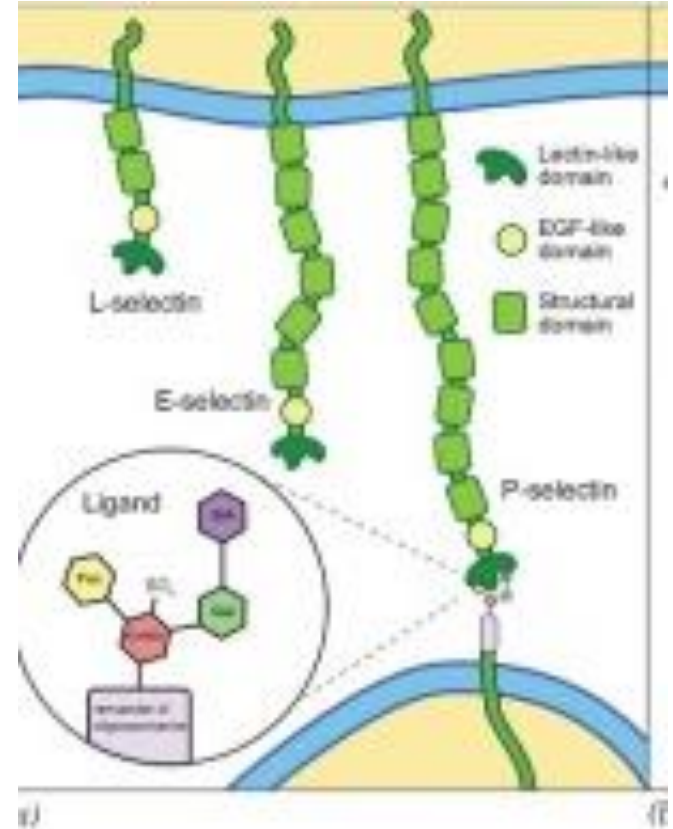
التهاب

جرح

1. ستة نطاقات (Six Ig domains) **Ig**: موجودة عند الطرف الخارجي للبروتين (N-terminal) وهي المسؤولة عن "المصافحة" مع الخلايا الأخرى.
2. قطع تشبه الفيبرونيكتين (Segments resemble fibronectin): تعطي البروتين الطول والمرونة اللازمة.

3. جزء عابر للغشاء (Transmembrane segment): يثبت البروتين في غشاء الخلية.

4. نطاق سيتوبلازمي صغير (Small cytoplasmic domain): موجود داخل الخلية لنقل الإشارات.

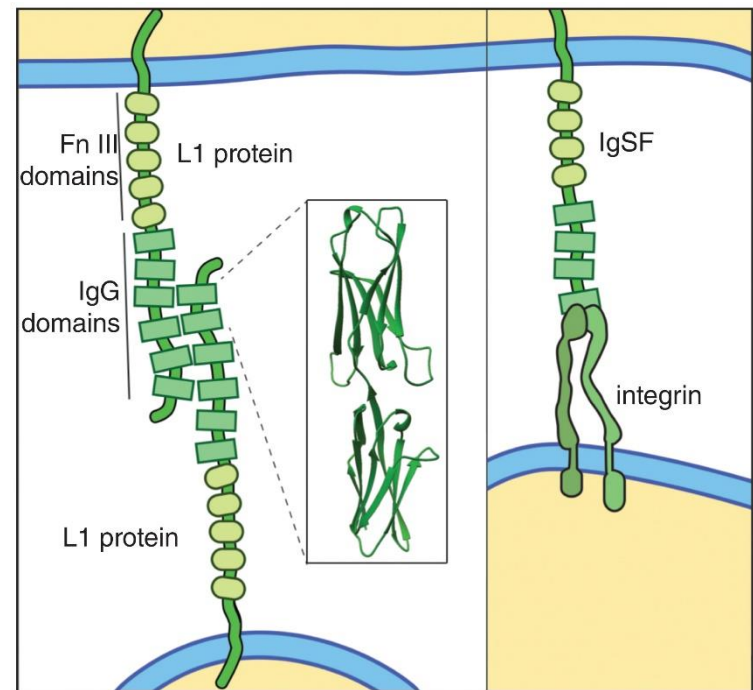


Schematic of the three selectins and their ligand

# 7.4 | Interactions of Cells with Other Cells (1 of 4)

## The Immunoglobulin Superfamily

- The human genome encodes 765 distinct Ig domains.
- These are members of the immunoglobulin superfamily.
- Immune functions for most
- Original function likely cell-adhesion mediators ( $\text{Ca}^{2+}$  independent)
- Developmental roles in neuronal growth and circuitry



Source: Inset from E. Yvonne Jones et al., *Nature* 373:540, 1995; © 1995, reprinted by permission from Macmillan Publishers Ltd.

Cell-cell adhesion from homotypic interactions of two L1 molecules through Ig domains at the N-termini.

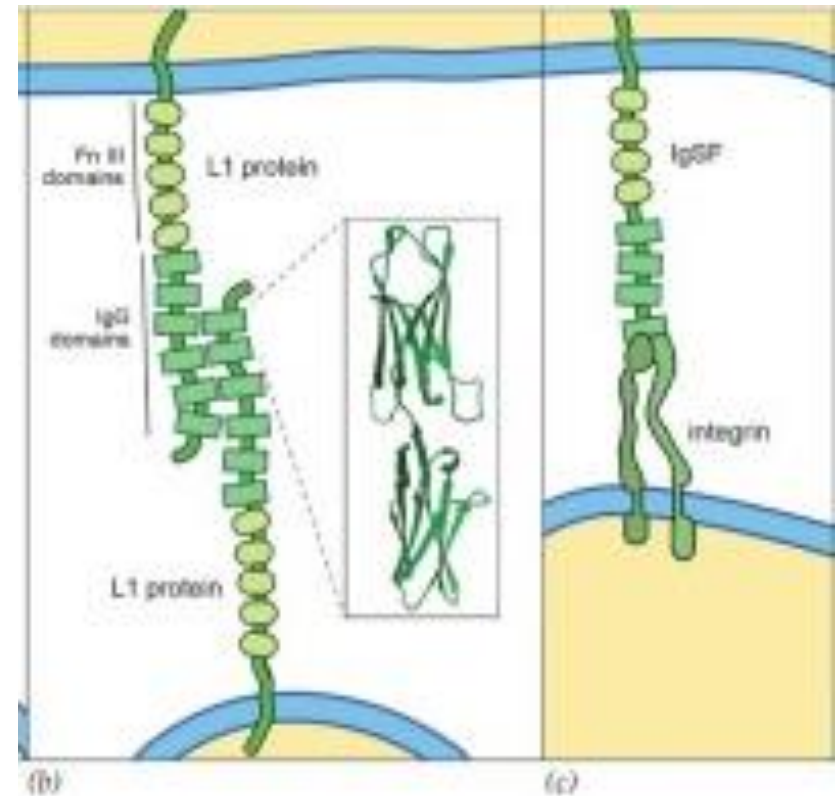
# The Immunoglobulin Superfamily

VCAM (vascular cell-adhesion molecule), NCAM (neural cell-adhesion molecule), and L1 (also called L1CAM), mediate adhesion between nonimmune cells.

NCAM and L1 have roles in nervous system development.

Various types of proteins serve as ligands for IgSF cell surface molecules, such as integrins.

لـ يرتبط بالعادة ECM  
لكن همه يرتبط بـ IgSF



Cell-cell adhesion from homotypic interactions of two L1 molecules through Ig domains at the N-termini.

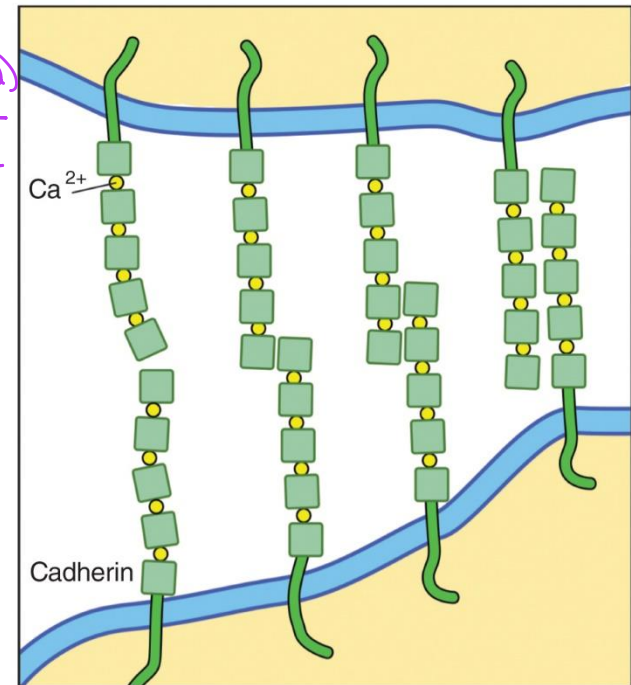
بـ ادرس  
ارجح للايقان

# 7.4 | Interactions of Cells with Other Cells

(2 of 4) Cadherins: most important cell-cell adhesion protein because of correlation with disorders. من اهم البروتينات للاتصال الخلية بخلية بسبب ارتباطها بالامراض والاضطرابات

## Cadherins

- Glycoprotein family (Cadherins with Cadherins bind) غير ذلك لا يعرف على شيء ثاني
- Cadherins typically join cells of similar type to one another (Ca<sup>2+</sup> dependent).
- Possibly the single most important factor in molding cells into cohesive tissues in the embryo and holding them together in the adult. تشكيل, تشكيل, مقاسمة, النسيجة
- Cadherin loss associated with malignancy له بسبب فقدان الالتصاق بين الخلايا تؤدي إلى الانفصال والانتشار tumor ←



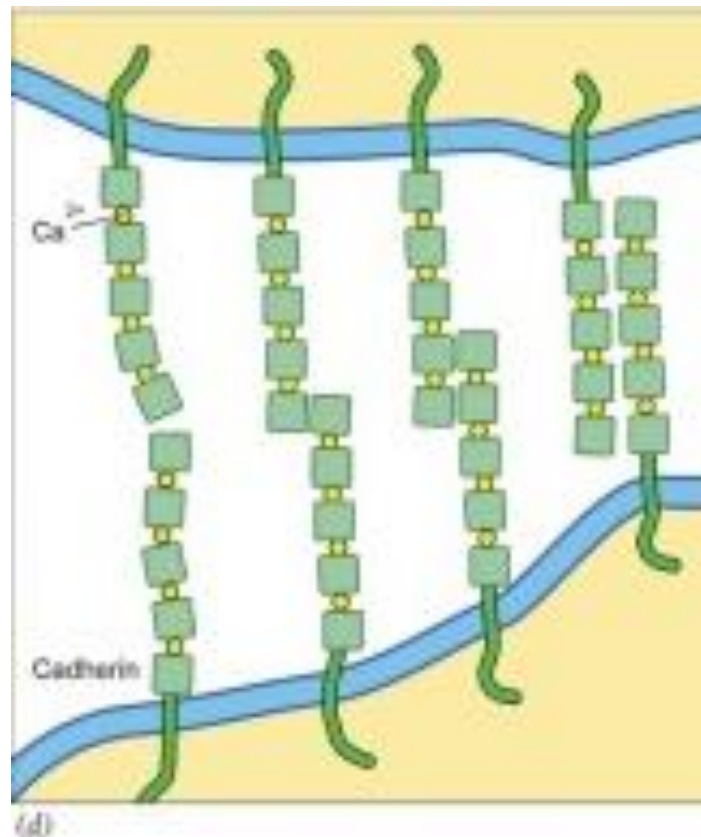
Schematic of two adhering cells due to interactions between cadherins projecting from the plasma membrane of each cell

# Cadherins

Cadherins are family of glycoproteins that mediate  $\text{Ca}^{2+}$ -dependent cell–cell adhesion and transmit signals from the ECM to the cytoplasm.

Cadherins typically join cells of similar type to one another and do so predominantly by binding to the same cadherin present on the surface of the neighboring cell.

Cadherins may be the single most important factor in molding cells into cohesive tissues in the embryo and holding them together in the adult.



Schematic of two adhering cells due to interactions between cadherins projecting from the plasma membrane of each cell

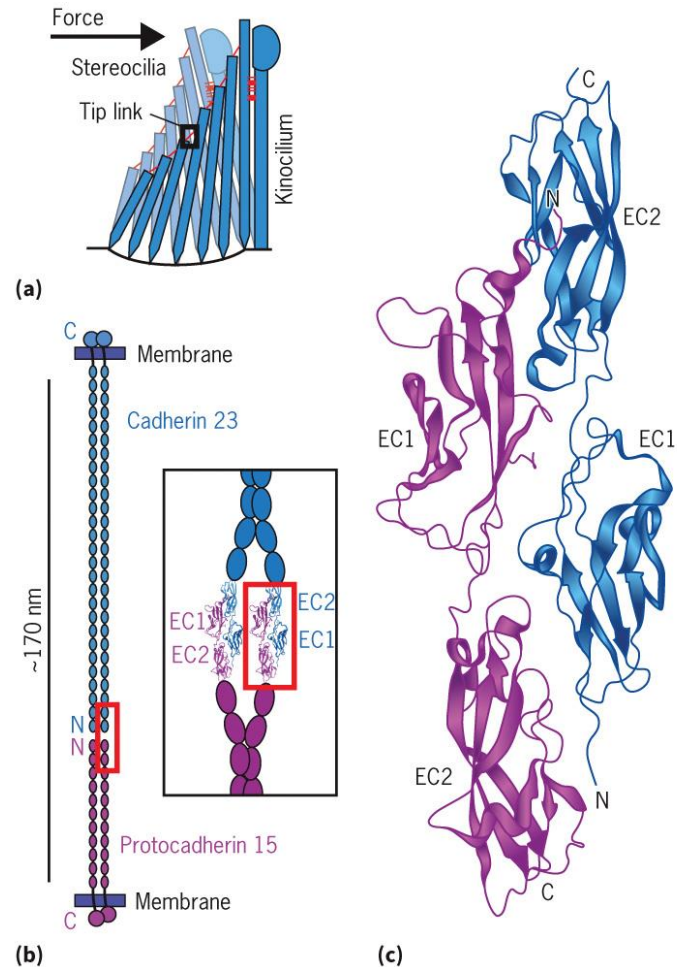
# 7.4 | Interactions of Cells with Other Cells (3 of 4)

## Cadherins

- Over 100 cadherins have been identified in humans.
- Usher syndrome is characterized by deafness and gradual loss of vision and can result from mutations in non-classical cadherins. → Classical + Non-Classical

Note: Cadherins play a role in maintaining the rigidity of the extracellular portion of the protein

Cadherins form tip links of stereocilia



# 7.4 | Interactions of Cells with Other Cells (4 of 4)

## Adherens Junctions and Desmosomes

- Cadherins are also found in specialized intercellular junctions.
- These are calcium-dependent linkages.
- The network of intermediate filaments provides structural continuity and tensile strength.   
استقرارية

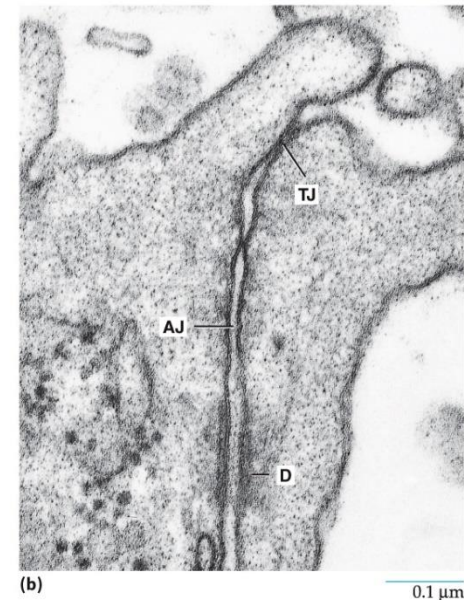
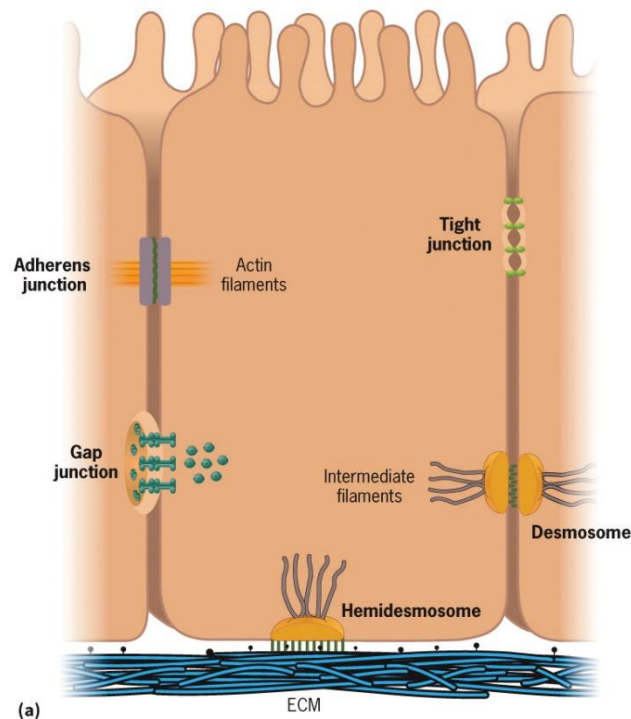


Diagram and EM showing the junctional complexes on the lateral surfaces of a simple columnar epithelial cell

# Adherens Junctions and Desmosomes

Cadherins are found in specialized intercellular junctions: **adherens junctions (AJs)** and **desmosomes**.

AJs are commonly found in epithelia as “belts” (*zonulae adherens*) that encircle cells near their apical surface, binding a cell to its surrounding neighbors.

These calcium-dependent linkages formed between the extracellular domains of cadherin molecules that bridge the 30-nm gap between neighboring cells.

منه ارجعها

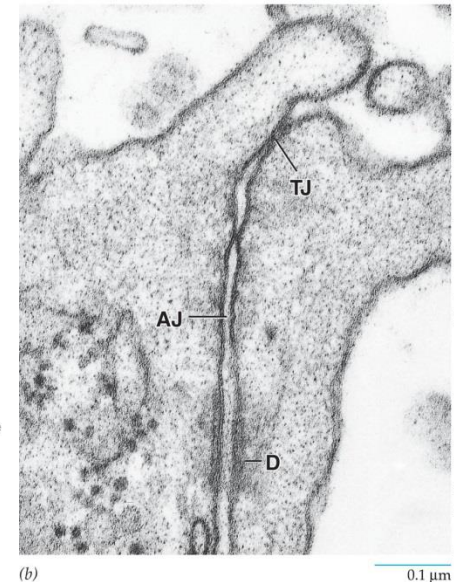
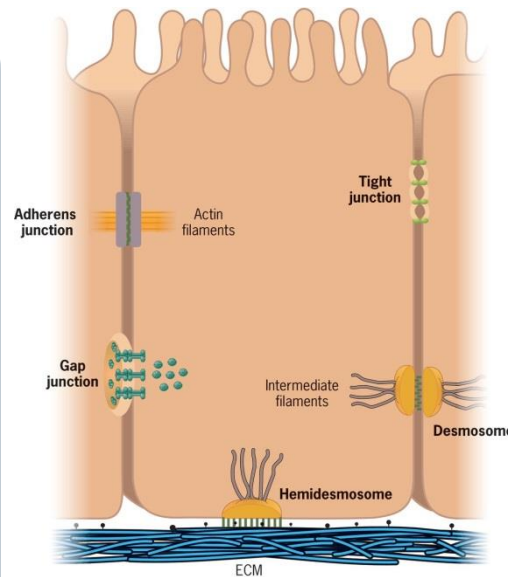


Diagram and EM showing the junctional complexes on the lateral surfaces of a simple columnar epithelial cell

# Adherens Junctions and Desmosomes

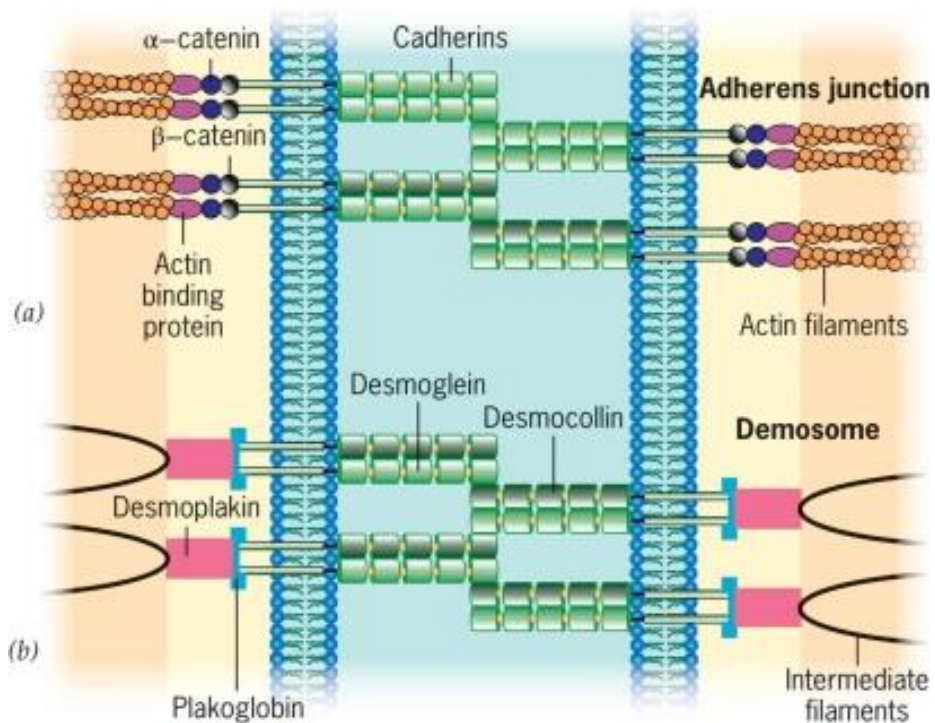
The cytoplasmic domain of cadherins is linked by  $\alpha$ - and  $\beta$ -catenins to cytoplasmic proteins including actin filaments.

Similar to integrins of a focal adhesion, the cadherin clusters of an adherens junction:

- (1) Connect the external environment to the actin cytoskeleton and
- (2) Provide a pathway for signals to be transmitted from the exterior to the interior

Adherens junctions situated that line the walls of blood vessels transmit signals that ensure the survival of the cells.

توس اشارات  
تضمن بناء الخلية



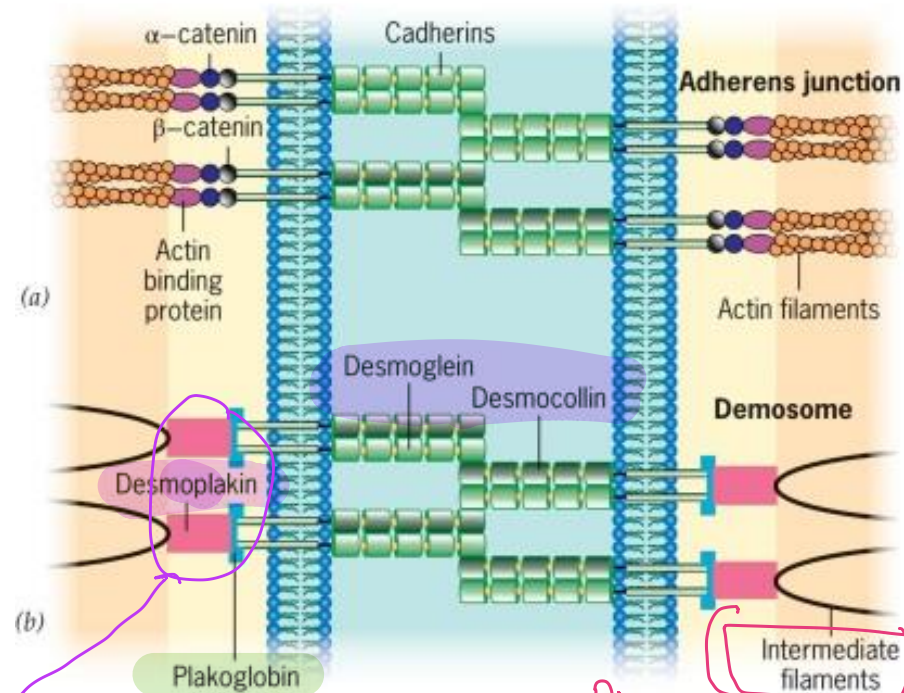
Cadherins link the two cells across a narrow extracellular gap

# Adherens Junctions and Desmosomes

Desmosomes (or *maculae adherens*) are disk-shaped adhesive junctions found in a variety of tissues subjected to mechanical stress, such as cardiac muscle, epithelial layers of the skin and uterine cervix.

Desmosomes contain cadherins with a different domain structure and are referred to as desmogleins and desmocollins.

Dense cytoplasmic plaques serve as sites of anchorage for looping intermediate filaments.

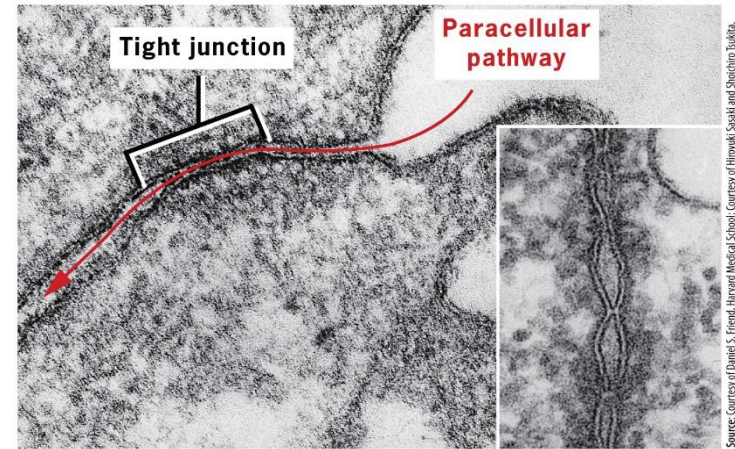


Model: molecular architecture of a desmosome

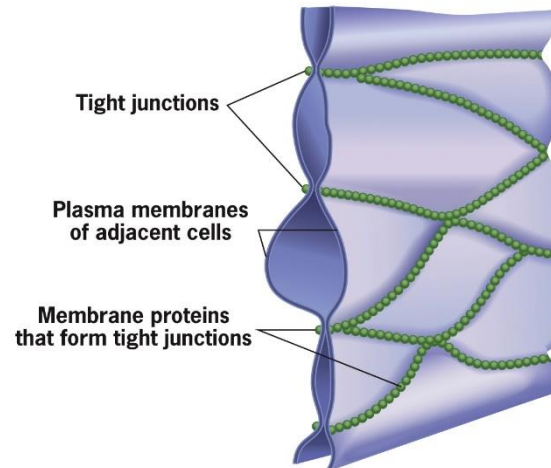
# 7.5 | Tight Junctions: Sealing the Extracellular Space

- Tight junctions occur between neighboring epithelial cells.
- Prevent solute distribution where different solute concentrations are in adjacent compartments
- The points of cell–cell contact are sites where integral proteins of two adjacent membranes meet within the extracellular space.

EM: apical region of adjoining epithelial cells



Three-dimensional view of tight junctions



Tight junction model showing intermittent contact points between proteins from two apposing membranes

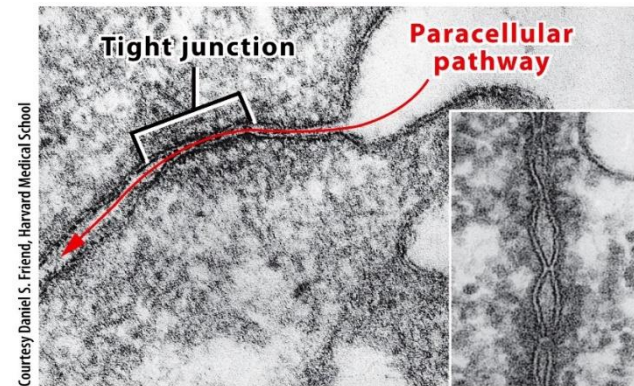
# Tight Junctions: Sealing the Extracellular Space

Tight junctions (*zonulae occludens*), occur between neighboring epithelial cells, and are located at the very apical end of the junctional complex between adjacent cells.

Electron Microscope

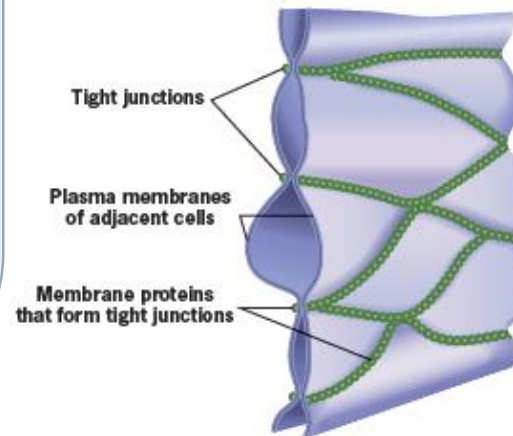
EM reveals that the adjoining membranes make contact at intermittent points, rather than being fused over a large surface area.

The points of cell-cell contact are sites where integral proteins of two adjacent membranes meet within the extracellular space.



EM: apical region of adjoining epithelial cells

Three-dimensional view of tight junctions

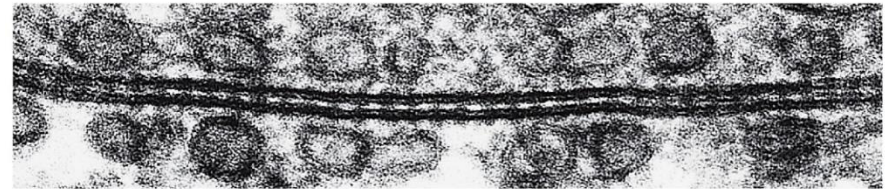


Tight junction model showing intermittent contact points between proteins from two apposing membranes

# 7.6 | Intercellular Communication (1 of 4)

## Gap Junctions *(transport material)*

- Plasma membranes of a gap junction contain channels that connect the cytoplasm of one cell with the cytoplasm of the adjoining cell.
- Gap junctions are sites between animal cells that are specialized for intercellular communication.
- Plasma membranes come very close to one another but do not make direct contact at gap junction.



0.15  $\mu\text{m}$

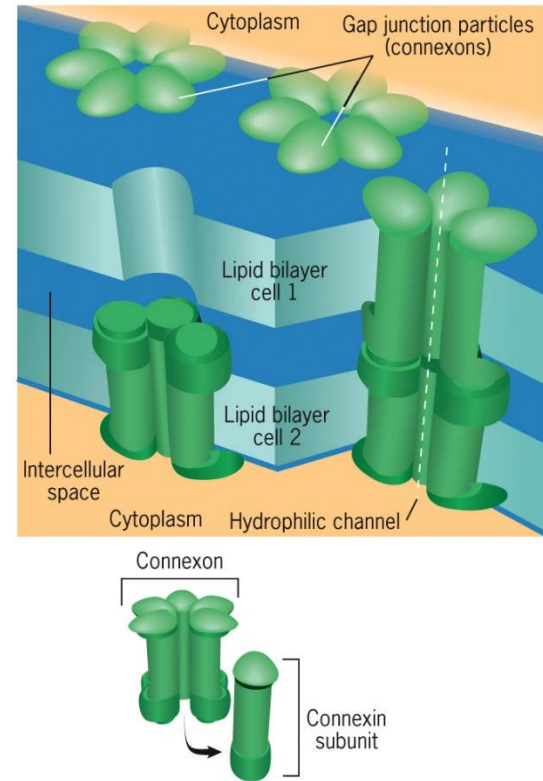
Source: ©1976 Camillo Peracchia et al. Originally published in *The Journal of Cell Biology* <http://doi.org/10.1083/jcb.70.2.419>.

Electron micrograph of a section through a gap junction perpendicular to the plane of the two adjacent membranes

# 7.6 | Intercellular Communication (2 of 4)

## Gap Junctions

- Gap junctions are molecular “pipelines” that pass through the adjoining plasma membranes and open into the cytoplasm of the adjoining cells.
- They are composed of an integral membrane protein **connexin**, and organized into multisubunit complexes, **connexons**, that span the membrane.



Schematic model of a gap junction showing the arrangement of six connexin subunits to form a connexon

# Gap Junctions

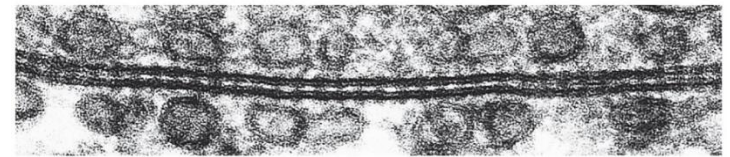
Plasma membranes of a gap junction contain channels that connect the cytoplasm of one cell with the cytoplasm of the adjoining cell.

The passage of ionic currents through gap junctions plays a pivotal role in numerous physiologic processes.

Gap junctions are sites between animal cells that are specialized for intercellular communication.

Gap junctions come very close to one another but do not make direct contact.

تقريباً أُنشئة الخلايا عند Gap Junctions ولا تلتصق  
يتميز فضاء صغير تسمى من خلاله الأنايب البروتينية



0.15  $\mu\text{m}$

From Camillo Peracchia and Angela F. Duhunt, *J. Cell Biol.* 70:426, 1976, Fig. 5; Reproduced with permission of the Rockefeller University Press.

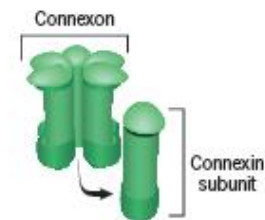
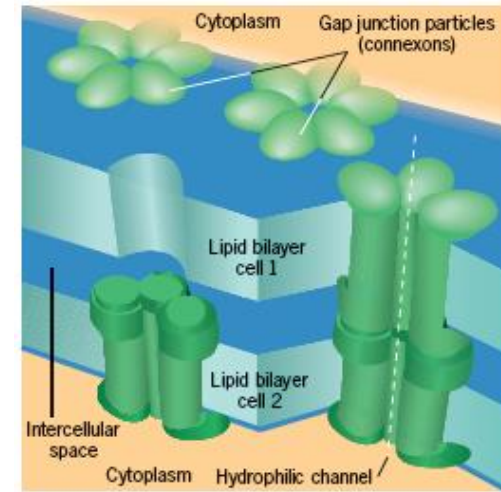
Electron micrograph of a section through a gap junction perpendicular to the plane of the two adjacent membranes

# Gap Junctions

Gap junctions are molecular “pipelines” that pass through the adjoining plasma membranes and open into the cytoplasm of the adjoining cells.

They are composed of an integral membrane protein *connexin*, and organized into multisubunit complexes, *connexons*, that span the membrane.

A connexon is composed of six connexin subunits arranged in a ring around a central opening, or *annulus*, around 1.5 nm in diameter at its extracellular surface.



Schematic model of a gap junction showing the arrangement of six connexin subunits to form a connexon

## 7.4 | The Human Perspective (1 of 3)

### The Role of Cell Adhesion in Inflammation and Metastasis

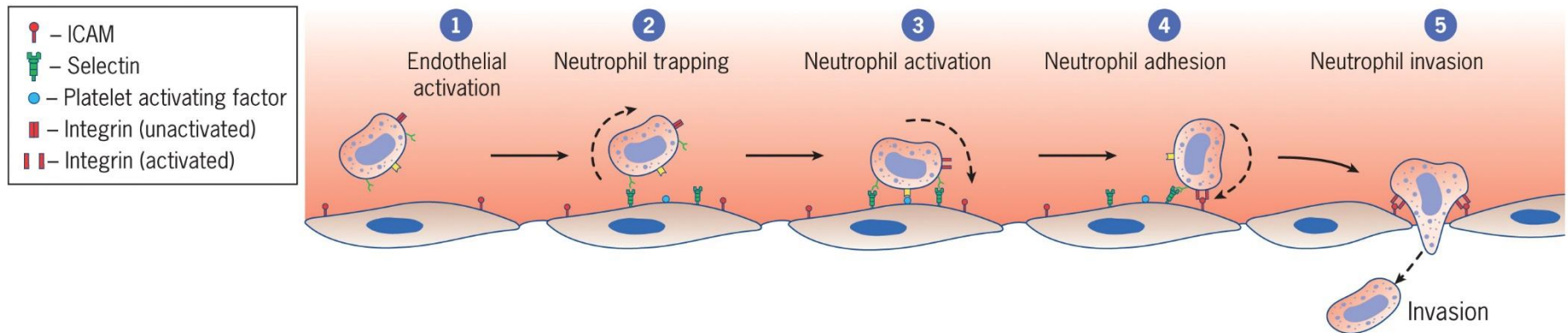
- Inflammation is one of the primary responses to infection, but can produce adverse side effects like fever, swelling, redness, and pain.
- Following a puncture wound to the skin, white blood cells (leukocytes) from the bloodstream are stimulated to traverse the endothelial layer that lines the smallest veins (venules) and enter the tissue.
- Leukocytes recruitment has focused on three types of cell adhesion molecules: selectins, integrins, and IgSF proteins.

نوع من أنواع الـ Cancer ينقل من عضو لآخر  
عن طريق Cell adhesion

## 7.4 | The Human Perspective (2 of 3)

### The Role of Cell Adhesion in Inflammation and Metastasis

- Endothelial cells that line venules become more adhesive to circulating neutrophils through display of P- and E-selectins.
- **Platelet activating factor (PAF)** on endothelial cells stimulates an increase in the integrin binding activity on neutrophils.
- Bound neutrophils then change their shape and squeeze between adjacent endothelial cells into the damaged tissue.

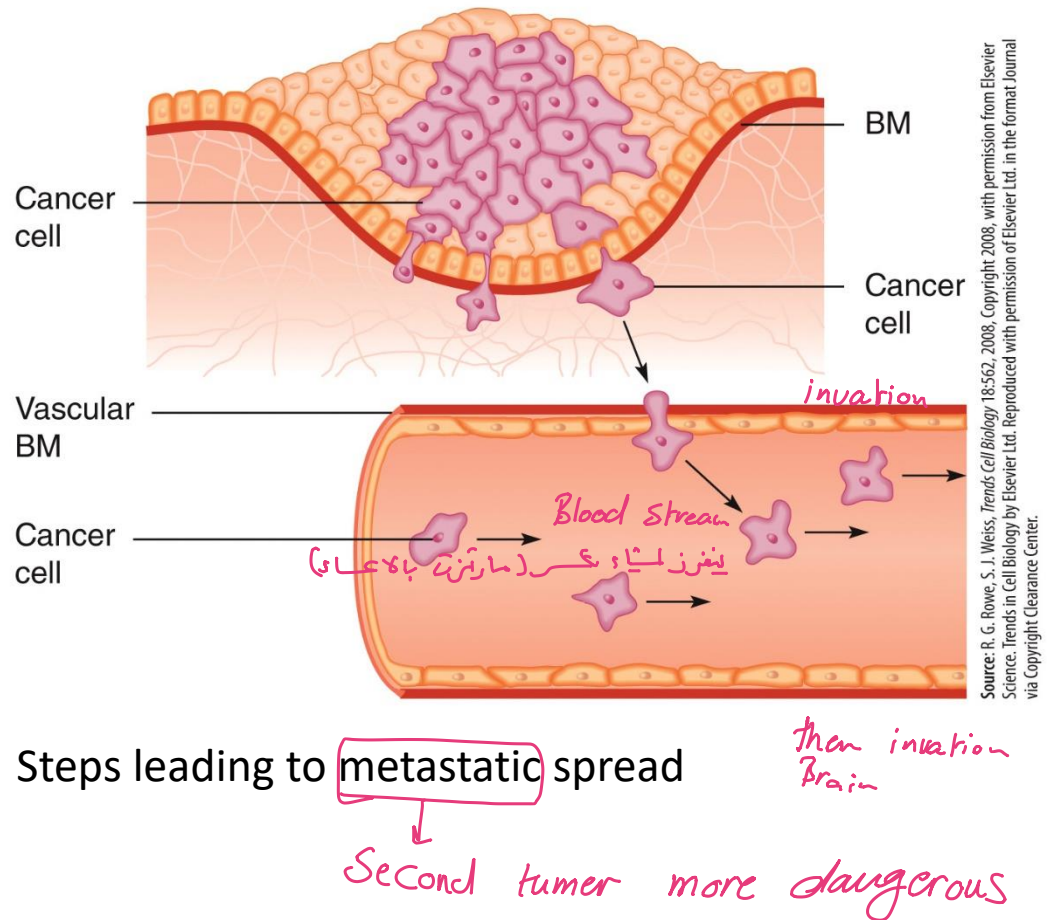


Movement of neutrophils during inflammation

# 7.4 | The Human Perspective (3 of 3)

## The Role of Cell Adhesion in Inflammation and Metastasis

- Cancer cells escape the normal growth control mechanisms and proliferate in an unregulated manner.
- Most malignant tumors are not readily contained.
- Metastatic cells are thought to have special cell-surface properties that are not shared by most other cells in the tumor.



Source: R. C. Rowe, S. J. Weiss, Trends Cell Biology 18:562, 2008. Copyright 2008, with permission from Elsevier Science. Trends in Cell Biology by Elsevier Ltd. Reproduced with permission of Elsevier Ltd. in the format Journal via Copyright Clearance Center.

Note: Adherens junctions and tight junctions circle the cell, while desmosomes and gap junctions are in specific sites. Hemidesmosomes are at the basal membrane of a cell.

Note: Catenins have dual roles: they tether cadherins to the cytoskeleton, and transmit signals to the nucleus and cytoplasm.

In adherens junctions, integral membrane proteins bind to cadherins through actin filaments using adapter proteins (vinculin, alpha catenin and beta catenin)

Adherens junctions situated that line the walls of blood vessels transmit signals that ensure the survival of the cells.

Both desmosomes and adherens junctions use cadherins.

Desmosomes (or maculae adherens) are disk-shaped adhesive junctions found in a variety of tissues subjected to mechanical stress, such as cardiac muscle, epithelial layers of skin and uterine cervix.

Desmosomes contain cadherins with a different domain structure and are referred to as desmogleins and desmocollins.

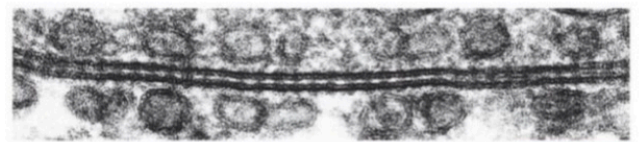
The network of intermediate filaments provides structural continuity and tensile strength.

In desmosomes, cadherin is connected intracellularly with intermediate filaments through adapter proteins called desmoplakins (plakins in desmosomes)

Dense cytoplasmic plaques serve as sites of anchorage for looping intermediate filaments.

ions and small RNAs, as well as glucose and fructose and **small** proteins (Molecules under the molecular weight of 1000 daltons)

Note: Short-range communication between cells is carried out by gap junctions, while mid-range communication is carried out by long tubules that stretch between cells, and long-range communication is carried out using extracellular vesicles.



From Camillo Peracchia and Angela F. Duhanty, J. Cell Biol. 70:426, 1976, Fig. 5; Reproduced with permission of the Rockefeller University Press.

Electron micrograph of a section through a gap junction perpendicular to the plane

The passage of ionic currents through gap junctions plays a pivotal role in numerous physiologic processes.

Plant cells have **plasmodesmata** which has same function of gap junctions.