

Harvey Lodish • Arnold Berk • Paul Matsudaira • Chris A.
Kaiser • Monty Krieger • Matthew P. Scott •
Lawrence Zipursky • James Darnell

Molecular Cell Biology

Fifth Edition

Chapter 6: Integrating Cells into Tissues

Copyright © 2004 by W. H. Freeman & Company

Cells in tissues can adhere directly to one another (cell-cell adhesion) through specialized integral membrane protein called cell adhesion molecules (CAMs)

Cells in animal tissues also adhere indirectly (cell-matrix adhesion) through the binding of adhesion receptors in the plasma membrane to components of the surrounding extracellular matrix (ECM); A complex interdigitating meshwork of proteins and polysaccharides secreted by cells into the spaces between them

CAMs and ECM can bind cell together, and transfer of information between the exterior and interior cells.

Cell Junctions are relatively stable, ultrastructurally (ie in EM) distinct sites where cells are joined to each other or the extracellular matrix.

- Adhesion molecules are one component of adhering junctions

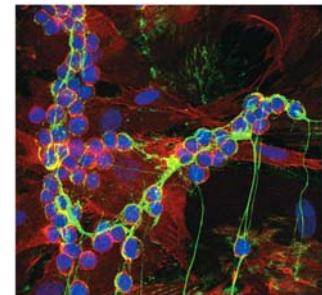
Adhesion Molecules are cell surface molecules that stick to each other to allow cell-cell or cell-ECM adhesion

- Usually less stable

Cell formed organ

Cells in the organism → organized into cooperative assemblies “tissue” → tissues associated in various combinations → organs

Cells in tissue → contact with complex network of secreted extracellular macromolecules (ECM) had “scaffold” function

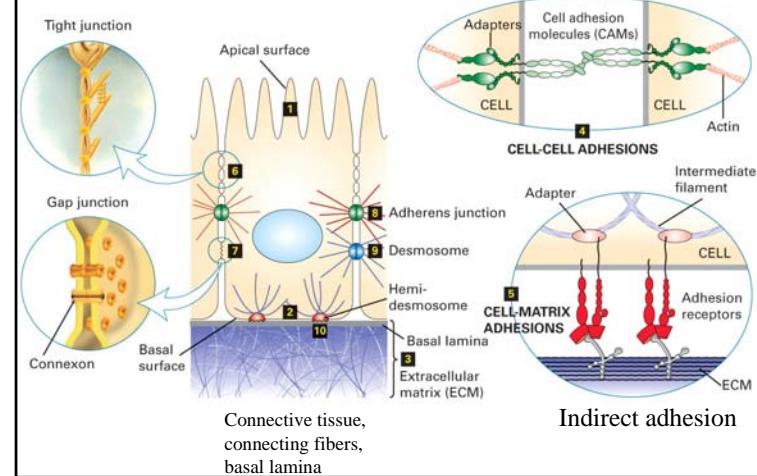


Blue: nuclei

Green: secrete hyaluronan

Inflammatory bowel disease:

Major adhesive interactions that bind cells to each other and the extracellular matrix



Cell-adhesion molecules bind to one another and to intracellular protein Cell Adhesion Molecules (CAMs)

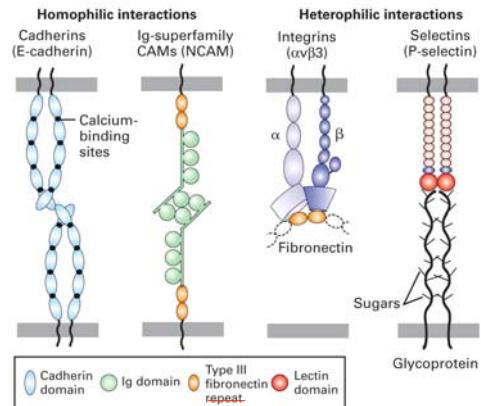
CAMs fall into four major families: 1. Cadherins; 2. immunoglobulin (Ig) superfamily; 3. integrins and 4. selectins

Homophilic adhesion: the same cell type adhesion.

Heterophilic adhesion: different cell type adhesion

Homotypic adhesion: the same adhesive molecule interaction

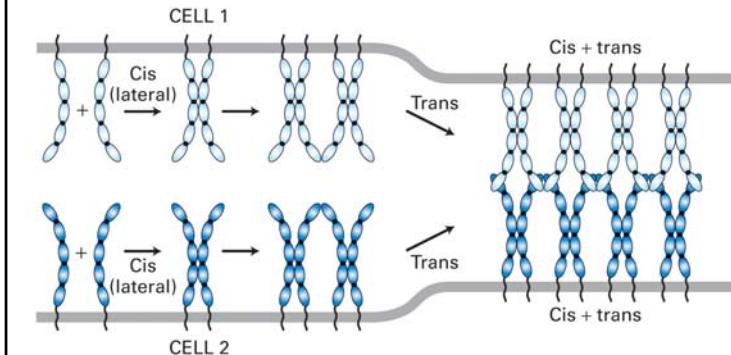
Heterotypic adhesion: different adhesive molecule interaction



Cell-cell adhesion of two types of molecular interaction

Cis (lateral) interaction: on one cell associated laterally through their extracellular domain or cytosolic domain or both into homodimers or higher-order oligomers in the plane of the cell's plasma membrane.

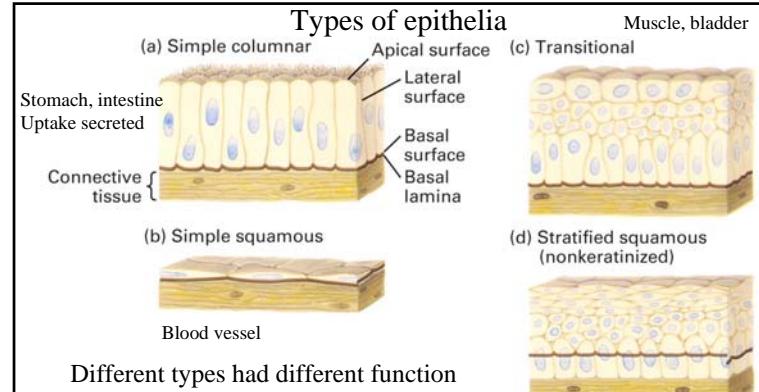
Trans interaction: on one cell bind to the same or different CAMs on an adjacent cell



Three abundant ECM

1. Proteoglycans, a glycoprotein
2. Collagens, protein that form fibers
3. Fibronectin, soluble multiadhesive matrix protein

Diversity of animal tissues depends on evolution of adhesion molecules with various properties



Epithelial tissues provide cellular coats that protect exposed internal & external surfaces from water loss and wear & tear

Seal surfaces

Regulate flow of materials across surface via secretion and transcytosis

Cell junctions key to formation and maintenance of epithelial sheets

The principal types of cell junctions that connect the columnar epithelial cells lining the small intestine

Classification of cell junctions

Occluding (封閉) junctions

tight junctions and septate (分開) junctions

Anchoring junctions

Actin filament attachment sites

1. Cell-cell (adherens junctions)
2. Cell-matrix (focal adhesions)

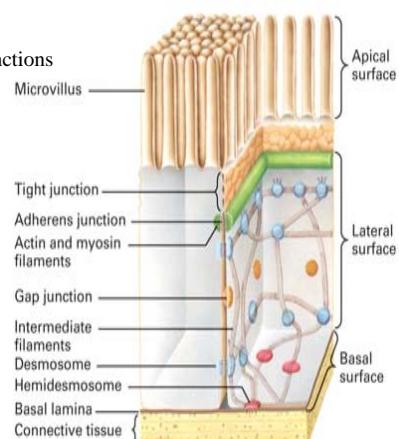
Intermediate filament attachment sites

1. Cell-cell (desmosomes)
2. Cell-matrix (hemi desmosomes)

Communicating junctions

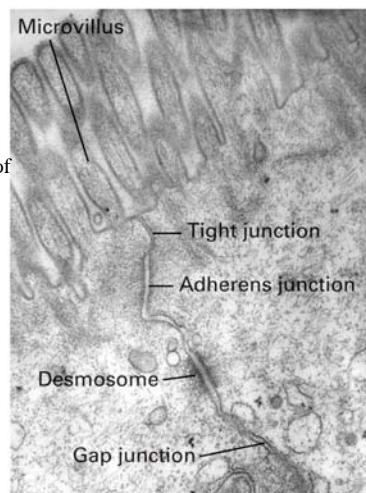
gap junctions

Specialized junctions help define the structure and functions of epithelial cells



The cadherin family of Ca^{2+} dependent cell-cell adhesion molecules comprises ~80 members

Most cadherins are integral membrane proteins that contain a specific number of extracellular cadherin (EC) domains



Cell Junctions

Occur at many points of **cell-cell** and **cell-matrix** contact in all tissues and can be classified according to their function

Cell membrane did not directly contact (fusion), need protein molecule

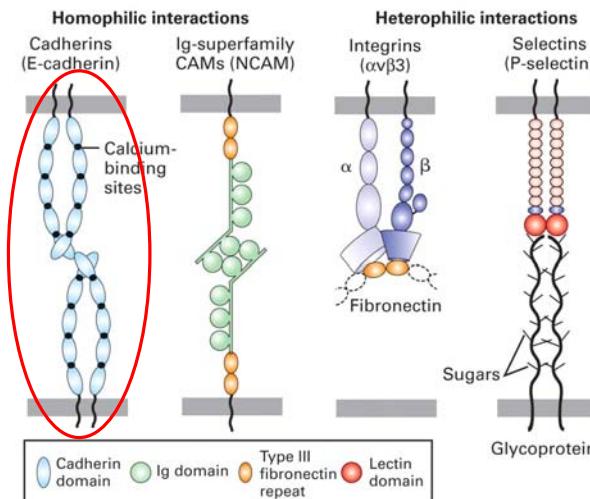
Classified into 3 functional groups:

Occluding/Tight Junctions: seal cells together in an epithelial sheet stops molecules from leaking from one side of the sheet to the other

Anchoring Junctions: mechanically attach cells (and their cytoskeleton) to their neighbors, or to ECM

Communicating Junctions: mediate passage of chemical, or electrical signals from one cell to its adjacent neighbor

Ca^{2+} dependent homophilic cell-cell adhesion in adherens junctions and desmosomes is mediated by cadherins



Cadherins mediate Ca^{2+} -dependent homophilic cell-cell adhesion

E-cadherin: expressed on early embryonic cells in mammals. Later becomes restricted to embryonic and adult epithelial tissue

P-cadherin: Trophoblast cells (placental)

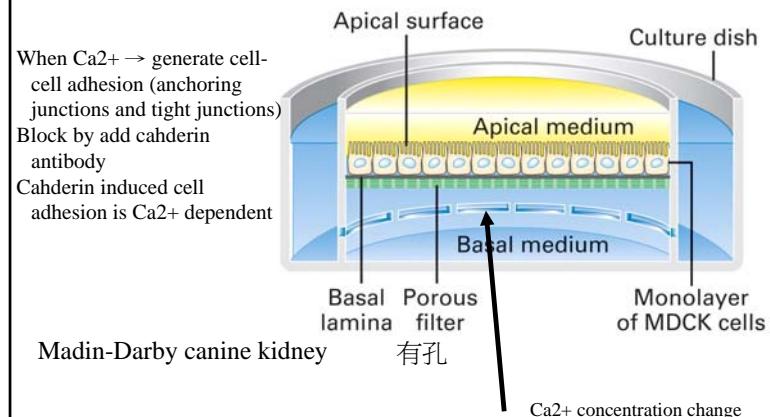
N-cadherin: First mesodermal, later CNS

EP-cadherin: frog blastomere adhesion

Protocadherins: not connected to catenin

- The C-terminal cytoplasmic domain associates with the cytoskeleton
- N-terminal extracellular domain forms dimers and, through homophil interactions, forms tetramers
- Each cadherin has a characteristic tissue distribution

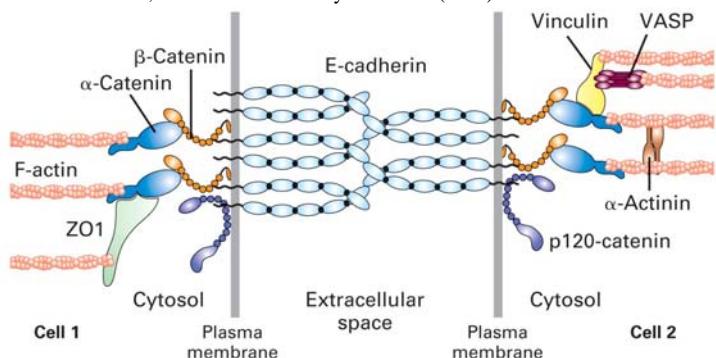
How to proof the Ca^{2+} dependent adhesion



Protein constituents (組成) of typical adherens junctions

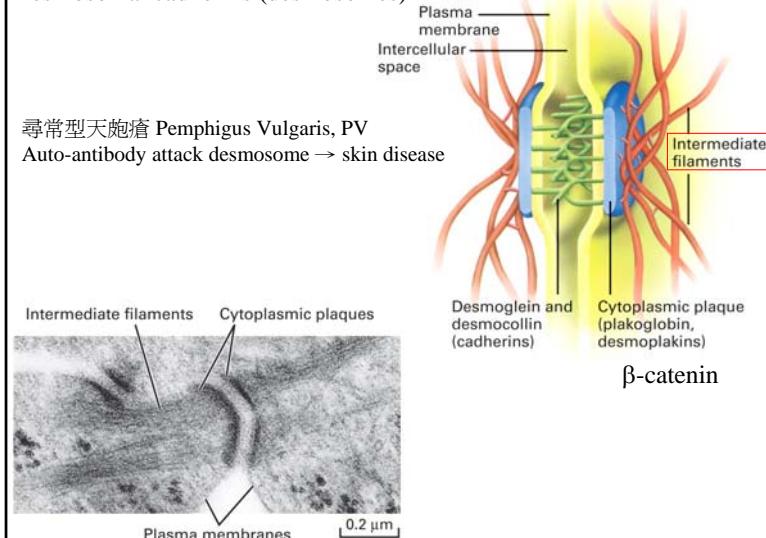
Binding partners:

catenins, and via catenins to cytoskeleton (actin)



Cytosolic domains of the E-cadherin bind direct or indirectly to multiple adapter protein that connect the junctions to cytoskeleton and participate in intracellular signaling pathways (catenin)

Desmosomal cadherins (desmosomes)



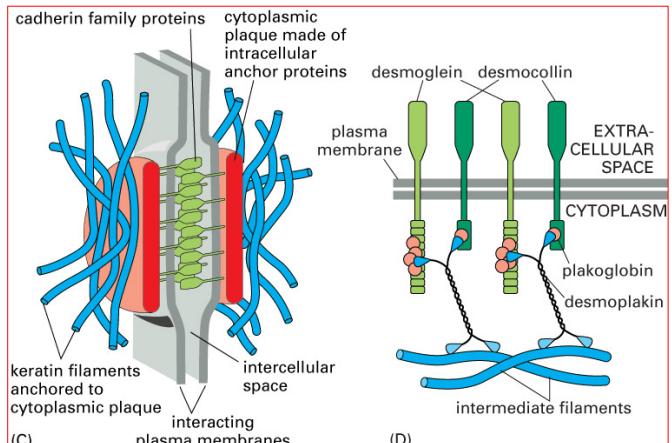
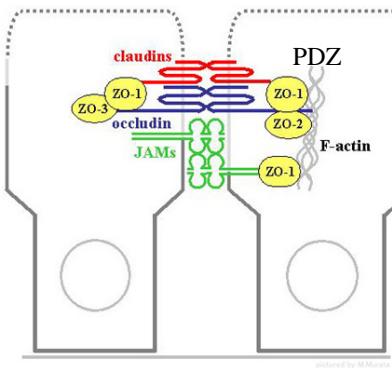
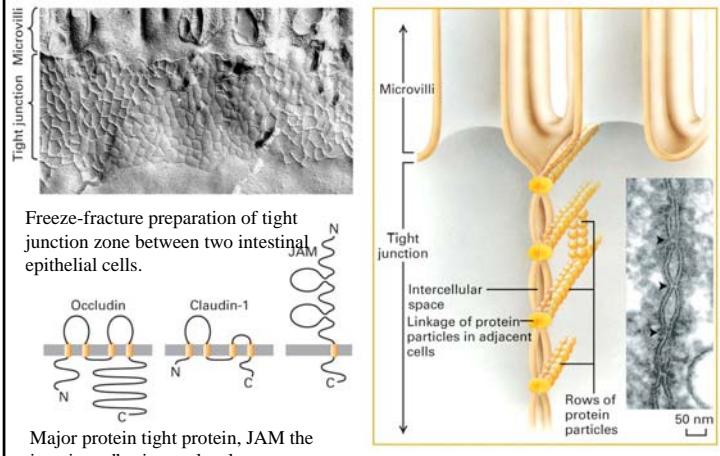


Figure 19-11 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Tight junctions seal off body cavities and restrict diffusion of membrane components



Occludin comes in two splice variants; TJs may form without occludin in certain cell types

Claudin (-1 and -2) appears to form the ridge backbone; cDNA-transfection into fibroblasts establishes TJs. Claudin expression is cell- and tissue specific
JAMs associate laterally with TJs (-> Adhesion Molecules)

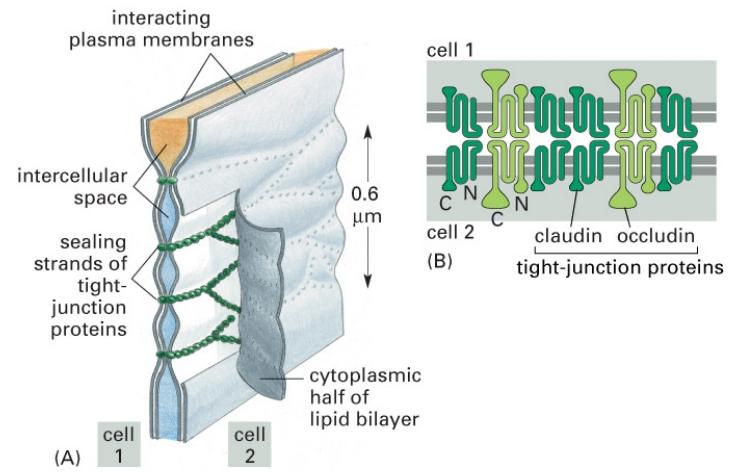


Figure 19-5. Molecular Biology of the Cell, 4th Edition.

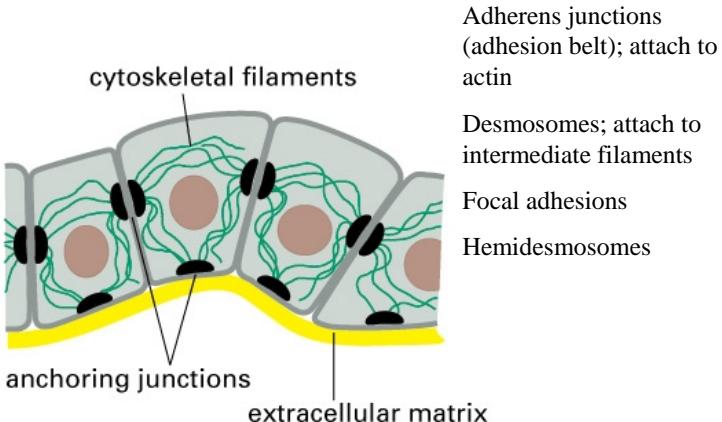
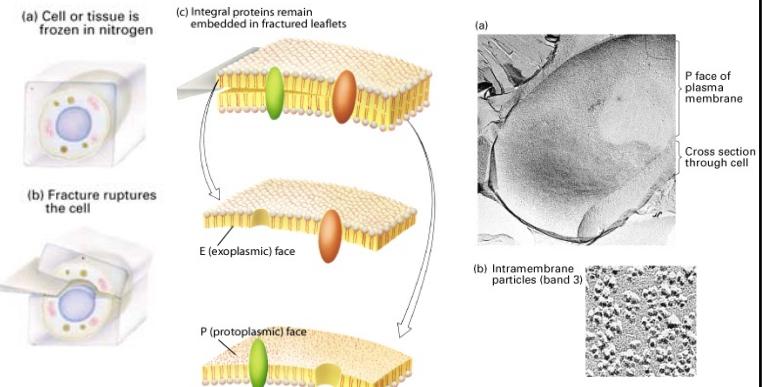
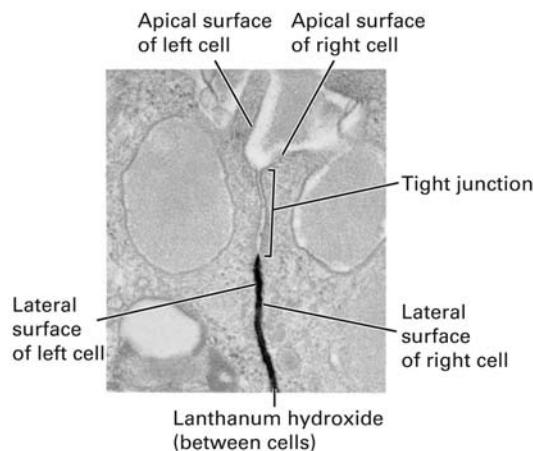


Figure 19-7. Molecular Biology of the Cell, 4th Edition.

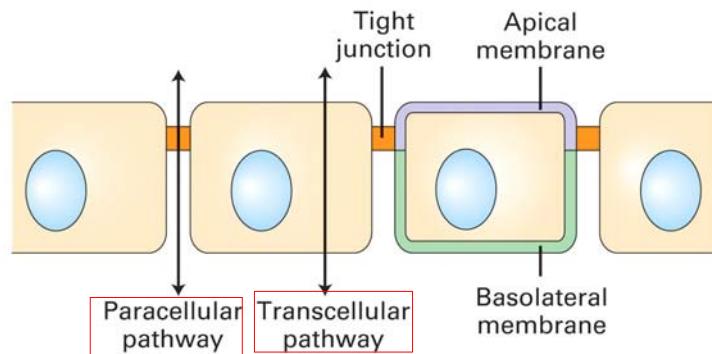
The freeze fracture, freeze etch method



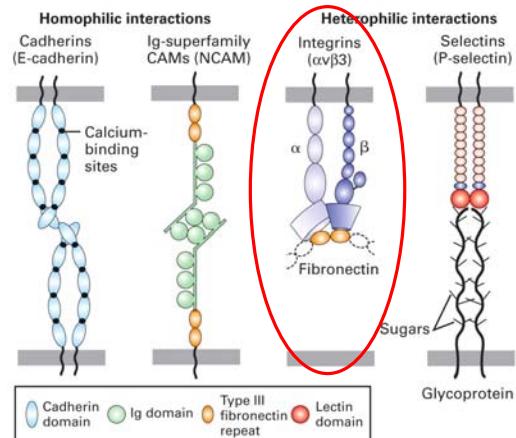
Exp: demonstrates the impermeability of certain tight junctions to many water-soluble substance



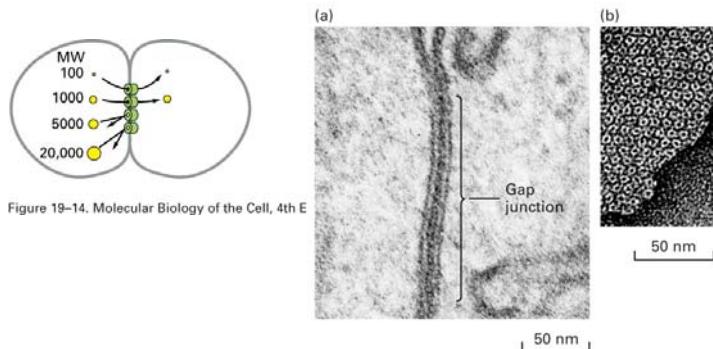
Differences in permeability of tight junctions can control passage of small molecules across



Many cell-matrix and some cell-cell interactions are mediated by integrins



Gap junction composed of connexins allow small molecules to pass between adjacent cells



Integrins mediate cell-matrix and cell-cell interactions

Part of family cell adhesion receptors; receptor proteins
Roles in binding ligand for cell signaling and in adhesion esp to matrix

Two transmembrane glycoprotein subunits, non-covalently bound, alpha and beta

Now, 18 alpha and 8 beta subunits to 24 integrins

Not all permutations viable, eg, $\beta 4$ can form only with $\alpha 6$, but $\beta 1$ can form partners with ten different α

•“Combinatorial Diversity” =small number of components to a large number of functions

P223

Adhesive interactions and nonepithelial cells

GAP JUNCTIONS

Connections at the lateral surfaces of cells that allow transport of ions and small molecules (as large as 12 nm)

Channels directly link the cytosol of adjacent cells

The extent to which channels are open is highly regulated (ex. very high calcium ion concentration closes the channels)

In neurons, the passage of ions can lead to propagation of action potentials

In smooth muscle, calcium transfer can induce contraction

Passage of cyclic AMP can lead to signal transduction

A hormonal stimulation of one cell can be passed to neighboring cells

6 connexin subunits on each cell form a connexon

Each connexin crosses the membrane fourtimes

Different connexins form junctions that differ in channel size and regulation

Hetero-oligomeric connexons can form heterotypic gap junction channels

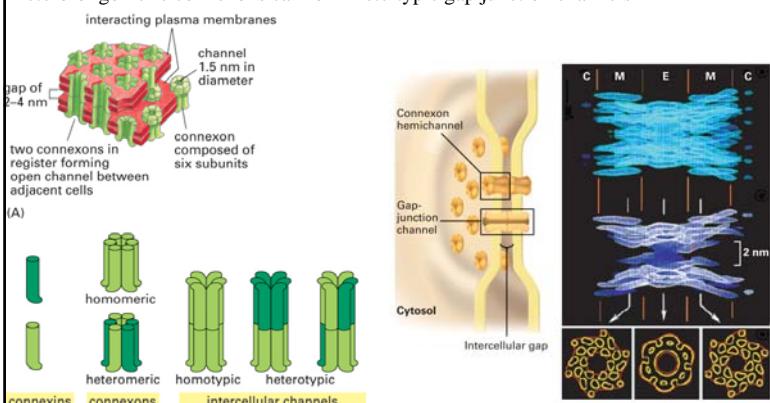


Figure 19-15. Molecular Biology of the Cell, 4th Edition.

Summary: Cell junctions

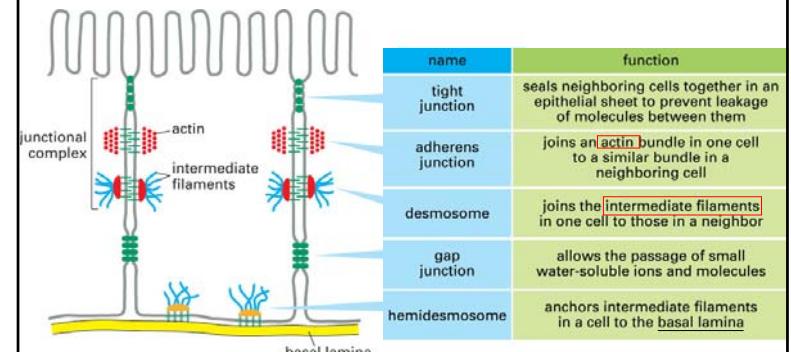
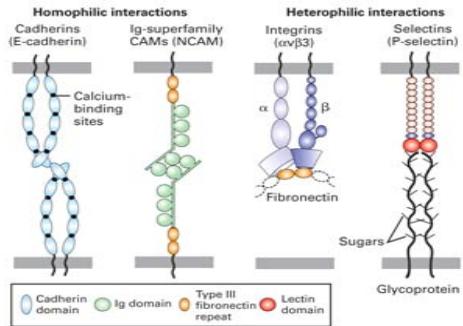


Figure 19-19 part 2 of 2. Molecular Biology of the Cell, 4th Edition.
Figure 19-19 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Cell adhesion molecules



cadherins: mainly Ca^{2+} -dependent cell-cell adhesion

immunoglobulin superfamily: Ca^{2+} -independent cell-cell adhesion in neuronal and other tissues

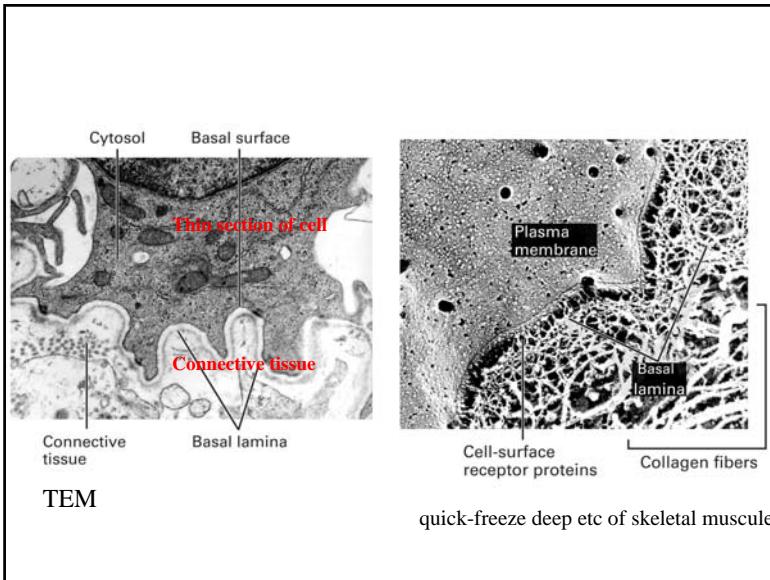
Integrins: mainly cell-ECM interaction

Selectins: movement of leucocytes into tissue

The extracellular matrix (ECM)

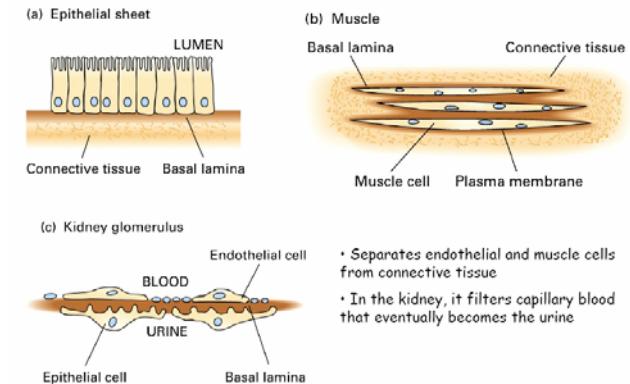
Three types of molecules are abundant in the extracellular matrix of all tissues:

1. proteoglycan: a glycoproteins, high viscosity, it can bind variety of ECMs
2. Collagen fibers: provide mechanical strength and resilience.
3. Soluble multiadhesive matrix proteins: bind to and cross-link cell-surface adhesion receptors and other ECM components

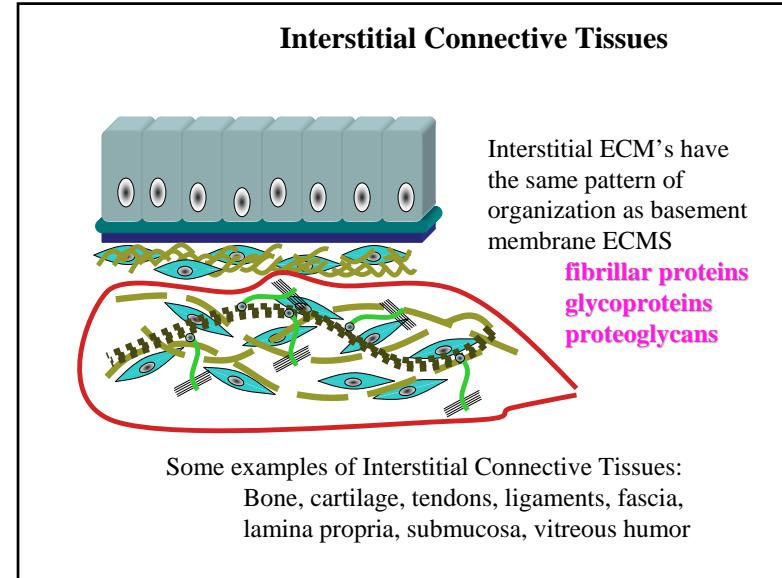
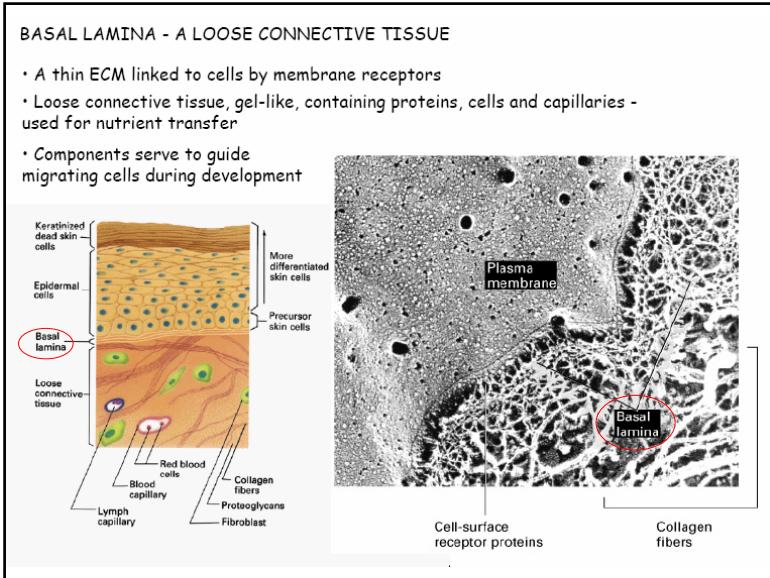


The basal lamina provides a foundation for epithelial sheets

BASAL LAMINA - IN VARIOUS TISSUES



Columnar and epithelia is a foundation on one surface of the cells rests
Muscle or fat the basal lamina surrounds each cell



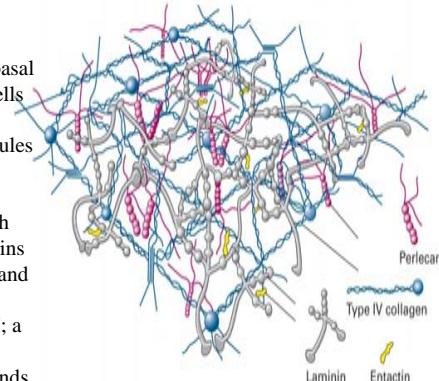
The basal lamina provides a foundation for epithelial sheets

Basal lamina has other function:

1. Helps four and eight-celled embryos adhere together
2. Development of neurons migrate
3. Tissue repair

Most of ECM components in the basal lamina are synthesized by the cells that rest. About four types:

1. **typeIV collagen**: trimeric molecules (rodlike & globular), form 2D network
2. **Laminins**: form 2D network with collagen, also can bind to integrins
3. **Entactin**: cross-link collagenIV and laminin, and helps incorporate other components into the ECM; a proteoglycan
4. **Perlecan**: a proteoglycan, can binds to and ECM and cell surface molecules



Sheet-forming type IV collagen is a major structural component in basal laminae (基底層)

20 types of collagen participate in the formation of ECM

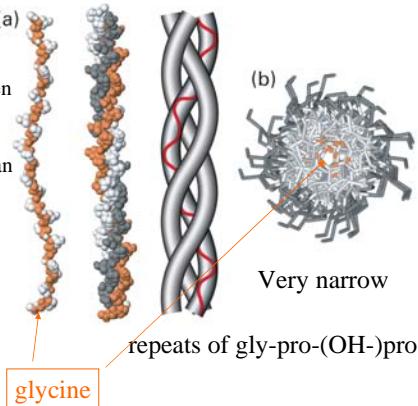
All collagen are **trimeric** protein made from three polypeptide called collagen a chain; May homotrimeric or heterotrimeric

Has **triple helical structure**, because of an unusual abundance of three amino acids: **glycine**, **proline**, and **hydroxyproline** (modified from proline)

The unique properties of each type of collagen by difference:

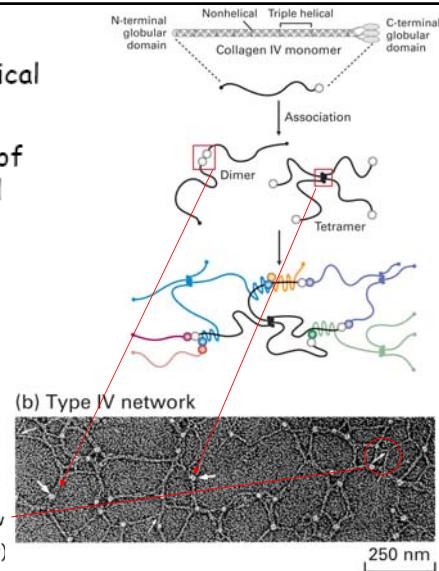
1. The number and lengths of the triple-helical segment
2. The segment effect 3-D structure
3. Covalent modification

Motif: Gly-X-Y, X and Y are any, but often are pro and (OH)-pro



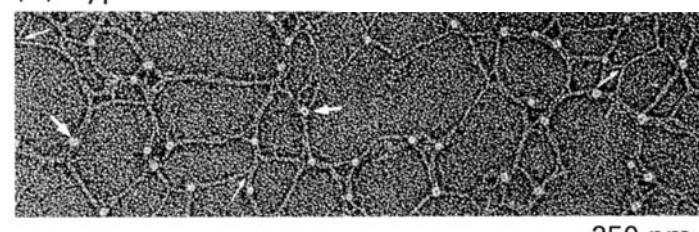
- The triple helix is interrupted by non-helical segments

- A lateral association of triple helices combined with C-terminal associations results in sheet formation



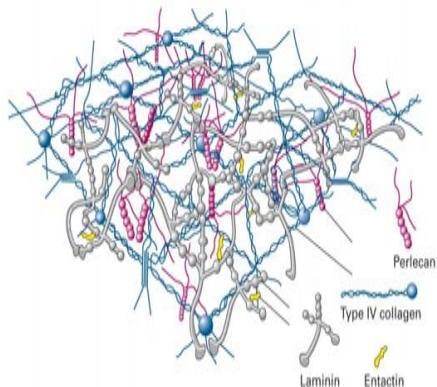
Type IV collagen assembly

(b) Type IV network



- EM of in vitro formed network
 - thin arrows- side-to-side binding
 - thick arrows- C-term domain binding
- Goodpasture's syndrome (dysfunction of basal lamina)
- Autoimmune disease
- Ab against $\alpha 3$ chains of type IV collagen of kidney and lungs
- Cellular damage, progressive renal failure and pulmonary hemorrhage

Laminins provide an adhesive substrate for cells



Laminin, a multiadhesive matrix protein helps cross-link components of the basal lamina

LAMININ: a heterotrimeric protein

found in all basal lamina

It binds to cell surface receptors as well as various matrix components

Multiadhesive matrix proteins

Long and flexible with multiple domains

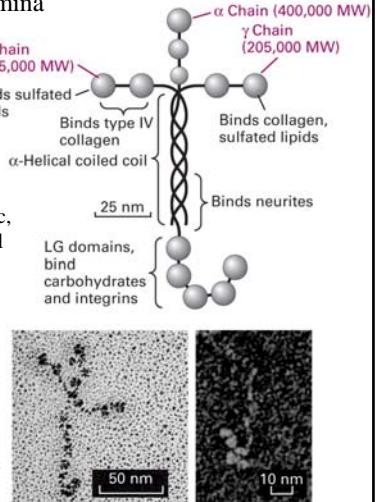
Bind collagen, other matrix proteins, polysaccharide adhesion receptors and extra-cell ligands

Function in organization of extracellular matrix, regulating cell-matrix adhesion, cell migration, and cell shape

Laminin, principle multiadhesive matrix protein in basal

Heterotrimeric 820,000 daltons

b: left, intact laminin molecule, characteristic cross appearance
right, carbohydrate binding LG domains



Secreted and cell surface **proteoglycan** are expressed by many cell type

Viscous proteins and glycoprotein, covalently linked to charged **glycosaminoglycan** also called GAG (specialized polysaccharide chains)

polysaccharides; protein + GAGs = proteoglycan

Found in all connective tissues, extracellular matrices and on the surface of many cells

A core protein is attached to one or more polysaccharides called **glycosaminoglycans*** (repeating polymers of disaccharides with sulfate residues)

Four classes: hyaluron, chondroitin sulfate, heparan sulfate, keratan sulfate

Proteoglycans are very diverse

Modifications in GAG chains can determine proteoglycan functions (Fig 6-19)

Gels of Polysaccharide and Protein Fill Spaces and Resist Compression

Dense, compact connective tissues (tendon, bone)

→ proportion of GAGs is small → very little water → matrix consists almost entirely of collagen

Other extreme = jelly-like substance in interior of eye → mainly one type of GAG → mostly water, → very little collagen.

GAGs in general:

strongly hydrophilic

adopt highly extended conformations

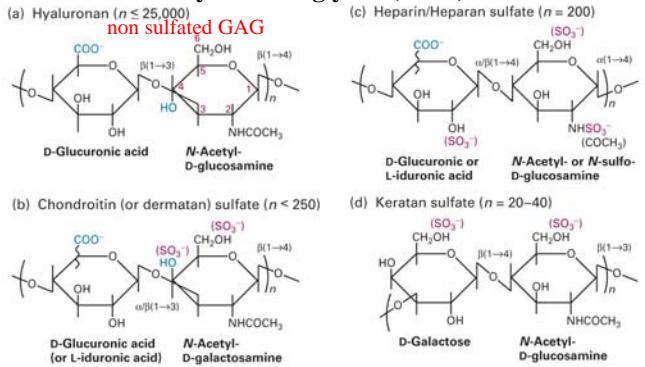
huge volume relative to their mass

form gels at very low concentrations

multiple -ve charges attract cations → osmotically active → large amounts of water adsorbed into matrix

Create swelling pressure that is counterbalanced by tension in the collagen fibres and interwoven with the PGs.

Glycosaminoglycan (GAG)



The repeating **disaccharides** of glycosaminoglycans (GAGs), the polysaccharide components of proteoglycans

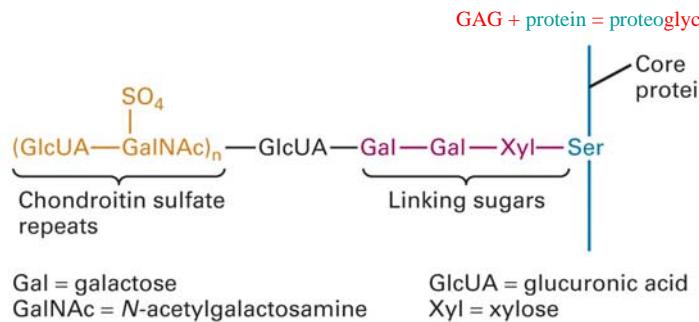
Localization

1. Cell surface receptors
2. Extracellular

Function

1. Bind & present growth factors
2. Extracellular matrix

Biosynthesis of heparan and chondroitin sulfate chains in proteoglycans

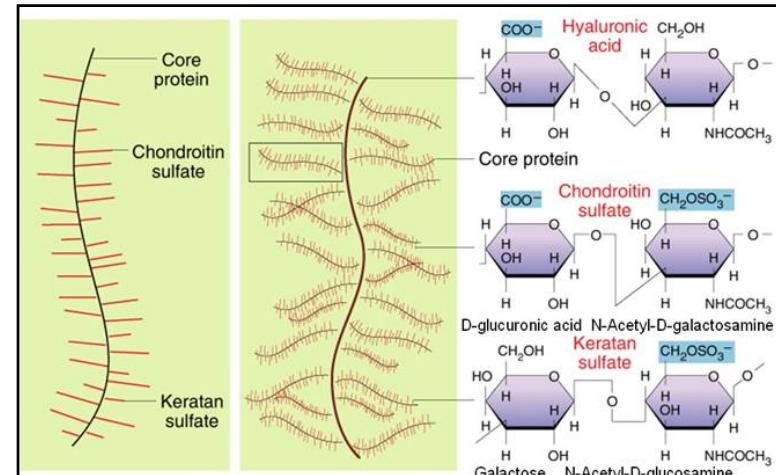
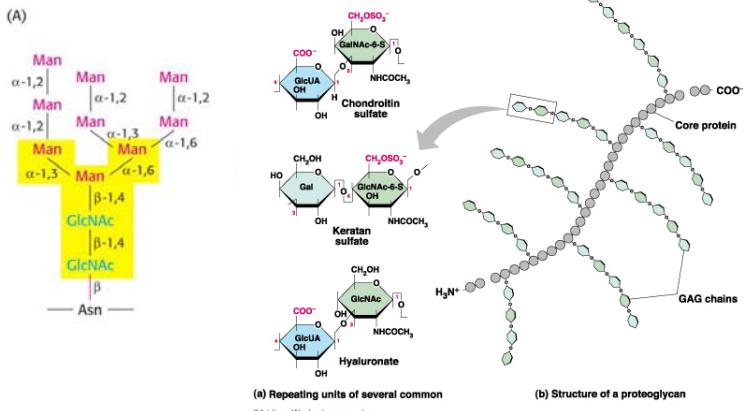


Glycosaminoglycans (heparan or chondroitin sulfate) are covalently linked to serine residues in the core protein via linking sugars (three); keratan sulfate attached to asparagine residues, N-linked oligosaccharides

Core protein synthesis at ER; GAG chains assembled in Golgi complex

Addition of keratan sulfate chains are oligosaccharide chains attached to asparagine residues: N-linked oligosaccharides

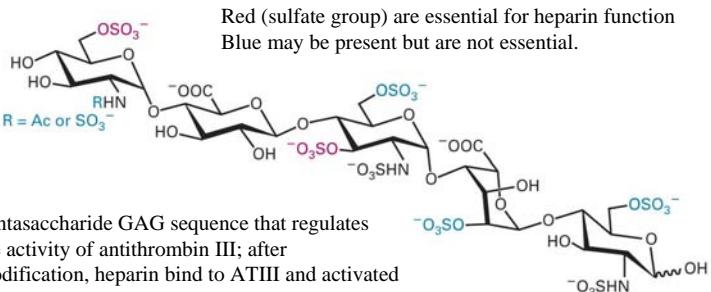
N-linked oligosaccharides



Single proteoglycan poly-proteoglycan

GAG

Modifications in GAG chains can determine proteoglycan functions



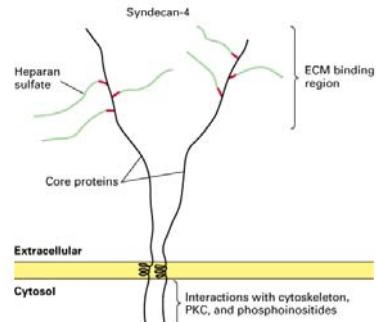
ECM can regulate many functions

Low-affinity co-receptors

HS syndecans have been implicated in numerous cellular processes:

- Receptor for growth factor
- Binds to Extracellular matrix components

- Enzymes involved in lipid metabolism
- Serine Protease Inhibitors



Membrane-associated proteoglycans are mostly heparan-sulfate substituted and are either transmembrane like syndecan or GPI-membrane-anchored

- The core protein spans the membrane with a short cytosolic domain
- The GAGs (heparan sulfate chains) are attached via the trisaccharide linker to Ser residues
- Syndecan binds extracellularly to collagens and fibronectin and intracellularly to the cytoskeleton

Syndecans

proteoglycan regulators of cell-surface microdomains

Four members:

- Syndecan-1/syndecan
 - Syndecan-2/fibroglycan
 - Syndecan-3/N-syndecan
 - Syndecan-4/ryudocan
- | Core Protein : | Syndecan-1 | Syndecan-2 | Syndecan-3 | Syndecan-4 |
|-------------------|------------|---------------|--------------|------------------------|
| Alternate names : | (Syndecan) | (Fibroglycan) | (N-Syndecan) | (Ryudocan Amphiglycan) |
| MW : | 33kD | 23kD | 43kD | 22kD |

Syndecans are proteoglycans that has an inherent transmembrane and cytoplasmic domain

- Syndecan-1 interacts with intracellular microfilaments
- Syndecan-1 has both HS and CS GAG chains
- Syndecan-4 connects to focal adhesion molecules

Heparan sulfate proteoglycans are cell surface coreceptors

Heparan sulfate proteoglycans are a subset of proteoglycans.

- They contain chains of the glycosaminoglycan heparan sulfate.

Most heparan sulfate is found on two families of membrane-bound proteoglycans:

- the syndecans

Heparan sulfates are composed of distinct combinations of more than 30 different sugar subunits.

- This allows for great variety in heparan sulfate proteoglycan structure and function.

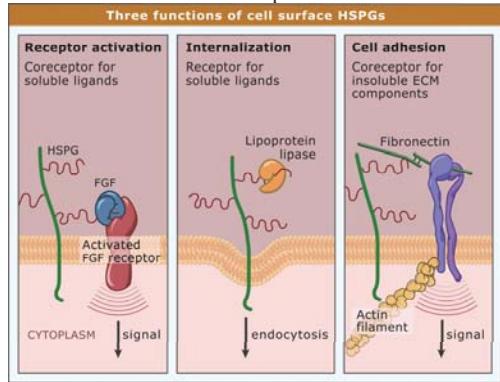
Cell surface heparan sulfate proteoglycans:

- are expressed on many types of cells
- bind to over 70 different proteins

Heparan sulfate proteoglycans are cell surface coreceptors

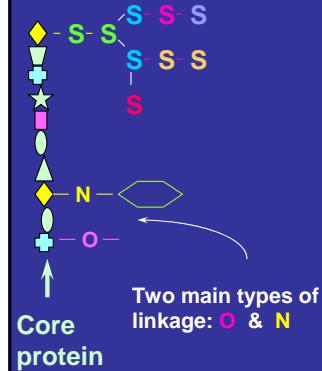
Cell surface heparan sulfate proteoglycans

- assist in the internalization of some proteins
- act as coreceptors for:
 - soluble proteins such as growth factors
 - insoluble proteins such as extracellular matrix proteins

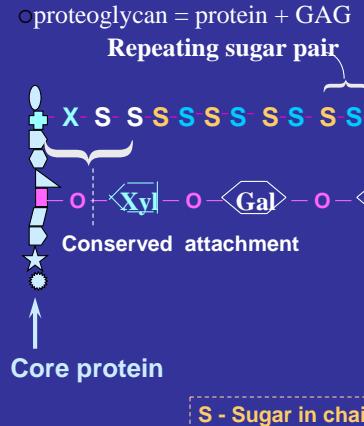


GLYCOPROTEINS VERSUS PROTEOGLYCANS

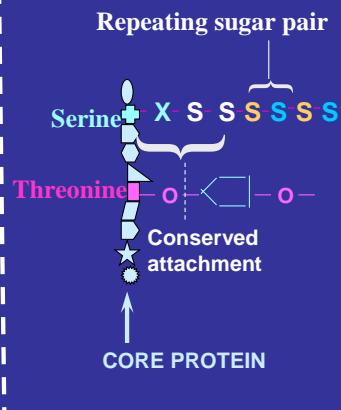
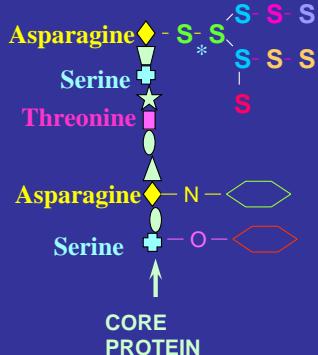
Glycoproteins are vast in number & structurally very diverse



Proteoglycans are few and share a simple structure



GLYCOPROTEINS VERSUS PROTEOGLYCANS



GLYCOPROTEINS VERSUS PROTEOGLYCANS

Sugars varied, not all hexose

Sugar chains short (sometimes very short, or a single sugar)

Less negative charge

Sugar chains can branch

Characteristic core proteins

Sugar chains are all glycose-aminoglycans (GAGs)

Sugar chains are long

GAGs often sulfated

Large negative charge

Sugar chains do not branch

Sugars - small repertoire

Own core proteins

GAG can be independent of protein or have PGs attached, e.g., hyaluronan

The ECM of nonepithelial tissue

Fibrillar (纖維) collagens are the major protein in the ECM of connective tissue

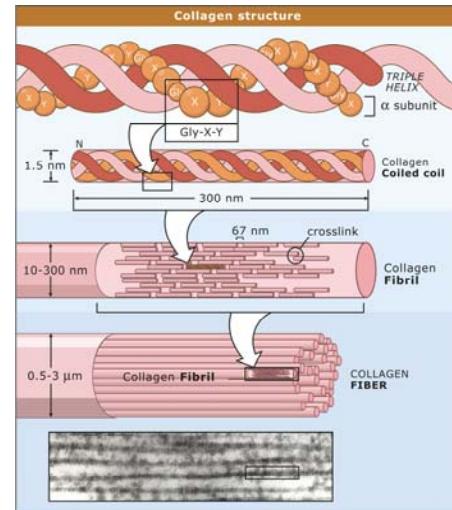
Most volume is made up of ECM rather than cell, and packed with **insoluble protein** fiber and contain proteoglycan, various multiadhesive proteins, and hyaluronan (non sulfated GAG.)

Collagen found in all multicellular animals, mammals; approx 25 different genes
Are main proteins in bone, tendon and skin → approx. 25% of total protein
Connective Tissue = mainly types I, II, III, V and XI, type-I by far most

common; 80-90% of the collagen in the body consists of types I, II and III.
Rope 繩 -like super-helix with 3 collagen polypeptide chains wound around each other

Packed together in ordered fashion → collagen fibrils = thin cables, 10-300 nm diameter → these pack together → thicker collagen fibers

Collagen provides structural support to tissues



All collagens are organized into triple helical, coiled-coil "collagen subunits."

- They are composed of three separate collagen polypeptides.

Collagen subunits are:

- secreted from cells
- then assembled into larger fibrils and fibers in the extracellular space

Characterizations of COLLAGEN

The various isoforms are the most abundant proteins in the animal kingdom

There are at least 16 types (or 24 types)

Types I, II and III are the most abundant and form fibrils

Type IV forms sheets (found in the basal lamina)

They form triple helices

They have unique segments that interrupt the triple helix and are responsible for the unique properties of individual collagen

They contain a three residue repeat of: glycine, proline, X

They are rich in hydroxyproline

There are three amino acids per turn of the helix, with pyrrolidone rings on the outside of the helix

The helix is stabilized by hydrogen bonds

The fibrous backbone of the extracellular matrix

TABLE 6-1 Selected Collagens

Type	Molecule Composition	Structural Features	Representative Tissues
FIBRILLAR COLLAGENS 細纖維			
I	$[\alpha 1(I)]_2[\alpha 2(I)]$	300-nm-long fibrils	Skin, tendon, bone, ligaments, dentin, interstitial tissues
II	$[\alpha 1(II)]_3$	300-nm-long fibrils	Cartilage, vitreous humor
III	$[\alpha 1(III)]_3$	300-nm-long fibrils; often with type I	Skin, muscle, blood vessels
V	$[\alpha 1(V)]_2[\alpha 2(V)]$, $[\alpha 1(V)]_3$	390-nm-long fibrils with globular N-terminal extension; often with type I	Cornea, teeth, bone, placenta, skin, smooth muscle
FIBRIL-ASSOCIATED COLLAGENS 細纖維			
VI	$[\alpha 1(VI)][\alpha 2(VI)]$	Lateral association with type I; periodic globular domains	Most interstitial tissues
IX	$[\alpha 1(IX)][\alpha 2(IX)][\alpha 3(IX)]$	Lateral association with type II; N-terminal globular domain; bound GAG	Cartilage, vitreous humor

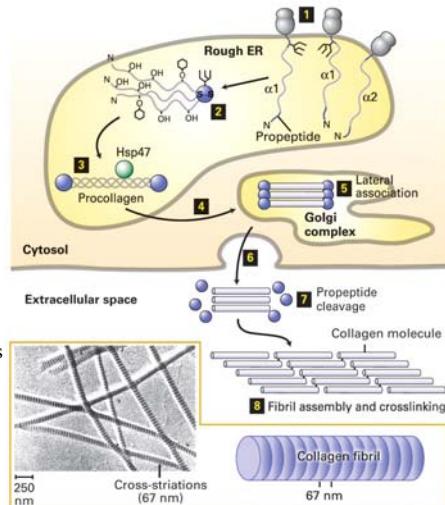
TABLE 6-1 Selected Collagens

Type	Molecule Composition	Structural Features	Representative Tissues
SHEET-FORMING AND ANCHORING COLLAGENS			
IV	$[\alpha 1(IV)]_2[\alpha 2(IV)]$	Two-dimensional network	All basal laminae
VII	$[\alpha 1(VII)]_3$	Long fibrils	Below basal lamina of the skin
XV	$[\alpha 1(XV)]_3$	Core protein of chondroitin sulfate proteoglycan	Widespread; near basal lamina in muscle
TRANSMEMBRANE COLLAGENS			
XIII	$[\alpha 1(XIII)]_3$	Integral membrane protein	Hemidesmosomes in skin
XVII	$[\alpha 1(XVII)]_3$	Integral membrane protein	Hemidesmosomes in skin
HOST DEFENSE COLLAGENS			
Collectins	Oligomers of triple helix; lectin domains	Blood, alveolar space	
C1q	Oligomers of triple helix	Blood (complement)	
Class A scavenger receptors	Homotrimeric membrane proteins	Macrophages	

SOURCES: K. Kuhn, 1987, in R. Mayne and R. Burgess, eds., *Structure and Function of Collagen Types*, Academic Press, p. 2; and M. van der Rest and R. Garrone, 1991, *FASEB J.* 5:2814.

Formation of collagen fibrils (細纖維) begins in the endoplasmic reticulum and is completed outside the cell

1. Synthesis of procollagen a on ribosomes (ER)
2. Formed trimers and glycosylation (modification)
3. Facilitate zipperlike (拉鍊) formation and stabilization of triple helices, and binding by chaperone Hsp47. it procollagen
4. Transport to golgi complex
5. folded procollagens
6. Secretion
7. N- and C-terminal propeptides removed
8. Trimers assemble into fibrils and are covalently the cross-link



PROCOLLAGEN:

Transfers to the Golgi

- There is a further addition of oligo-saccharides
- There is further processing to remove disulfide-containing regions and insertion into transport vesicles
- Exocytosis results in the removal of termini by extracellular enzymes and assembly of cross-linked fibers

Synthesized by fibroblasts in connective tissue

Made by osteoblasts in bone

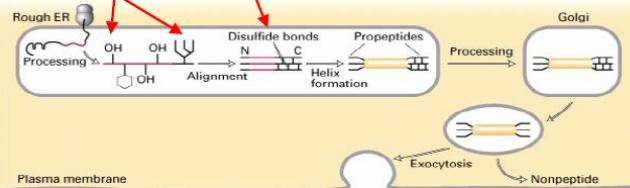
Secreted by cells as “procollagen” → collagenase cuts off terminal domains at each end → assembly only after molecules emerge into extracellular space

Propeptides function to:

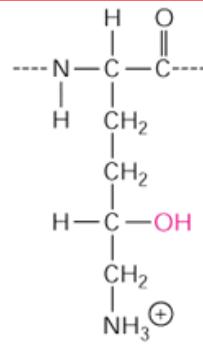
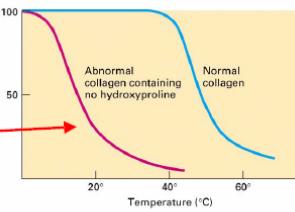
- guide intracellular formation of triple-strand structure
- prevent intracellular formation of large collagen fibrils

PROCOLLAGEN:
Assembles in the rough ER (RER)

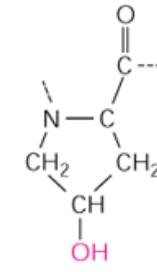
- Some prolines are hydroxylated *
- The absence of hydroxyproline yields a collagen that is susceptible to denaturation
- Glycosylation occurs in the RER
- The termini are held together by intrachain disulfide bonds



* Ascorbic acid is required to prevent scurvy, characterized by fragile tendons, skin and blood vessels



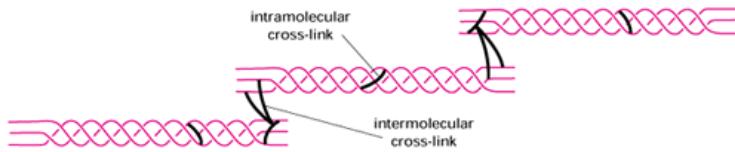
hydroxylysine
in protein



hydroxyproline
in protein

Figure 19-42 Hydroxylysine and hydroxyproline residues. These modified amino acids are common in collagen; they are formed by enzymes that act after the lysine and proline are incorporated into procollagen molecules

Collagen \rightarrow collagen fibril



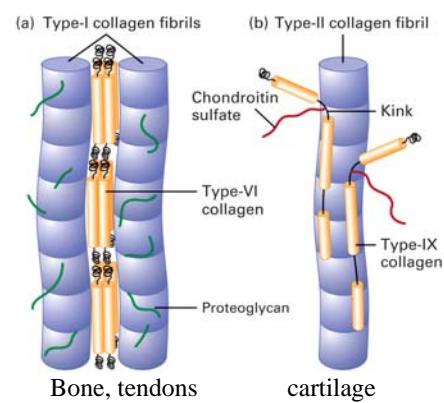
The covalent intramolecular and intermolecular cross-links formed between modified lysine side chains within a **collagen fibril**. The cross-links are formed in several steps. First, certain lysine and hydroxylysine residues are deaminated by the extracellular enzyme **lysyl oxidase** to yield **highly reactive aldehyde groups**. The aldehydes then react spontaneously to form **covalent bonds** with each other or with other **lysine or hydroxylysine** residues. Most of the cross-links form between the short nonhelical segments at each end of the collagen molecules.

Type I and II collagens from diverse structure and associate with different **non-fibrillar** (非纖維) collagens

Strong
Includes Types VI and IX

Type IX cannot form fibrils due to interruptions in the helical structure, but it can associate with fibrils of other collagen types

Type VI is bound to the sides of Type I fibrils, linking them together. Non-helical regions anchor Types VI and IX to proteoglycans/other ECM components



Interaction of fibrous collagens with nonfibrous associated collagens

Characterization and functions of collagen

Collagen found in all multicellular animals, mammals; approx 25 different genes
Are main proteins in bone, tendon and skin → approx. 25% of total protein
Connective Tissue = mainly types I, II, III, V and XI, type-1 by far most common
Rope-like super-helix with 3 collagen polypeptide chains wound around each other
Packed together in ordered fashion → collagen fibrils = thin cables, 10-300 nm diameter → these pack together → thicker collagen fibres
Synthesized by fibroblasts in connective tissue
Made by osteoblasts in bone
Secreted by cells as “procollagen” → collagenase cuts off terminal domains at each end → assembly only after molecules emerge into extracellular space

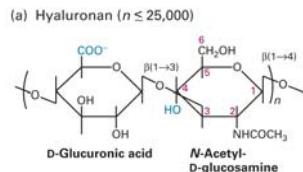
Propeptides function to:
guide intracellular formation of triple-strand structure
prevent intracellular formation of large collagen fibrils

Summary - Collagen

All 16 collagen types contain a repeating gly-pro-X sequence and form triple helices
Collagens vary in their associations to form sheets, fibrils and cross-linkages
Most collagen is fibrillar - made of Type I molecules
The basal lamina contains Type IV collagen
Fibrous collagen molecules (I,II & III) form fibrils stabilized by aldol cross-links
Procollagen chains are assembled into triple helices in the RER, aligned by disulfide bonds among propeptides (which are subsequently removed)
Fibrous collagen is subject to mutations which exhibit a dominant phenotype

Hyaluronan resists compression and facilitates cell migration

Also called hyaluronic acid (HA), is a nonsulfated GAG.
A long, negatively charged polysaccharide that forms hydrated gels. It is synthesized by a plasma membrane bound enzyme (HA synthase) and is directly secreted into extracellular space.
It is not covalently linked to a protein
It imparts stiffness, resilience and lubricating qualities to connective tissues
Behaves as a random coil in solution
Takes up water (1000-fold its own weight) in the ECM
Binds via the CD44 receptor to the surface of migrating cells – keeping them apart
Degraded by the action of hyaluronidase, an extracellular enzyme



ECM Proteoglycans: Aggrecan

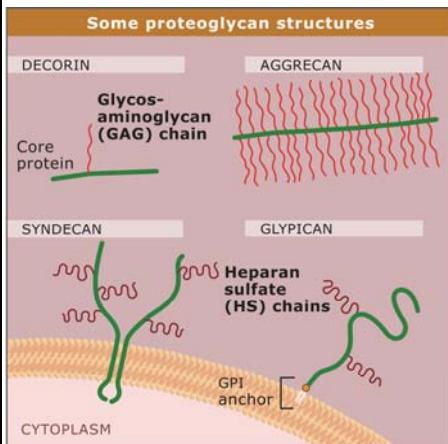
In cartilage the key proteoglycan is aggrecan (MW: 2×10^8)

- The central component of aggrecan is **hyaluronan**
- At 40 nm intervals aggrecan core proteins are attached (assisted by a linker protein) to a decasaccharide sequence in hyaluronan
- Attached to the aggrecan core protein are multiple GAGs
- The major GAGs in aggrecan are chondroitin sulphate and keratin sulphate

• 1-10% of cartilage glycosaminoglycans is hyaluronan

- Form aggregates- important for cartilage function

Proteoglycans provide hydration to tissues



Proteoglycans consist of a central protein "core" to which long, linear chains of disaccharides, called glycosaminoglycans (GAGs), are attached.

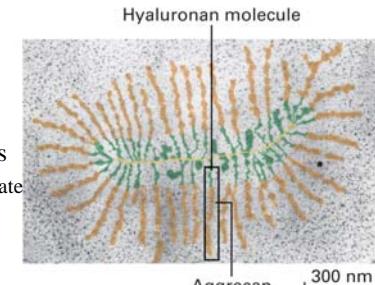
GAG chains on proteoglycans are negatively charged.

- This gives the proteoglycans rodlike, bristly shape due to charge repulsion.

Association of hyaluronan and proteoglycans forms large, complex aggregates

Proteoglycans form large aggregates

- proteoglycans attached to a hyaluronate backbone
- can be as long as 4000 nm and a diameter of 500 nm



Function of aggregation:

- increased water retention
- increased stiffness
- regulate collagen fibril deposition

Aggregated proteoglycans

Structure of proteoglycan aggregate from cartilage

Aggrecan aggregate

Proteoglycans form large aggregates

Aggrecan monomer:

- a protein backbone of 210-250 kDa
- both chondroitin sulphate and keratan sulphate chains attached to backbone
- chondroitin sulphate chains (100 - 150 per monomer), being located in the C terminal 90%
- the keratan sulphate (30 - 60 per monomer) is preferentially located towards the N terminal

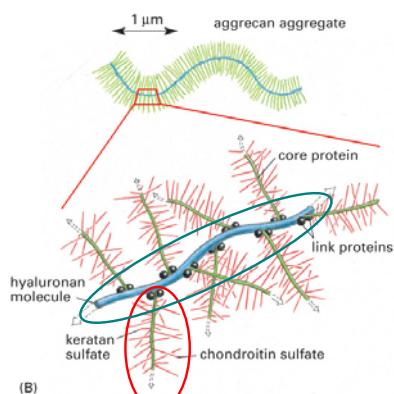


Figure 19-41 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

Hyaluronan is a glycosaminoglycan enriched in connective tissues

Hyaluronan is a glycosaminoglycan.

– It forms enormous complexes with proteoglycans in the extracellular matrix. These complexes are especially abundant in **cartilage**.

- There, hyaluronan is associated with the proteoglycan aggrecan, via a linker protein.

Hyaluronan is highly **negatively charged**.

- It binds to cations and water in the extracellular space.
 - This increases the stiffness of the extracellular matrix .
 - This provides a water cushion (墊子) between cells that absorbs compressive forces.

Unlike other glycosaminoglycans, hyaluronan chains are:

- **synthesized on the cytosolic surface of the plasma membrane**
- translocated out of the cell

Cells bind to hyaluronan via a family of receptors known as hyaladherins.

- Hyaladherins initiate signaling pathways that control:

- cell migration
- assembly of the cytoskeleton

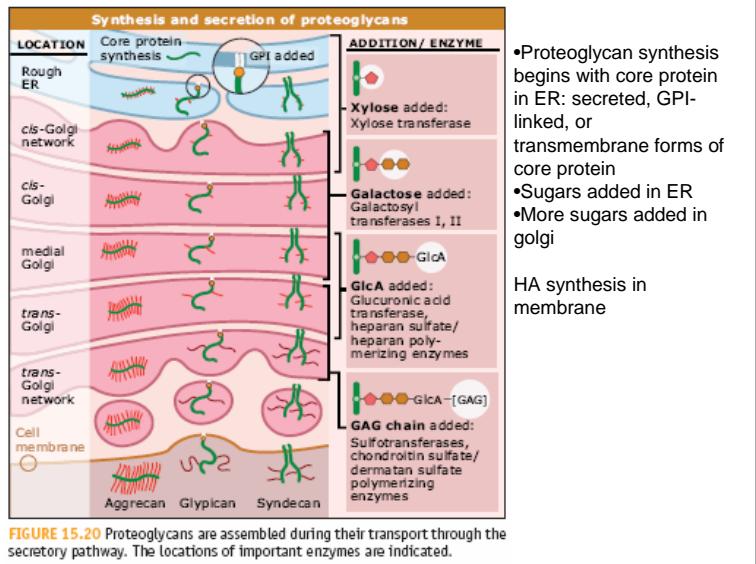
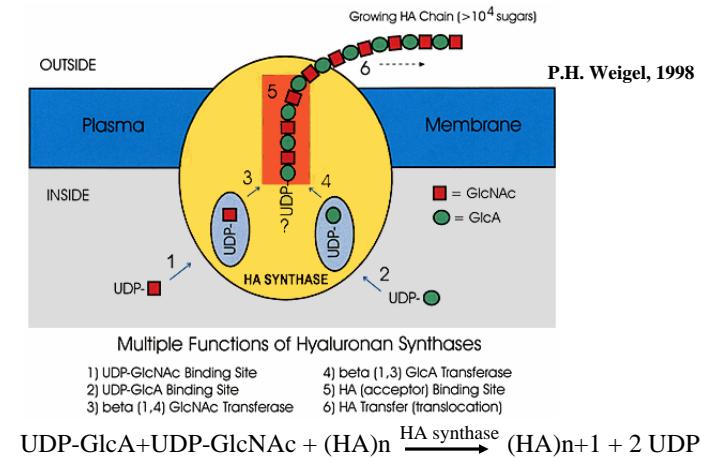


FIGURE 15.20 Proteoglycans are assembled during their transport through the secretory pathway. The locations of important enzymes are indicated.

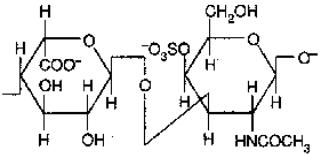
Hyaluronan synthesis



Glycosaminoglycans

GAG	Localization
Hyaluronate	synovial fluid, vitreous humor, ECM of loose connective tissue
Chondroitin sulfate	cartilage, bone, heart valves
Heparan sulfate	basement membranes, components of cell surfaces
Heparin	mast cells lining the arteries of the lungs, liver and skin
Dermatan sulfate	skin, blood vessels, heart valves
Keratan sulfate	cornea, bone, cartilage aggregated with chondroitin sulfates

Dermatan Sulphate:
absent in cartilage
identified in meniscus, tendon, skin and joint capsule



The extracellular matrix (ECM)

Three types of molecules are abundant in the extracellular matrix of all tissues:

1. proteoglycan: a glycoproteins, high viscosity, it can bind variety of ECMs
2. Collagen fibers: provide mechanical strength and resilience.
3. Soluble multiadhesive matrix proteins: bind to and cross-link cell-surface adhesion receptors and other ECM components

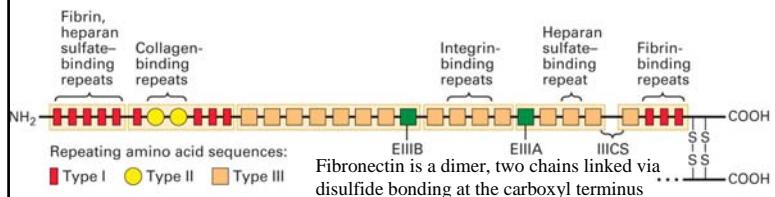
Fibronectins connect many cells to fibrous collagens and other matrix components

Fibronectin = example of “**adhesive**” ECM protein
Is a protein with multiple domains with number of specific binding sites for macromolecules and for receptors on cell surface.

Plasma Fibronectin; soluble, circulates in the blood and other body fluids → enhances **blood clotting**, wound healing and phagocytosis

Fibronectin Fibrils; insoluble → assemble on surface of cells & deposited in ECM

Fibrils assemble on surface of cells via fibronectin-binding integrins.
Usually aligned with adjacent intracellular actin fibres.



Fibrin, heparan sulfate proteoglycan, and collagen:

- bind to distinct regions in fibronectin
- integrate fibronectin fibers into the extracellular matrix network

Some cells express integrin receptors that bind to the Arg-Gly-Asp (RGD) sequence of fibronectin.

At least 20 different forms of fibronectin have been identified.

- All of them arise from alternative splicing of a single fibronectin gene.

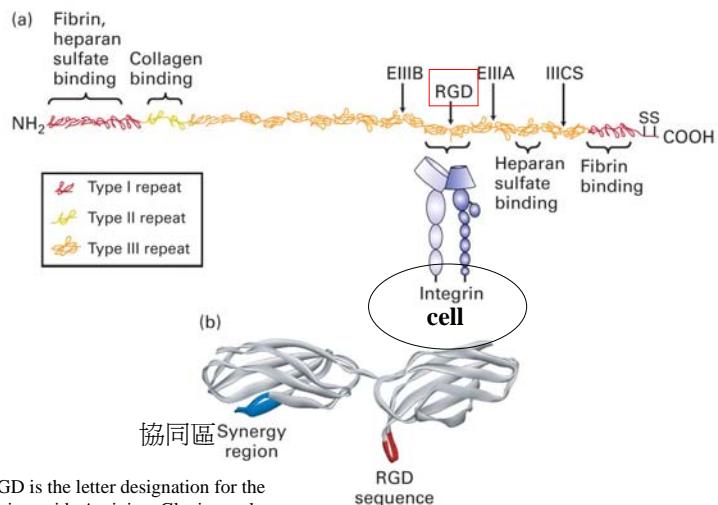
The soluble forms of fibronectin are found in tissue fluids.

The insoluble forms are organized into fibers in the extracellular matrix.

Fibronectin fibers consist of crosslinked polymers of fibronectin homodimers.

Fibronectin proteins contain six structural regions.

- Each has a series of repeating units.



FIBRONECTINS: attach cells to collagen matrices

Regulates cell shape/cytoskeleton

Dimers of two similar polypeptides linked by disulfide bonds

Forms fibrils when exposed to cells expressing integrins

Circulating fibronectin can bind to fibrin, with the result that platelets associate at the site of blood clots via integrin binding

◆ 纖連蛋白是高分子量糖蛋白 (220-250KD)

◆ 纖連蛋白模型

◆ 纖連蛋白的主要功能：

◆ 介導細胞黏著，進而調節細胞的形狀和細胞骨架的組織，促進細胞鋪展；

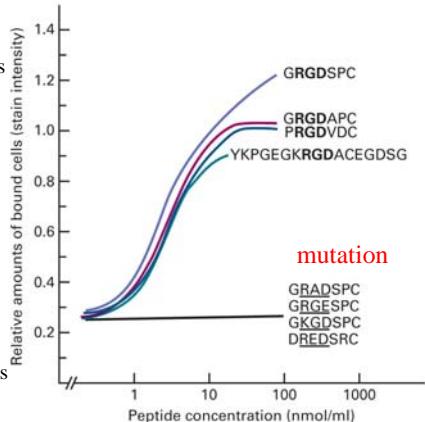
◆ 在胚胎發生過程中，纖連蛋白對於許多類型細胞的遷移和分化是必需的；

◆ 在創傷修復中，纖連蛋白促進巨噬細胞和其它免疫細胞遷移到受損部位；

◆ 在血凝塊形成中，纖連蛋白促進血小板附著于血管受損部位。

Specific tripeptide sequence RGD is important role of the cell-bind region of fibronectin is require adhesion of cells

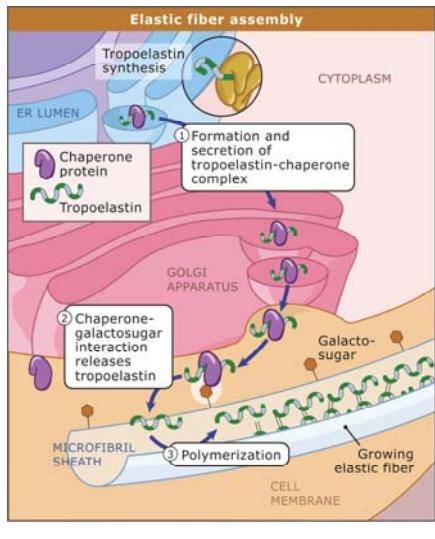
- Arg-Gly-Asp
- Cell binding region
- Type III repeat/binds integrins



Assembly of tropoelastin into fibers:

- occurs in the extracellular space
- is controlled by a three step process

Mutations in elastin give rise to a variety of disorders, ranging from mild skin wrinkling to death in early childhood.



Elastic fibers impart flexibility to tissues

The principal function of elastin is to impart **elasticity** to tissues.

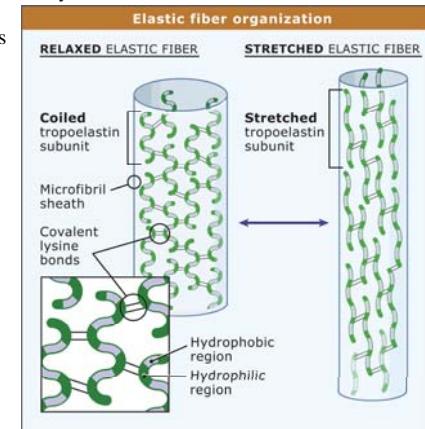
Elastin monomers (known as tropoelastin subunits) are organized into fibers.

The fibers are so strong and stable they can last a lifetime.

The strength of elastic fibers arises from covalent **crosslinks** formed between **lysine** side chains in adjacent elastin monomers.

The elasticity of elastic fibers arises from the hydrophobic regions, which:

- are stretched out by tensile forces
- spontaneously reaggregate when the force is released



In animals the ECM is composed of:

- Structural fiber -> Collagen and elastin
- Matrix -> proteoglycans
- Adhesive -> fibronectins & laminin
- Receptors -> integrin

Summary -Components of the ECM

Laminin, a multiadhesive protein in basal lamina, binds heparan sulfate, type IV collagen and other cell surface proteins

Fibronectins, multiadhesive proteins linking collagen, other matrix proteins, attach cell to matrix

Glycosaminoglycans are sulfated disaccharides (like chondroitin sulfate, heparin, heparan sulfates)

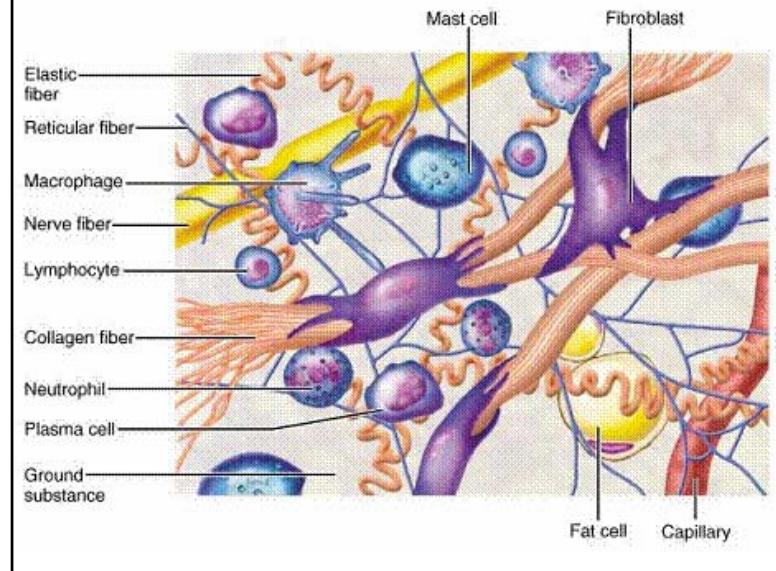
Proteoglycans have a protein core and branching glycosaminoglycan chains

Aggrecan is a proteoglycan in cartilage – forms large aggregates

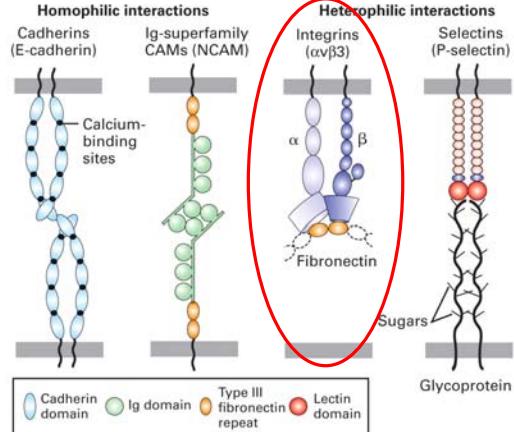
Smaller proteoglycans attach to cell surface and facilitate cell-matrix interactions

Hyaluronan is a long, negatively charged polysaccharide that forms viscous, hydrated gels that resist compression; can inhibit cell-cell adhesion, facilitate cell migration

Multiadhesive Matrix Proteins - Long and flexible, they bind collagens and other proteins, polysaccharides, cell-surface proteins and signaling molecules (growth factors, hormones)



Many cell-matrix and some cell-cell interactions are mediated by integrins



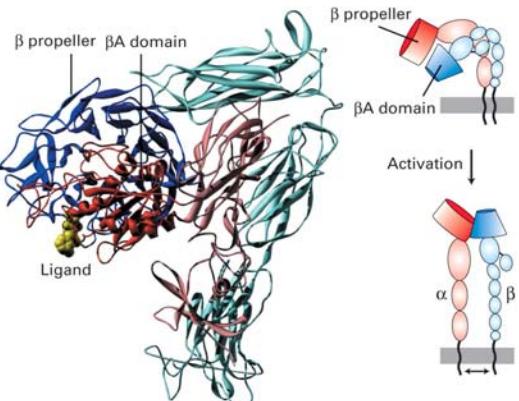
At least 12 distinct α -subunits and 9 β -subunits identified; single subunit can associate with more than one partner

Difficult to crystallize and therefore 3D structures not readily available

Cloning experiments indicate that integrins have short cytoplasmic tail (~ 50 amino acids) and 4 Ca^{2+} binding sites identified in the α subunit

Numerous disulfide bonds- difficult identify all of them

Integrins



Integrin superfamily 的黏著分子主要參與細胞與細胞外基質的黏附，使細胞得以附著而形成 integration。此外，這些分子還參與白血球與血管內皮細胞的黏附。

這些分子都是由 α 、 β 兩條鏈以非共價鍵連接組成的 heterodimer 。

α 鏈的分子量為 120~180kD, β 鏈的分子量為 90~110kD, 不同的 α 鏈或 β 鏈胺基酸組成和序列有不同程度的同源性，在架構上有其共同的特點。

α 鏈和 β 鏈均由胞漿區、穿膜區、胞膜外區三部分組成。胞漿區一般較短，可能與細胞骨架相聯。穿膜區富含疏水胺基酸。

α subunits 和 β subunits 組合構成並不是隨機的，多數 α subunits 只能與一種 β subunits 結合成 heterodimer，而大部分 β subunits 則可以結合數種不同 α subunits。目前依 β subunits 的不同將與動脈粥狀硬化相關的 integrin superfamily 分為 3 個不同的組。

Integrin 在與 ligand 結合時所識別的只是 ligand 分子中由數個胺基酸組成的序列，例如 Arg-Gly-Asp (RGD) 序列。不同的 integrin 可以識別相同的序列或同一個 ligand 中不同的序列。

Integrins 在體內分佈很廣泛，多數 integrins 可以表現於多種組織、細胞，如 VLA 組的 integrins 在體內廣泛分佈於各種組織、細胞，而多數細胞可同時表达數種不同的 integrins 。

Cell-matrix adhesion is modulated by changes in the activity and number of integrins
De-adhesion factors promote cell migration and can remodel the cell surface

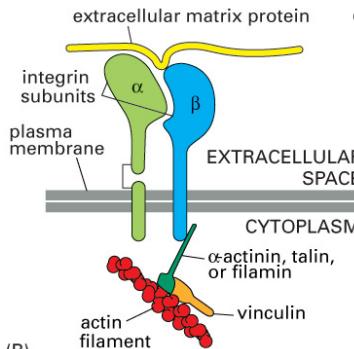
TABLE 6-2 Selected Vertebrate Integrins*

Subunit Composition	Primary Cellular Distribution	Ligands
$\alpha 1\beta 1$	Many types	Mainly collagens; also laminins
$\alpha 2\beta 1$	Many types	Mainly collagens; also laminins
$\alpha 4\beta 1$	Hematopoietic cells	Fibronectin; VCAM-1
$\alpha 5\beta 1$	Fibroblasts	Fibronectin
$\alpha 1\beta 2$	T lymphocytes	ICAM-1, ICAM-2
$\alpha M\beta 2$	Monocytes	Serum proteins (e.g., C3b, fibrinogen, factor X); ICAM-1
$\alpha IIb\beta 3$	Platelets	Serum proteins (e.g., fibrinogen, von Willebrand factor, vitronectin); fibronectin
$\alpha 6\beta 4$	Epithelial cells	Laminin

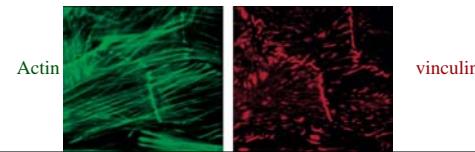
*The integrins are grouped into subfamilies having a common β subunit. Ligands shown in red are CAMs; all others are ECM or serum proteins. Some subunits can have multiply spliced isoforms with different cytosolic domains.

SOURCE: R. O. Hynes, 1992, *Cell* 69:11.

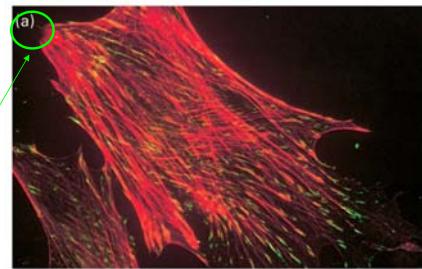
Focal adhesions



Laminin and fibronectin provide an adhesive substrate for cells

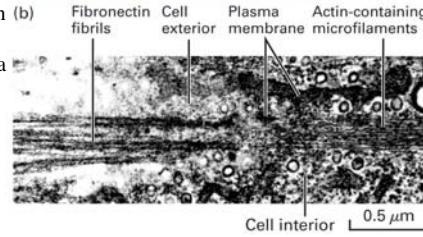


Integrins mediate linkage between fibronectin in the extracellular matrix and the cytoskeleton



Green: integrin
Red: actin

Stress fiber are long bundles of actin microfilament that radiate inward from points where the cell contacts a substratum



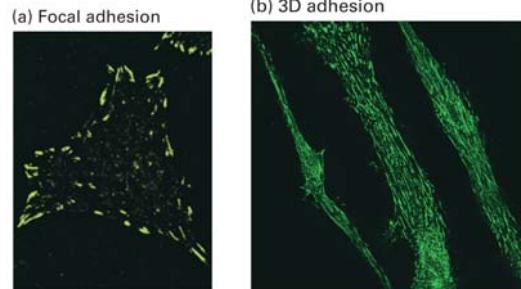
Adhesive interaction and non-epithelial cells

Integrin containing adhesive structures physically and functionally connect the ECM and cytoskeleton in nonepithelial cells

fibroblast

(B) Anchoring junctions display greater adhesion and mobility.

increased rates of cell proliferation and spindle shaped morphology



Culture dish

3D matrix of ECM

Adhesive interaction and non-epithelial cells

Integrin containing adhesive structures physically and functionally connect the ECM and cytoskeleton in nonepithelial cells

Characterization of integrin

1. tie the matrix to the cell's cytoskeleton
2. principal cell receptors for binding most ECM proteins
3. large family of homologous transmembrane linker proteins
4. heterodimer structure
5. non-covalently associated α and β subunits
6. cells can regulate the activity of their integrins
7. often need to be activated before they can mediate cell adhesion
8. short cytoplasmic domains, no kinase activity

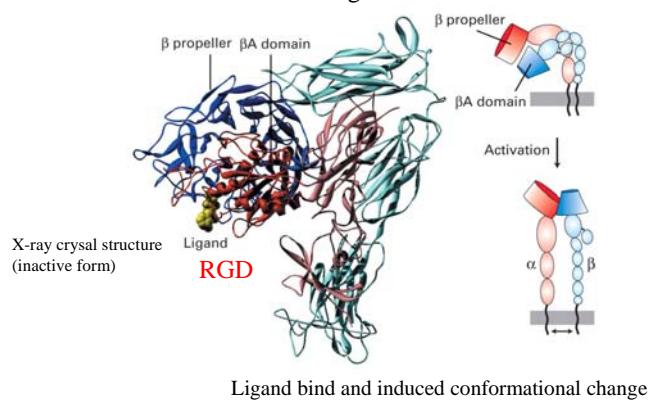
α and β subunits ($\alpha 1, \alpha 2, \dots$ and $\beta 1, \beta 2, \dots$) associate in pairs e.g. $\alpha 1-\beta 1$ binds collagen, $\beta 2-\alpha$ binds fibrinogen; α subunits attach to membrane, lack cytoplasmic domain; β subunit attaches to membrane-cytoplasmic domain interacts with cytoskeleton bind ligands including ECM components and serum proteins

ligand binding changes integrin conformation

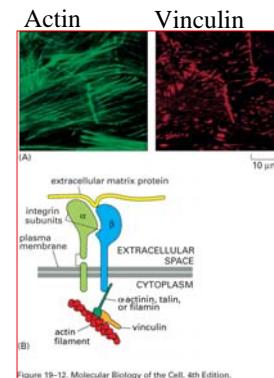
Diversity of ligand-integrin interaction contributes to number biological processes

Cell-matrix adhesion is modulated by changes in the binding activity and number of integrins

Model for integrin activation



Focal Contacts (adhesion plaques, focal adhesions)



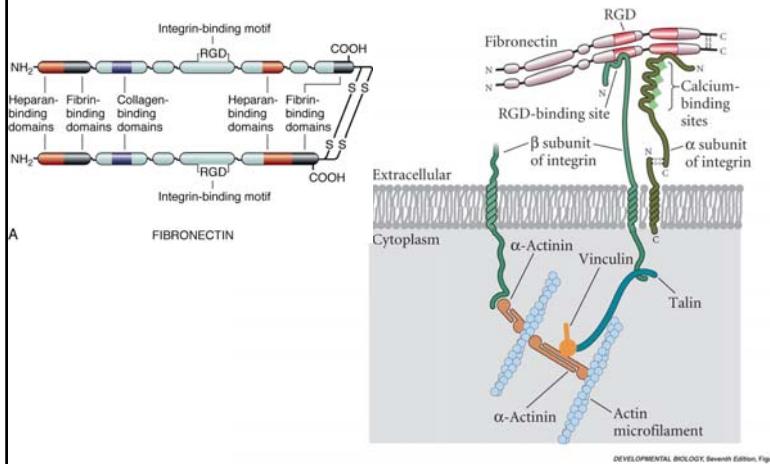
Found in cells (i.e., fibroblasts) where actin bundles (stress fibers) are anchored to the plasma membrane. Important in cell movement and wound healing.

Transmembrane linker proteins are integrins

Integrins bind to various ECM Proteins
Intracellular attachment proteins bind integrins to actin

Figure 19-12, Molecular Biology of the Cell, 4th Edition.

The Binding of Cytoskeleton to the Extracellular Matrix Through the Integrin Molecule



Integrin vs Receptor

Integrins are signaling receptors that control both:

- cell binding to extracellular matrix proteins
- intracellular responses following adhesion

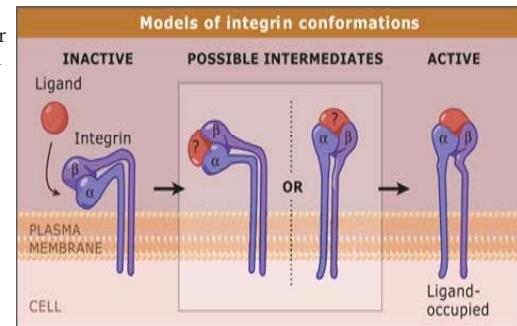
Integrins have no enzymatic activity of their own.

- Instead, they interact with adaptor proteins that link them to signaling proteins.

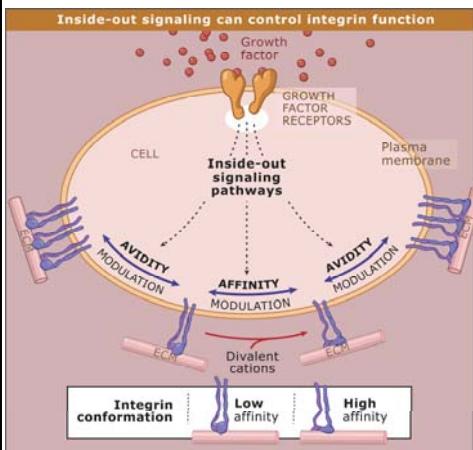
Changes in integrin receptor conformation are central to both types of modulation.

They can result from changes:

- at the cytoplasmic tails of the receptor subunits **or**
- in the concentration of extracellular cations



Integrin receptors participate in cell signaling

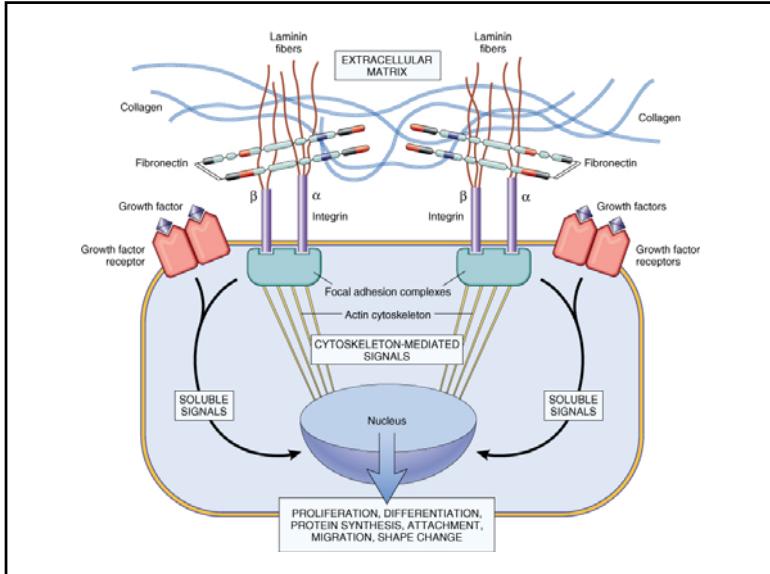


In inside-out signaling, changes in receptor conformation result from intracellular signals that originate elsewhere in the cell.

- For example, at another receptor

In outside-in signaling, signals initiated at a receptor are propagated to other parts of the cell.

- For example, upon ligand binding



Muscular dystrophy: connections between the ECM and cytoskeleton are defective

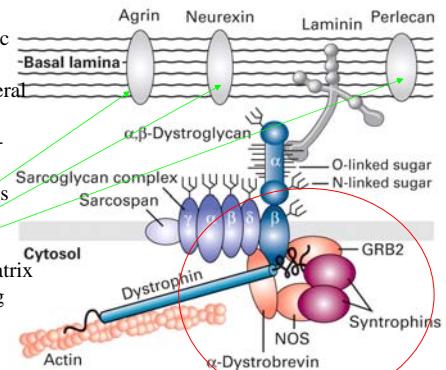
About 1/3300 boys, heart or lung failure

Mutation of dystrophin (a cytosolic protein), bind to dystroglycan

Dystroglycan: α -subunit (peripheral protein) plus β -subunit (transmembrane protein); the α -subunit also has O-linked oligosaccharides to bind various basal lamina components

DGC (dystrophin glycoprotein complex) links extracellular matrix to the cytoskeleton and signaling pathways enzyme for muscle's function

Mutations in components of this pathway (e.g. muscular dystrophy) results in mechanical instability of muscle cells.



Ca²⁺ independent cell-cell adhesion in neuronal and other tissue is mediated by CAMs (IgCAM) in the **immunoglobulin superfamily**

Movement of leukocytes into tissue depends on a precise sequence of combinatorially diverse set of adhesive interactions.

Movement across an endothelial cell layer of:

- Monocytes (macrophage precursors - cells that ingest foreign particles)
- Neutrophils (release antibacterial)
- T and B Lymphocytes (antigen-specific)

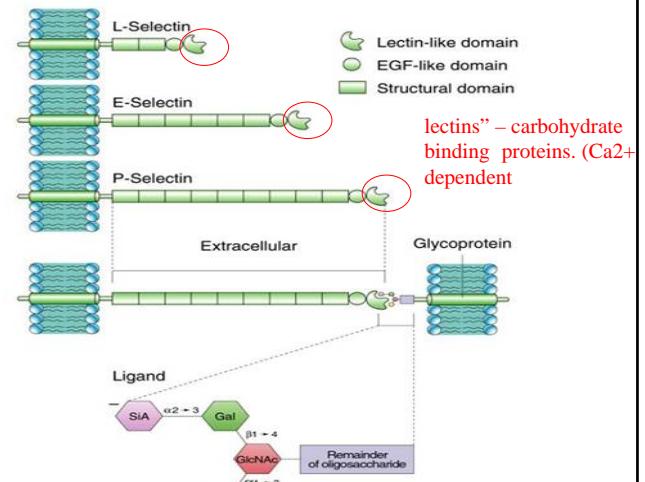
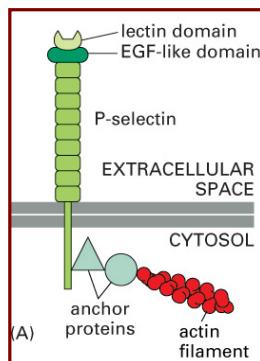
Movement is mediated by selectins, a class of CAMs specific for leukocyte/vascular cell interactions

- Activate integrin binds ICAM-1 and ICAM-2
- Cells move from the blood into infected or inflamed tissue

Selectins: mediate transient cell-cell adhesion in the bloodstream

White blood cells (WBCs) utilize the adhesive properties of selectins (and integrins) in order to move: blood \leftrightarrow tissue.

- Selectins are “lectins” – carbohydrate binding proteins. (Ca²⁺ dependent)
- TM protein with a highly conserved lectin domain that binds to a specific oligosaccharide.
- Transient, calcium-dependent interactions.
- Selectin types:
 - ✓ L-selectin: WBCs
 - ✓ P-selectin: platelets and endothelial cells
 - ✓ E-selectin: activated endothelial cells



目前已發現selectin家族中有三個成員：L-selectin、P-selectin和E-selectin，L、P和E分別表leukocyte, platelet和endothelium，是最初發現相應selectin分子的三種細胞，故得名。

P-selectin，分子量140KD，由單核巨細胞跟內皮細胞形成，貯存於血小板的α顆粒及內皮細胞的Weibel-Palade小體。當受到thrombin跟histamine刺激時，P-selectin會迅速到達血小板或內皮細胞表面，介導白血球與內皮細胞的起始黏附。

E-selectin，分子量115KD，正常的內皮細胞表面並無E-selectin存在，細胞內也沒有儲存。當受到IL-1及TNF- α 等細胞因子的刺激時，會活化內皮細胞，刺激E-selectin的合成。E-selectin會幫助白血球與內皮細胞的黏附作用。

L-selectin廣泛存在於各種白血球的表面，參與發炎部位白血球的出血管過程。白血球表面L-selectin分子上的SLeA與活化的內皮細胞表面的P-selectin及E-selectin之間的識別與結合，可召集血液中快速流動的白血球在發炎部位的血管內皮上減速滾動（即透過黏附、分離、再黏附……，如此循環往複），最後穿過血管進入發炎部位。

2. Non calcium dependent adhesion molecules

Evolutionarily ancient; widely expressed

Belong to the immunoglobulin (Ig) superfamily

Structure: single pass, transmembrane proteins which may bind to the cytoskeleton inside cells

Type of adhesion:

Can have both homophilic and heterophilic interactions;

homo – neural specific Ig Cell Adhesion molecules (IgCAMs);

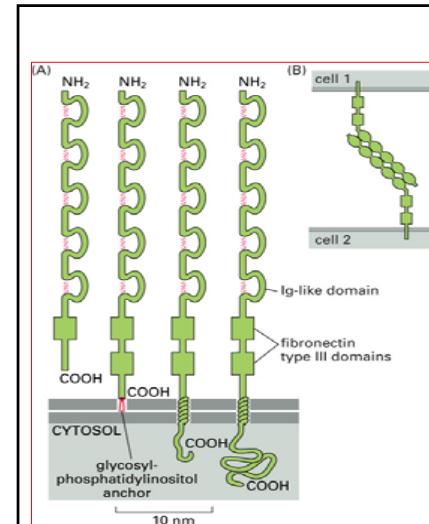
hetero systemic IgCAMs

Functions:

neurite outgrowth, myelination, and firm adhesion of leukocytes

Immunoglobulin superfamily

Immunoglobulin Superfamily CAMs (ICAMs)



Schematic drawing of four forms of NCAM. The extracellular part of the polypeptide chain in each case is folded into five immunoglobulinlike domains (and one or two other domains called fibronectin type III repeats for reasons that will become clear later). Disulfide bonds (shown in red) connect the ends of each loop forming each Ig-like domain.

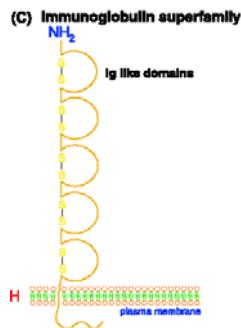
Figure 19-31. Molecular Biology of the Cell, 4th Edition.

Immunoglobulin superfamily的家族成員眾多，且均與immunoglobulin 有一定的同源性，其分子架構中含有多個90-100個胺基酸的Ig-like domains。廣泛分佈於淋巴細胞、單核細胞、內皮細胞等多種細胞的表面。

重要的成員有intercellular adhesion molecule-1、2、3 (ICAM-1、2、3) 、vascular cell adhesion molecule-1 (VCAM-1) 和platelet-endothelial cell adhesion molecule (PECAM) 。

該家族的主要功能是參與不同細胞間的識別與黏附，在與免疫、發炎有關的細胞黏附中發揮重要作用。

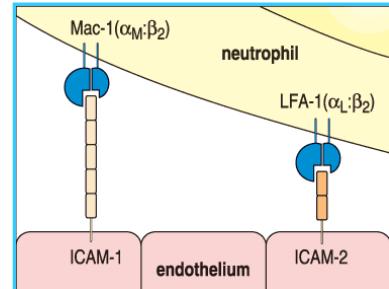
ICAM-1是最早發現的immunoglobulin superfamily 黏附分子之一，以後又相繼發現了ICAM-2和ICAM-3，它們的胺基酸序列具有同源性，且都可以結合LFA-1分子(一種integrin)。不同的ICAM分子在體內的分佈範圍有較大差異，ICAM-1分子分佈廣泛，如白血球、內皮細胞、某些腫瘤細胞、上皮細胞、肝細胞、平滑肌細胞等，IL-1、TNF- α 、和LPS可促進ICAM-1分子的表現；ICAM-2則分佈較局限，主要表現在血管內皮細胞；而ICAM-3表現在T細胞、單核細胞。



VCAM-1為110KD跨膜糖蛋白，由6個Ig同源區組成，與ICAM-1有很高的相似性。可在內皮細胞、上皮細胞、樹突細胞、巨噬細胞表現，並透過ligand VLA-4參與白血球對血管內皮細胞的黏附。

PECAM-1為130KD的單鏈糖蛋白，由6個Ig同源區組成。PECAM-1除表現於血管內皮細胞表面外，還可表現於血小板及白血球，細胞因子如TNF- α 、IL-1和IFN可刺激其表現，其配體為 β_2 integrin。PECAM-1主要參與內皮細胞間的黏附，亦與單核和中性粒細胞穿越內皮進行遷移有關，此外內皮受損時PECAM-1可促使血小板黏附形成血栓。

Ig superfamily has homophilic interaction and heterophilic interaction



IgCAMs comprise a diverse group of adhesion receptors, that are defined by the presence of one or several Ig folds; classical examples are:

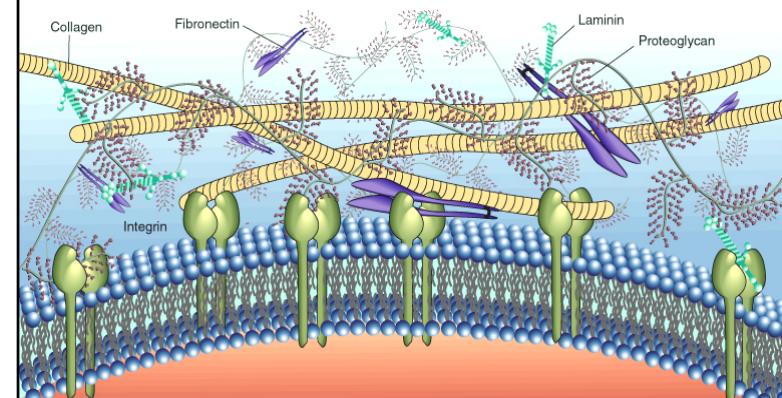
Neuronal CAM (NCAM) is implicated in neuronal guidance and establishment of new synapses

NCAM forms homotypic contacts

Intercellular CAM (ICAM) interacts heterotypically with integrins

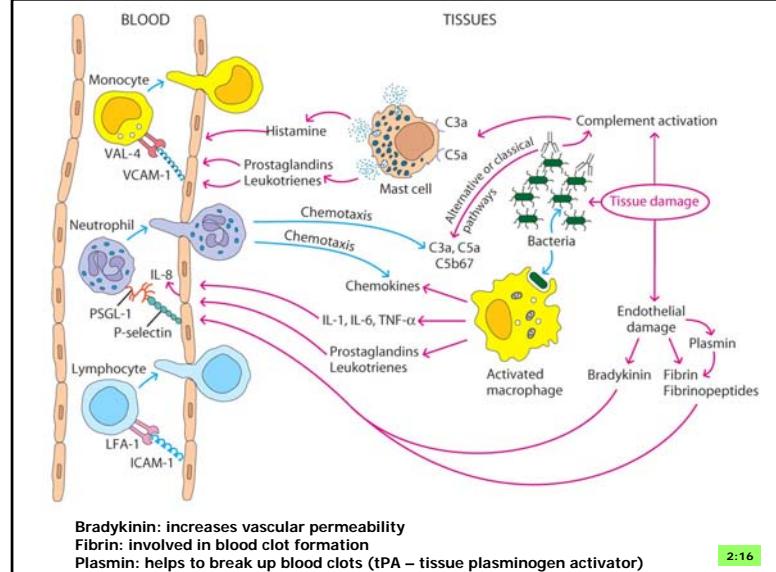
CAMs differ widely in their cytoplasmic binding partners

MACROMOLECULAR ORGANIZATION OF ECM

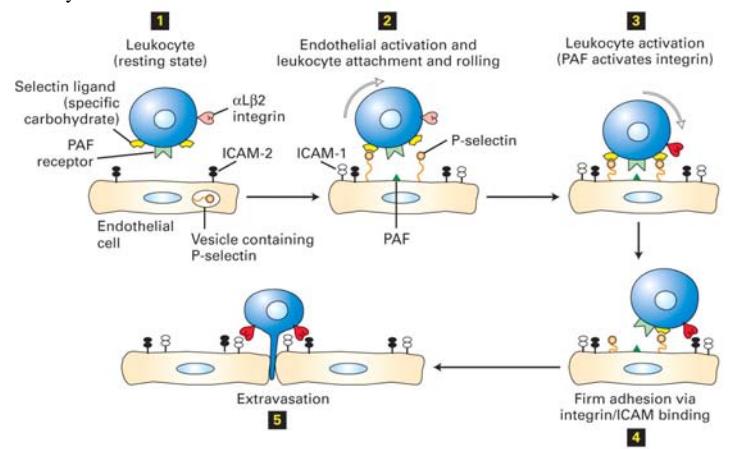


Movement of leukocytes into tissue depends on a precise sequence of combinatorially diverse set of adhesive interaction

Bacterial, infection or inflammation → tissue dysfunction → blood (leukocyte) → expressed special adhesion molecules at endothelial surface → bind leukocyte → induced adhesion molecule activation → extravasation → extracellular

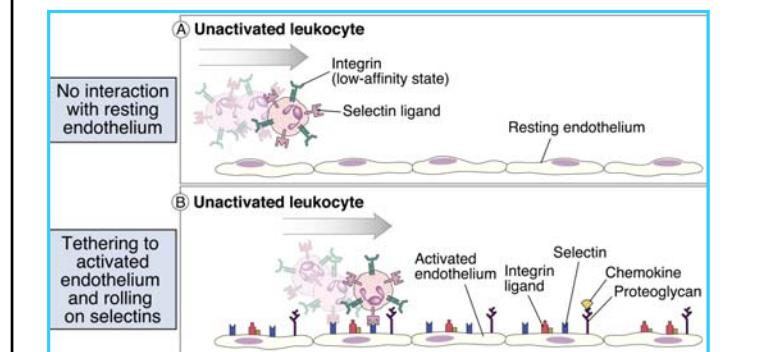


P-selectin, a lectin (protein that binds carbohydrates) on activated endothelial cells, binds a specific ligand (an oligosaccharide sequence) on T cells
 PAF (Platelet Activating Factor - a phospholipid) activates integrin on the leukocyte surface

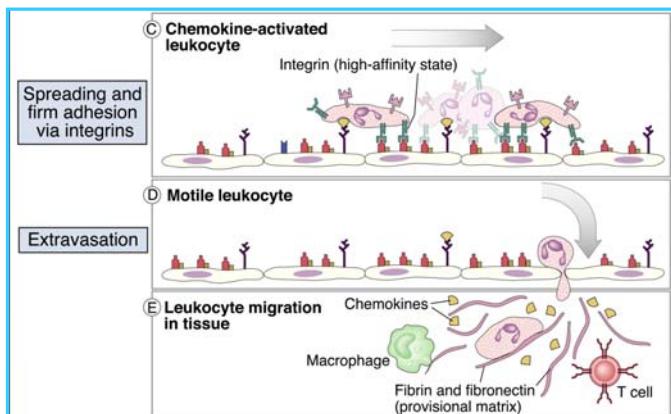


CAM directly bind to leukocyte

1. Endothelium activation → selectin or carbohydrate ligand → weak, reversible binding
2. Infection or inflammation signal → chemokines or PAF → expressed special molecules → attached leukocyte
3. Additional activation dependent CAM, integrins → strong adhesion



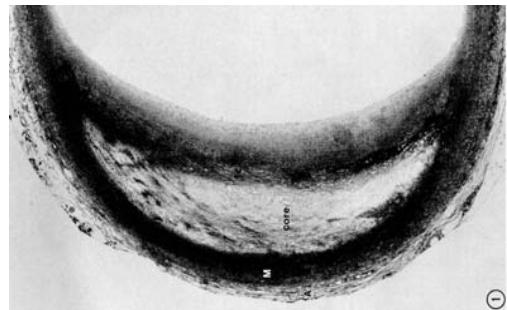
Multi-step Model of Leukocyte Adhesion and Extravasation



When leukocyte extravasation in artery ????????????

Artery wall is so strong and thick → leukocyte did not pass through

Atheroma



Inflammation and atherosclerosis

Cell adhesion molecules:

Selectins(*Selective lectins*)

Integrins(*Integrating proteins*)

IgG adhesion molecules

- P-selectin, a lectin (protein that binds carbohydrates) on activated endothelial cells, binds a specific ligand (an oligosaccharide sequence) on T cells
- PAF (Platelet Activating Factor - a phospholipid) activates integrin on the leukocyte surface

Reversible interaction of leukocytes to vascular endothelium via carbohydrate ligand (**s-lex**) on leukocytes and **E-selectin** on the endothelium cannot anchor the leukocyte because of the shearing force of the blood flow and instead just slows them down and allows for the possibility of stronger binding when other adhesion molecules on the leukocyte (**LFA-1**) interacts with other induced cell adhesion molecules (**ICAM-1**)

This arrests the rolling and allows the leukocyte to extravasate (squeeze between two endothelial cells)

Inside the tissue the leukocyte migrates along a chemokine concentration gradient (**IL-8** in this example) secreted by cells at the site of infection

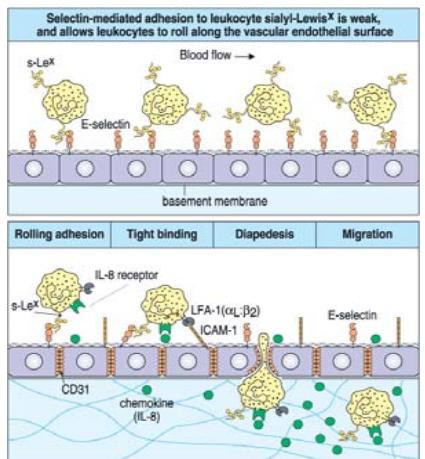
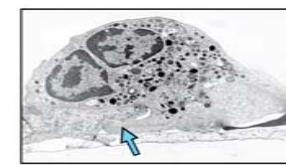
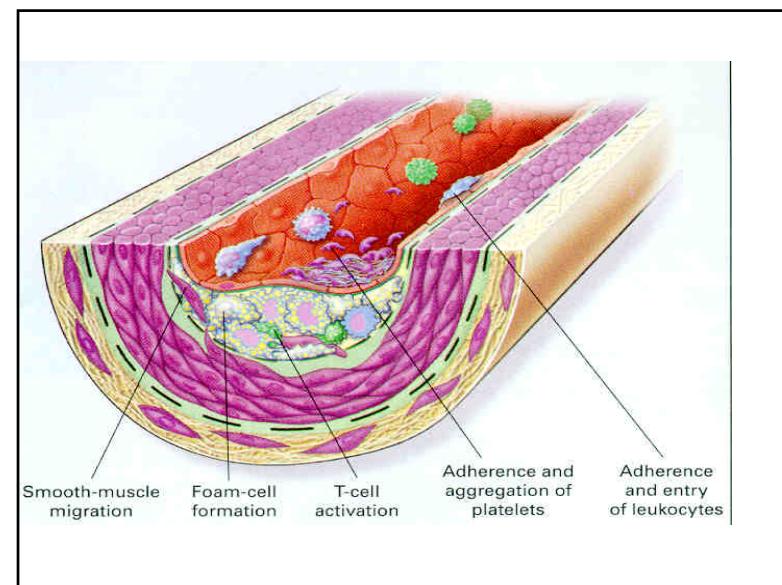
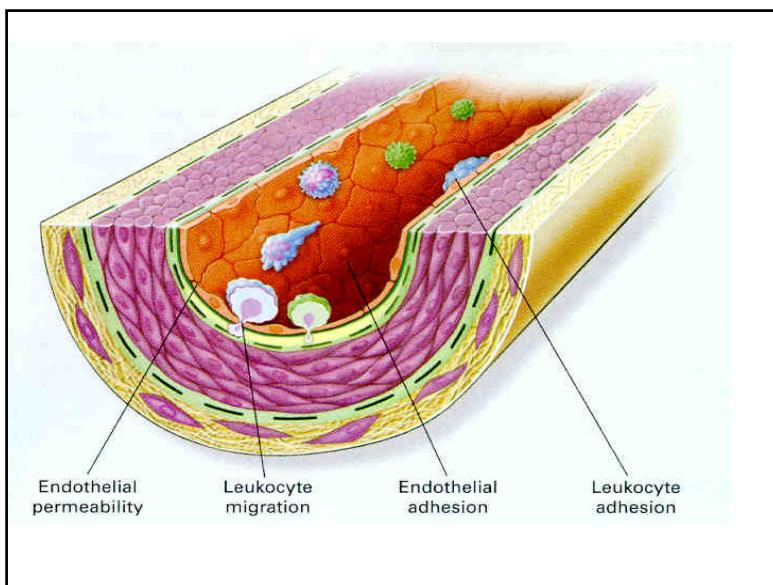
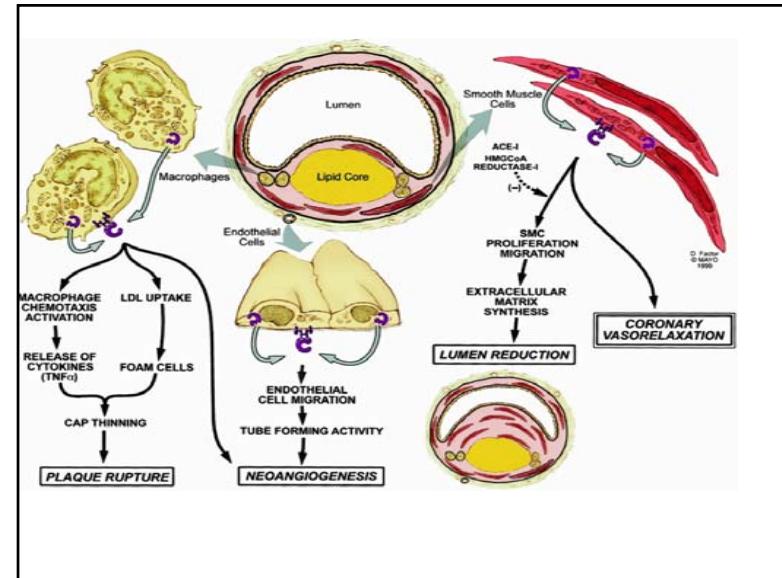
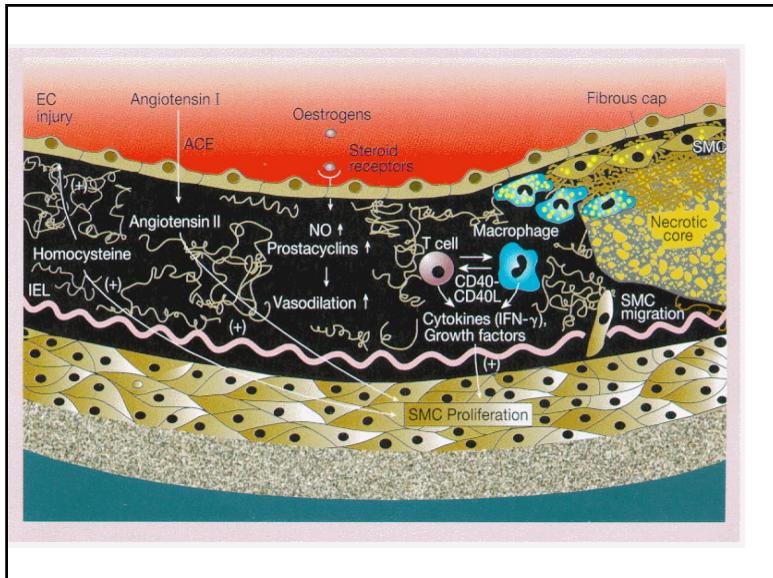
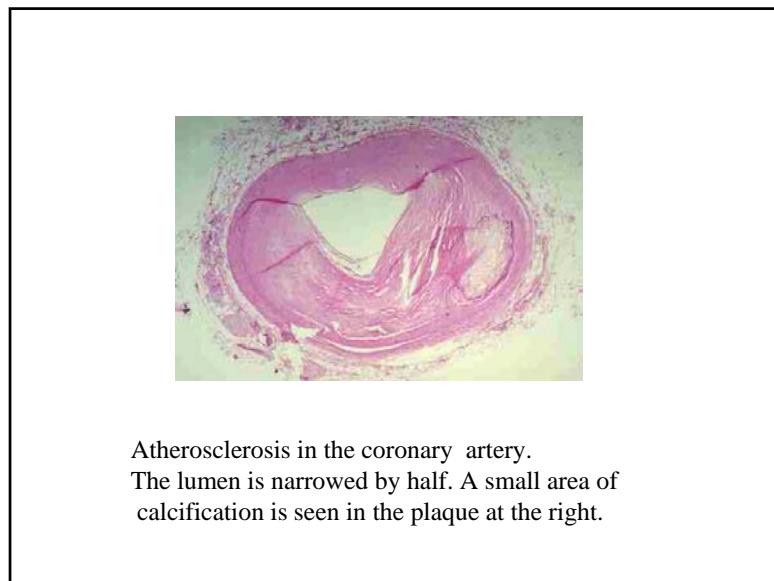
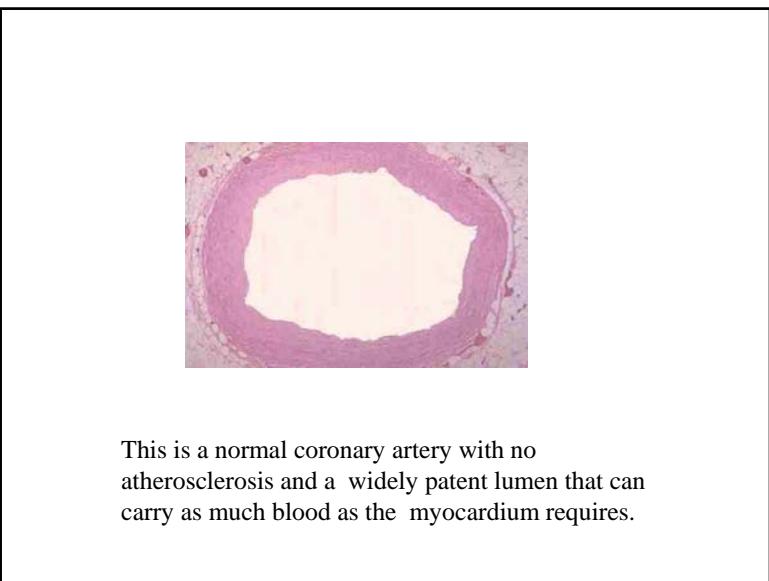
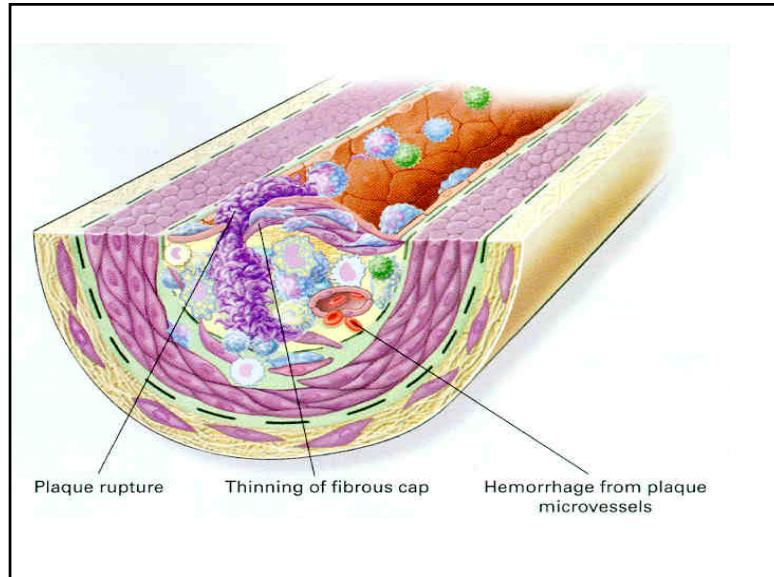
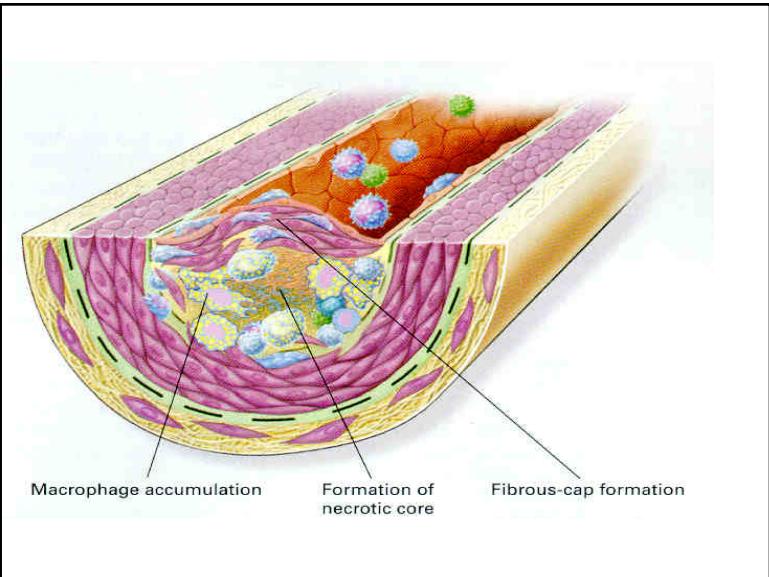
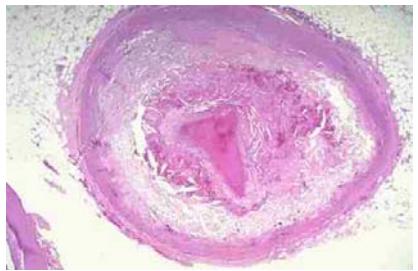


Fig 2.36 part 1 of 2 © 2001 Garland Science

note: even in the absence of infection, monocytes continuously migrate into tissues and differentiate into macrophages

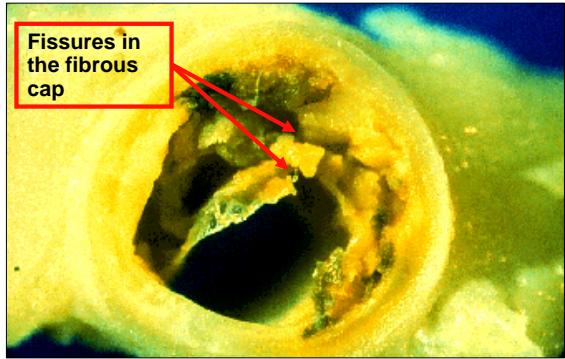






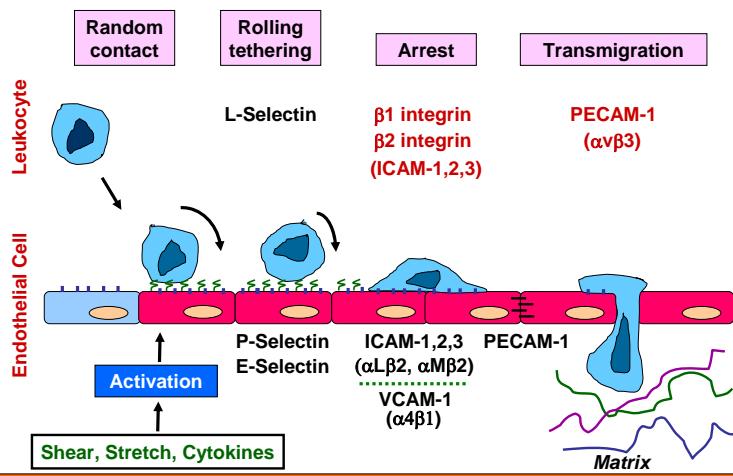
A coronary thrombosis is occluding the lumen of this coronary artery.

The Matrix Skeleton of Unstable Coronary Artery Plaque

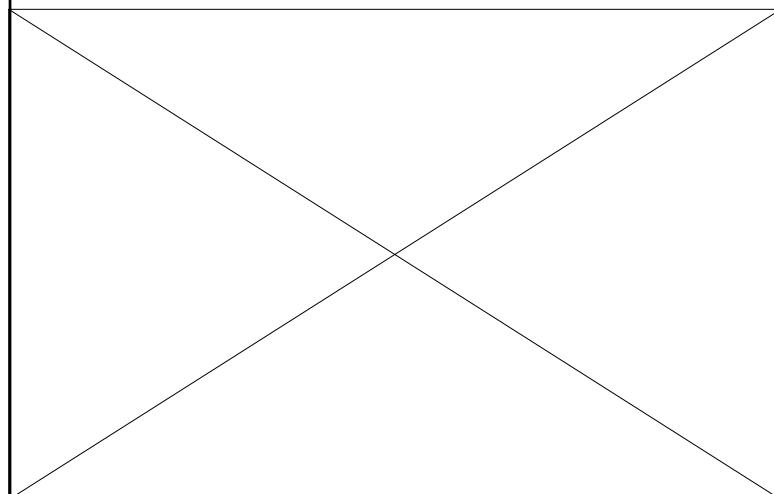


Davies MJ. *Circulation*. 1996;94:2013-2020.

More Detailed T-Cell Endothelial Cell Interactions



Cell-cell adhesion in leukocyte extravasation



Soluble Adhesion Molecules and Cardiovascular Risk Prediction

Type of Population	sICAM-1	sVCAM-1	sE-Selectin	sP-Selectin
Healthy Individuals	++	-	+	+
Patients at risk with established CAD	++	+++	+	+
Acute Coronary Syndrome	+	+++	+	++

+++ strong evidence;
 ++ moderate evidence
 + weak evidence
 - no evidence.

Atherosclerosis, 170:191-203, 2003

Functions of cell walls:

For plants:

Mechanical strength--> plant heights

Glue cells together--> dictate the way in which plant develop

Exoskeleton--> control cell shapes

Control balance between cell turgor pressure and cell volume

Diffusion barrier for macro-molecules and pathogens

Food reserves: endosperm cell walls degrade during seed during germination

Signaling

Plant tissue

Unlike animals, plants **do not** replace or repair old or damaged cells or tissues; only grow new organs

Plant only four broad types of cells (form four basic classes of tissue)

1.dermal tissue: interact with environment

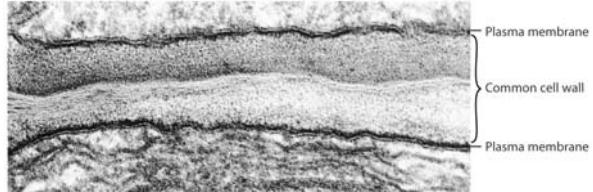
2.vascular tissue: transport water and dissolved substances

3.ground tissue: space filling

4.sporogenous tissue: forms the reproductive organs

Contain polysaccharides: cellulose (tensile 張力 拉力 strength), hemicellulose

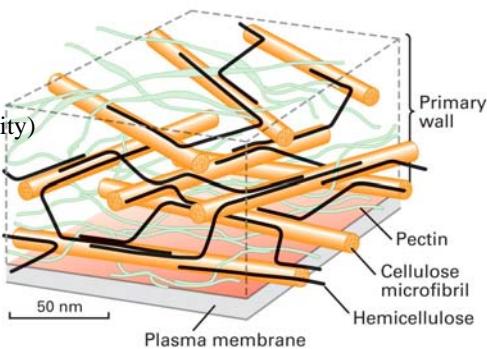
Allow soluble factor to pass to cell membrane, but less permeable than animal cell matrix



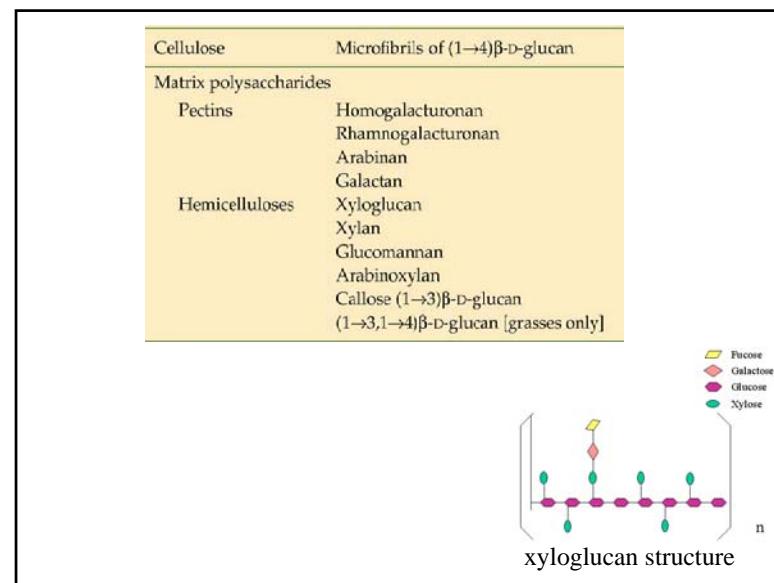
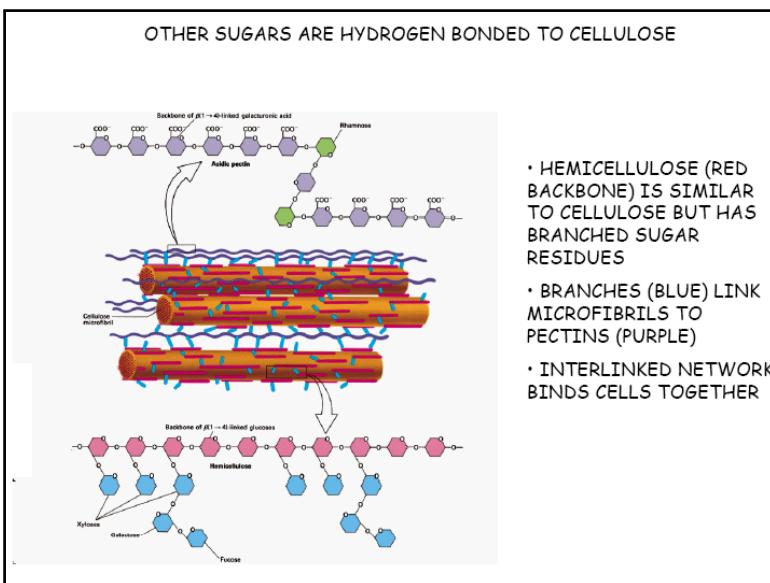
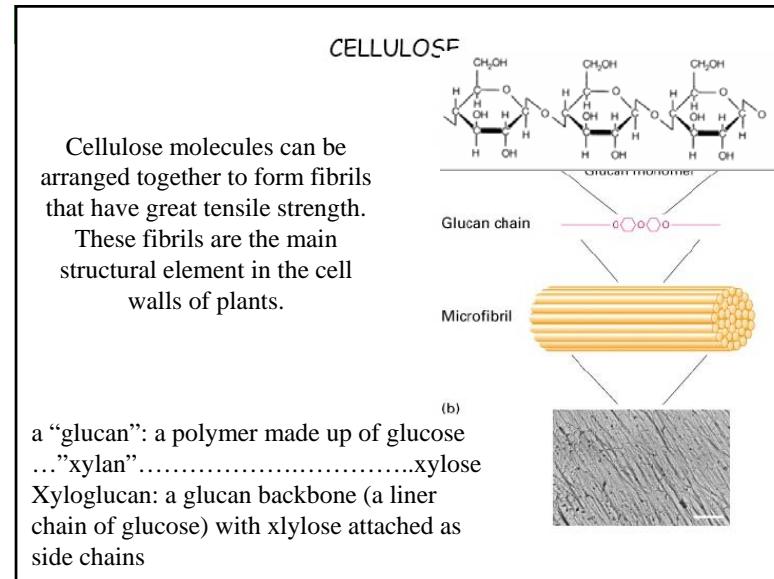
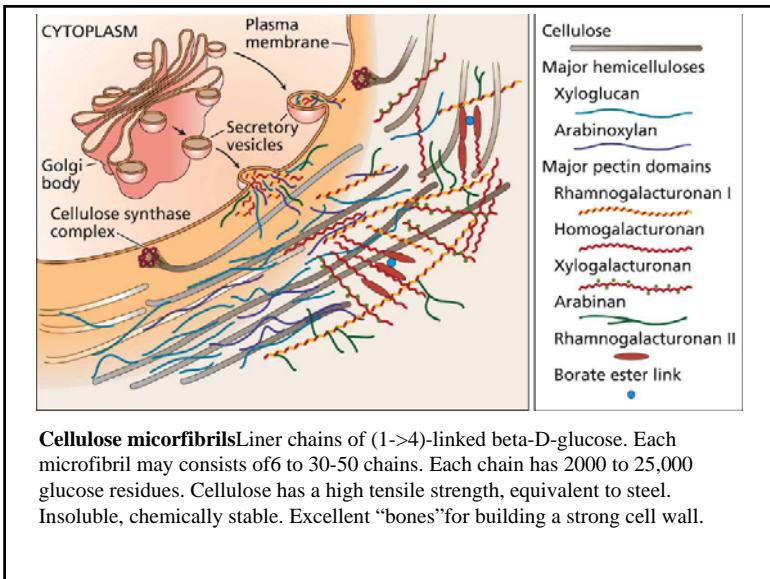
The plant cell wall is a laminate (薄板) of cellulose fibrils in a matrix of **glycoprotein**

Primary wall consists of the following basic features

- Cellulose (strength)
- Hemicellulose
- Pectins (flexibility)
- Structural proteins (rigidity)
- Non-structural proteins



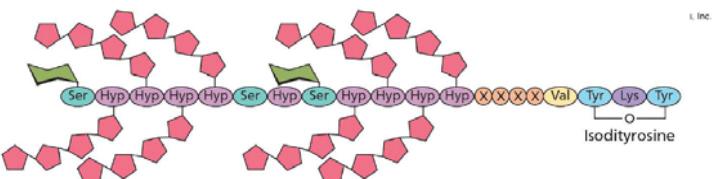
CELLULOSE AND HEMICELLULOSE ARE PRESENT IN A MATRIX OF PECTIN POLYMERS



Walls also contain some **proteins**. They may serve structure purposes or function in signaling.

TABLE 15.2
Structural proteins of the cell wall

Class of cell wall proteins	Percentage carbohydrate	Localization typically in:
HRGP (hydroxyproline-rich glycoprotein)	~55	Phloem, cambium, sclereids
PRP (proline-rich protein)	~0-20	Xylem, fibers, cortex
GRP (glycine-rich protein)	0	Xylem



A repeated hydroxyproline-rich motif from a molecule of HRGP from tomato

Loosening of the cell wall permits elongation of plant

Auxin → induced weakening of cell wall → water into cell
→ expansion of intracellular vacuole → elongation of cell

Cell Wall Structure

The middle lamella, primarily pectin, 'glues' neighbouring cells together.

Primary cell wall:

The first wall laid down during growth.

This is **soft** and **flexible** so that the cell can expand during growth.

It contains a mixture of biopolymers, with typically **~20-30% cellulose**

Once growth has stopped, the secondary cell wall is laid down, which provides structural support for the cells.

Secondary Cell Wall Structure:

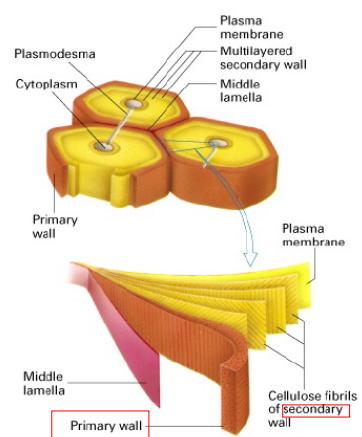
Some cells have very **thick** secondary cell walls, to provide maximum support.

In the case of flax it can be μm in thickness (compared with $\sim 100\text{nm}$ for the primary wall), and this was why flax was used for this study.

Typical **cellulose content is ~50%**, though can reach $\sim 100\%$ for e.g. cotton.

Structure is complex, and thought to consist of aligned **排列直線** layers of cellulose microfibrils in a general biopolymer matrix, with systematic misorientations between the layers.

THE SECONDARY CELL WALL CONTAINS A SERIES OF CELLULOSE LAYERS



- THE PRIMARY CELL WALL CONTAINS EXTENSIN, A GLYCOPROTEIN SIMILAR TO COLLAGEN, THAT IS INCORPORATED INTO THE INSOLUBLE POLYSACCHARIDE NETWORK.

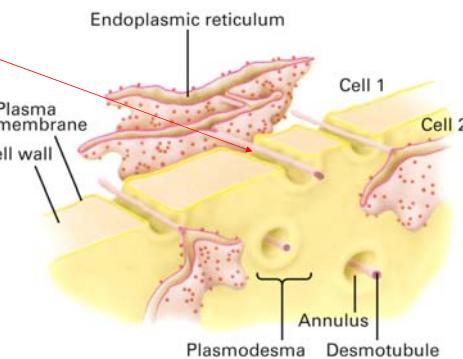
- THE INNER SECONDARY WALL LAYER IS LAID DOWN AS CELLS MATURE

PLASMODESMATA INTERCONNECT CYTOPLASMS OF ADJACENT PLANT CELLS

60 nM diameter allows passage of molecules of up to 1000 MW

ER extensions (desmotubule) can pass through, allowing transit of membrane bound molecules

Elevation of cytosolic calcium inhibits transports (similar to gap junction)



Plasmodesmata Plasma membrane Cell wall

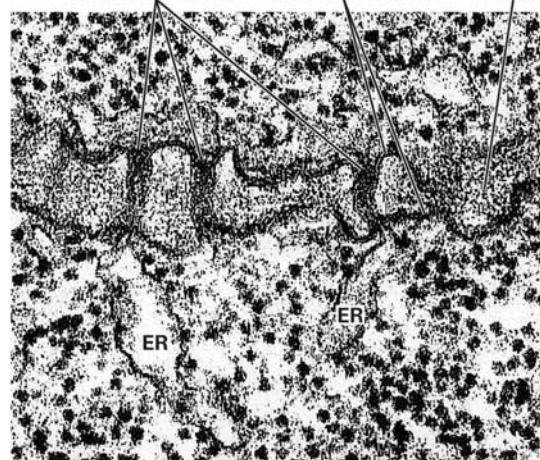


Table 11-1 Extracellular Structures of Eukaryotic Cells

Kind of Organism	Extracellular Structure	Structural Fiber	Components of Hydrated Matrix	Adhesive Molecules
Animals	Extracellular matrix	Collagens (ECM)	Proteoglycans and elastins	Fibronectins and laminins
Plants	Cell wall	Cellulose	Hemicelluloses	Pectins and extensins

Copyright © 2003 Pearson Education, Inc., publishing as Benjamin Cummings.

The extracellular matrix and the cell wall are the **“outside”** of the cell

Extracellular matrix (ECM): consists of collagen fibers and proteoglycan. Collagen are a group of insoluble glycoproteins that contain large amount of glycine and the hydroxylated forms of lysine and proline. (examples, tendons, cartilage, and bone)

Cell wall: consists cellulose microfibrils embedded in a matrix of other polysaccharides and small amounts of proteins (extensins)

Primary cell wall: cellulose fibrils and gel like polysaccharides, thus flexible and extensible

Secondary cell wall: additional cell wall materials deposited on the inner surface of the primary cell wall, thus thicker and rigid. Second cell wall also contains high concentration of lignin, a major component of wood

Communication between cells:

Plasmodesmata: cytoplasmic bridges between plant cells

Animal cells: gap junctions, tight junctions and adhesive junctions

Prokaryotes: cell walls consist of peptidoglycans with GlcNAc-MurNAc units