Biomechanical interaction between cells and environment

Cell/tissue structures acting in this interaction:

- Cell membrane
- Cell junctions
- Cytoskeleton
- Extracellular matrix

Biological events controlled/modulated by this interaction:

- cell proliferation, cell death
- cell motility
- tissue development, regeneration, healing

Cell junctions

- Specialized ultrastructures of the cell membrane gathering cytoskeleton to specialized elements of plasmalemma and assuring the cell ability to attach one to another or to the substratum (extracellular matrix), in order to organize tissues and organs respectively
- Classification respects both their structural appearance/morphology and functions

Classification of cell junctions

- Occluding junctions (tight junctions)
- Anchoring junctions (Adhering junctions);
  - Actin filament attachment:
    - cell-to-cellcell junctions (adherens junctions/adhesion belt or *zonula adherens*)
    - cell-to-matrix junctions (focal adhesions/focal contacts).
  - Intermediate filament attachment:
    - cell-to-cell junctions (desmosomes or *macula adherens*);
    - cell-to-matrix junctions (hemidesmosomes)
- Communicating junctions:
  - channel-forming junctions (gap junctions or *macula communicans*)
  - synapses/signal-relaying junctions:
    - chemical synapses
    - immunological synapses
    - stromal synapses

Ordering of various types of junctions in unicellular epithelia

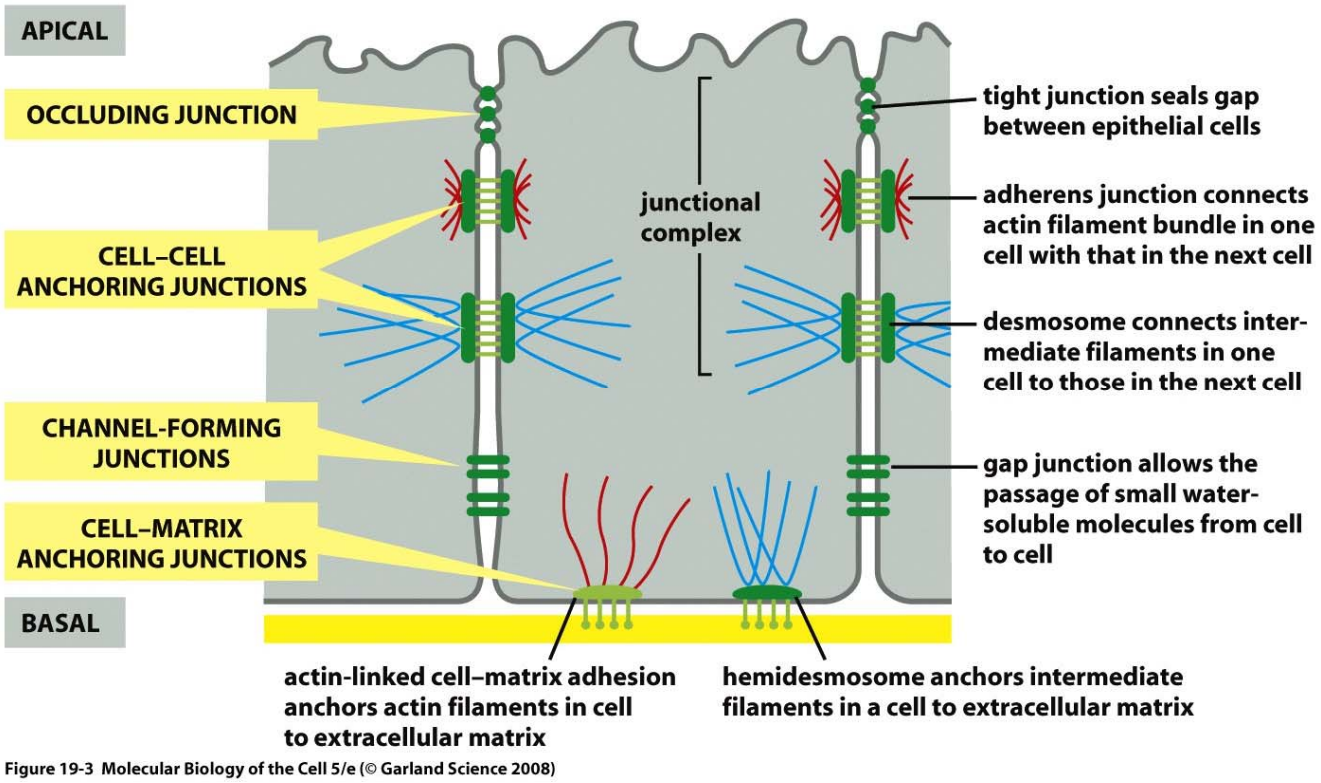
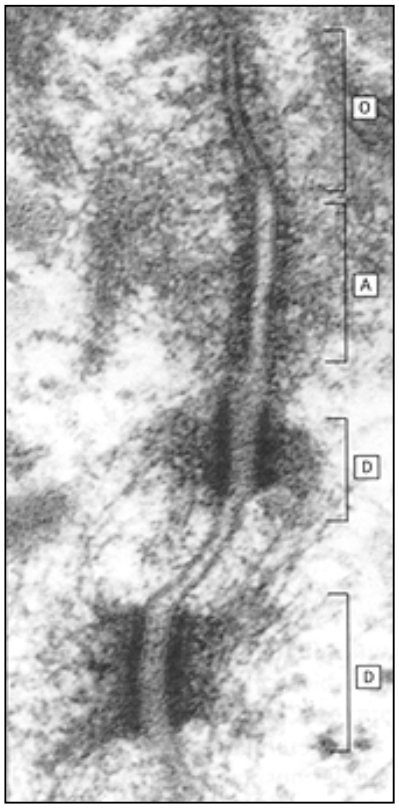


Figure 19-3 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Occluding junction organization

Transmembrane proteins involved: occludin (65kDa), claudins (20-27kDa)



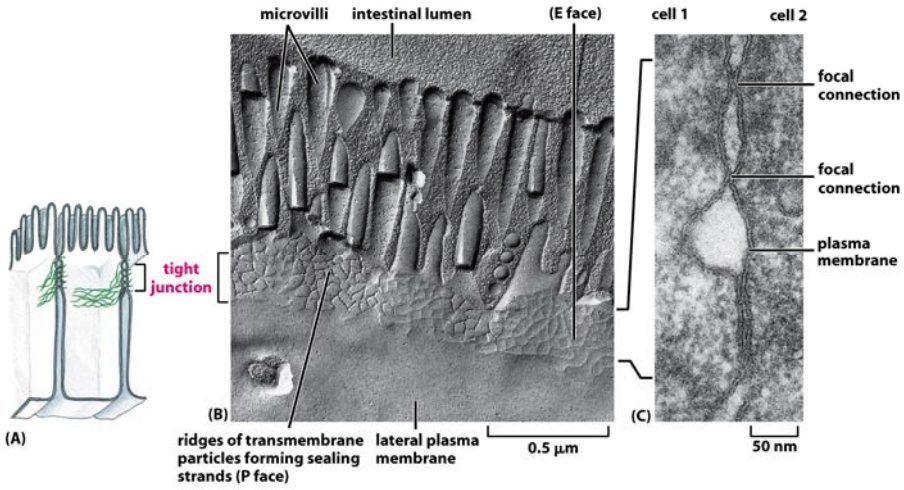


Figure 19-25 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Location: mainly in unicellular/monolayer epithelia (polarized cells), but multi-layered epithelia (urothelium, epidermis) express occludin and/or claudins

Roles:

- assures the sealing between luminal compartment of the organ and the tissue;
- maintains membrane polarization (luminal ***versus*** lateral-basal)

Molecular organization of tight junctions – *zonula occludens*

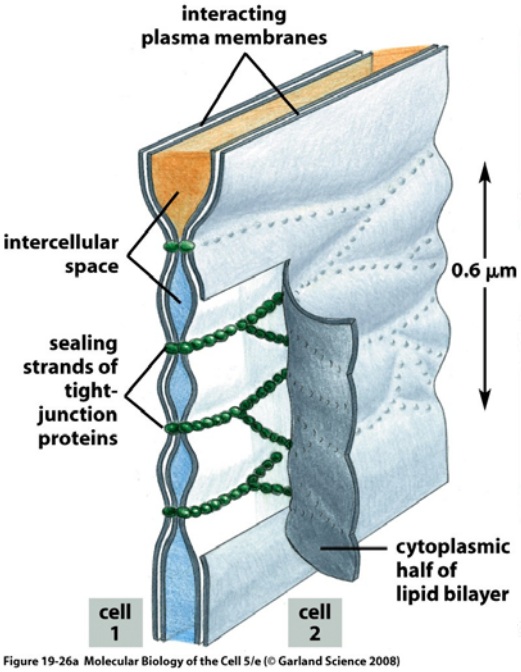


Figure 19-26a Molecular Biology of the Cell 5/e (© Garland Science 2008)

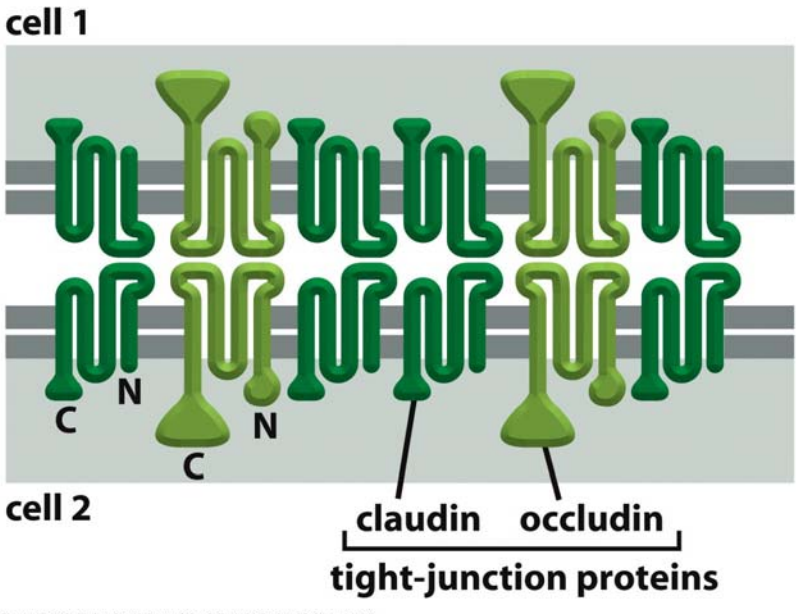
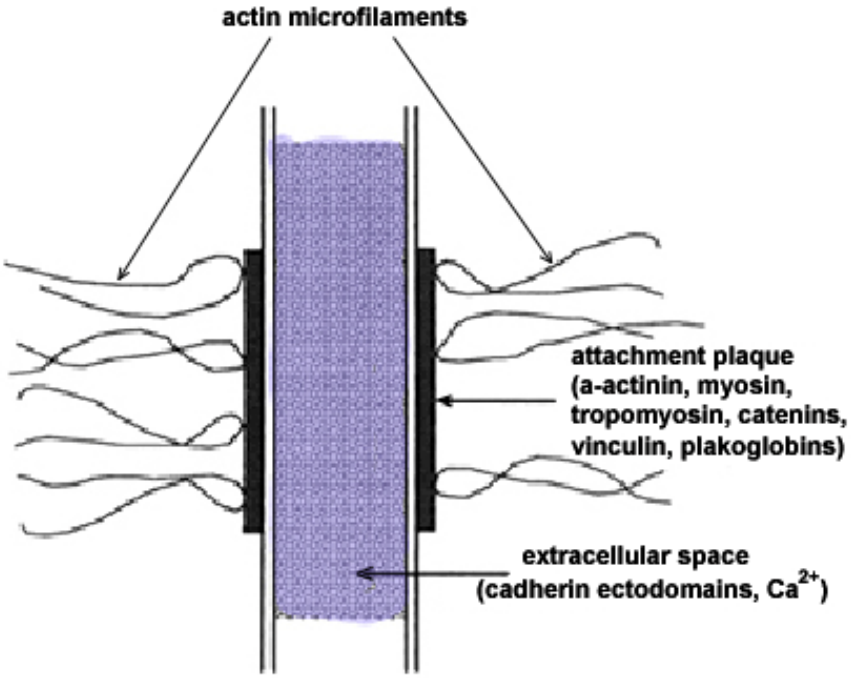


Figure 19-26b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cell-to-cell anchoring junction

1. Adhesion belt (*zonula aderens*)



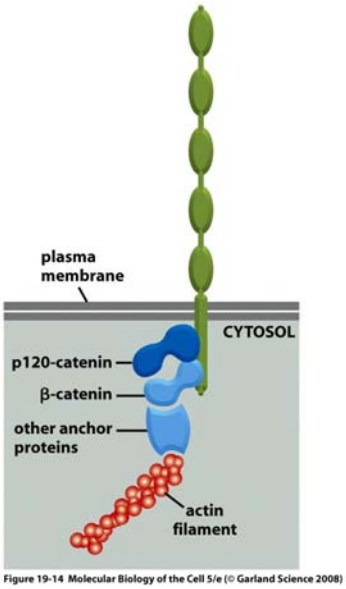


Figure 19-14 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Role: assure mechanical power for cell-to-cell interactions to maintain tissue integrity (mainly underneath tight junctions) and control cell shape

Cadherin role

Cadherin interactions in adhesion belt

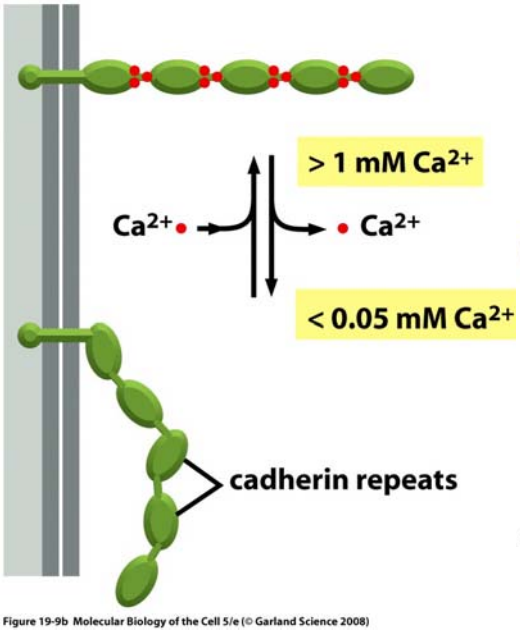


Figure 19-9b Molecular Biology of the Cell 5/e (© Garland Science 2008)

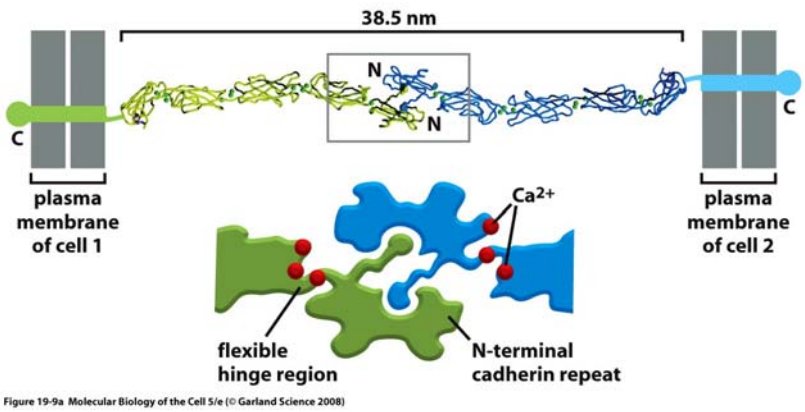
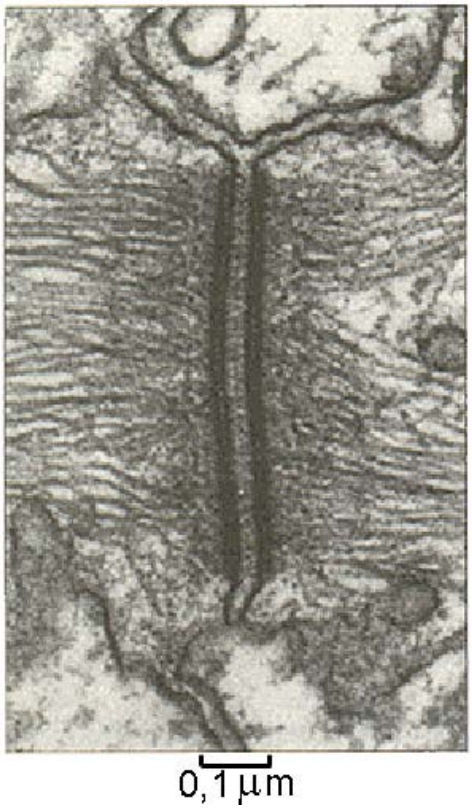


Figure 19-9a Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cell-to-cell anchoring junction

2. Desmosome (*macula aderens*)



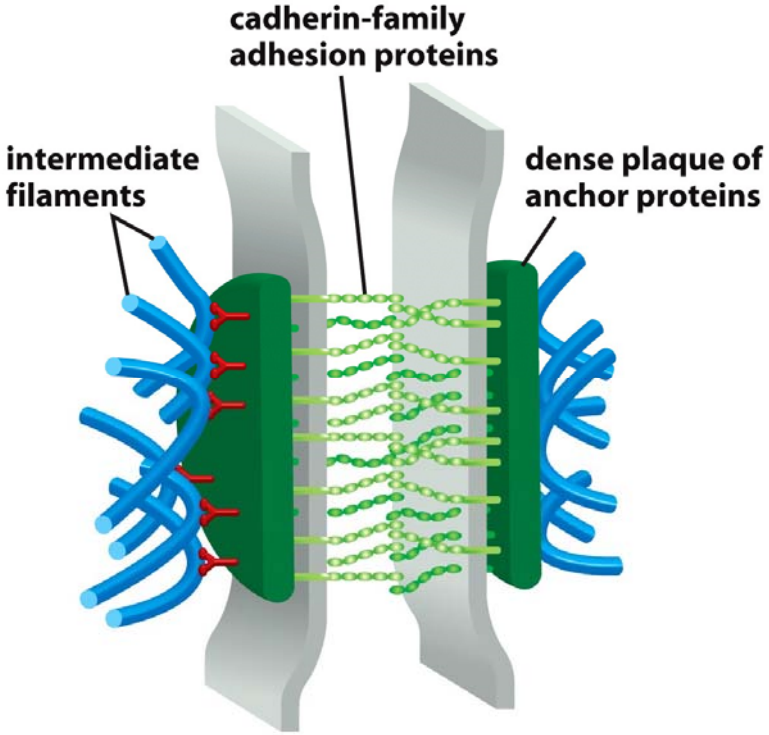


Figure 19-17a Molecular Biology of the Cell 5/e (© Garland Science 2008)

Molecular organization of desmosomes

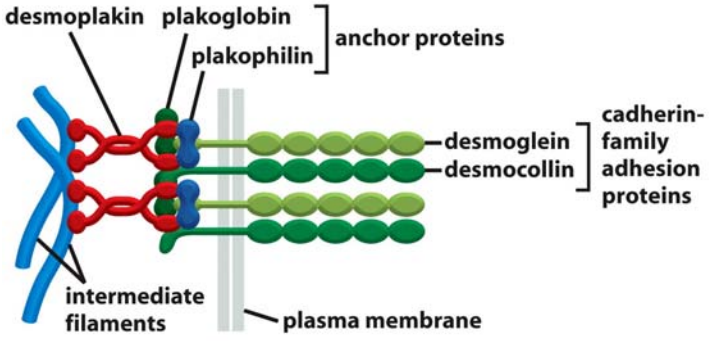


Figure 19-17b Molecular Biology of the Cell 5/e (© Garland Science 2008)

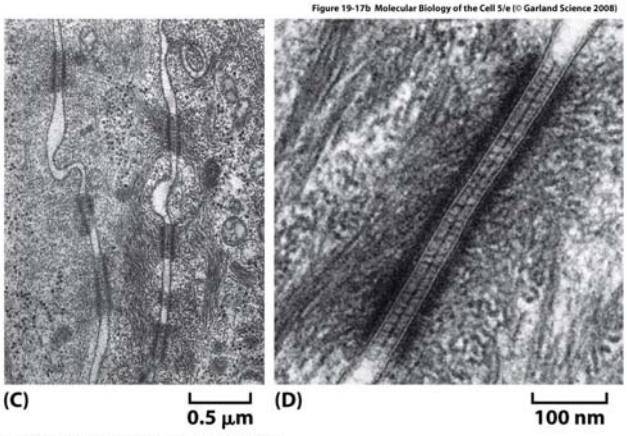
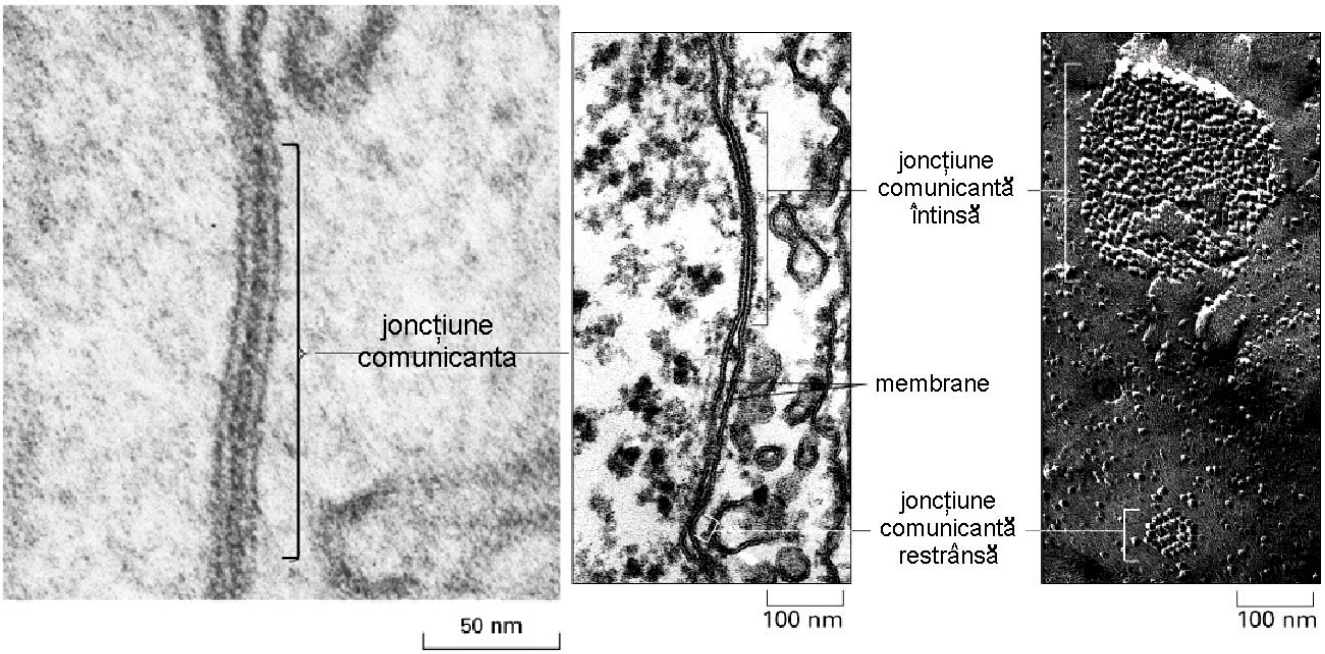


Figure 19-17cd Molecular Biology of the Cell 5/e (© Garland Science 2008)

Role: assures mechanical power for cell-to-cell interactions to maintain tissue integrity and cell shape

Gap junction structure
(*macula communicans*)



Transmembrane proteins involved: connexins (23-62kDa)

Molecular organization of gap junctions

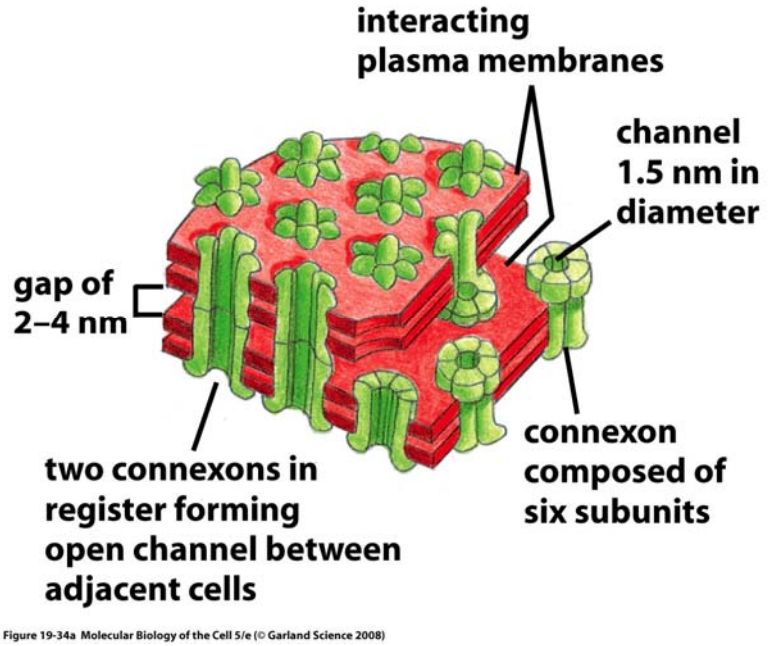
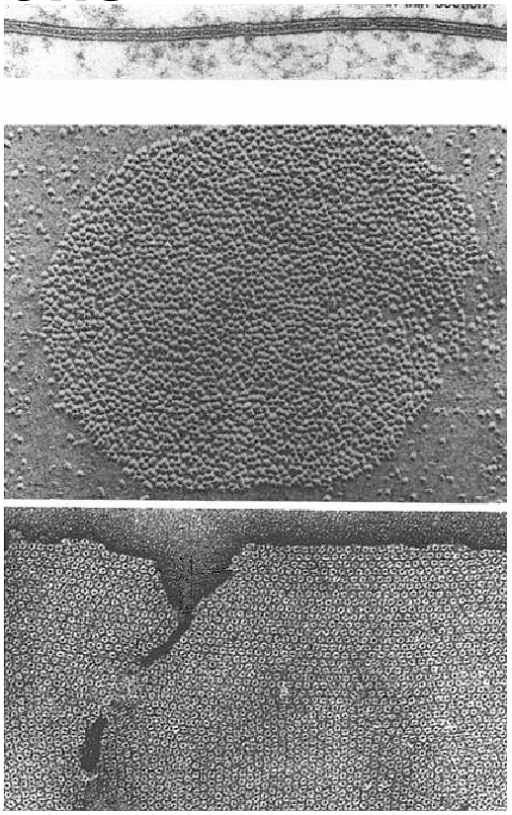


Figure 19-34a Molecular Biology of the Cell 5/e (© Garland Science 2008)

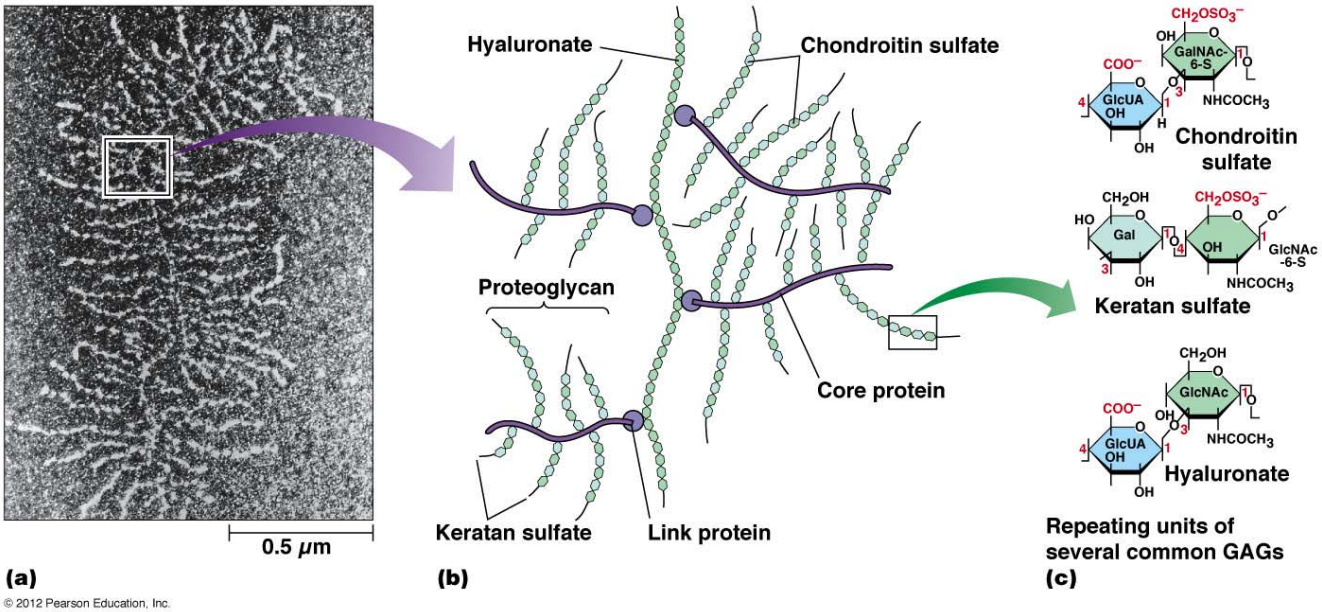


Role: allow direct communication between the cytoplasm of linked cells (passage of molecules and ions; e.g. second messengers)

Extracellular matrix

- Definition;
- Biological significance;
- Components:
  - proteoglycans
  - Structural proteins:
    - collagen;
    - elastin.
  - Specialized proteins (adhesive):
    - fibronectin;
    - laminin.
  - Accessory proteins

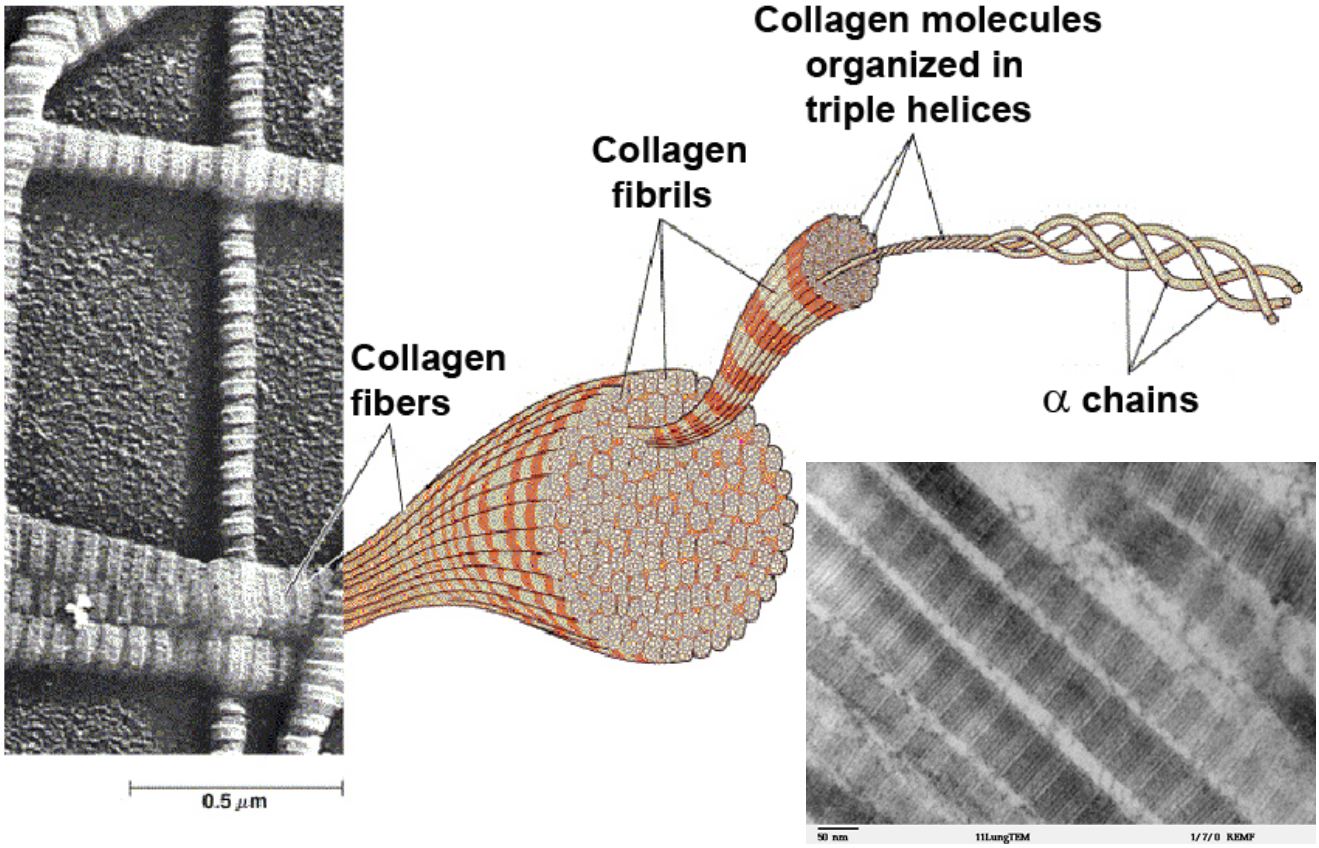
Proteoglycans



http://www.mun.ca/biology/desmid/brian/BIOL2060/BIOL2060-17/17_17.jpg

Roles: - hydration of the extracellular space;
- stocking by absorption a large variety of molecules.

Structural proteins: 1. Collagen



http://de.wikipedia.org/wiki/Kollagen#mediaviewer/File:Fibers_of_Collagen_Type_I_-_TEM_.jpg

Types of collagen

Table 19–7 Some Types of Collagen and Their Properties

	TYPE	POLYMERIZED FORM	TISSUE DISTRIBUTION	MUTANT PHENOTYPE
Fibril-forming (fibrillar)	I	fibril	bone, skin, tendons, ligaments, cornea, internal organs (accounts for 90% of body collagen)	severe bone defects, fractures
	II	fibril	cartilage, invertebral disc, notochord,	cartilage deficiency, dwarfism vitreous humor of the eye
	III	fibril	skin, blood vessels, internal organs	fragile skin, loose joints, blood vessels prone to rupture
	V	fibril (with type I)	as for type I	fragile skin, loose joints, blood vessels prone to rupture
	XI	fibril (with type II)	as for type II	myopia, blindness
Fibril-associated	IX	lateral association	cartilage with type II fibrils	osteoarthritis
Network-forming	IV	sheetlike network	basal lamina	kidney disease (glomerulonephritis), deafness
	VII	anchoring fibrils	beneath stratified squamous epithelia	skin blistering
Transmembrane	XVII	non-fibrillar	hemidesmosomes	skin blistering
Proteoglycan core protein	XVIII	non-fibrillar	basal lamina	myopia, detached retina, hydrocephalus

Note that types I, IV, V, IX, and XI are each composed of two or three types of α chains (distinct, nonoverlapping sets in each case), whereas types II, III, VII, XII, XVII, and XVIII are composed of only one type of α chain each. Only 10 types of collagen are shown, but about 27 types of collagen and 42 types of α chains have been identified in humans.

Table 19-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Fibril associated collagen

Type IX (associated to collagen II) and type XII (associated to collagen I and III)
Features:
- flexible, non-helical parts, alternant with helical parts
- pro-peptides not removed
- unable to organize fibrils

Role: organize collagen fibrils in extracellular matrix

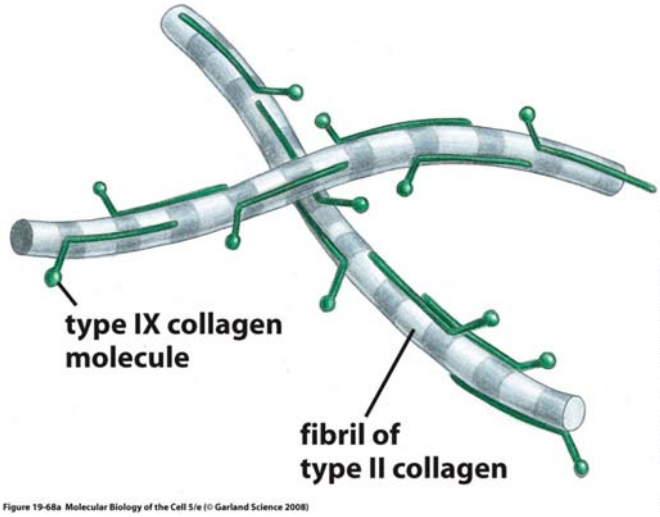


Figure 19-68a Molecular Biology of the Cell 5/e (© Garland Science 2008)

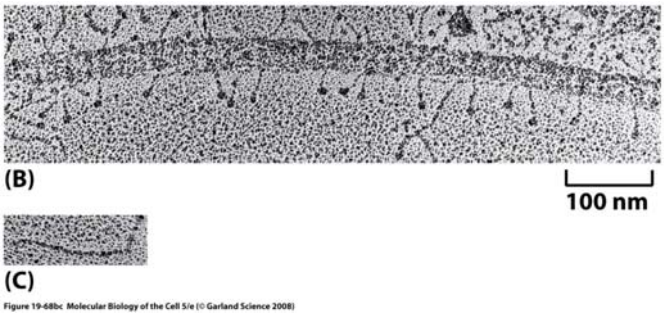


Figure 19-68bc Molecular Biology of the Cell 5/e (© Garland Science 2008)

Structural proteins: 2. Elastin

Highly hydrophobic protein organized as monomer network
Biosynthesized and secreted as tropoelastin (Mr ~70kD)
Alternant structural domains:
- hydrophilic (rich in Lys and Ala); assure networking by cross-linking
- hydrophobic (rich in Val, Pro, Ala and Gly, with VPGVG or VGGVG as repetitive units); responsible for the elasticity

Fibers' 3D organization:
- random twisting

Molecular organization:
- an elastin core covered by fibrillin microfibrils

Fibrillin: glycoprotein ~350kD; organizes microfibrils under transglutaminase activity; microfibrils associate head-to-tail forming a shield around the elastin netwok

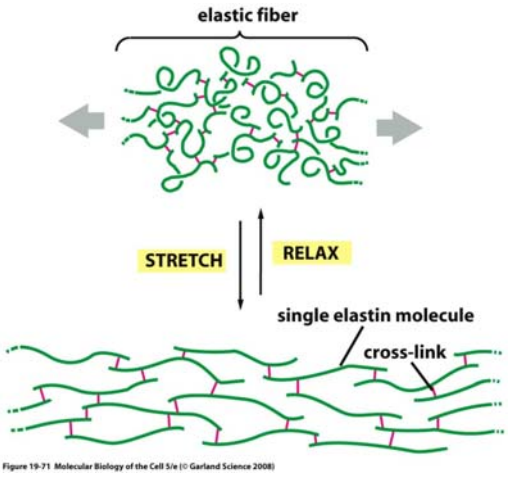
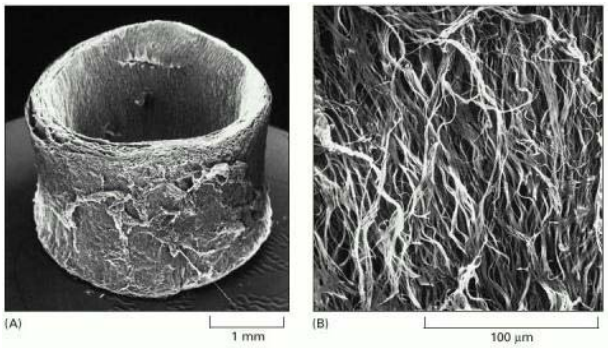


Figure 19-71 Molecular Biology of the Cell 5/e (© Garland Science 2008)



Elastin elongation

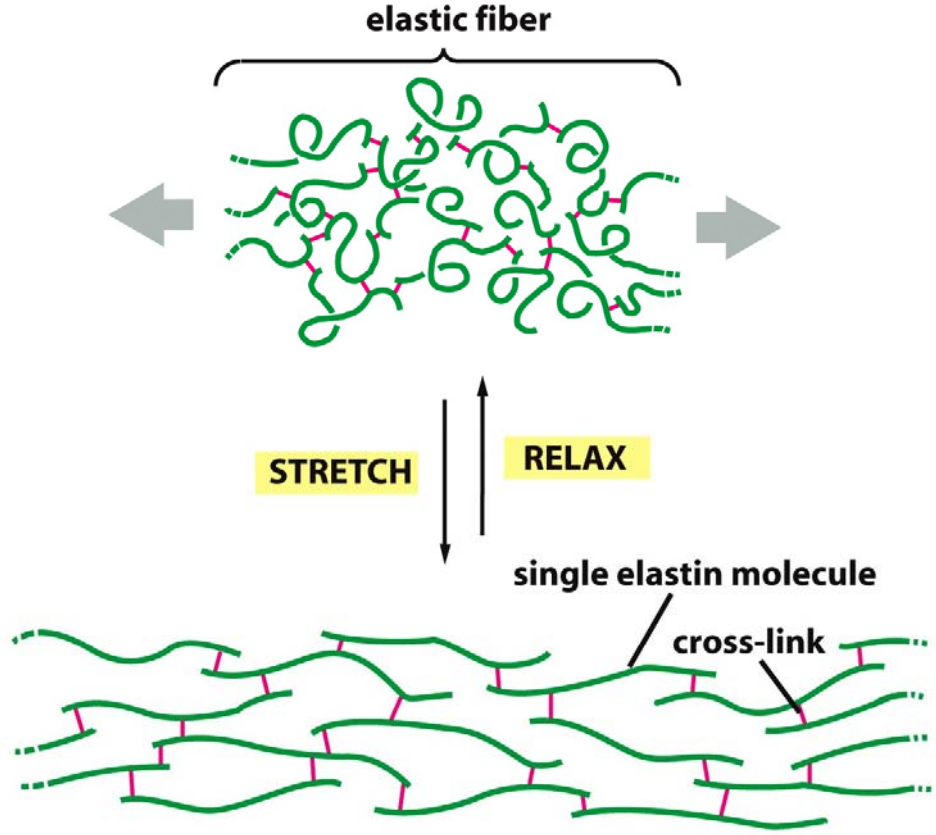


Figure 19-71 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Basement membrane

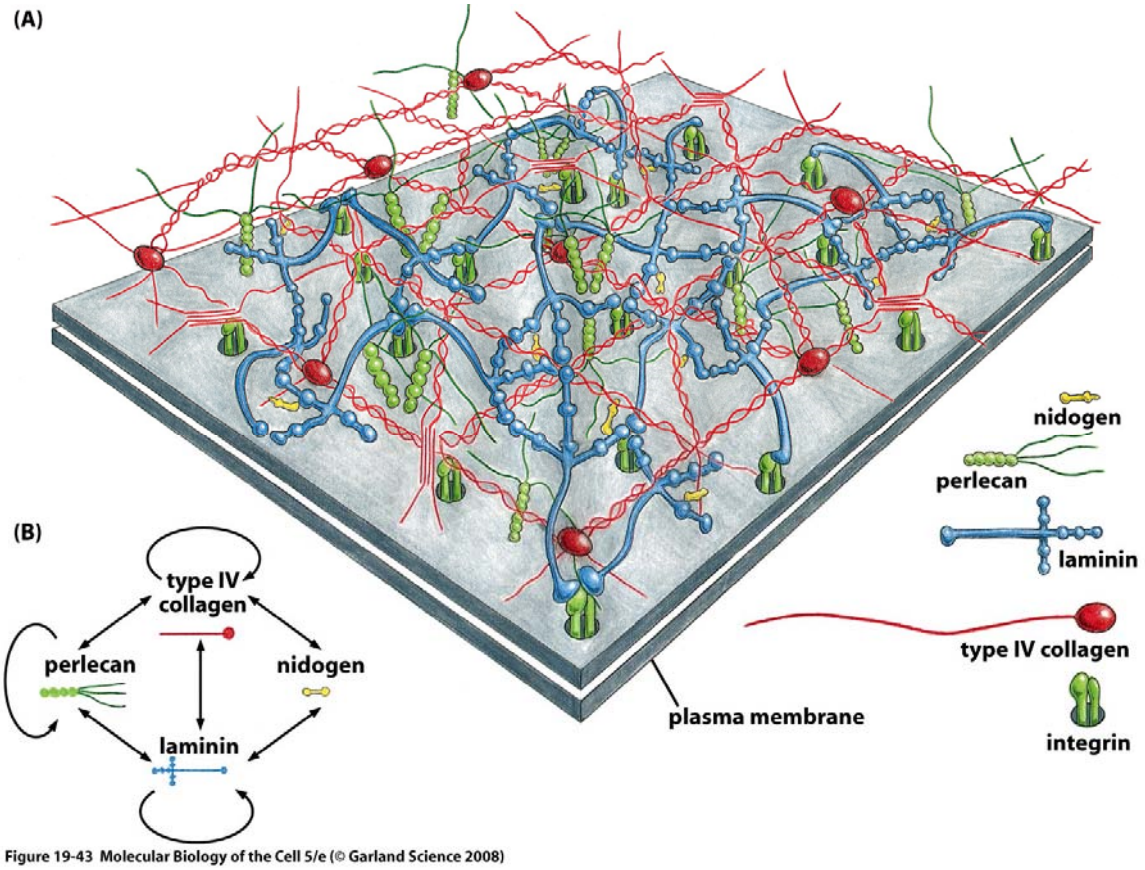
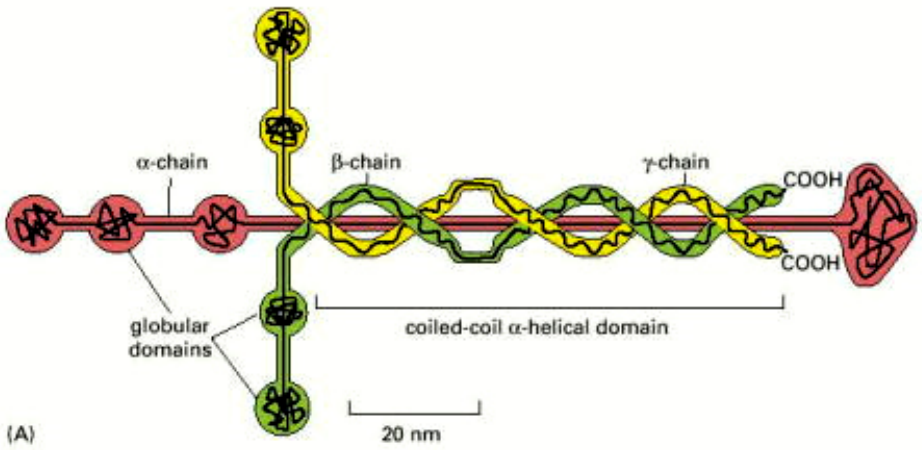
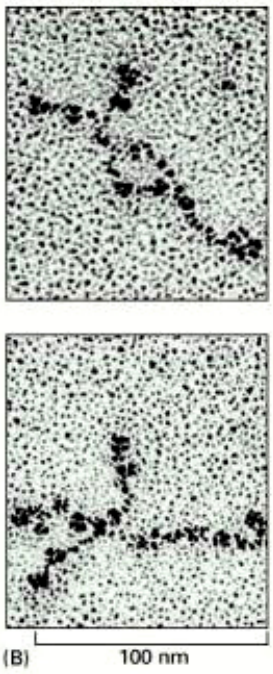


Figure 19-43 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Adhesive proteins: 1. Laminin

A protein complex with three subunits (α, β, γ or α, β_1, β_2);
Mr ~850kD;
Identified subunits: 5 α types, 4 β types and 3 γ types, forming 18 laminin isoforms;
3D organization of the complex: cross shape (length ~70nm).





Laminin interactivity

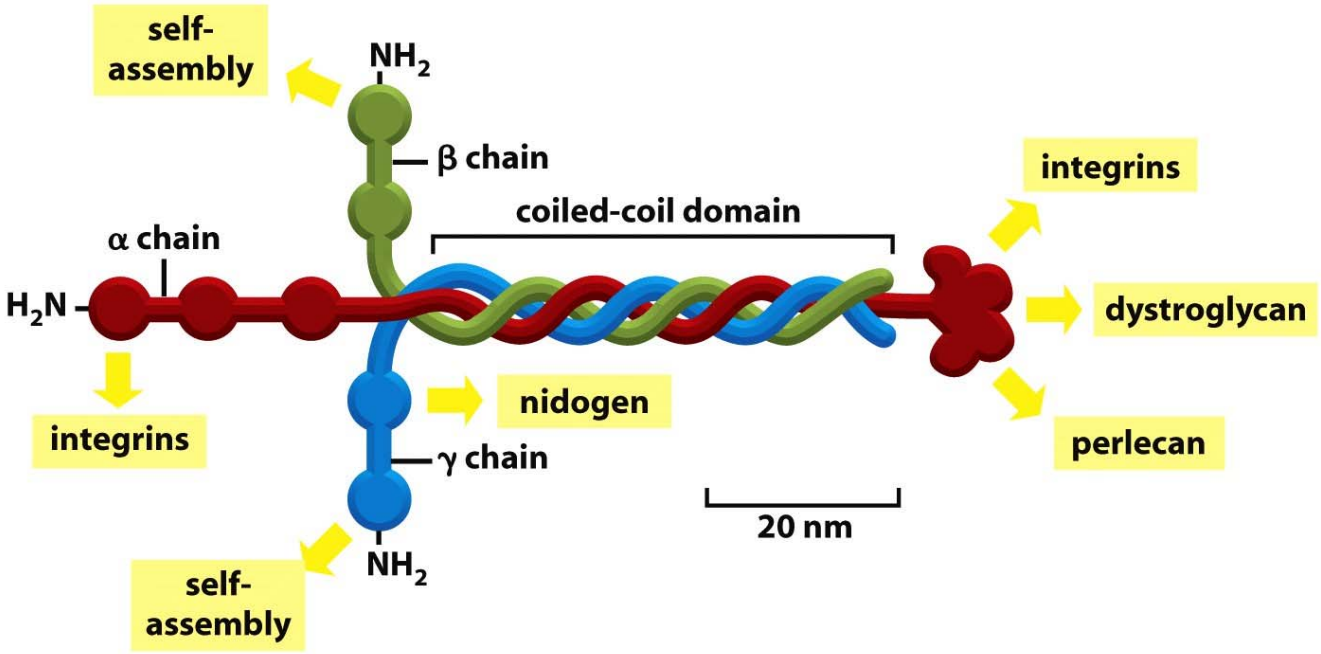
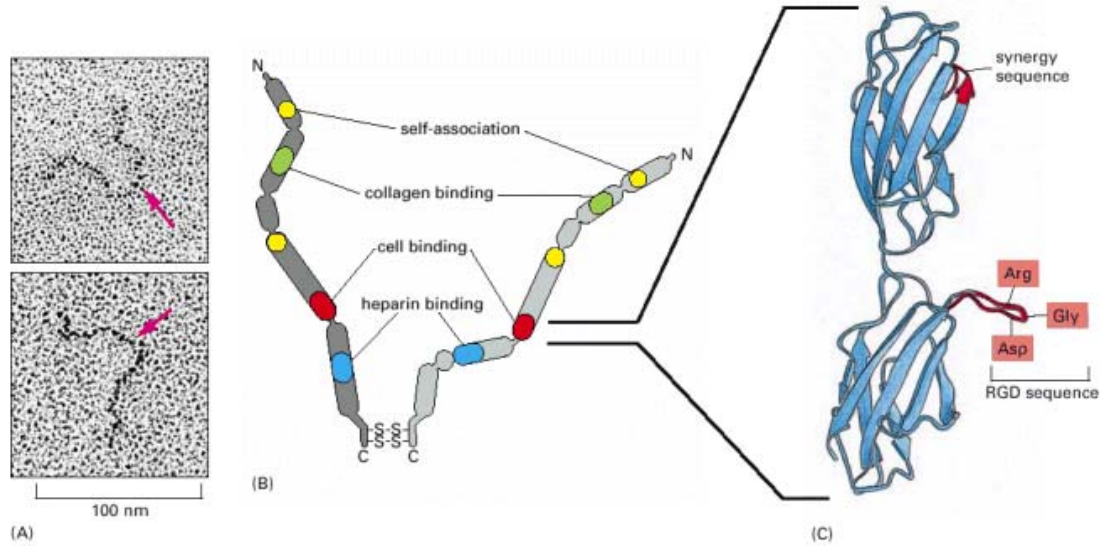


Figure 19-42a Molecular Biology of the Cell 5/e (© Garland Science 2008)

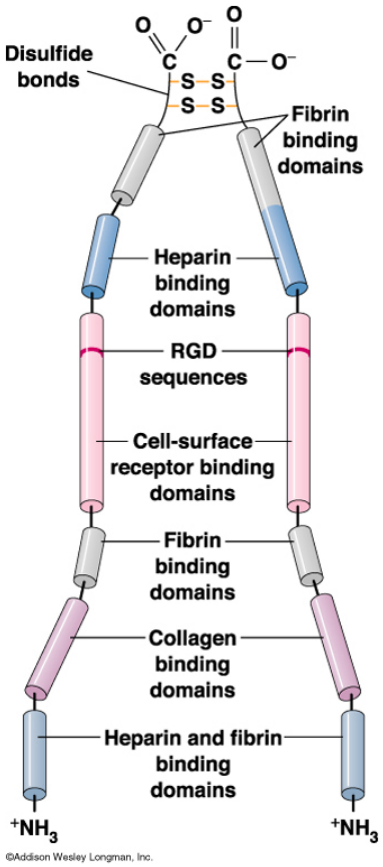
Adhesive proteins: 2. Fibronectin

Dimeric protein, 2 similar subunits (but not identical);
Dimerization by two -S-S- bridges, near C-terminal ends of the subunits;
Every subunit ~2500 aa, ~230kD;
Multiple functional domains;
Repetitive structures: type III repetitive module of fibronectin (~90 aa).



Roles: essential in embryogenesis; cell migration (wound healing)

Fibronectin interactivity



Extracellular matrix dynamics

- Matrix proteins are long live components (half time period: 10 years for collagen, 70 years for elastin);
- However, the extracellular matrix is not immovable;
- Multiple physiological and pathological events need cell migration, requesting matrix degradation and regeneration;
- Two classes of matrix protein proteases exist:
  - Matrix metalloproteases, Ca^{2+} or Zn^{2+}-dependent (MMP)
  - Serine proteases (e.g. urokinase-type plasminogen activator)
- Some proteases are transmembrane proteins, other of them are soluble;
- Proteases activity control and modulation by activation/ inhibition:
  - Tissue inhibitors of metalloproteases (TIMP) – for MMP
  - Serpins – for serine proteases

Matrix related pathologies

- Scurvy: deficient extracellular organization of collagen, due to lack in proline and lysine (modifications dependent by vitamin C);

- Genetic defects:
  - mutations in collagen genes:
    - Osteogenesis imperfecta (mutations in collagen type I gene)
    - Chondrodysplasias (mutations in collagen type II gene)
    - Ehlers-Danlos syndrome (mutations in collagen type III gene)
    - Epidermolysis bullosa (mutations in collagen type VII gene)
  - Mutations in fibrillin gene
    - Marfan syndrome
    - Congenital scleroderma (stiff skin syndrome)

INTEGRINS

Cellular components (transmembrane proteins) acting as partners for matrix proteins

Structural and functional considerations

INTEGRINS

Molecular organization and functions

Membrane glycoproteins, dimers with one α and one β subunit;

Each subunit: transmembrane protein, single-pass, type I;

Ectodomains abundant (structured by several domains), responsible for matrix protein binding;

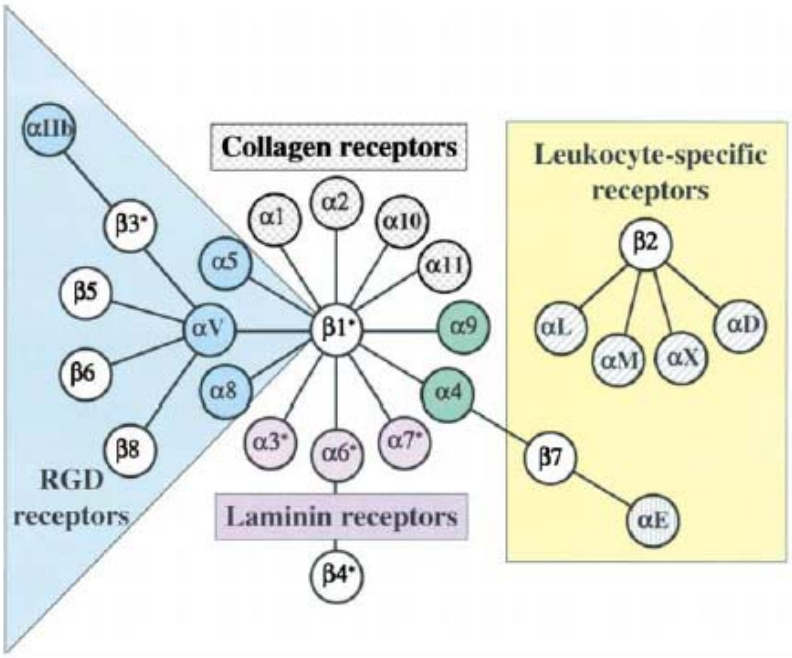
Endodomains short, responsible for cytoskeletal component binding, and interactions with signaling pathways effectors;

18 α subunits, 8 β subunits, but 24 integrins (dimers αβ);

Correspondence integrin – matrix protein: degenerated, but not redundant

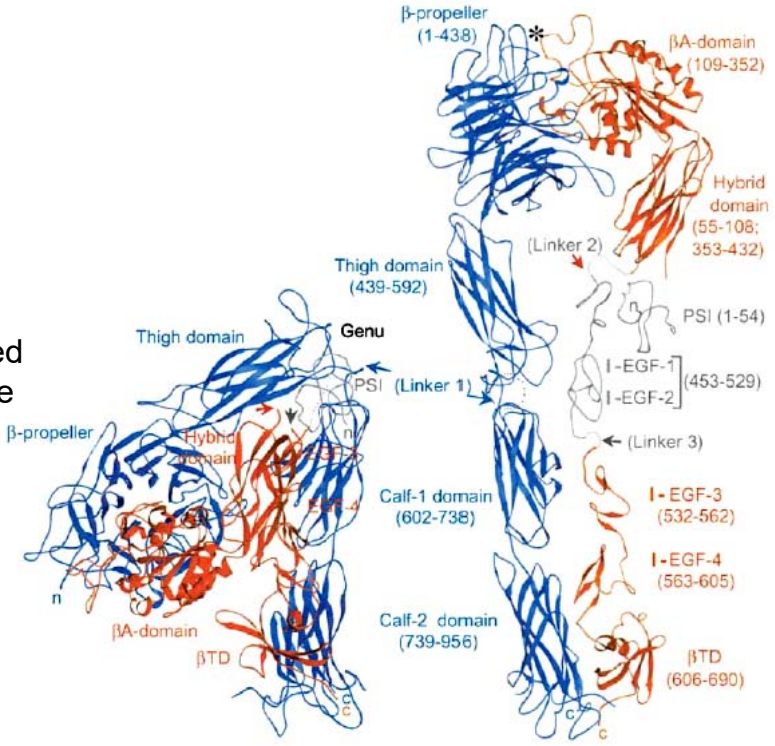
Integrins' diversity

αβ heterodimers; both subunits – singlepass transmembrane proteins, type I
18 α type subunits, 8 β type subunits, 24 typs of integrins



Quaternary sequence of integrin ectodomain

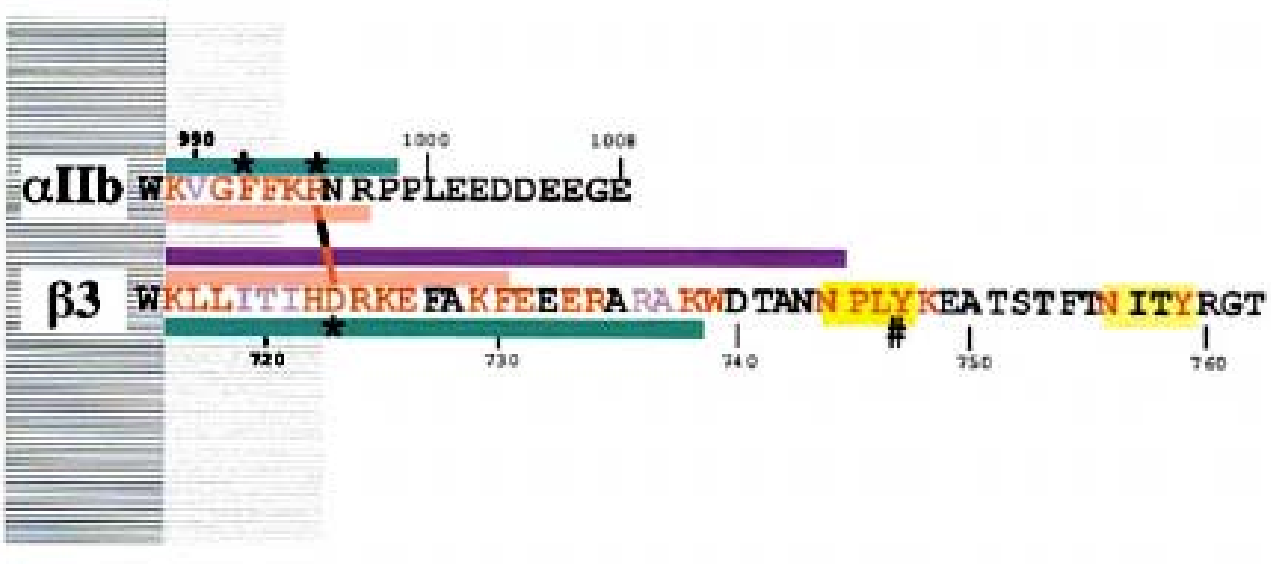
Inactive – folded (bended) shape



Active – erected shape, able to interact with matrix proteins

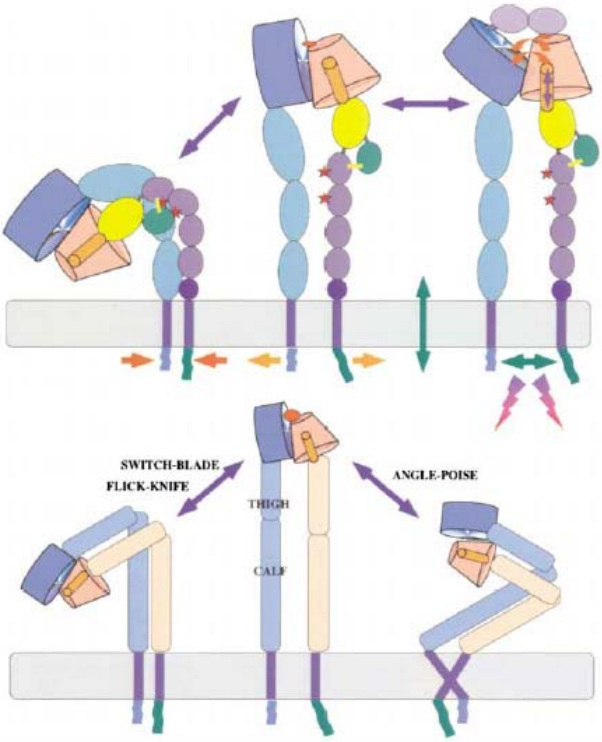
Richard O. Hynes, **Integrins: Bidirectional, Allosteric Signaling Machines.** ***Cell***, **110**, 673–687 (2002)

Integrin endodomain structure

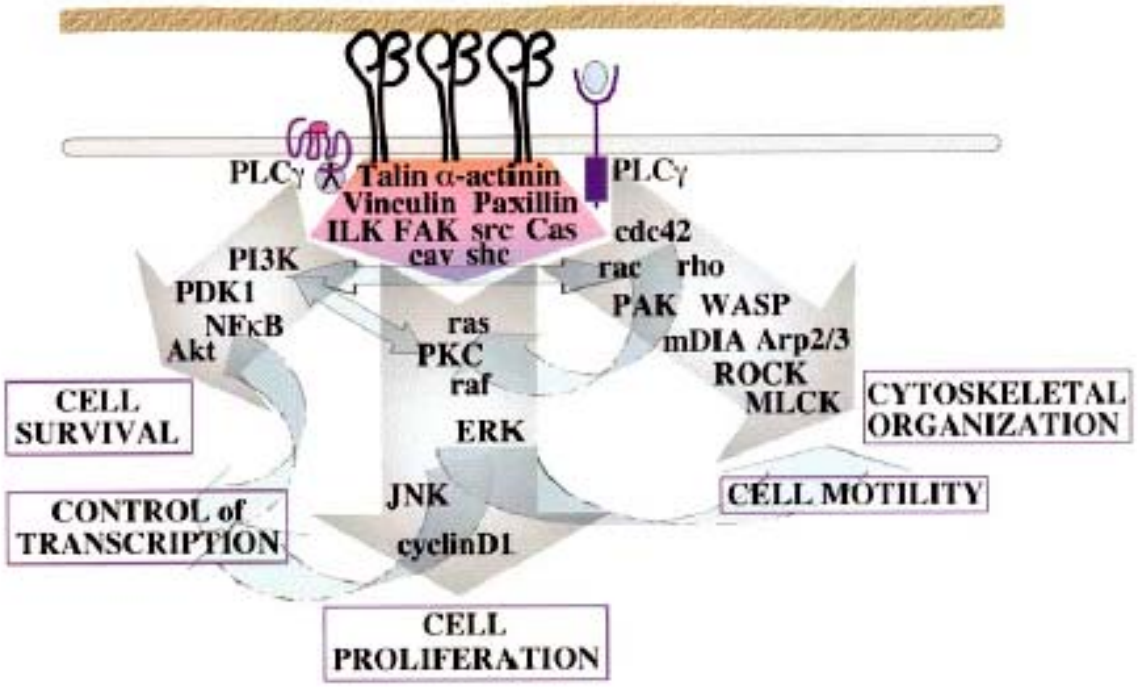


Control heterodimer activation, interact with cytoskeletal components in a dynamic manner

Conformational changes elicited by integrin activation



Integrin Roles



Cell-to-matrix junctions

- Hemidesmosomes (integrins as transmembrane linking elements and intermediate filaments)
- Focal contacts/adhesions (integrins as transmembrane linking elements and actin filaments)

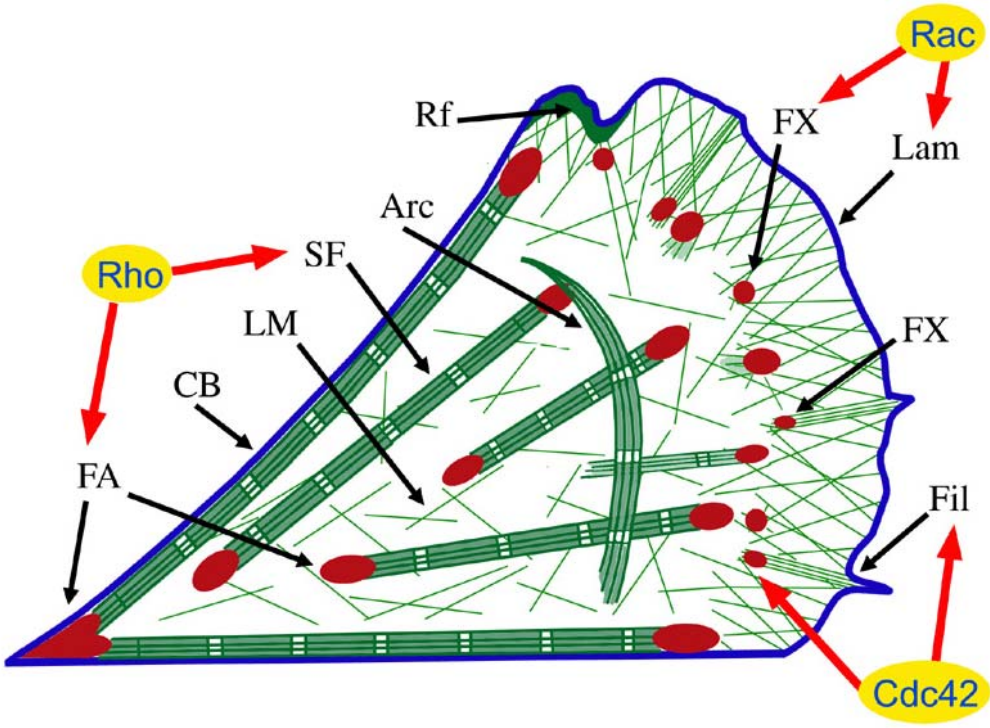
Cell motility

- A complex cellular event depending on integrin's, membrane receptor's and cytoskeleton's function

- Stages:
  - Cell stimulation
  - Cell morphology polarization
  - Membrane components polarization
  - Cytoskeleton reorganization (mainly actin cytoskeleton)
  - Filopodia and lamellipodia extension toward migration front
  - Forming and stabilizing of new focal adhesions
  - Stress fiber formation and traction force development
  - Cell tail retraction and cell location in the new position

  N.B. *Small GTP-ases are involved (Rho, Rac, Cdc42).*

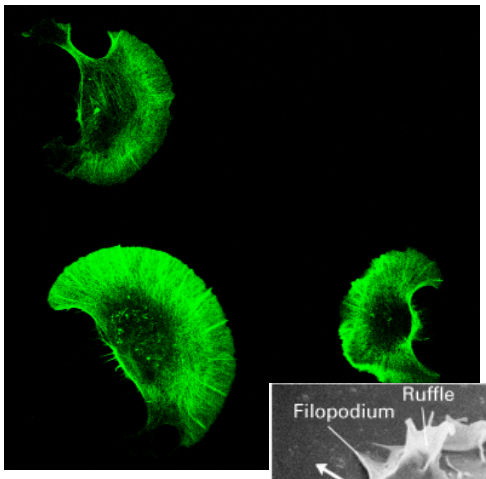
Dynamical structures in migrating cells

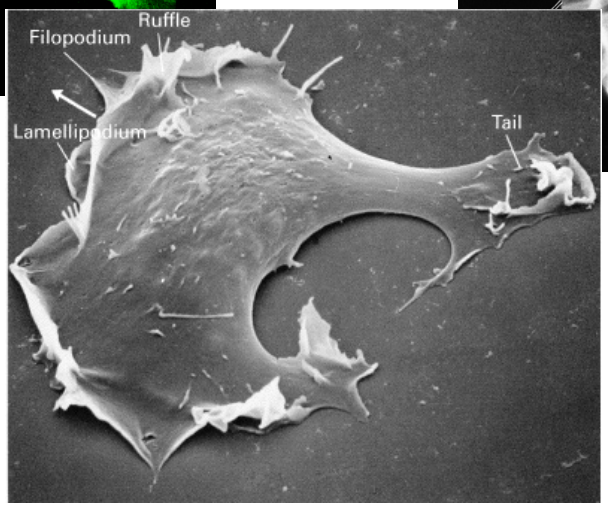


http://www.mit.edu/~kardar/research/seminars/motility/Videotour/video_tour_9.html

Morphological changes in migrating cells

http://bioweb.wku.edu/courses/biol22000/27Actin/default.html





Summary

- Cells are continuously related to environment (other cells, extracellular matrix) by both information, and mechanically – biomechanical interaction
- Cell interaction with neighboring cells assured by cell junctions
- Cell-to-matrix interactions are assured by integrins and specific cell-to-substratum junctions
- The two cell-to-environment interactions are cellular means to collect information
- Behavioral cell integration in the environment, answering to the specific “state of affairs” needs an effective cross-talk between integrin/cell adhesion molecule (cadherin) signaling and cell signaling by other receptors (receptors for cytokines, chemokines, growth factors)