Intercellular contacts

Andrei Leitão

Cell junctions & cytoskeleton

Due to its close association with the cytoplasmic surface of the plasma membrane, the membrane - skeleton meshwork directly influences the functions of the plasma membrane. As a consequence of the membrane – skeleton meshwork, the plasma membrane is effectively partitioned into mesoscale domains, or compartments, with sizes varying between 30 and 250 nm.

In the plasma membrane, there are three types of major mesoscale domains (*meso* domains):

(1) membrane compartments delineated by the actin-based membrane skeleton;
(2) raft domains, where specific proteins, glycosphingolipids, and cholesterol are concentrated;
(3) the protein oligomer domains.

Cellular Domains, First Edition. Edited by Ivan R. Nabi.

Cell junctions

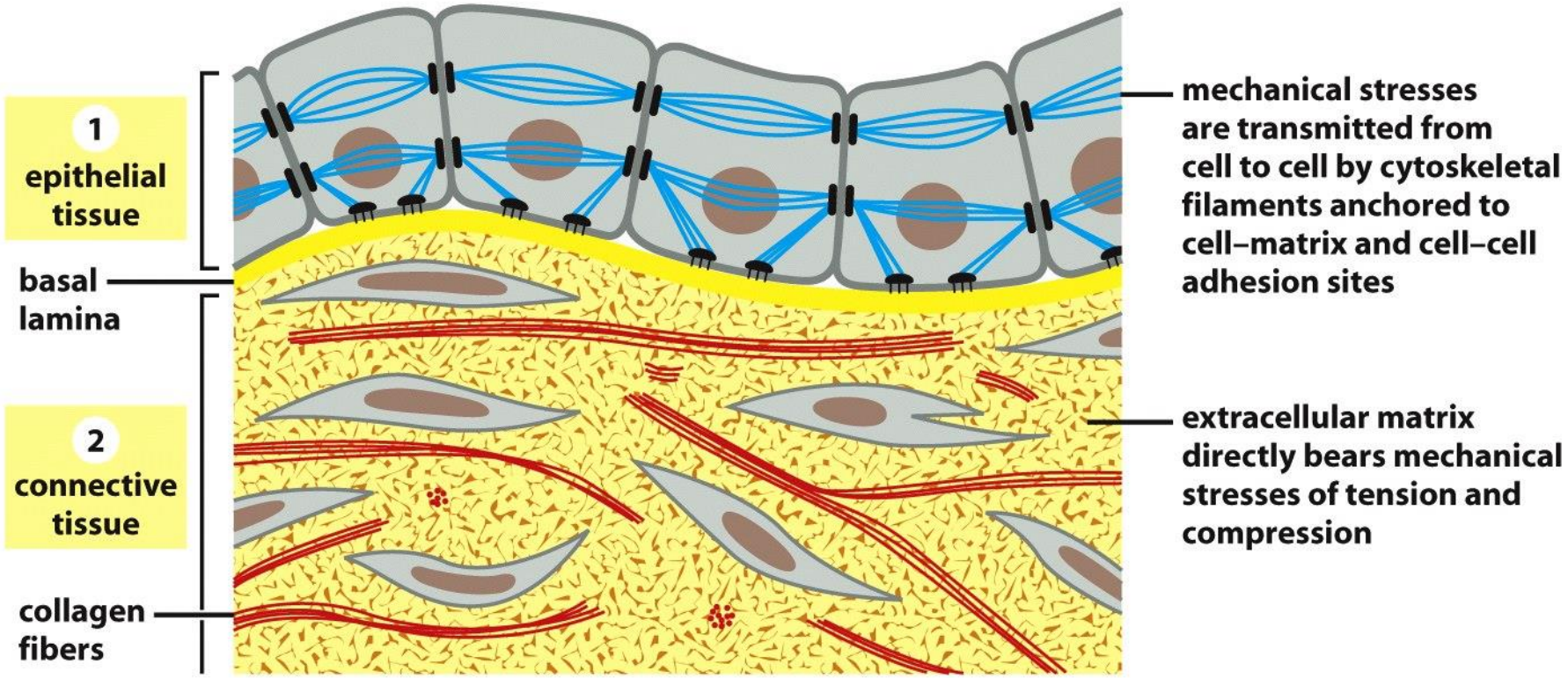
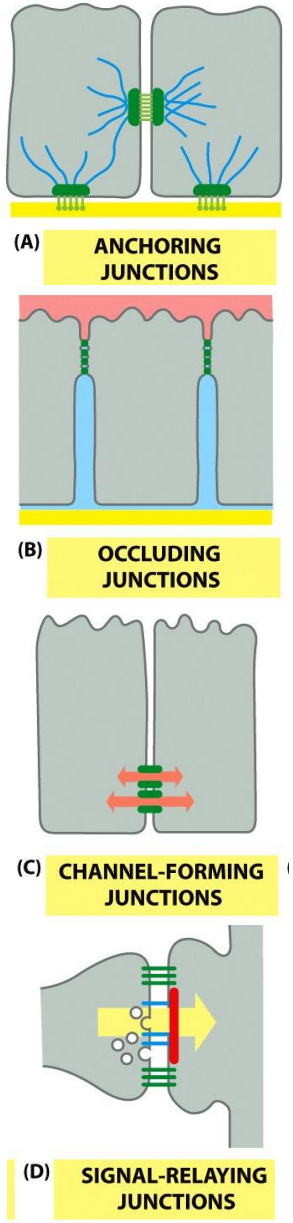


Figure 19-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Classification of cell junctions

Table 19–1 A Functional Classification of Cell Junctions

ANCHORING JUNCTIONS	**Usually cadherin and integrin**
Actin filament attachment sites	
1. cell–cell junctions (adherens junctions)	
2. cell–matrix junctions (actin-linked cell–matrix adhesions)	
Intermediate filament attachment sites	
1. cell–cell junctions (desmosomes)	
2. cell–matrix junctions (hemidesmosomes)	
OCCLUDING JUNCTIONS	**Involves claudin**
1. tight junctions (in vertebrates)	
2. septate junctions (in invertebrates)	
CHANNEL-FORMING JUNCTIONS	**Composed by connexin and innexin**
1. gap junctions (in animals)	
2. plasmodesmata (in plants)	
SIGNAL-RELAYING JUNCTIONS	
1. chemical synapses (in the nervous system)	
2. immunological synapses (in the immune system)	
3. transmembrane ligand–receptor cell–cell signaling contacts (Delta-Notch, ephrin-Eph, etc.). Anchoring, occluding, and channel-forming junctions can all have signaling functions in addition to their structural roles	



Classification of anchoring junctions

Table 19–2 Anchoring Junctions

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

Table 19-2 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Classification of cadherins

Cadherins are present in animals.

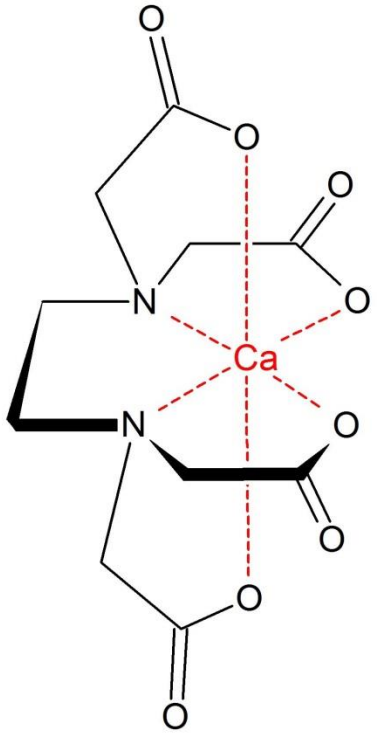
They depend on Ca^{2+}.

EDTA forms a complex with calcium ions.

Trypsin cleaves the extracellular part of this protein.

There are more than 180 cadherins described in humans.

Important cell-cell anchoring point.



Cadherin types

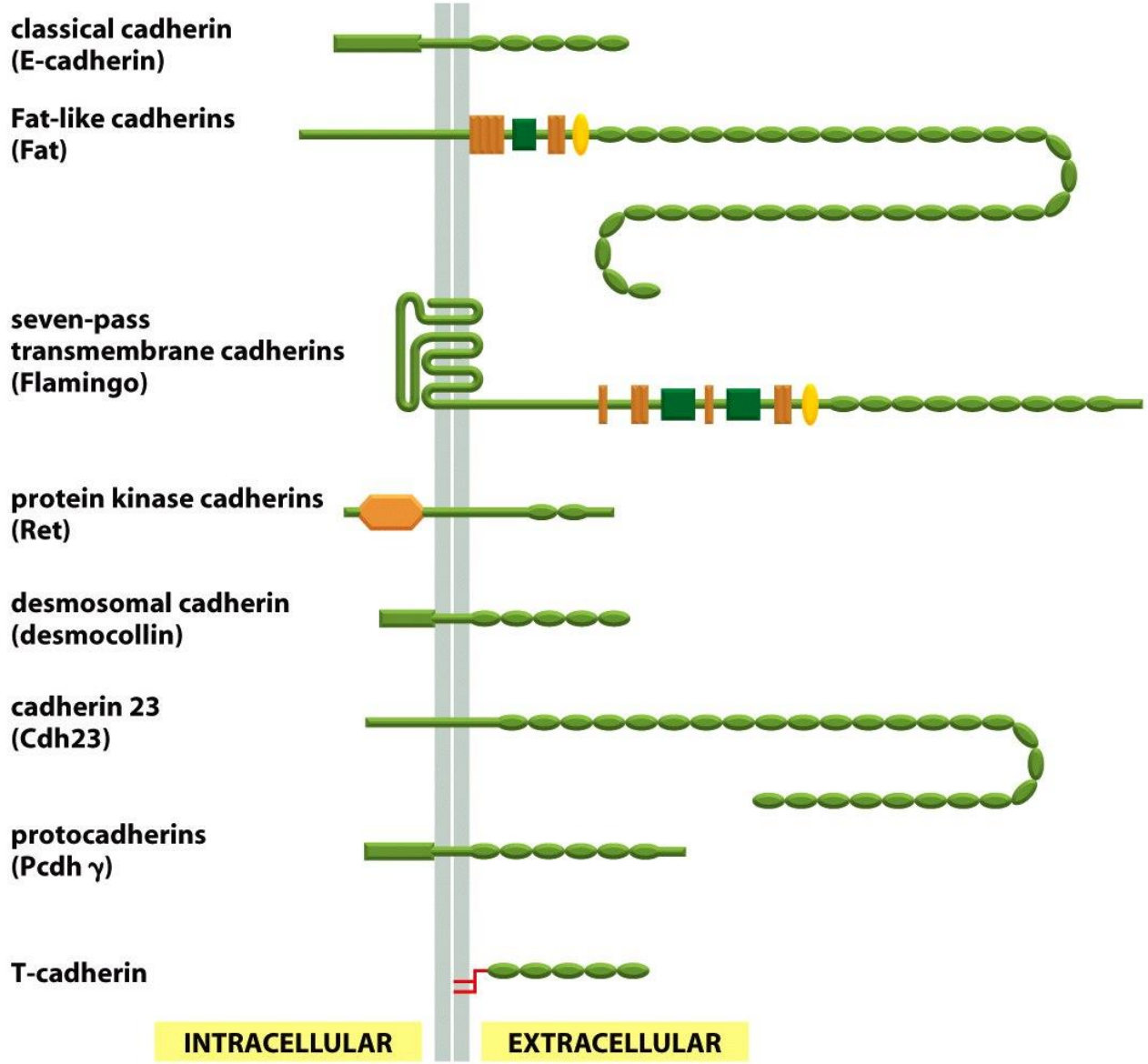


Figure 19-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Classification of cadherins

Table 19–3 Some Members of the Cadherin Superfamily

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

Cadherin-cadherin interactions

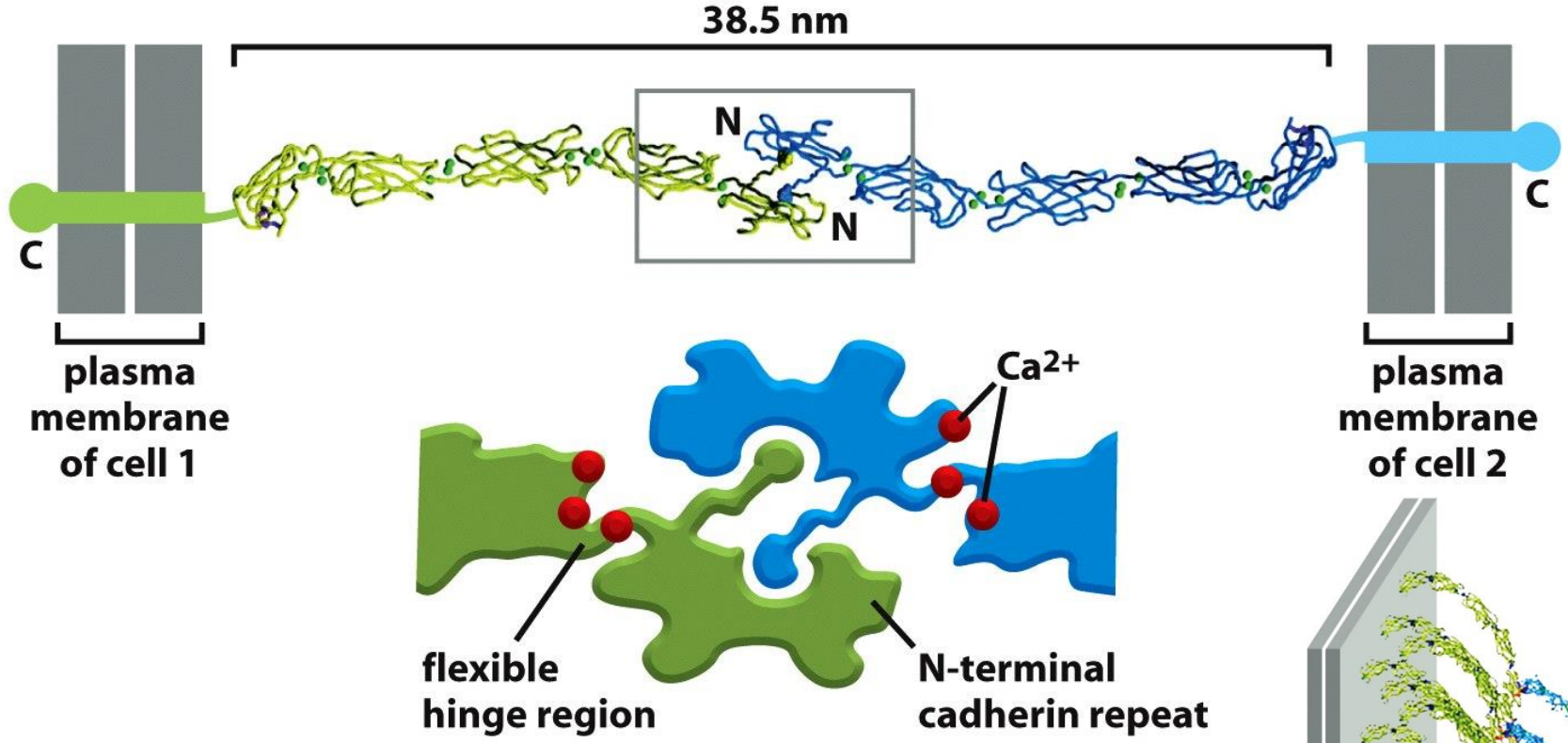
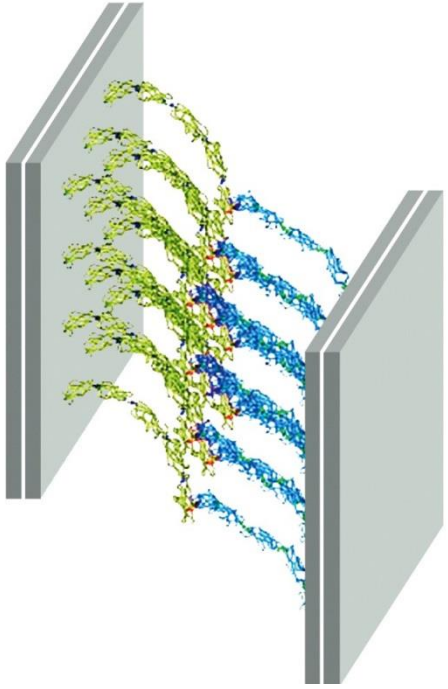
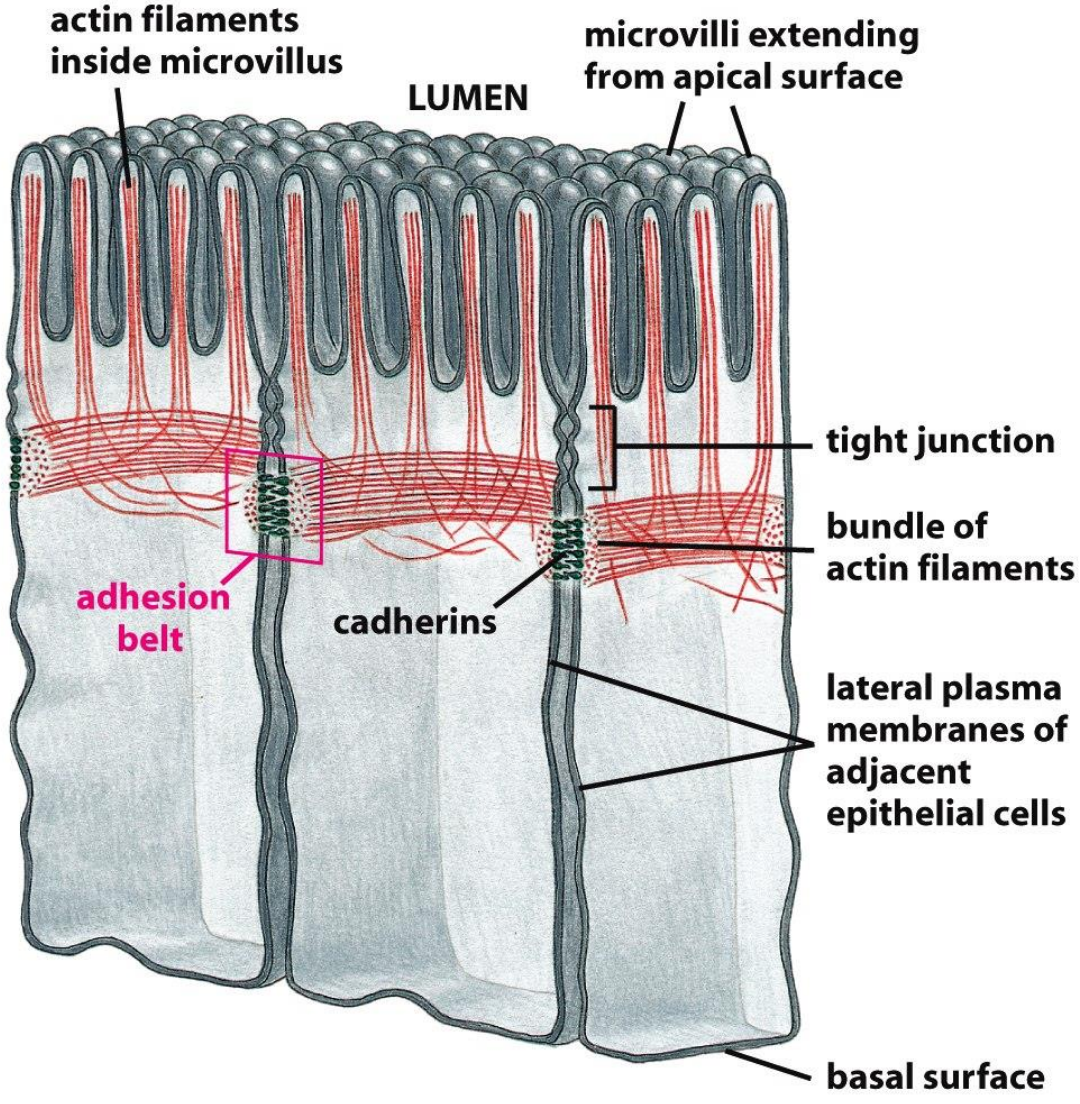


Figure 19-9a Molecular Biology of the Cell 5/e (© Garland Science 2008)

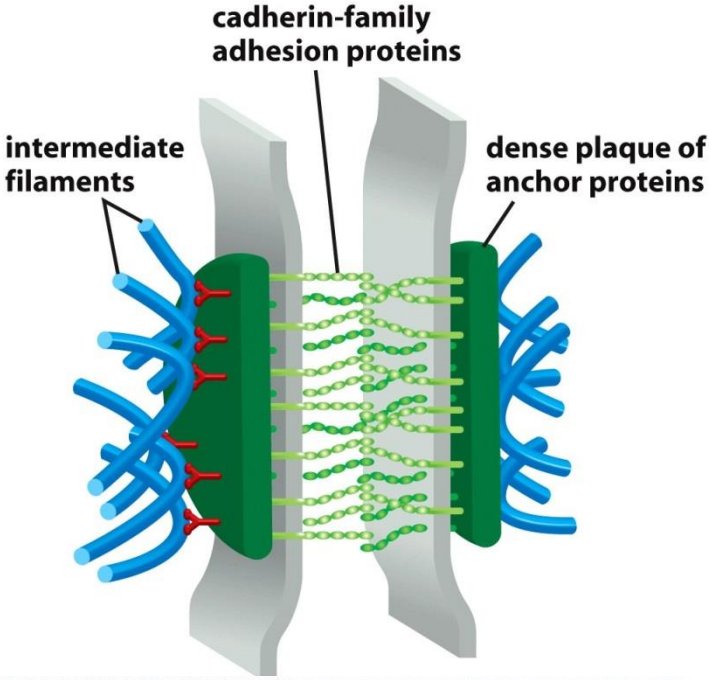


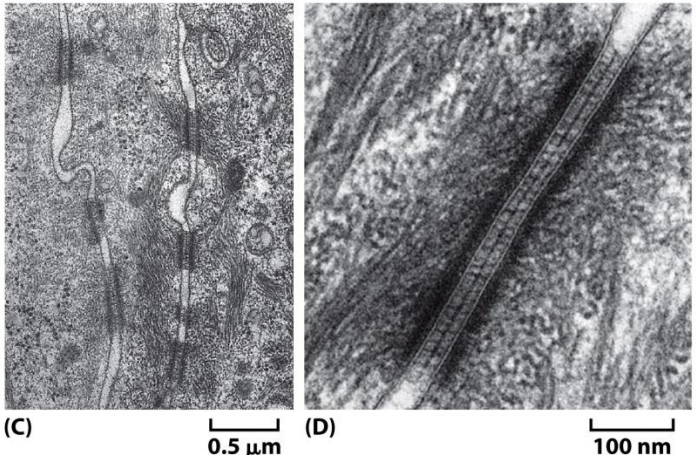
Cadherin for cell junction

Adherens junctions



Desmosomes





Sellectins

They interact with carbohydrates from the other cell membrane and are also calcium dependent.

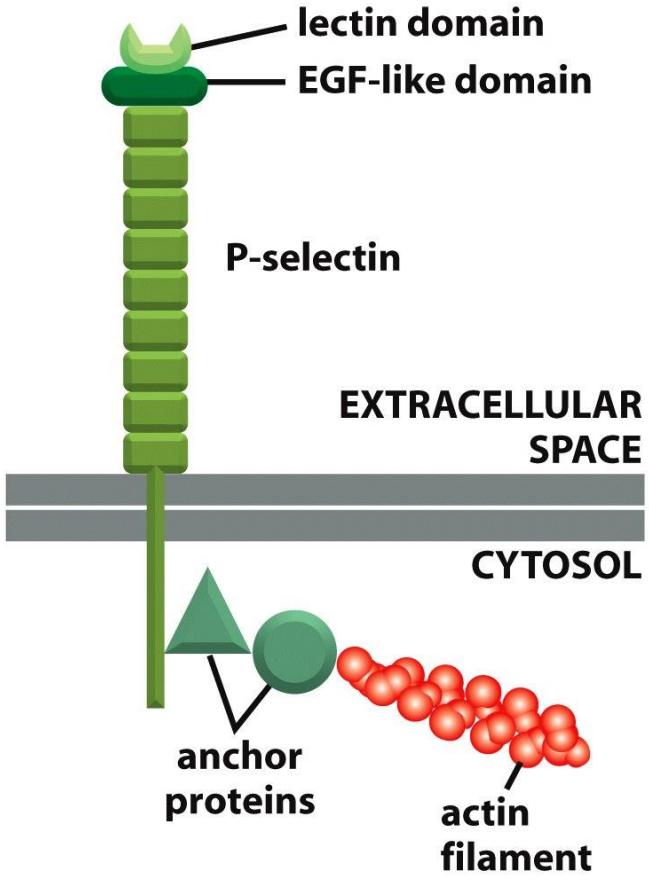


Figure 19-19a Molecular Biology of the Cell 5/e (© Garland Science 2008)

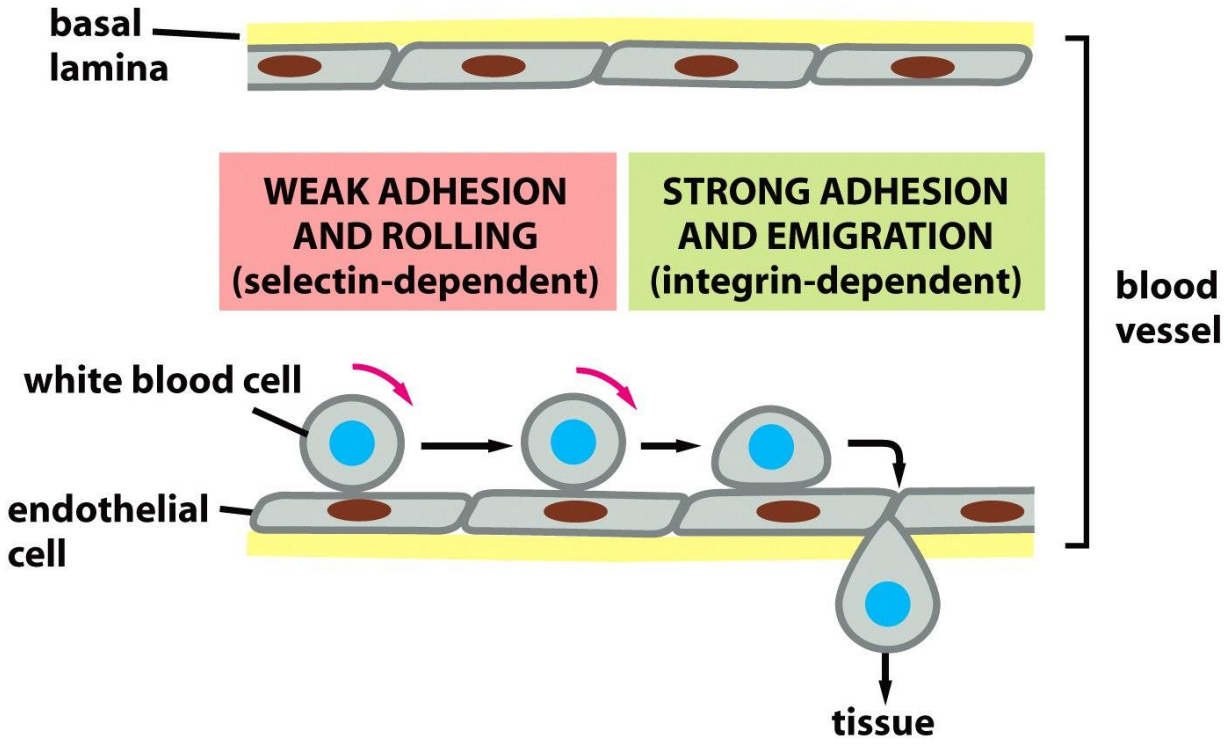


Figure 19-19b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Immunoglobulins for cell adhesion

These Ig-like do not present immune defense activity.

They are calcium independent proteins.

Intercellular cell adhesion molecules (ICAM), vascular (VCAM) and neural (NCAM) compose the set of Ig.

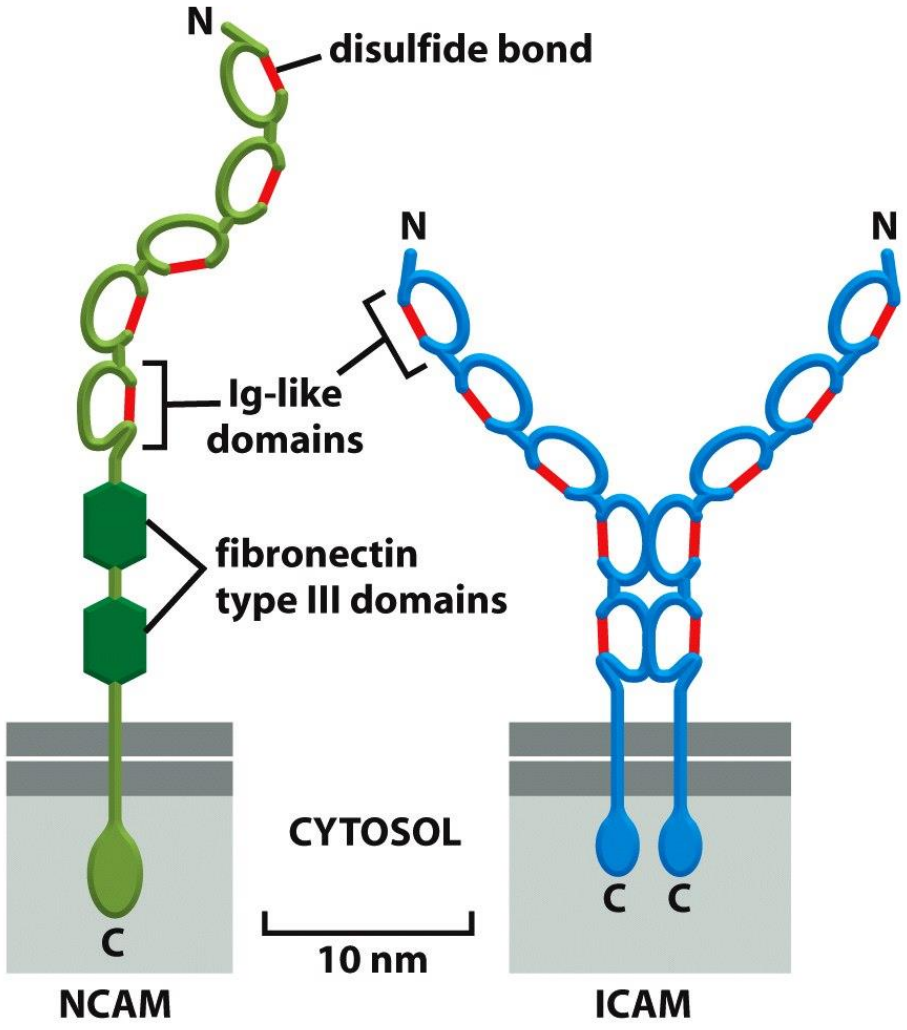


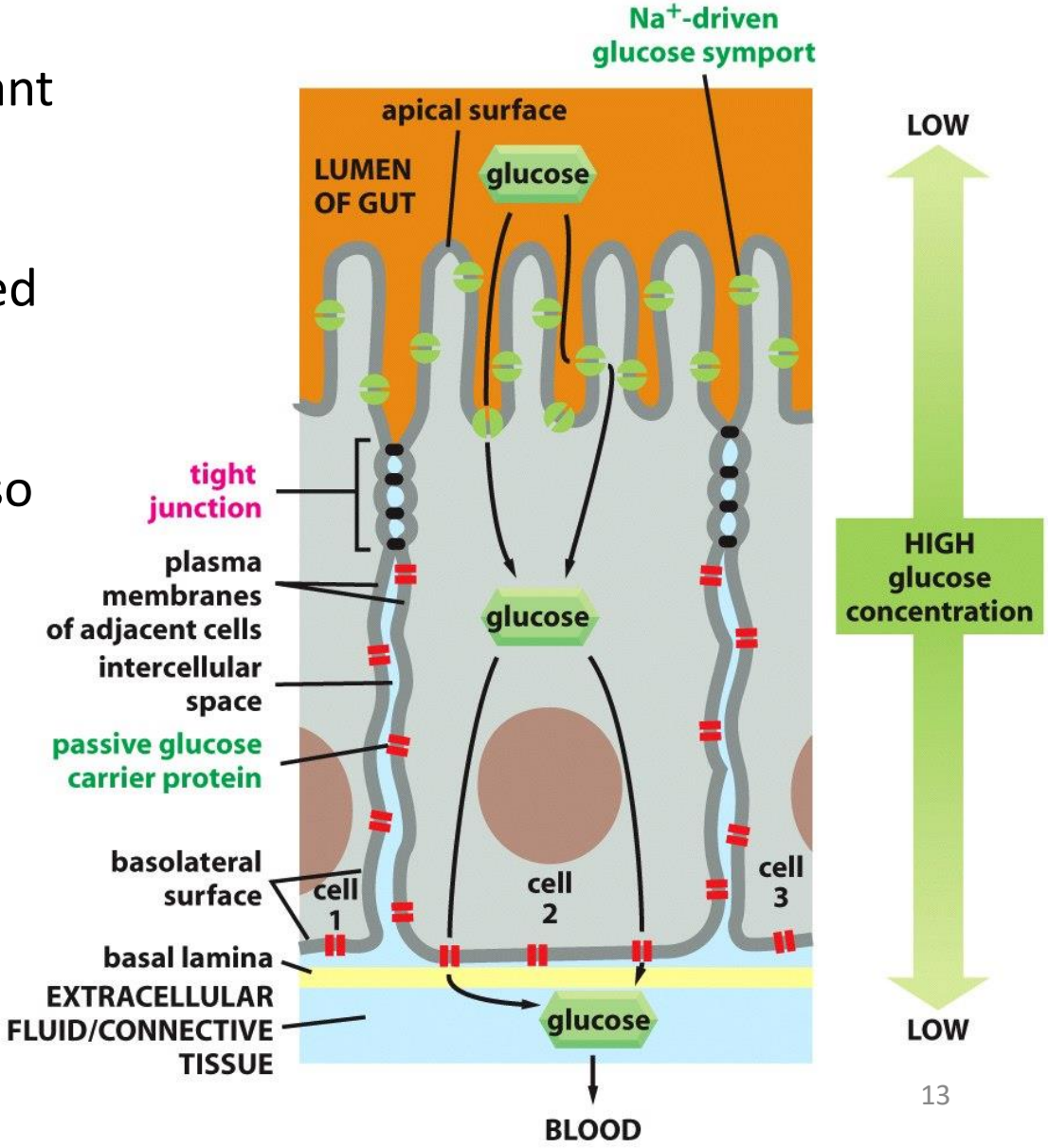
Figure 19-20 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Tight junctions

Claudins are the most important proteins for this junctions.

There are 24 claudins described in the human.

Occludin and Tricellulin are also found.



Tight junctions

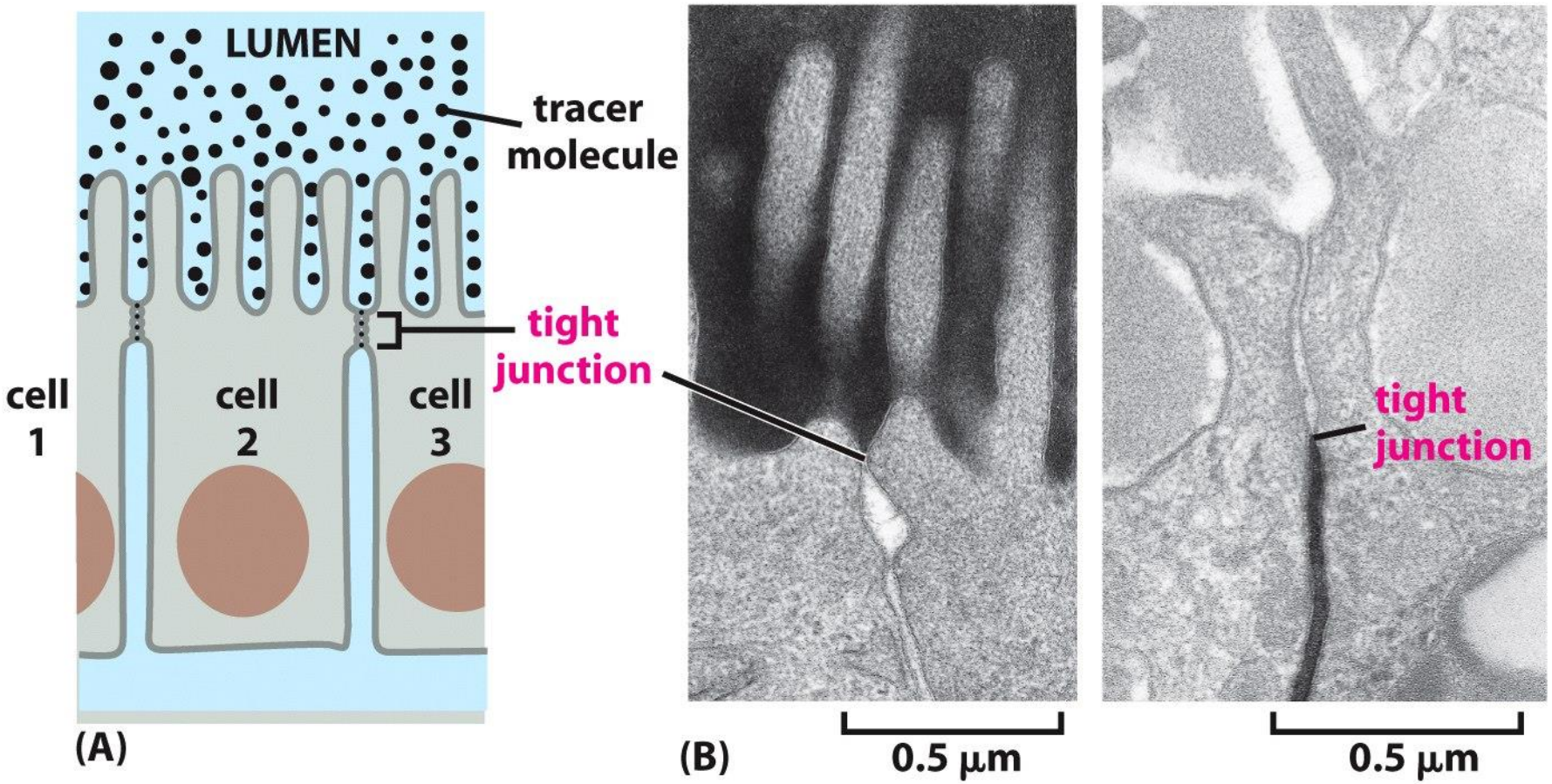


Figure 19-24 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cell junction and polarization

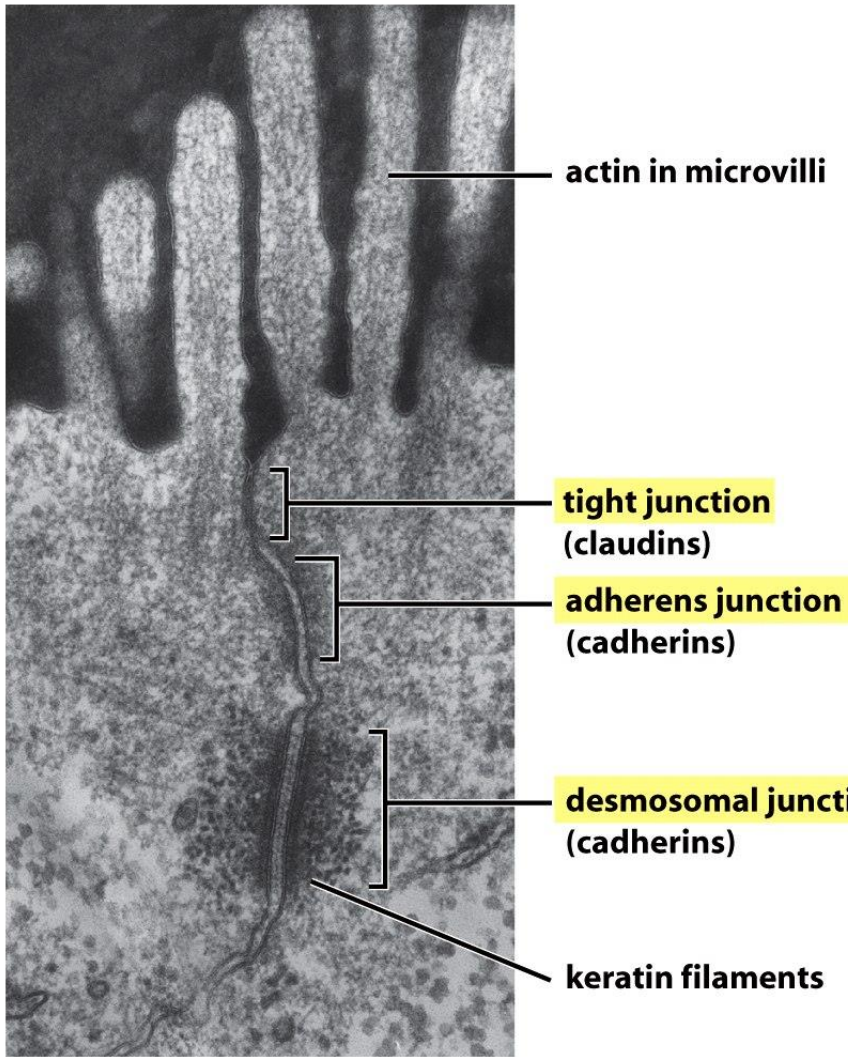


Figure 19-27 Molecular Biology of the Cell 5/e (© Garland Science 2008)

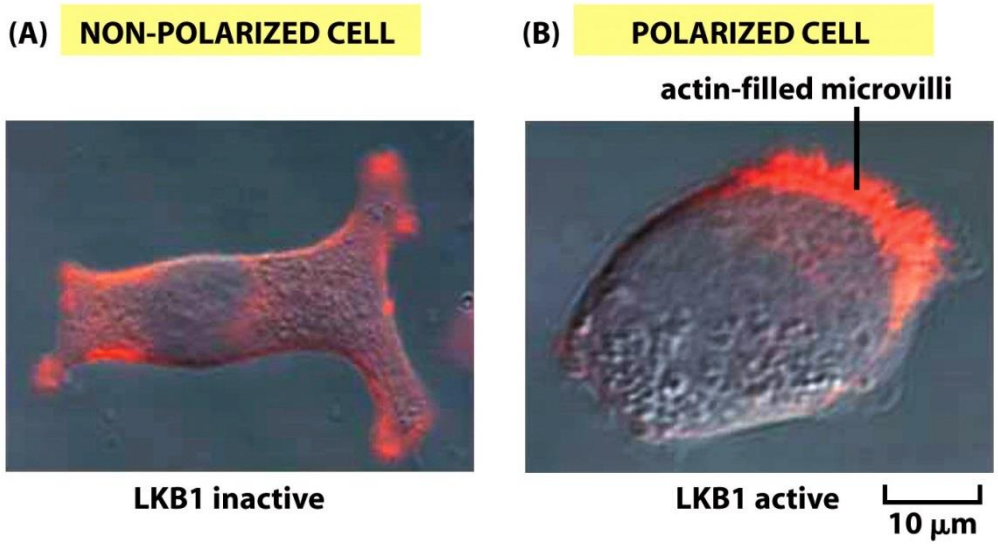


Figure 19-30 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Epithelial polarity

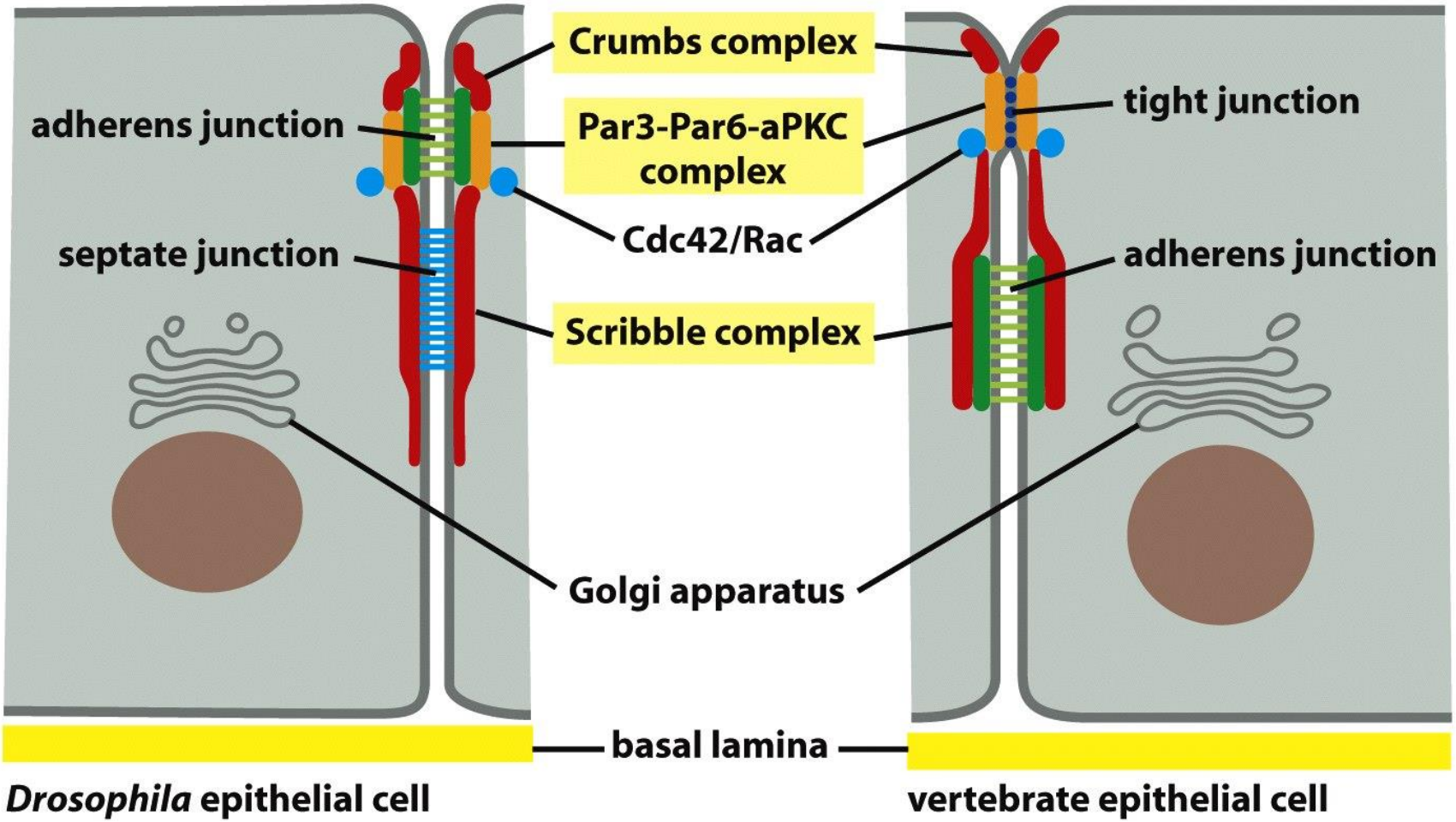


Figure 19-31 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Planar cell polarity

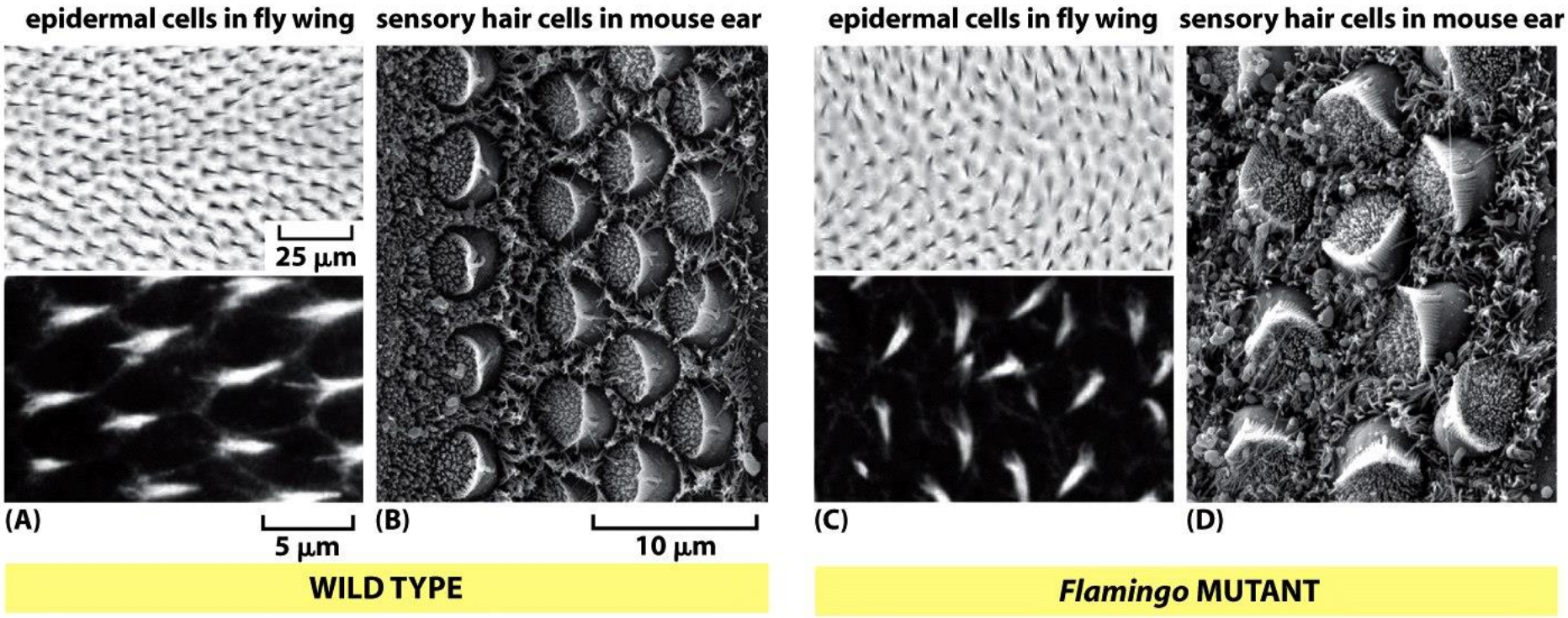


Figure 19-32 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Passage gateways – gap junctions

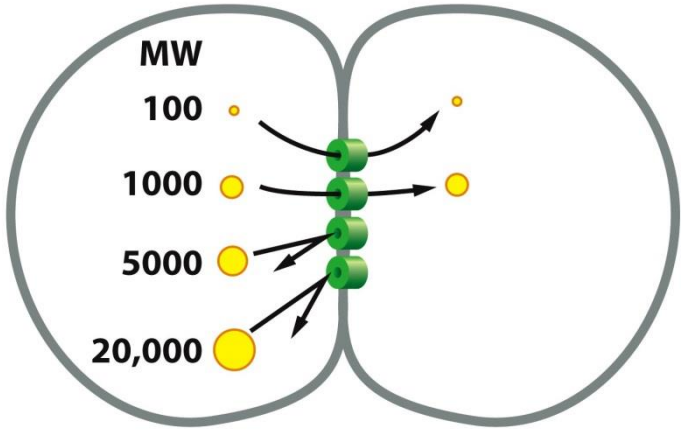


Figure 19-33 Molecular Biology of the Cell 5/e (© Garland Science 2008)

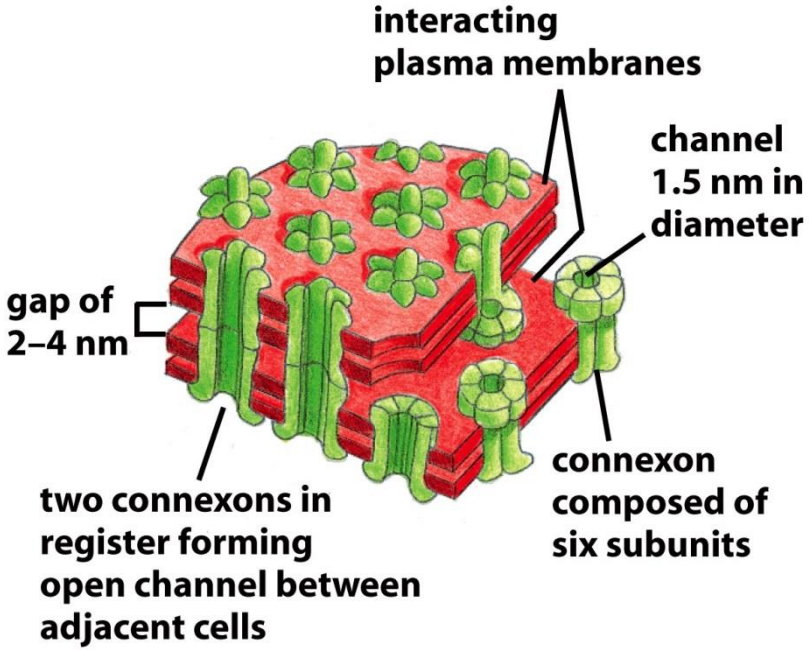


Figure 19-34a Molecular Biology of the Cell 5/e (© Garland Science 2008)

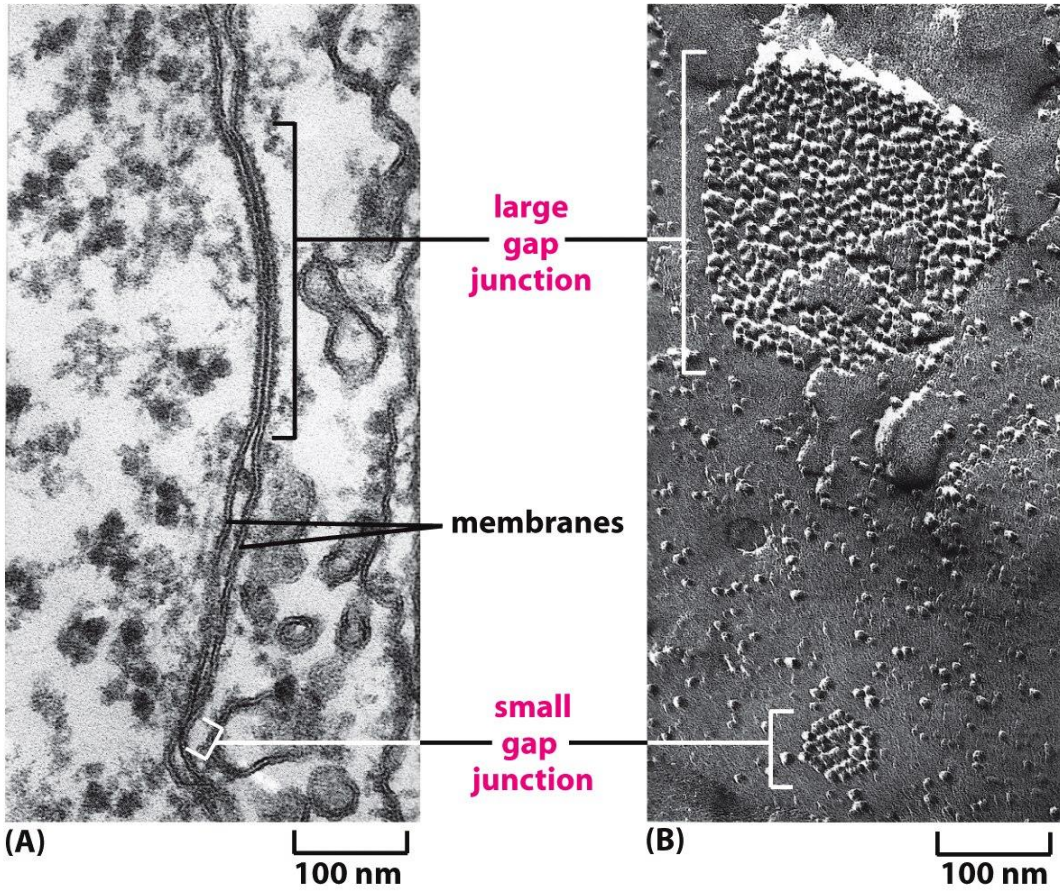


Figure 19-35 Molecular Biology of the Cell 5/e (© Garland Science 2008)

The basal lamina

40-120 nm thick

Important for many cellular processes, including replication, survival, differentiation and migration.

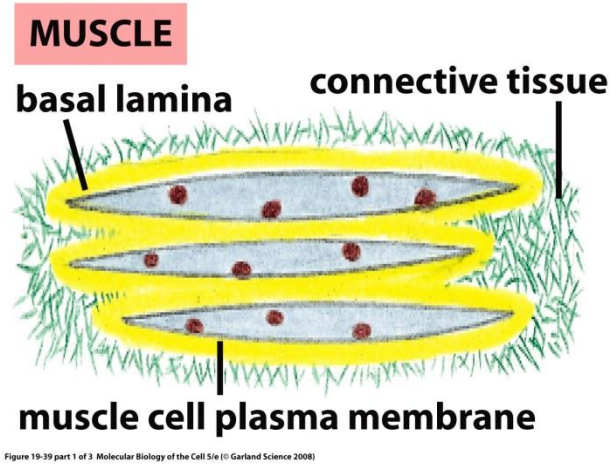


Figure 19-39 part 1 of 3 Molecular Biology of the Cell 5/e (© Garland Science 2008)

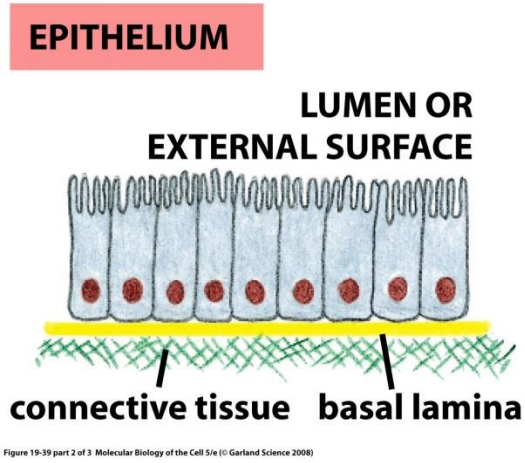


Figure 19-39 part 2 of 3 Molecular Biology of the Cell 5/e (© Garland Science 2008)

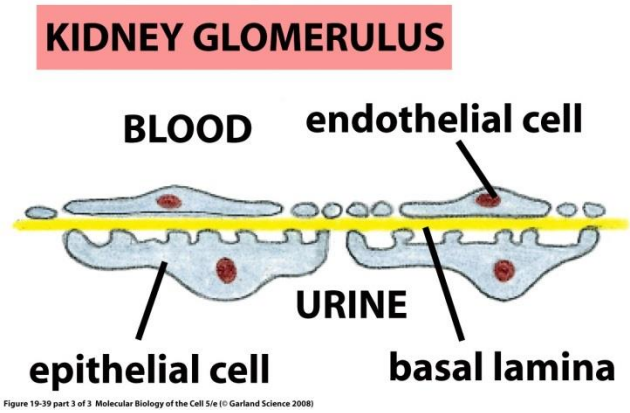


Figure 19-39 part 3 of 3 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Extracellular Cell Matrix (ECM)

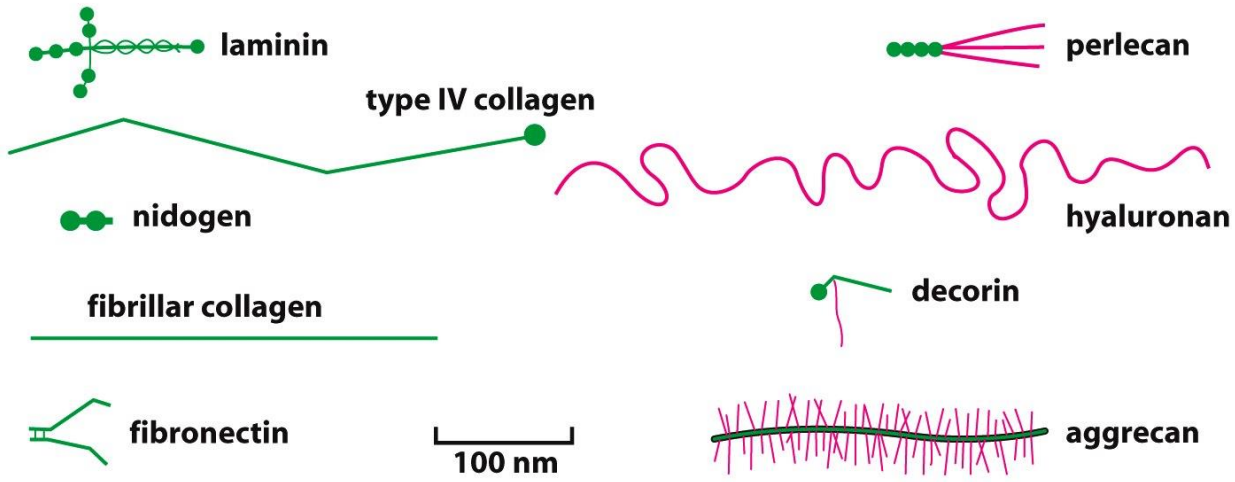


Figure 19-41 Molecular Biology of the Cell 5/e (© Garland Science 2008)

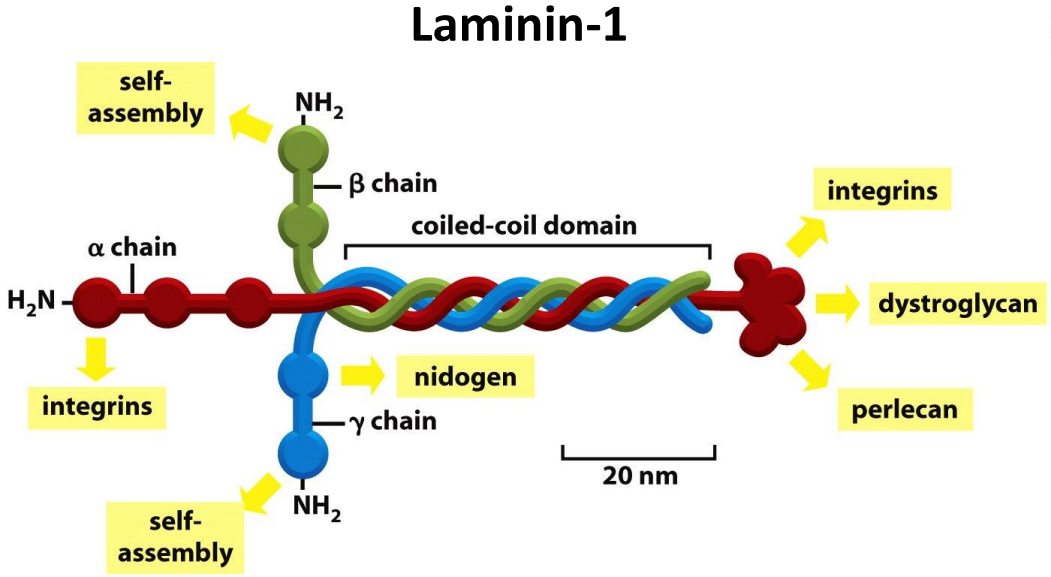


Figure 19-42a Molecular Biology of the Cell 5/e (© Garland Science 2008)

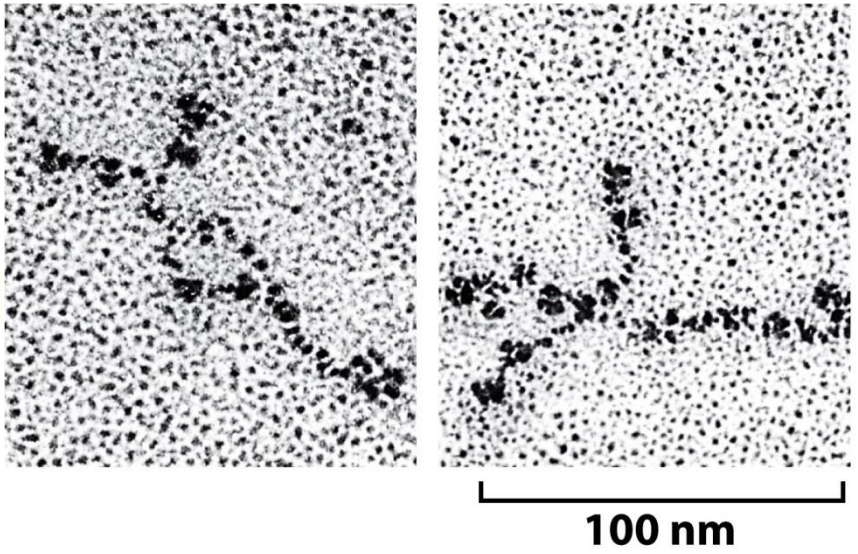


Figure 19-42b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Basal lamina model

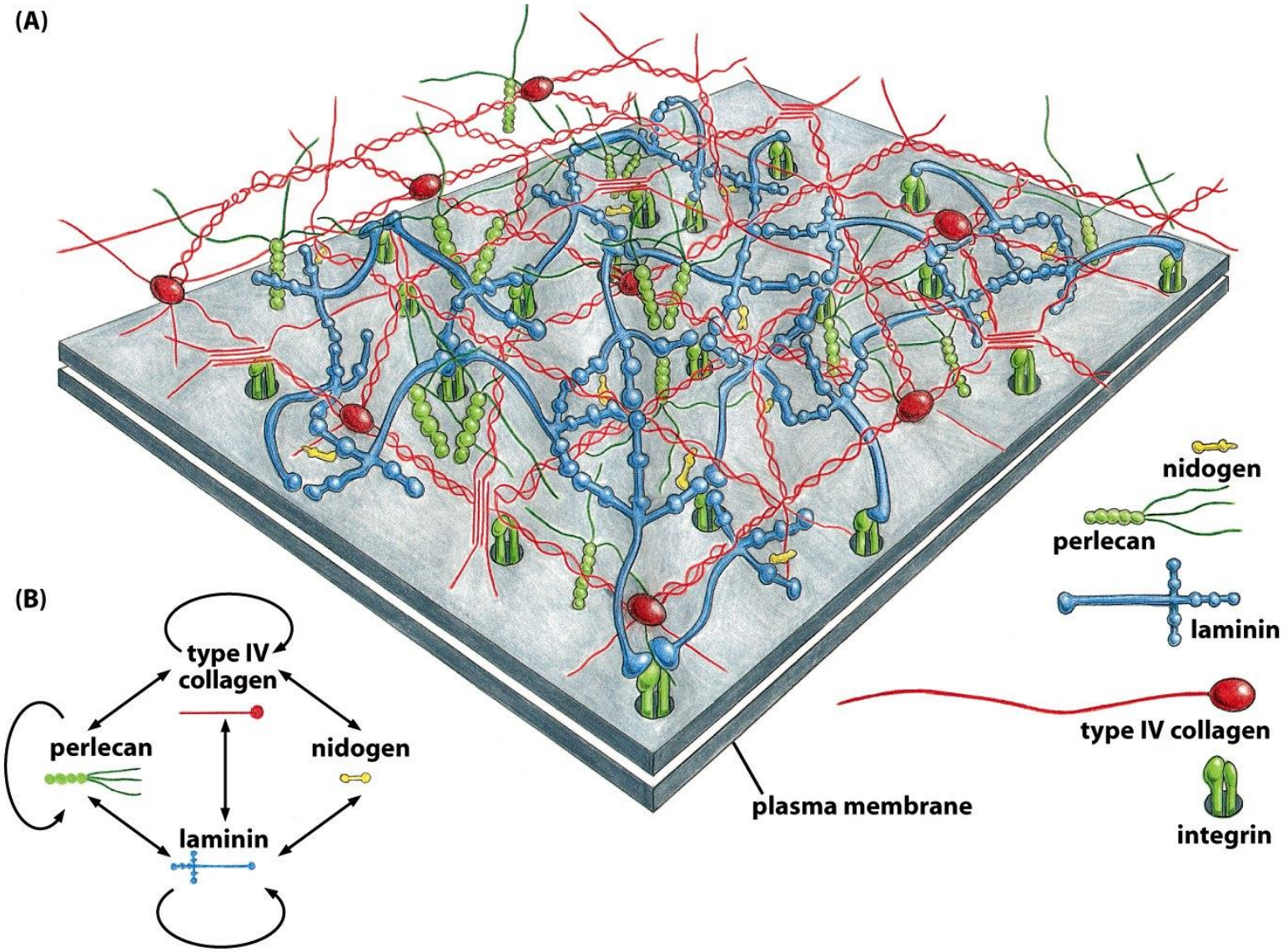


Figure 19-43 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cell-matrix contacts - Integrins

These are them most important adhesion proteins for cell-matrix contacts.

At least 24 different types of integrins were already described in human cells (8 β–chain genes and 18 α–chain genes).

All follow the same dimeric structure with α and β subunits.

They mediate the anchorage dependence of cells.

Integrin and hemidesmosomes

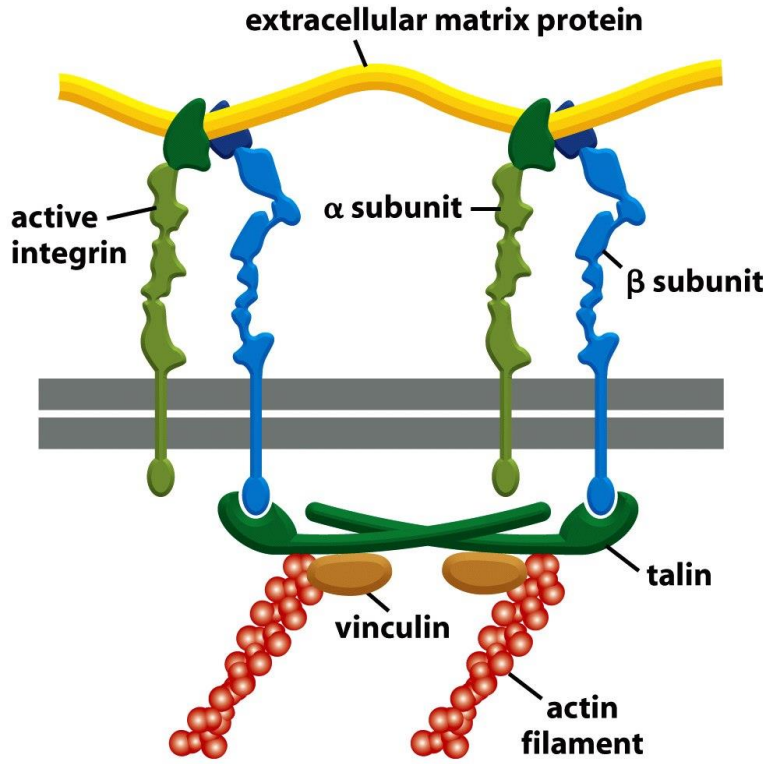


Figure 19-45 Molecular Biology of the Cell 5/e (© Garland Science 2008)

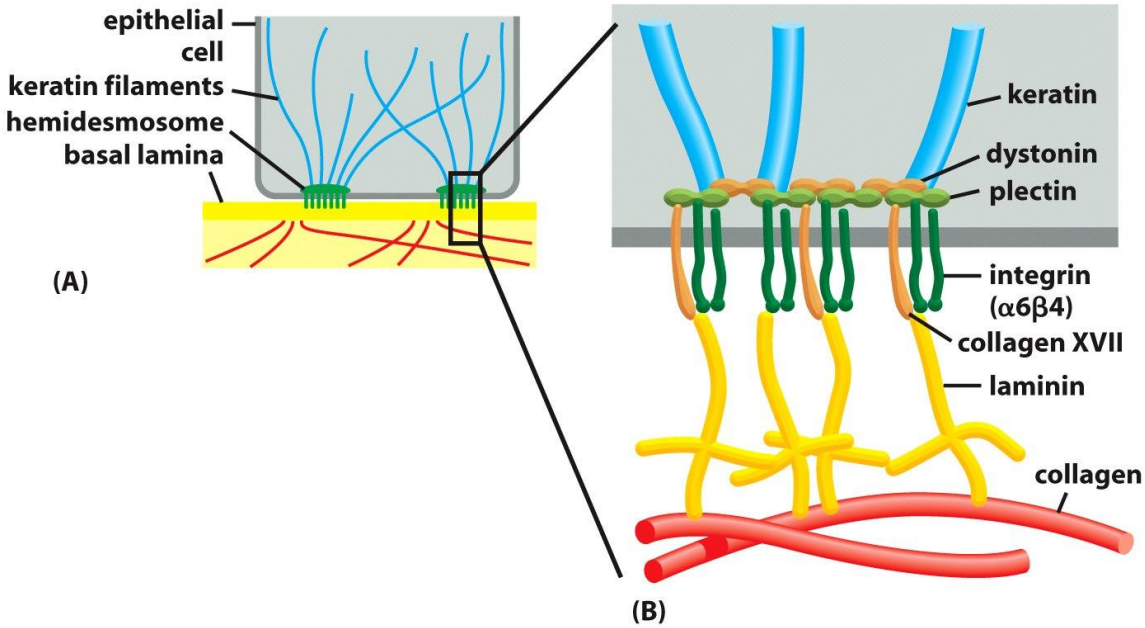


Figure 19-46 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Integrin activation

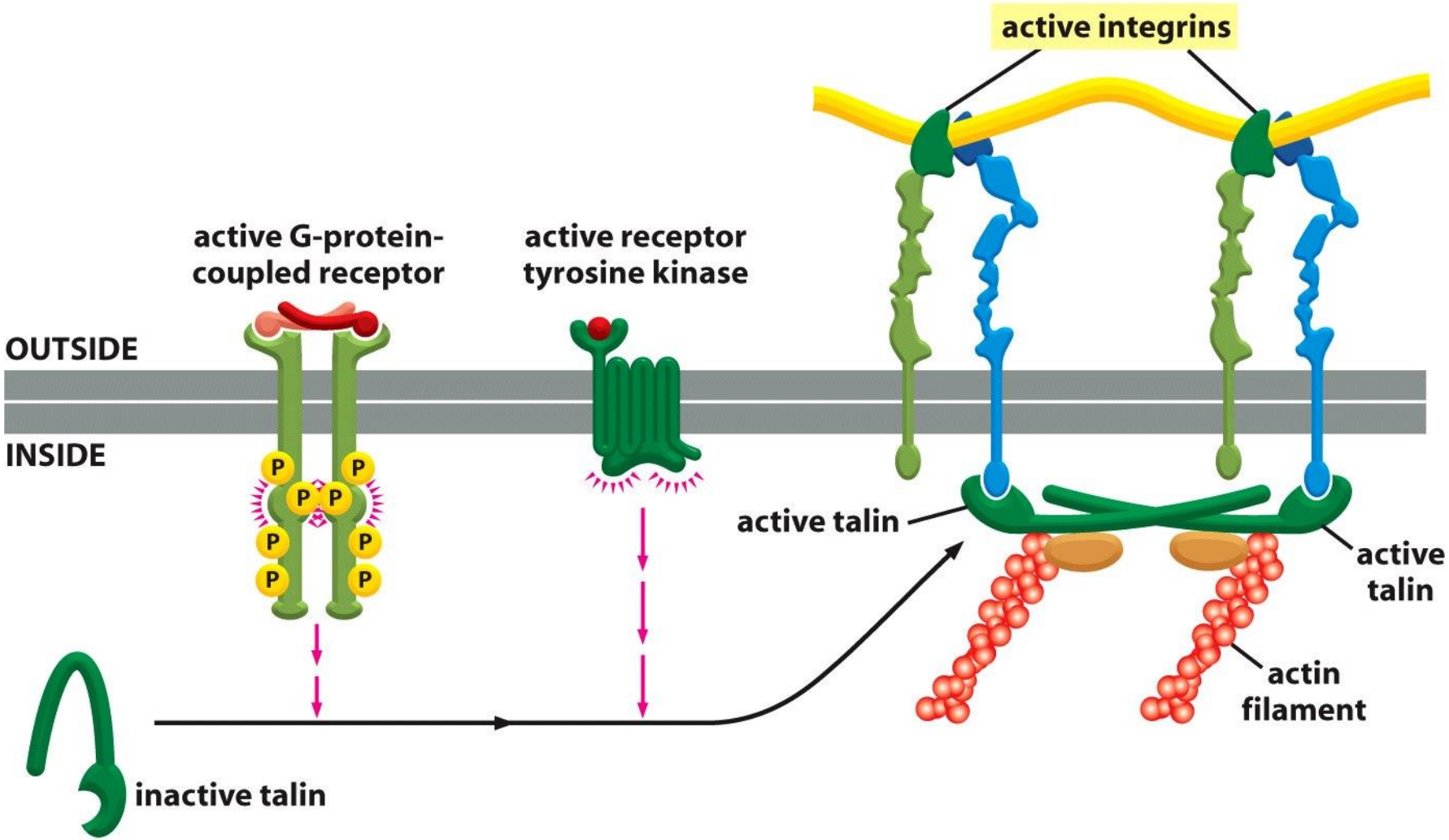


Figure 19-49 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Integrin and anchorage dependence

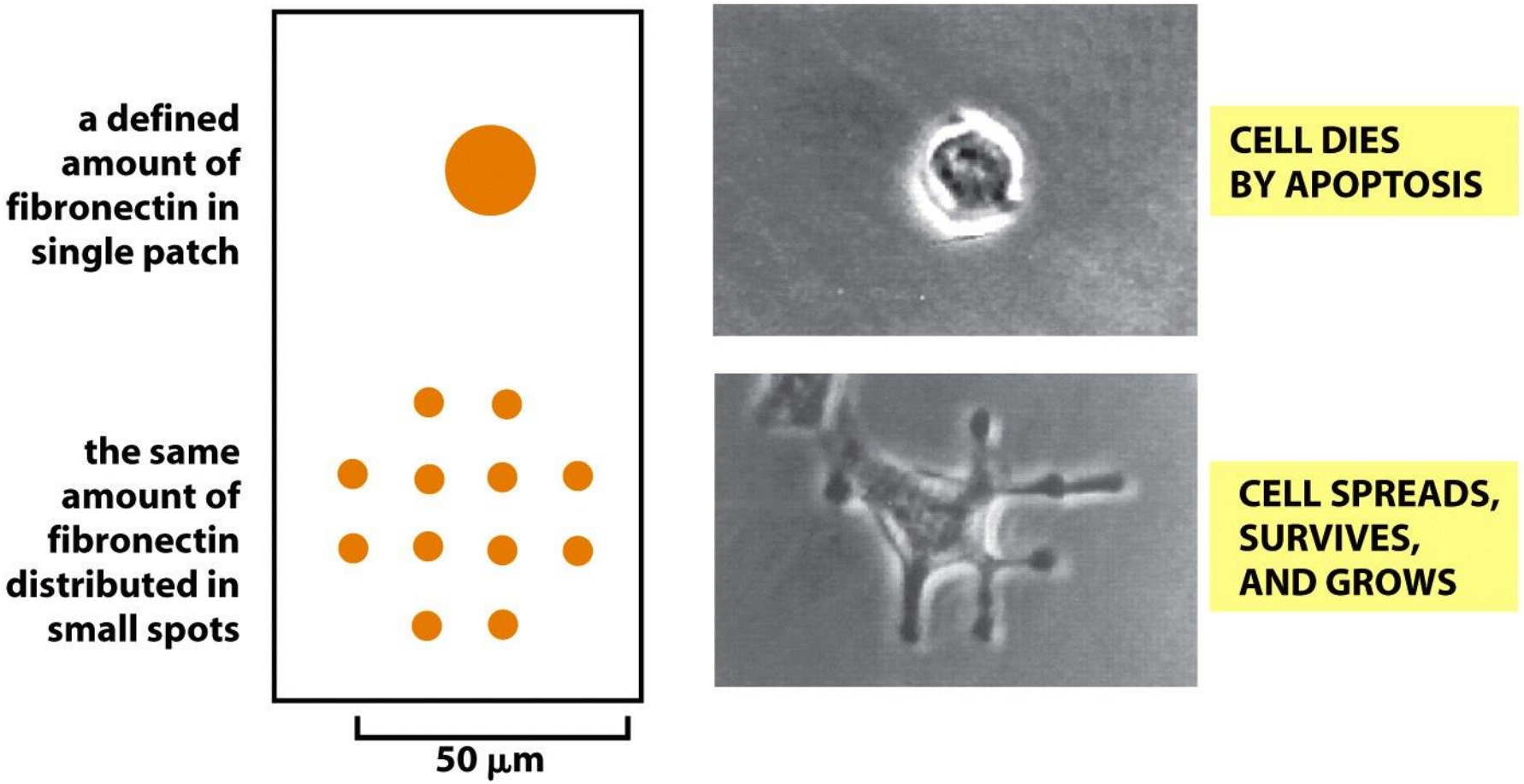


Figure 19-51 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Integrin and cell morphology

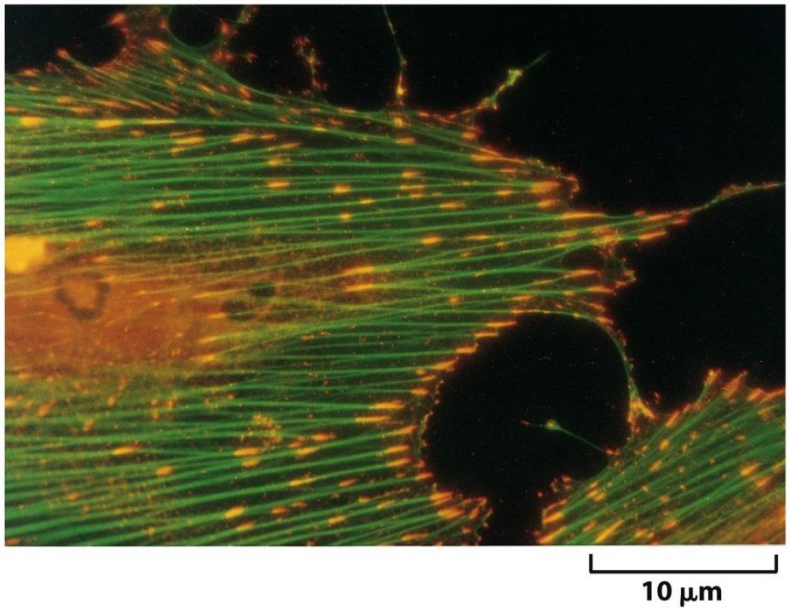


Figure 19-52a Molecular Biology of the Cell 5/e (© Garland Science 2008)

Phosphotyrosine (active protein): red
Actin: green

FAK: focal adhesion kinase

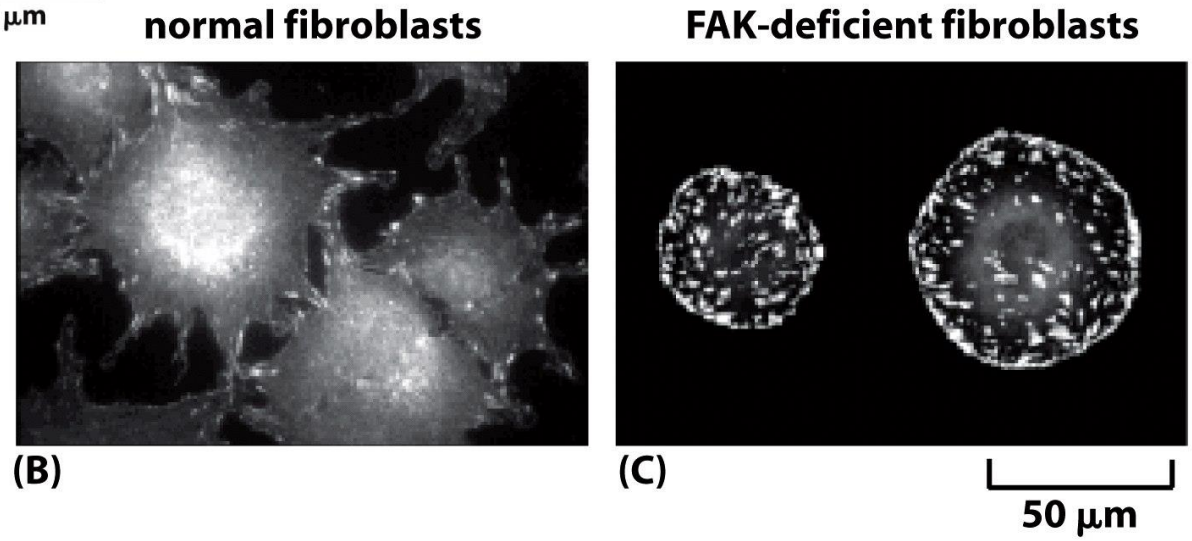


Figure 19-52bc Molecular Biology of the Cell 5/e (© Garland Science 2008)

Classification of integrins

Table 19–4 Some Types of Integrins

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

*Not all ligands are listed.

Table 19-4 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cell adhesion molecules

Table 19–5 Cell Adhesion Molecule Families

	SOME FAMILY MEMBERS	Ca^{2+} OR Mg^{2+} DEPENDENCE	HOMOPHILIC OR HETEROPHILIC	CYTOSKELETON ASSOCIATIONS	CELL JUNCTION ASSOCIATIONS
Cell–Cell Adhesion					
Classical cadherins	E, N, P, VE	yes	homophilic	actin filaments (via catenins)	adherens junctions, synapses
Desmosomal cadherins	desmoglein, desmocollin	yes	homophilic	intermediate filaments (via desmoplakin, plakoglobin, and plakophilin)	desmosomes
Ig family members	N-CAM, ICAM	no	both	unknown	neuronal and immunological synapses
Selectins (blood cells and endothelial cells only)	L-, E-, and P-selectins	yes	heterophilic	actin filaments	(no prominent junctional structure)
Integrins on blood cells	αLβ2 (LFA1)	yes	heterophilic	actin filaments	immunological synapses
Cell–Matrix Adhesion					
Integrins	many types	yes	heterophilic	actin filaments (via talin, paxillin, filamin, α-actinin, and vinculin)	focal adhesions
	α6β4	yes	heterophilic	intermediate filaments (via plectin and dystonin)	hemidesmosomes
Transmembrane proteoglycans	syndecans	no	heterophilic	actin filaments	(no prominent junctional structure)

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

The extracellular matrix (ECM)

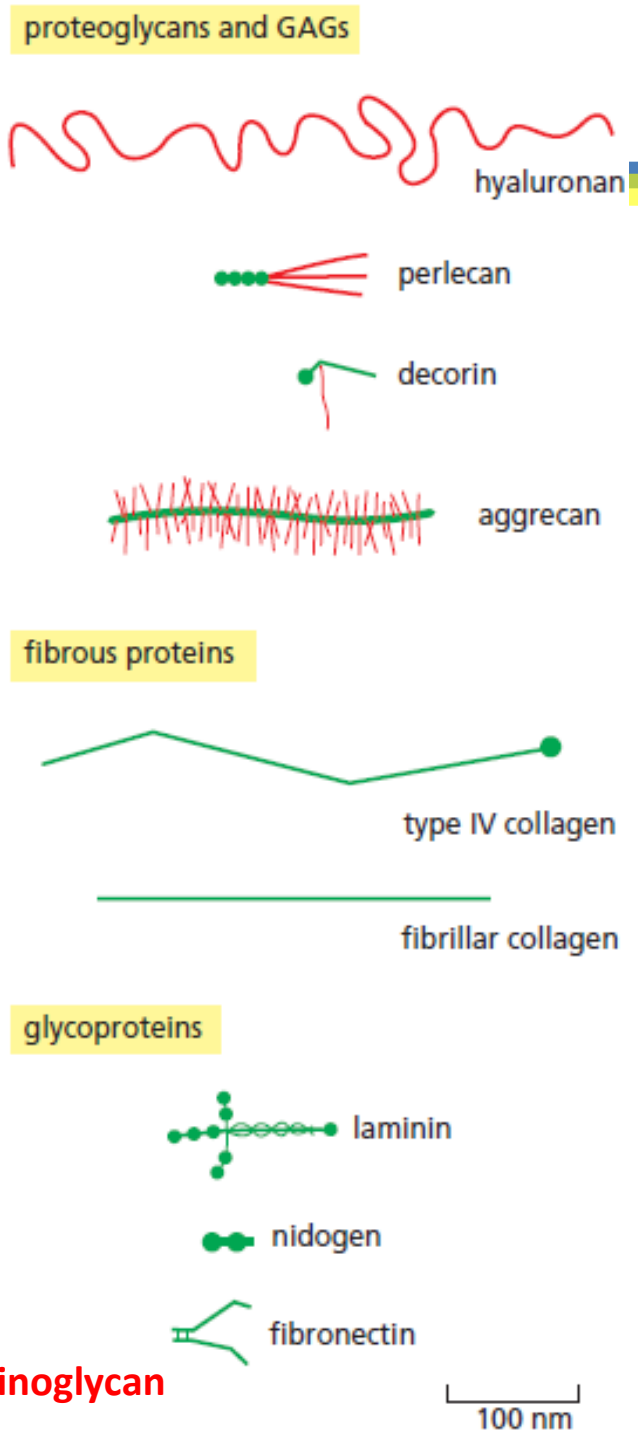
The extracellular matrix is constructed from three major classes of macromolecules:

(1) glycosaminoglycans (*GAGs*): large and highly charged polysaccharides that are usually covalently linked to protein in the form of *proteoglycans*;

(2) fibrous proteins: primarily members of the *collagen* family;

(3) a large class of noncollagen *glycoproteins*, which carry conventional asparagine-linked oligosaccharides.

Mammals are thought to have almost 300 matrix proteins, including about 36 proteoglycans, about 40 collagens, and over 200 glycoproteins.

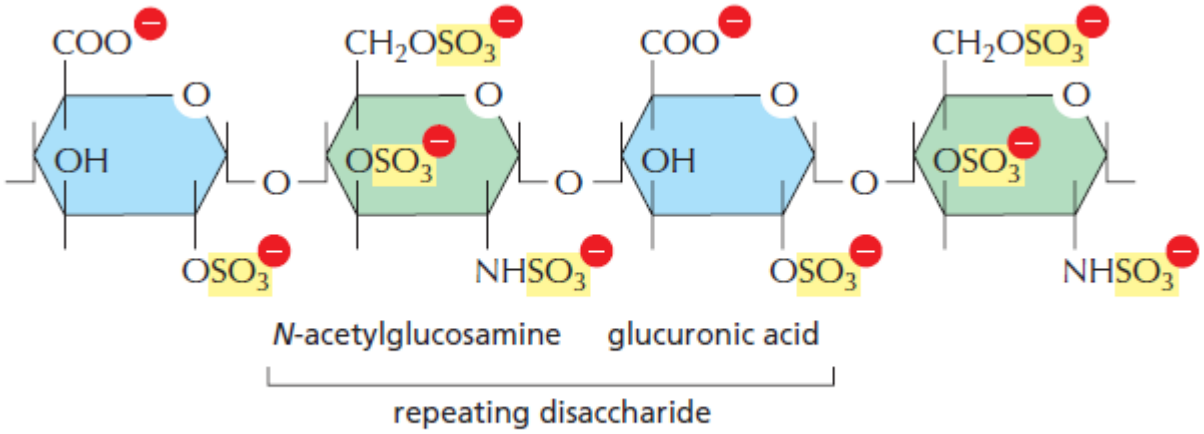


Green: Protein

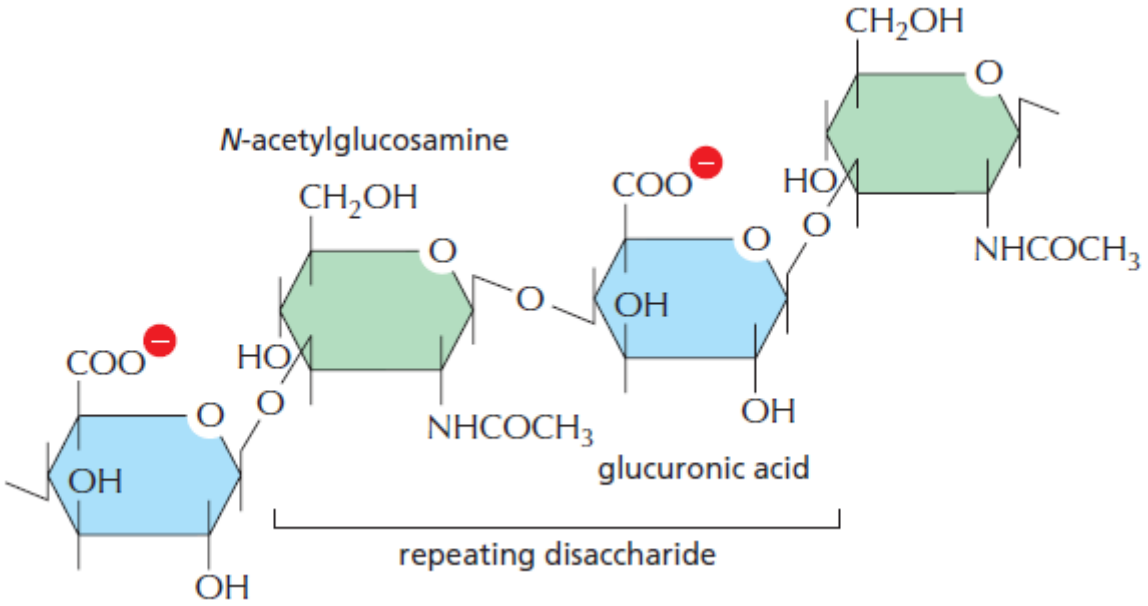
Red: glycosaminoglycan

ECM saccharides

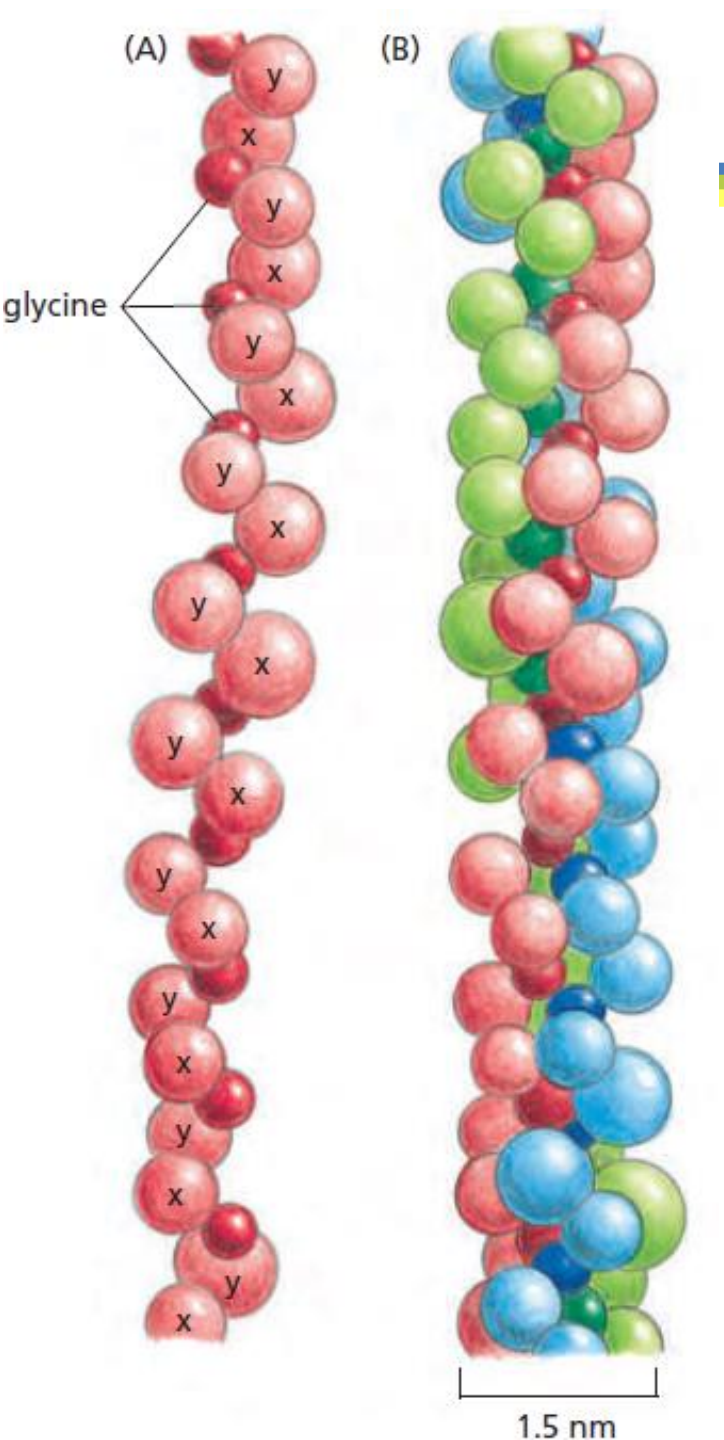
Glycosaminoglycan (GAG) chain: heparan sulphate



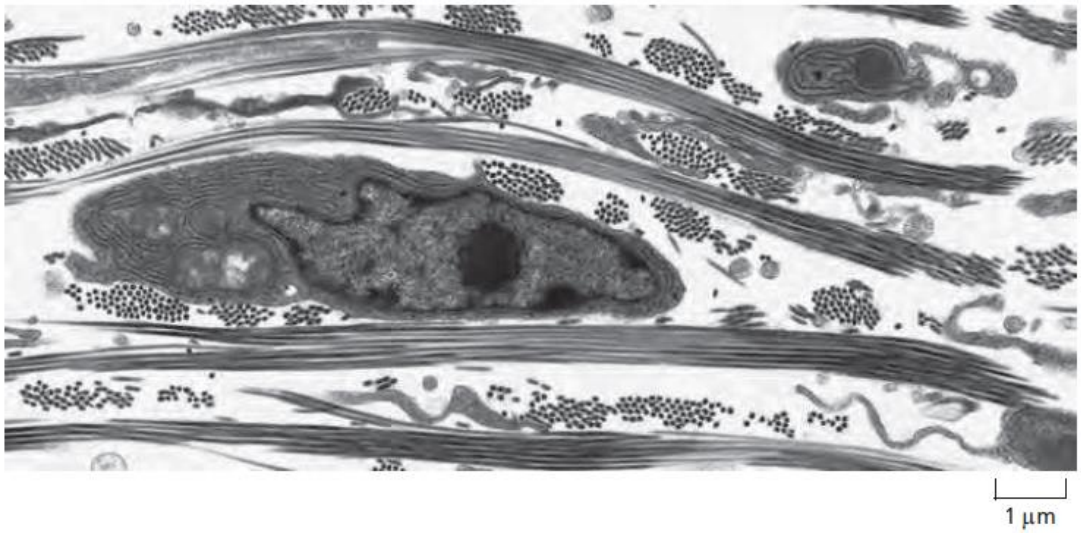
Disaccharide (hyaluronan)



ECM protein



Collagen



Fibroblast cell from chick embrio

Other types: fibronectin, elastin

Proteoglycans

Table 19–6 Some Common Proteoglycans

PROTEOGLYCAN	APPROXIMATE MOLECULAR WEIGHT OF CORE PROTEIN	TYPE OF GAG CHAINS	NUMBER OF GAG CHAINS	LOCATION	FUNCTIONS
Aggrecan	210,000	chondroitin sulfate + keratan sulfate (in separate chains)	~130	cartilage	mechanical support; forms large aggregates with hyaluronan
Betaglycan	36,000	chondroitin sulfate/ dermatan sulfate	1	cell surface and matrix	binds TGFβ
Decorin	40,000	chondroitin sulfate/ dermatan sulfate	1	widespread in connective tissues	binds to type I collagen fibrils and TGFβ
Perlecan	600,000	heparan sulfate	2–15	basal laminae	structural and filtering function in basal lamina
Syndecan-1	32,000	chondroitin sulfate + heparan sulfate (in separate chains)	1–3	cell surface	cell adhesion; binds FGF and other growth factors
Dally (in *Drosophila*)	60,000	heparan sulfate	1–3	cell surface	co-receptor for Wingless and Decapentaplegic signaling proteins

Table 19-6 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cell junction and polarization

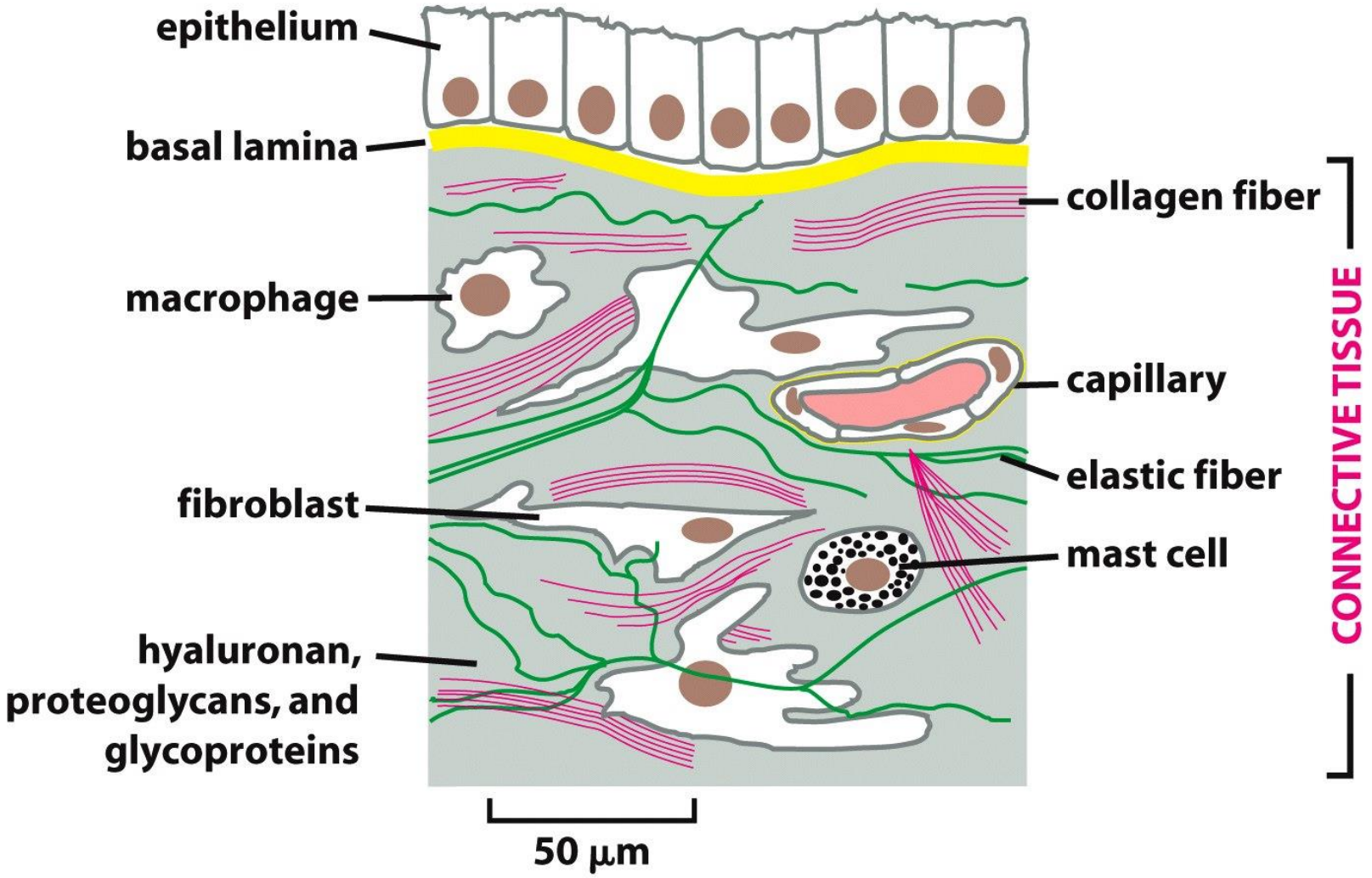


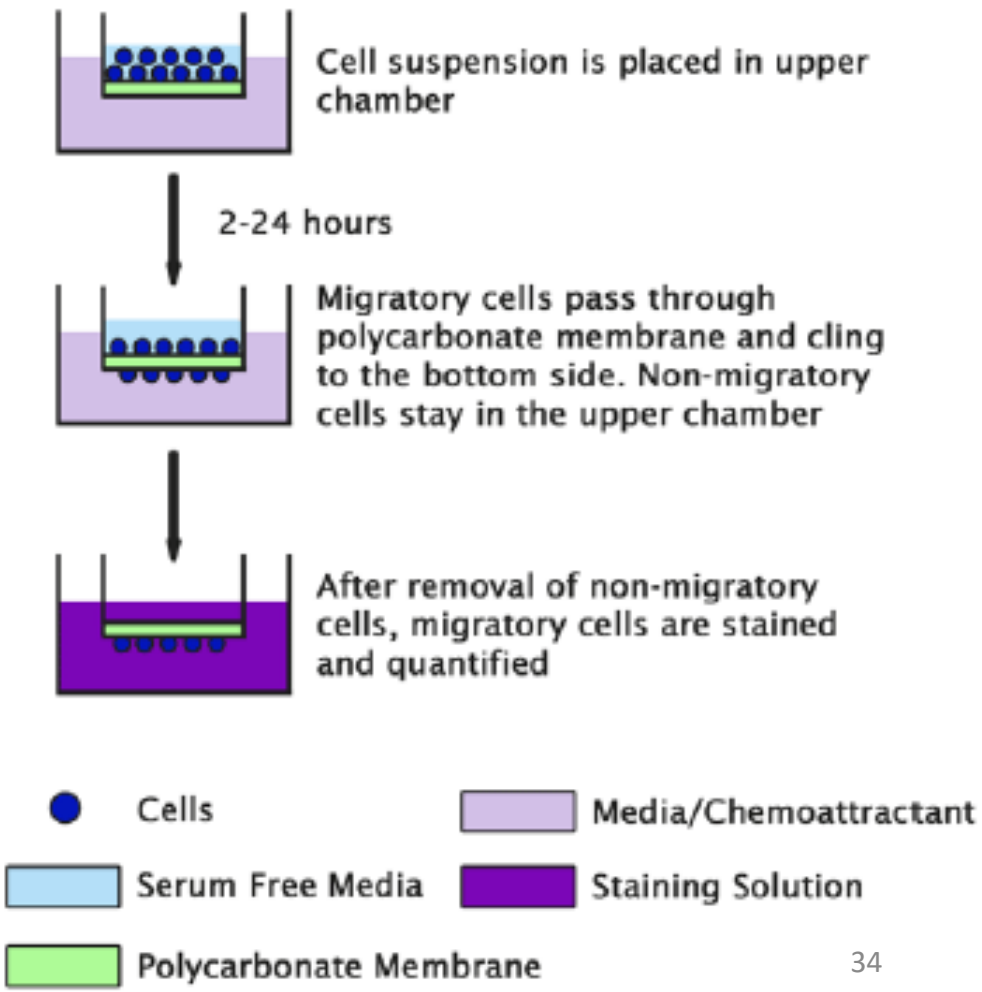
Figure 19-53 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Membrane composition and metastasis

Sphingosylphosphorylcholine caused an increase in the elasticity of cancer cells, which provided an explanation for how metastatic cells squeeze through membrane pores.

Beil, M. *et al.* Sphingosylphosphorylcholine regulates keratin network architecture and visco-elastic properties of human cancer cells. *Nature Cell Biol.* **5**, 803–811 (2003).

In vitro: cell migration (hapoptaxis assay)



http://www.biocat.com/cell-biology/cell-migration/haptotaxis-assays