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Cell Junctions

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What are cell junctions

- **Definition:**
  - Specialized areas where two or more cells come into direct contact
  - Provide connections between adjacent cells and between cells and the extracellular matrix
  - Essential for maintaining tissue integrity and coordinating cellular activities
- **Functions:**
  - Cell-to-cell adhesion
  - Sealing epithelial sheets
  - Direct intercellular communication
  - Mechanical strength and stability
- **Why Important?**
  - Form organized multicellular structures
  - Coordinate activities of individual cells
  - Maintain tissue organization and function

Classification of cell junction

Category	Function	Types
OCCLUDING JUNCTIONS	Seal extracellular space	Tight Junctions, Septate Junctions
ANCHORING JUNCTIONS	Mechanical attachment	**Cell-Cell:** Adherens Junctions, Desmosomes; **Cell-Matrix:** Focal Adhesions, Hemidesmosomes
COMMUNICATING JUNCTIONS	Allow molecular exchange	Gap Junctions, Plasmodesmata

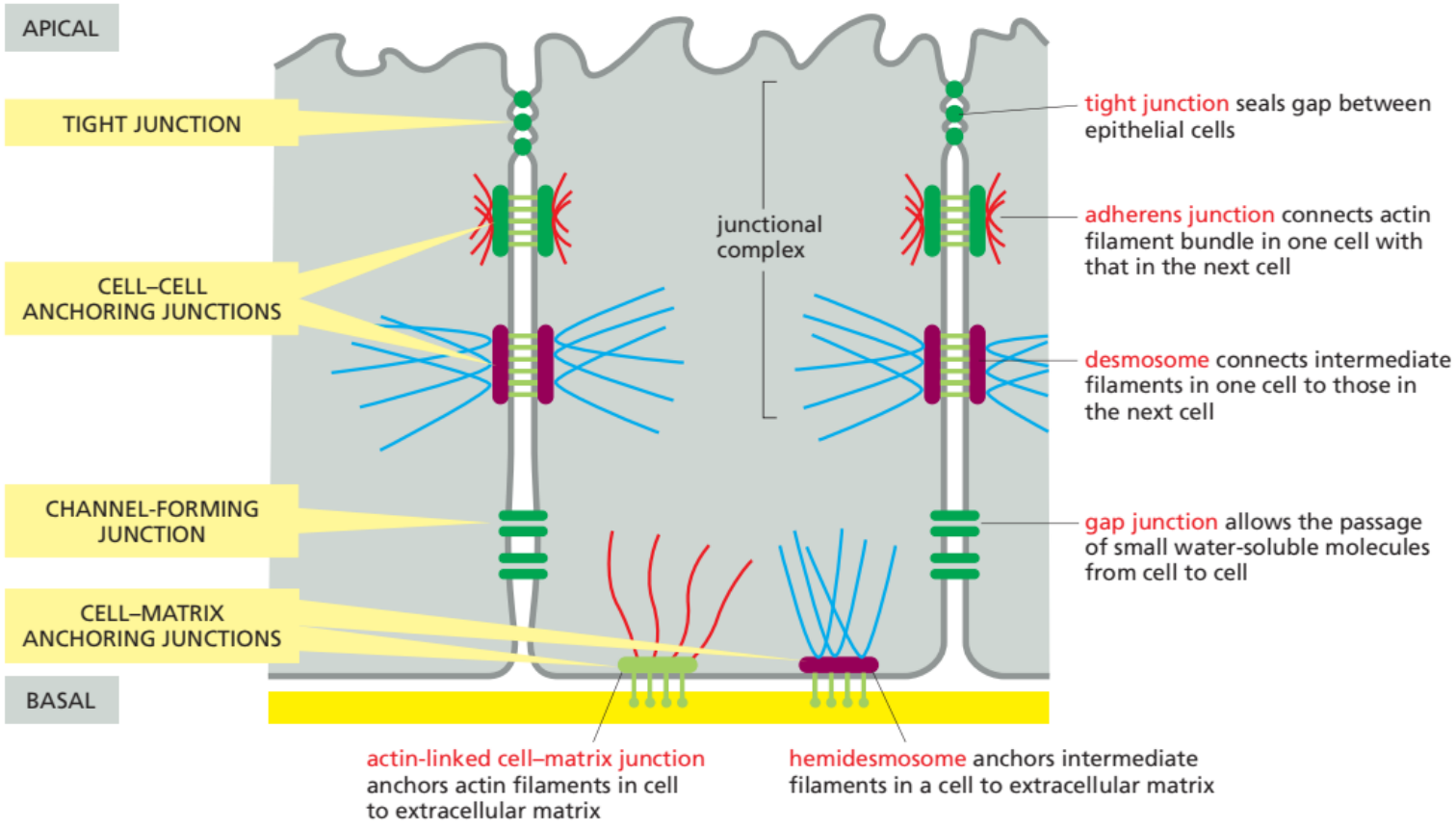


Figure 19–2 A summary of the various cell junctions found in a vertebrate epithelial cell, classified according to their primary functions. In the most apical portion of the cell, the relative positions of the junctions are the same in nearly all vertebrate epithelia. The tight junction occupies the most apical position, followed by the adherens junction (adhesion belt) and then by a special parallel row of desmosomes; together these form a structure called a junctional complex. Gap junctions and additional desmosomes are less regularly organized. Two types of cell-matrix anchoring junctions tether the basal surface of the cell to the basal lamina. The drawing is based on epithelial cells of the small intestine.

Junctional Complex Overview

Typical Epithelial Cell Junction Arrangement (Apical to Basal):

Tight Junctions (Zonula Occludens)
- Located most apically
- Seals intercellular space

Adherens Junctions (Zonula Adherens)
- Forms continuous belt
- Links actin filaments

Desmosomes (Macula Adherens)
- Scattered spots of adhesion
- Links intermediate filaments

Gap Junctions
- Allow molecular communication
- Located basolaterally

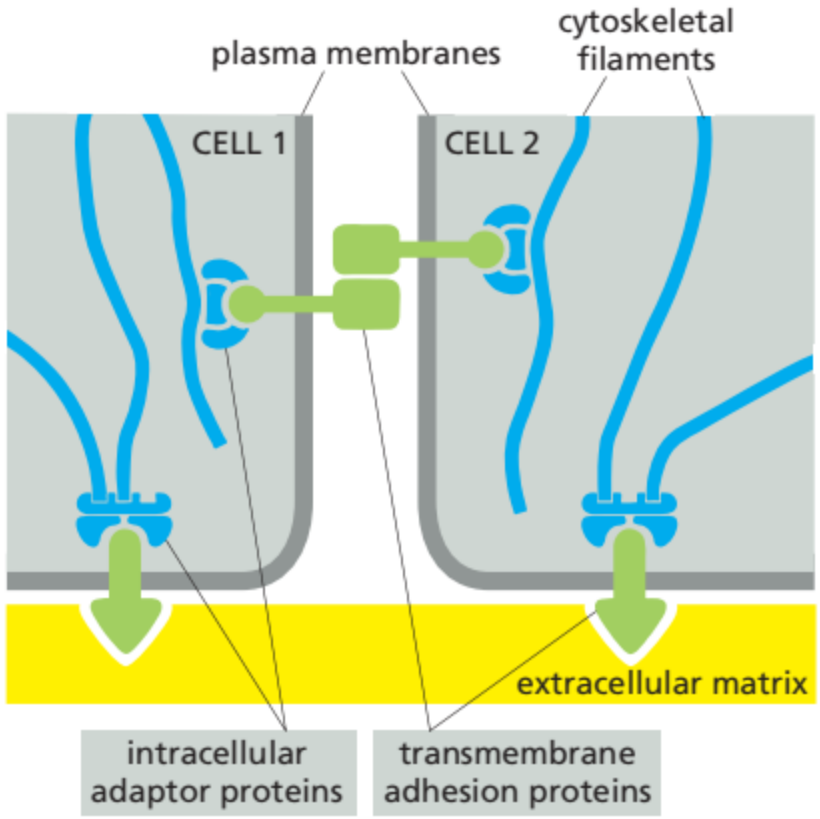


Figure 19–3 Transmembrane adhesion proteins link the cytoskeleton to extracellular structures. The external linkage may be either to other cells (cell–cell junctions, mediated typically by cadherins) or to extracellular matrix (cell–matrix junctions, mediated typically by integrins). The internal linkage to the cytoskeleton is generally indirect, via intracellular adaptor proteins, to be discussed later.

TABLE 19–1 Anchoring Junctions

Junction	Transmembrane adhesion protein	Extracellular ligand	Intracellular cytoskeletal attachment	Intracellular adaptor proteins
Cell–Cell				
Adherens junction	Classical cadherins	Classical cadherin on neighboring cell	Actin filaments	α-Catenin, β-catenin, plakoglobin (γ-catenin), p120-catenin, vinculin
Desmosome	Nonclassical cadherins (desmoglein, desmocollin)	Desmoglein and desmocollin on neighboring cell	Intermediate filaments	Plakoglobin (γ-catenin), plakophilin, desmoplakin
Cell–Matrix				
Actin-linked cell–matrix junction	Integrin	Extracellular matrix proteins	Actin filaments	Talin, kindlin, vinculin, paxillin, focal adhesion kinase (FAK), numerous others
Hemidesmosome	$\alpha_6\beta_4$ Integrin, type XVII collagen	Extracellular matrix proteins	Intermediate filaments	Plectin, BP230

Part I

Occluding Junctions

Tight Junctions - Structure & Function

- **Definition:**
  - Junction that seals the gap between adjacent epithelial cells
  - Prevents molecules from leaking between cells (paracellular pathway)
  - Acts as a "fence" maintaining plasma membrane domain polarity
- **Location:**
  - Most apical region of epithelial cell sheets
  - Found in intestinal epithelium, kidney tubules, blood-brain barrier
- **Primary Functions:**
  - **Barrier Function** – Blocks paracellular transport
  - **Fence Function** – Prevents mixing of apical and basolateral membrane proteins
  - **Ion Selectivity** – Some tight junctions allow selective ion passage

Tight Junction Molecular Components

Main transmembrane protein

Protein	Function	Characteristics
Claudins	Primary sealing component	24 different types in humans; forms main structure
Occludin	Regulatory protein	Determines permeability; not essential for structure
Tricellulin	Three-cell sealing	Prevents leakage where 3 cells meet

Cytoplasmic Scaffold Proteins (ZO proteins)

- ZO-1, ZO-2, ZO-3 (Zonula Occludens proteins)
- These protein has different domains:
  - PDZ interacts with claudin and ZO proteins
  - GK interacts with occluding
  - P interacts with actin
  - SH3 interacts with signalling protein

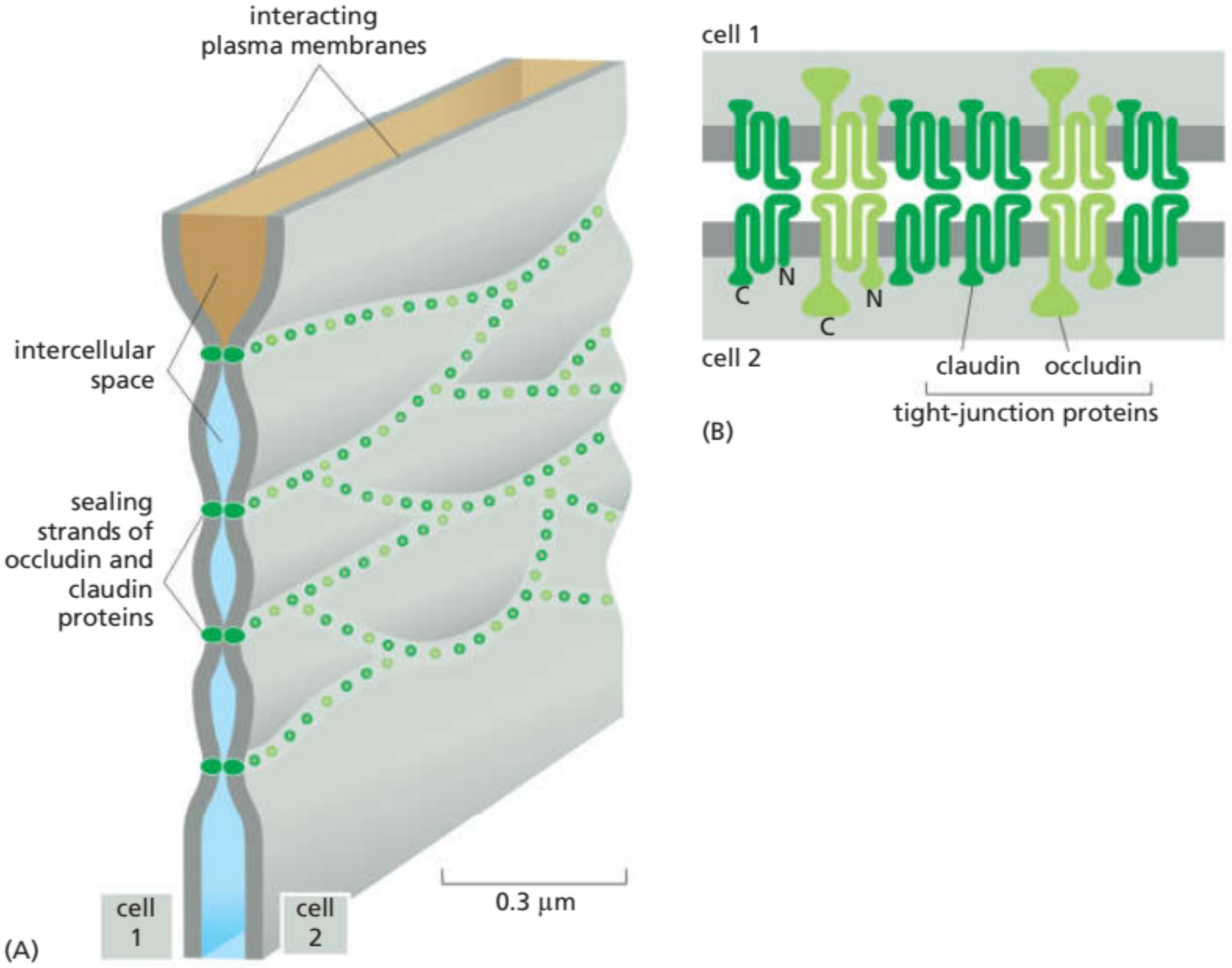


Figure 19–21 A model of a tight junction. (A) The sealing strands hold adjacent plasma membranes together. The strands are composed of transmembrane proteins that make contact across the intercellular space and create a seal. (B) The molecular composition of a sealing strand. The major extracellular components of the tight junction are members of a family of proteins with four transmembrane domains. One of these proteins, claudin, is the most important for the assembly and structure of the sealing strands, whereas the related protein occludin has the less critical role of determining junction permeability. The two termini of these proteins are both on the cytoplasmic side of the membrane, where they interact with large scaffolding proteins that organize the sealing strands and link the tight junction to the actin cytoskeleton (not shown here, but see Figure 19–22).

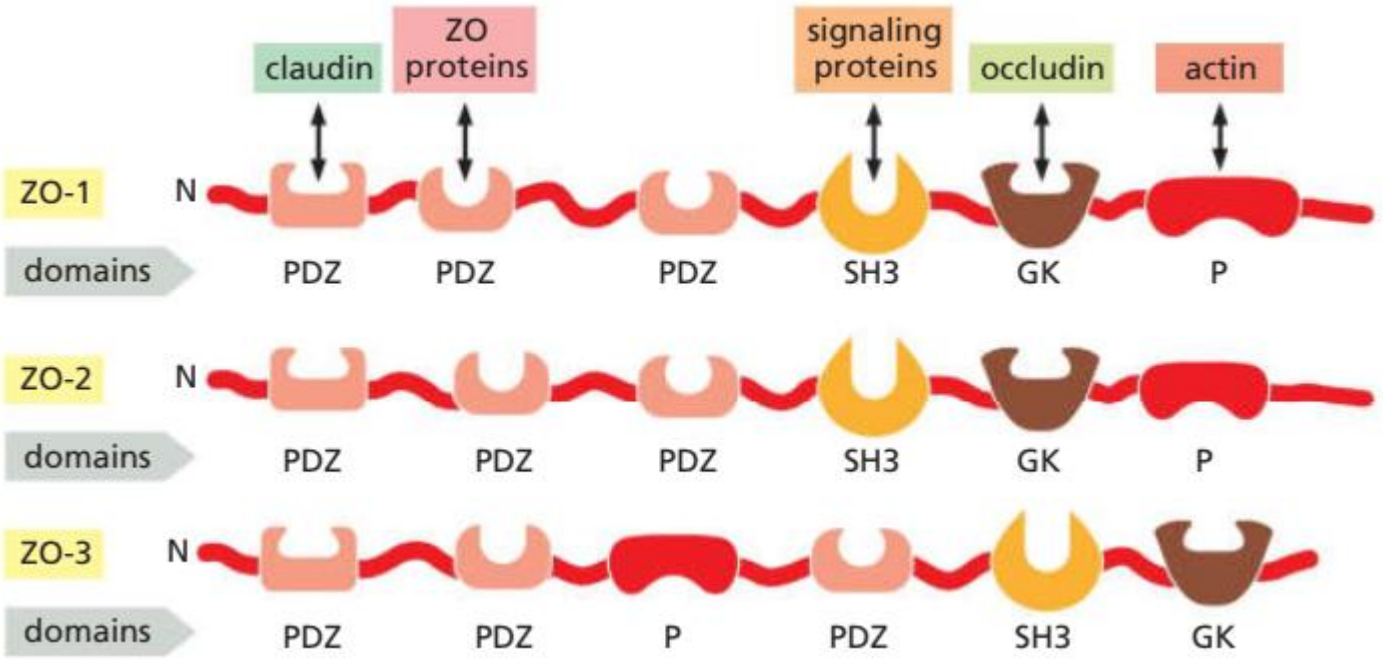
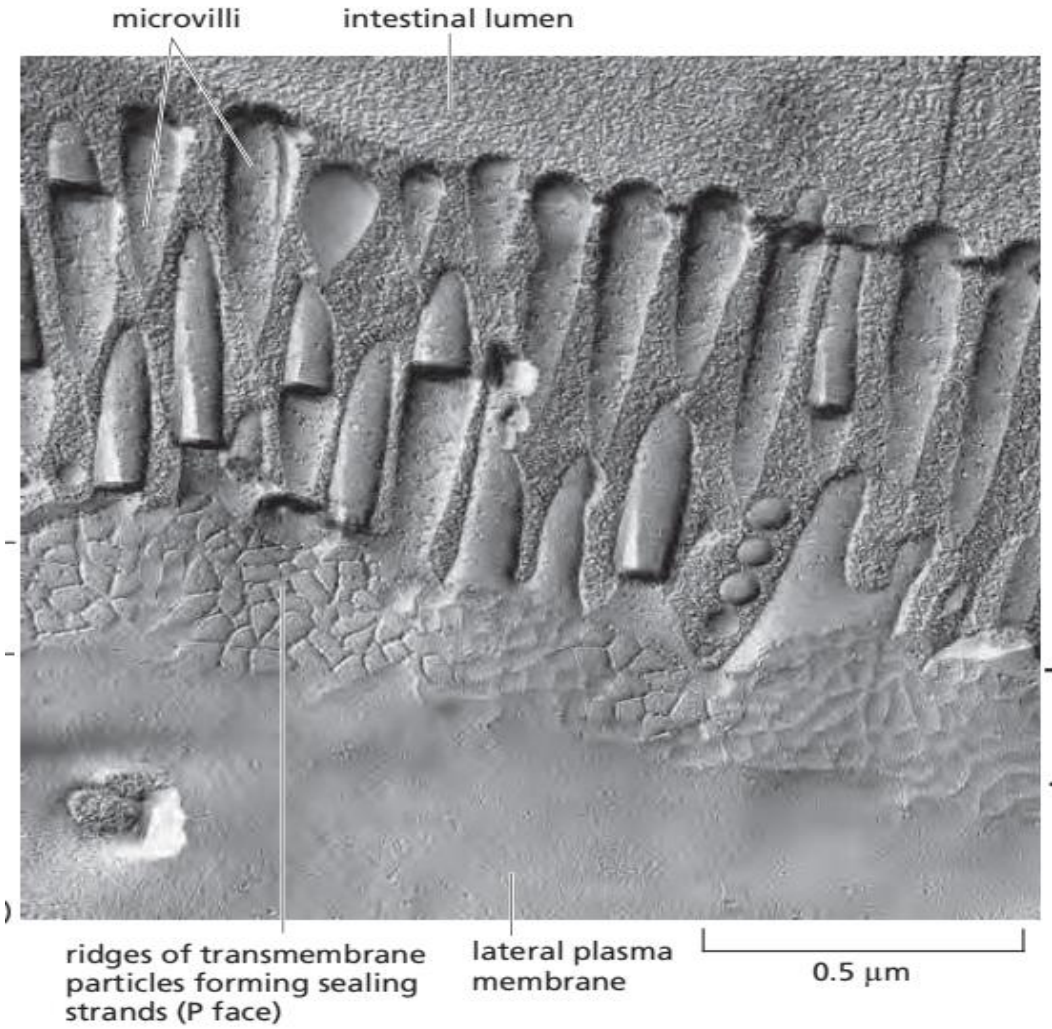
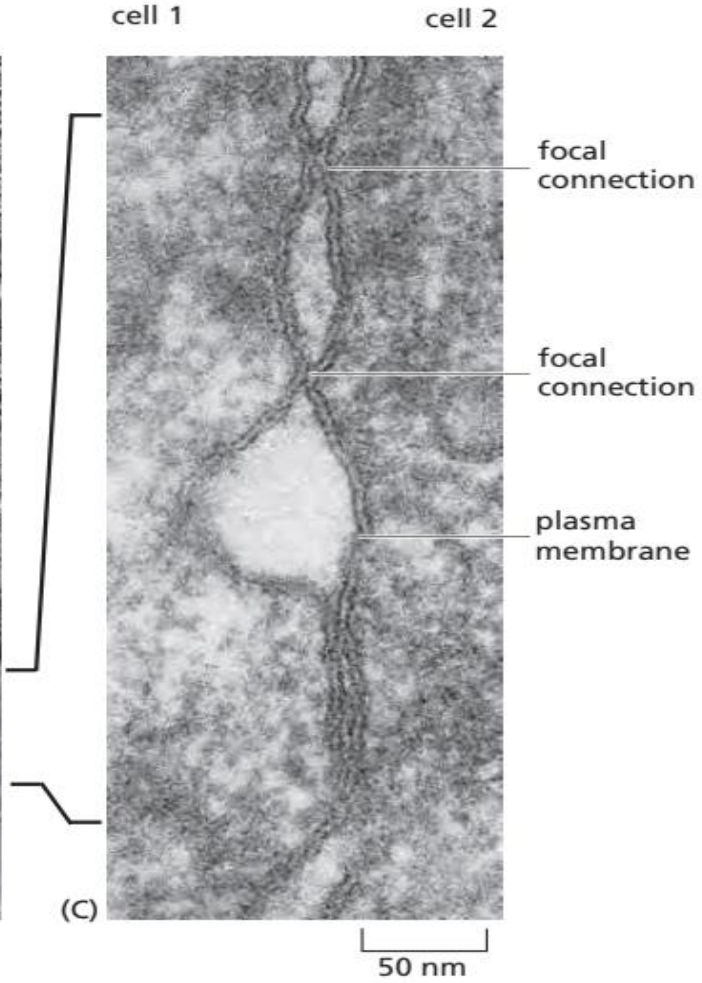
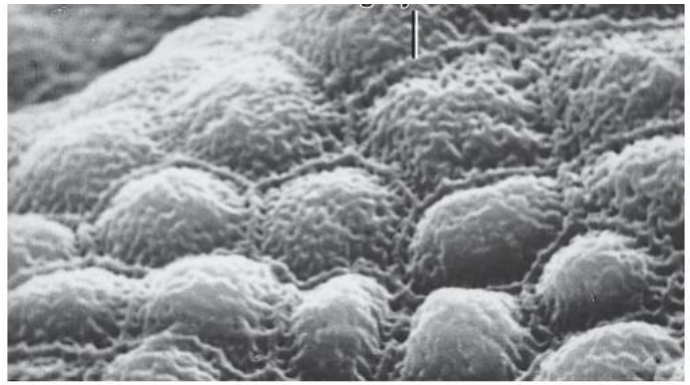


Figure 19–22 Scaffold proteins at the tight junction. The scaffold proteins ZO-1, ZO-2, and ZO-3 are concentrated beneath the plasma membrane at tight junctions. Each of the proteins contains multiple protein-binding domains, including three PDZ domains, an SH3 domain, and a GK domain, linked together like beads on a flexible string. These domains enable the proteins to interact with each other and with numerous other partners, as indicated here, to generate a tightly woven protein network that organizes the sealing strands of the tight junction and links them to the actin cytoskeleton. Scaffold proteins with similar structure help organize other junctional complexes, including those at neural synapses.







Tight Junction Structure (Electron Microscopy View)

Freeze-Fracture Appearance:

- Appears as branching network of sealing strands
- Strands completely encircle each epithelial cell
- Strands run parallel to apical cell surface

Conventional EM View:

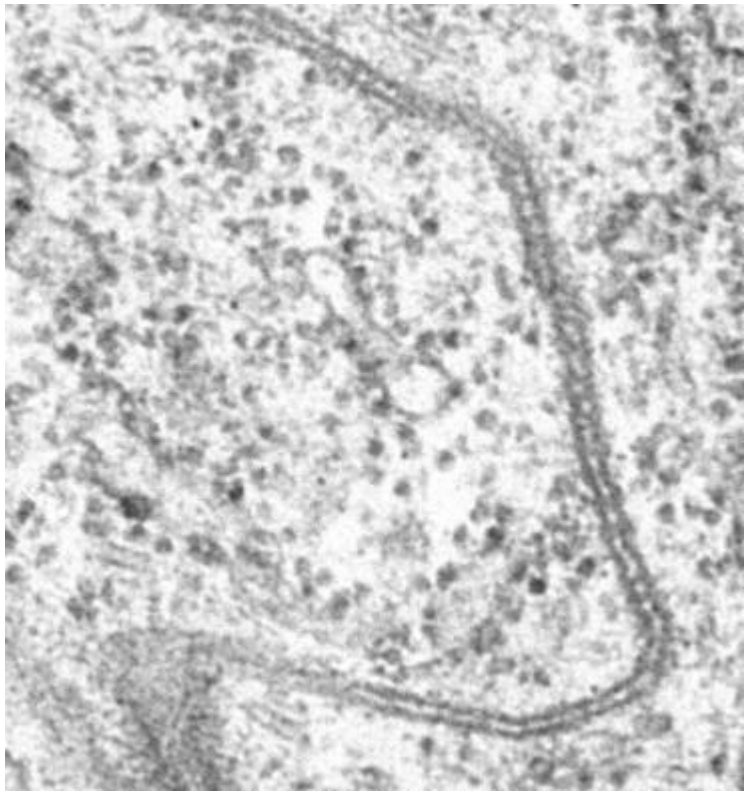
- Shows focal connections between outer plasma membrane leaflets
- Creates intermittent sealing points across intercellular gap
- Maintains 10-20 nm intercellular space

Permeability and Ion Selectivity

- **Paracellular Transport Control:**
  - Variable permeability depending on claudin composition
  - Intestinal tight junctions: 10,000x more permeable to Na+ than bladder TJs
  - Kidney tubule thick ascending limb: selective Mg^{2+} permeability via claudin-16
  - Shows claudins form selective pores in the extracellular space
- **Clinical Example:**
  - Claudin-16 mutation → abnormally low Mg^{2+} blood levels
  - Mg^{2+} is lost in urine instead of being reabsorbed
  - Demonstrates the importance of claudin selectivity

Septate Junctions

- **Definition:**
  - Occluding junctions found primarily in invertebrates (Drosophila, other arthropods)
  - Occasionally found in some vertebrate tissues
- **Structure:**
  - Rows of sealing strands with characteristic 10-15 nm spacing
  - Septate (septa = walls between) appearance
  - Appear as ladder-like structures under EM
- **Function:**
  - Block paracellular diffusion
  - Seal epithelial sheets
  - Maintain barrier function (similar to tight junctions)
- **Molecular Components:**
  - Different proteins than mammalian tight junctions
  - Includes neurexin, contactin, and other cell adhesion molecules (CAMs)
  - Shows evolutionary variation in junctional mechanisms



Sepate junction in developing trachea in *Drosophila*

Tight Junction Diseases and Dysfunction

Condition	What is wrong at the junction/barrier?	Simple effect
Claudin-1 deficiency	Mutation in claudin-1 tight-junction protein in skin	Very leaky skin barrier → severe water loss, dehydration (lethal in mice)
Crohn's disease	Tight junctions in intestinal epithelium become "leaky" (change in claudin pattern)	Increased paracellular leak → inflammation of gut wall
Type 2 diabetes (kidney)	Thickening of glomerular and tubular basement membranes, plus changes in junction/claudin expression in renal epithelium	Protein starts leaking into urine; progressive diabetic kidney disease

Part II

Anchoring Junctions

Anchoring Junctions - Overview

- **Definition:**
  - Junctions that mechanically attach cells to other cells or to extracellular matrix
  - Transmit mechanical forces across tissues
  - Provide structural strength to tissues
- **A. CELL-CELL ANCHORING JUNCTIONS:**
  - **Adherens Junctions** (Zonula Adherens)
    - Link actin filaments between cells
  - **Desmosomes** (Macula Adherens)
    - Link intermediate filaments between cells
- **B. CELL-MATRIX ANCHORING JUNCTIONS:**
  - **Focal Adhesions**
    - Link actin filaments to the extracellular matrix
  - **Hemidesmosomes**
    - Link intermediate filaments to the basement membrane

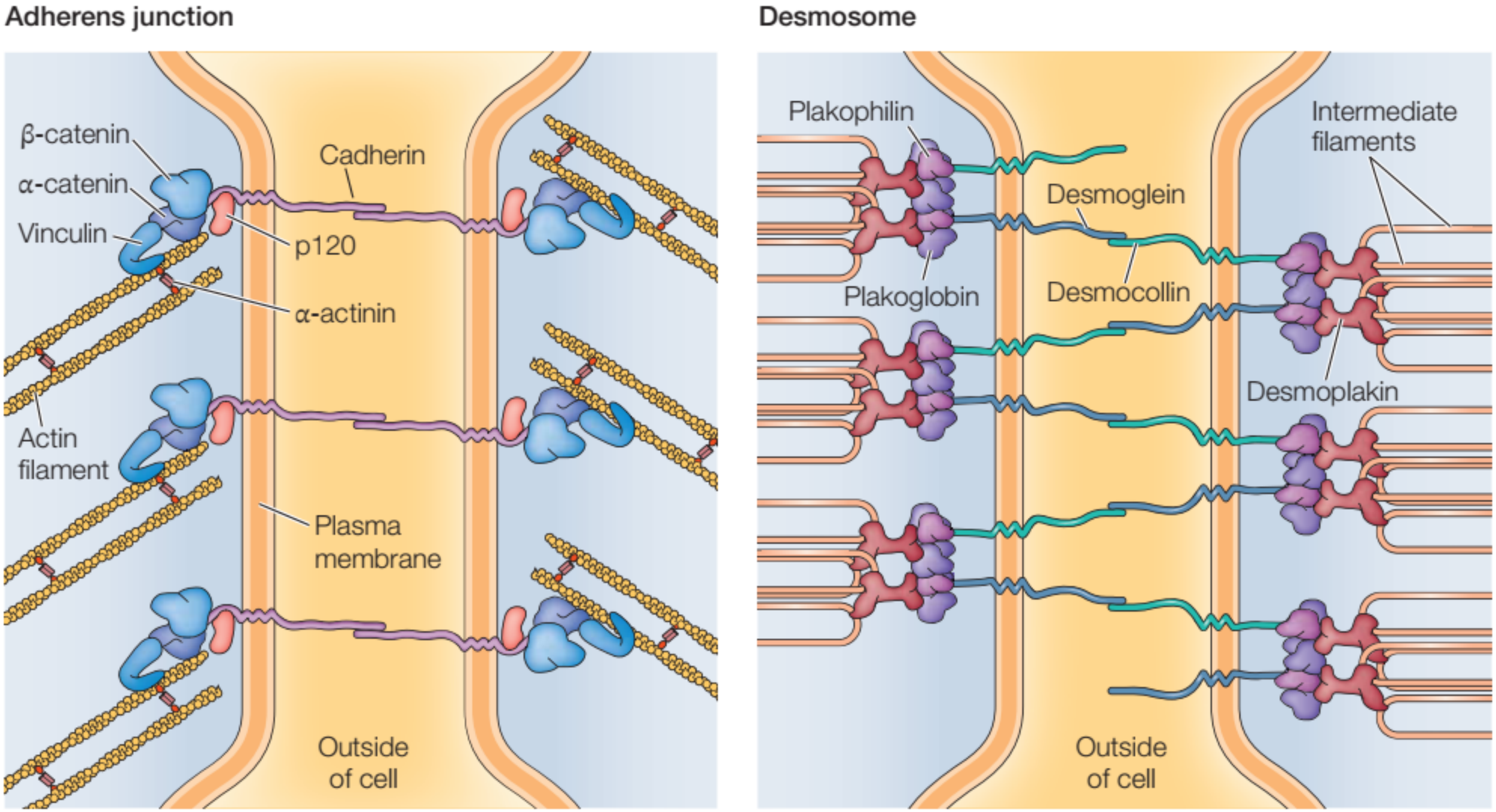
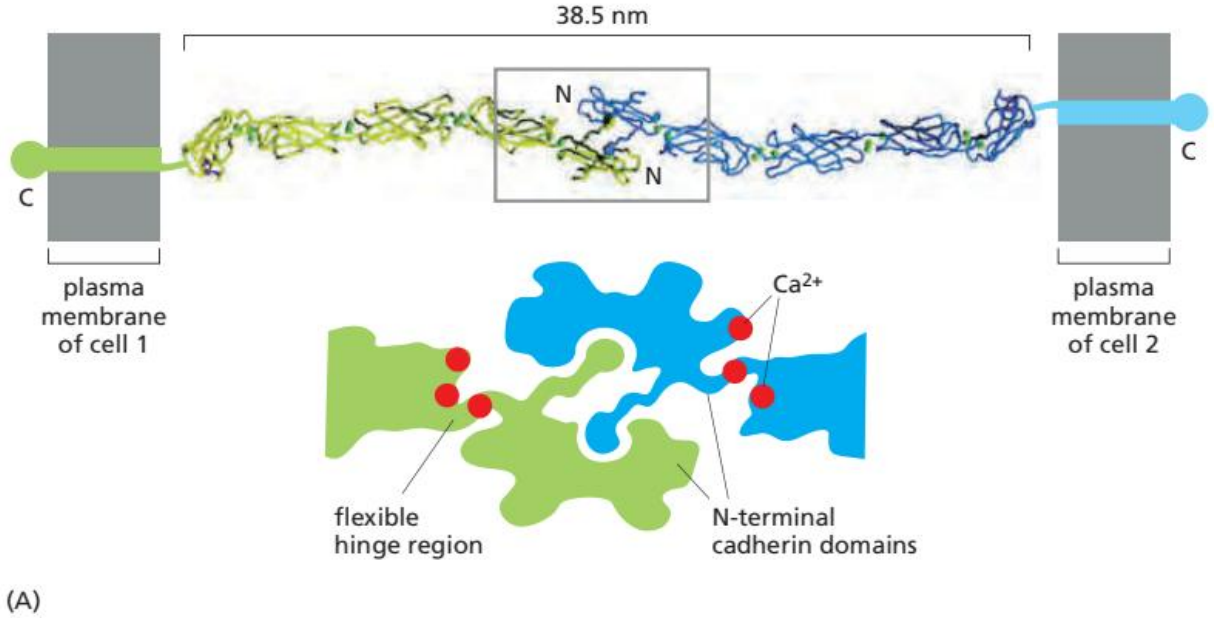


Figure 16.19 Adherens junctions and desmosomes In adherens junctions, cadherins link the actin filaments (cytoskeleton) of one cell to the actin filaments of another. In desmosomes, the desmosomal cadherins (desmoglein and desmocollin) link to intermediate filaments of adjacent cells.

Adherens Junctions - Structure

- **Transmembrane Component:**
  - Classical cadherins (E-cadherin, N-cadherin, P-cadherin)
  - Ca^{2+}-dependent adhesion proteins
  - Homophilic binding (same cadherin to same cadherin on adjacent cells)
- **Cadherin Structure:**
  - 5 extracellular cadherin domains
  - Each domain joined by hinge regions
  - Ca^{2+} ions bind near hinges → maintain rigidity
  - Without Ca^{2+} → hinges become flexible, adhesion fails



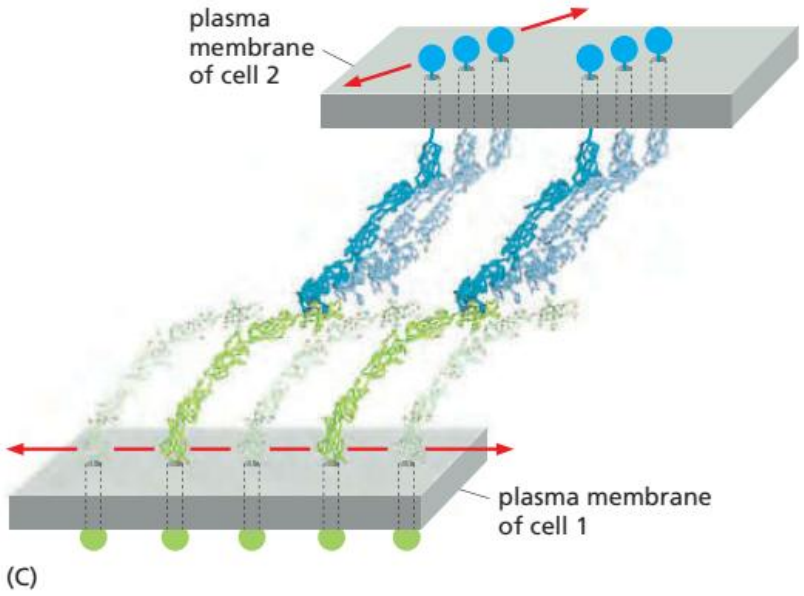


Figure 19–6 Cadherin structure and function. (A) The extracellular region of a classical cadherin contains five copies of the extracellular cadherin domain (see Figure 19–4) separated by flexible hinge regions. Ca^{2+} ions *(red dots)* bind in the neighborhood of each hinge, preventing it from flexing. As a result, the extracellular region forms a rigid, curved structure as shown here. To generate cell–cell adhesion, the cadherin domain at the N-terminal tip of one cadherin molecule binds the N-terminal domain from a cadherin molecule on another cell. The structure was determined by x-ray diffraction of the crystallized C-cadherin extracellular region. (B) In the absence of Ca^{2+}, increased flexibility in the hinge regions results in a floppier molecule that is no longer oriented correctly to interact with a cadherin on another cell—and adhesion fails. (C) At a typical cell–cell junction, an organized array of cadherin molecules functions like Velcro to hold cells together. Cadherins on the same cell are thought to be coupled by side-to-side interactions between their N-terminal head regions, resulting in a linear array like the alternating *green* and *light green* cadherins on the lower cell shown here. These arrays are thought to interact with similar linear arrays on an adjacent cell (*blue* cadherin molecules, top cell). The linear arrays on one cell are perpendicular to those on the other cell, as indicated by the *red arrows*. Multiple perpendicular arrays on both cells interact to form a tight-knit mat of cadherin proteins. (A, based on T.J. Boggon et al., *Science* 296:1308–1313, 2002; C, based on O.J. Harrison et al. *Structure* 19:244–256, 2011.)

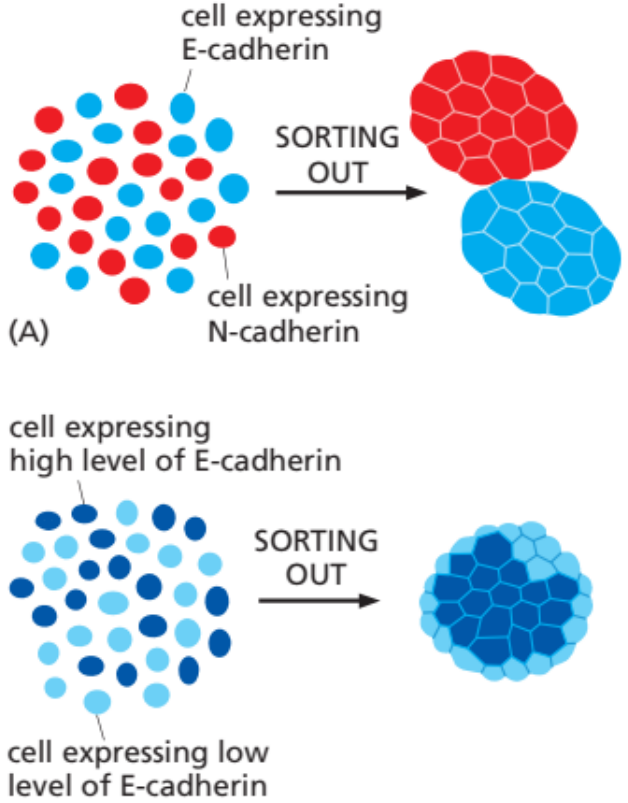


Figure 19–9 Cadherin-dependent cell sorting. Cells in culture can sort themselves out according to the type and level of cadherins they express. This can be visualized by labeling different populations of cells with dyes of different colors. (A) Cells expressing N-cadherin sort out from cells expressing E-cadherin. (B) Cells expressing high levels of E-cadherin sort out from cells expressing low levels of E-cadherin. The cells expressing high levels adhere more strongly and end up internally.

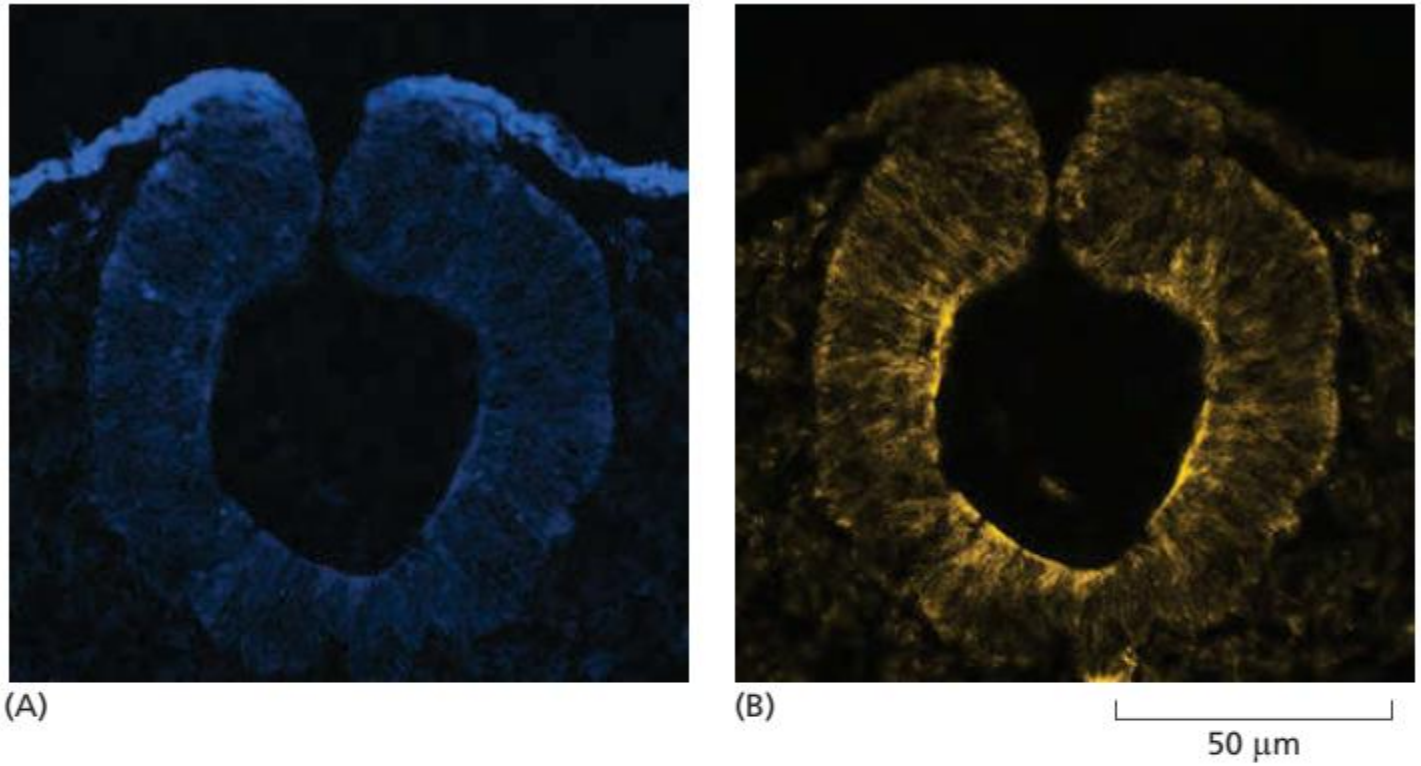


Figure 19–8 Changing patterns of cadherin expression during construction of the vertebrate nervous system. The figure shows cross sections of the early chick embryo, as the neural tube detaches from the ectoderm and then as neural crest cells detach from the neural tube. (A, B) Immunofluorescence micrographs showing the developing neural tube labeled with antibodies against (A) E-cadherin *(blue)* and (B) N-cadherin *(yellow)*. (C) As the patterns of gene expression change, the different groups of cells segregate from one another according to the cadherins they express. (Micrographs courtesy of Miwako Nomura and Masatoshi Takeichi.)

Adherens Junctions - Cytoplasmic Linkage

- Adaptor Proteins Linking Cadherins to Actin:

Protein	Function
ß-catenin	Bridges cadherin tail to α-catenin
α-catenin	Recruits actin-binding proteins
p120-catenin	Regulates cadherin stability
Vinculin	Reinforces linkage to actin filaments

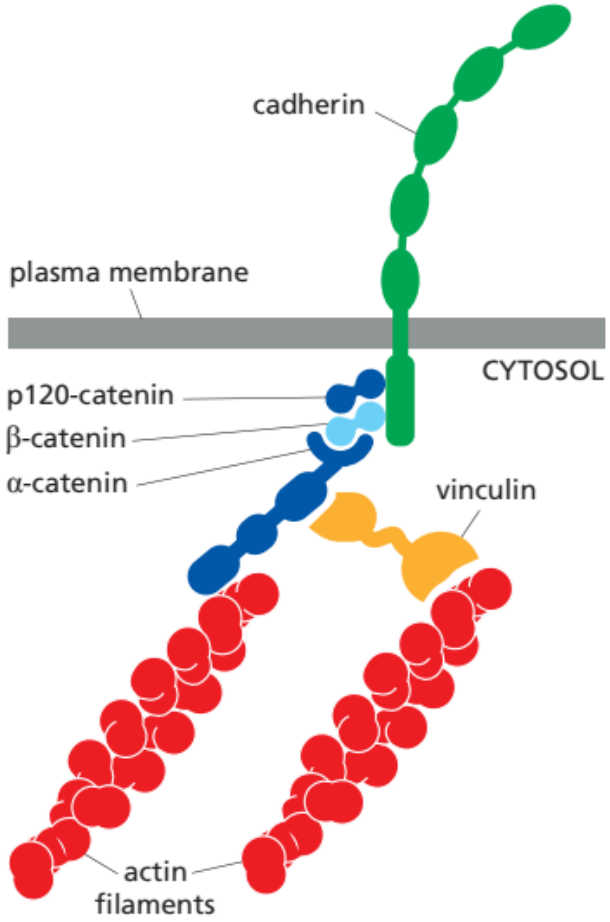


Figure 19–10 The linkage of classical cadherins to actin filaments. The cadherins are coupled indirectly to actin filaments through an adaptor protein complex containing p120-catenin, β-catenin, and α-catenin. Other proteins, including vinculin, associate with α-catenin and help provide the linkage to actin. β-Catenin has a second, and very important, function in intracellular signaling, as we discuss in Chapter 15 (see Figure 15–60). For clarity, this diagram does not show the cadherin of the adjacent cell in the junction.

- **Result:**
  - Cadherin clusters connected to contractile actin-myosin bundles
  - Creates "Velcro-like" adhesion with strength from multiple weak interactions
  - Junctions are dynamic and can be regulated

Adherens Junctions in Epithelia

- **Location and Arrangement:**
  - Form continuous adhesion belt (zonula adherens) near apical surface
  - Encircle each epithelial cell
  - Connected to contractile actin bundles running parallel to plasma membrane
- **Function in Tissue Morphogenesis:**
  - Enable coordinated contraction across epithelial sheets
  - Drive folding and invagination during development
  - Form tubes and vesicles (e.g., neural tube formation)

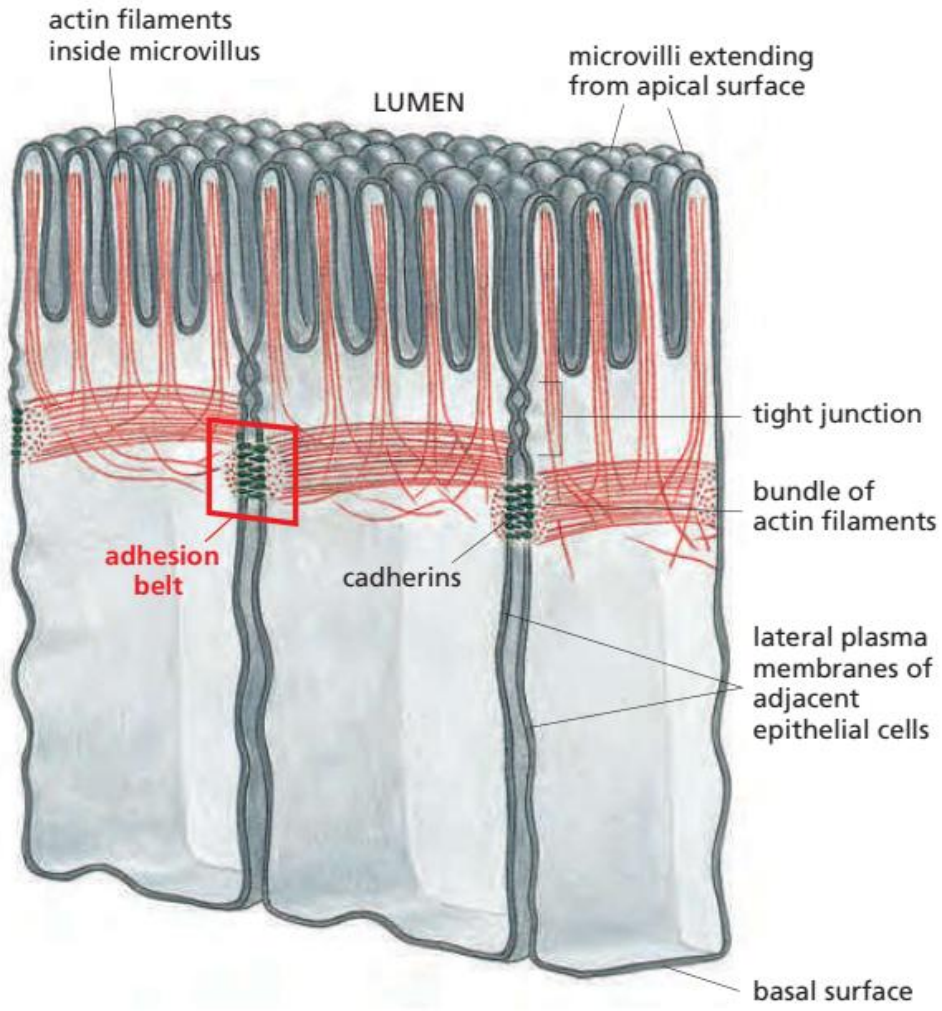


Figure 19–13 Adherens junctions between epithelial cells in the small intestine. These cells are specialized for absorption of nutrients; at their apex, facing the lumen of the gut, they have many microvilli (protrusions that increase the absorptive surface area). The adherens junction takes the form of an *adhesion belt*, encircling each of the interacting cells. Its most obvious feature is a contractile bundle of actin filaments running along the cytoplasmic surface of the junctional plasma membrane. The actin filament bundles are tethered by intracellular proteins to cadherins, which bind to cadherins on the adjacent cell. In this way, the actin filament bundles in adjacent cells are tied together. For clarity, this drawing does not show most of the other cell–cell and cell–matrix junctions of epithelial cells (see Figure 19–2).

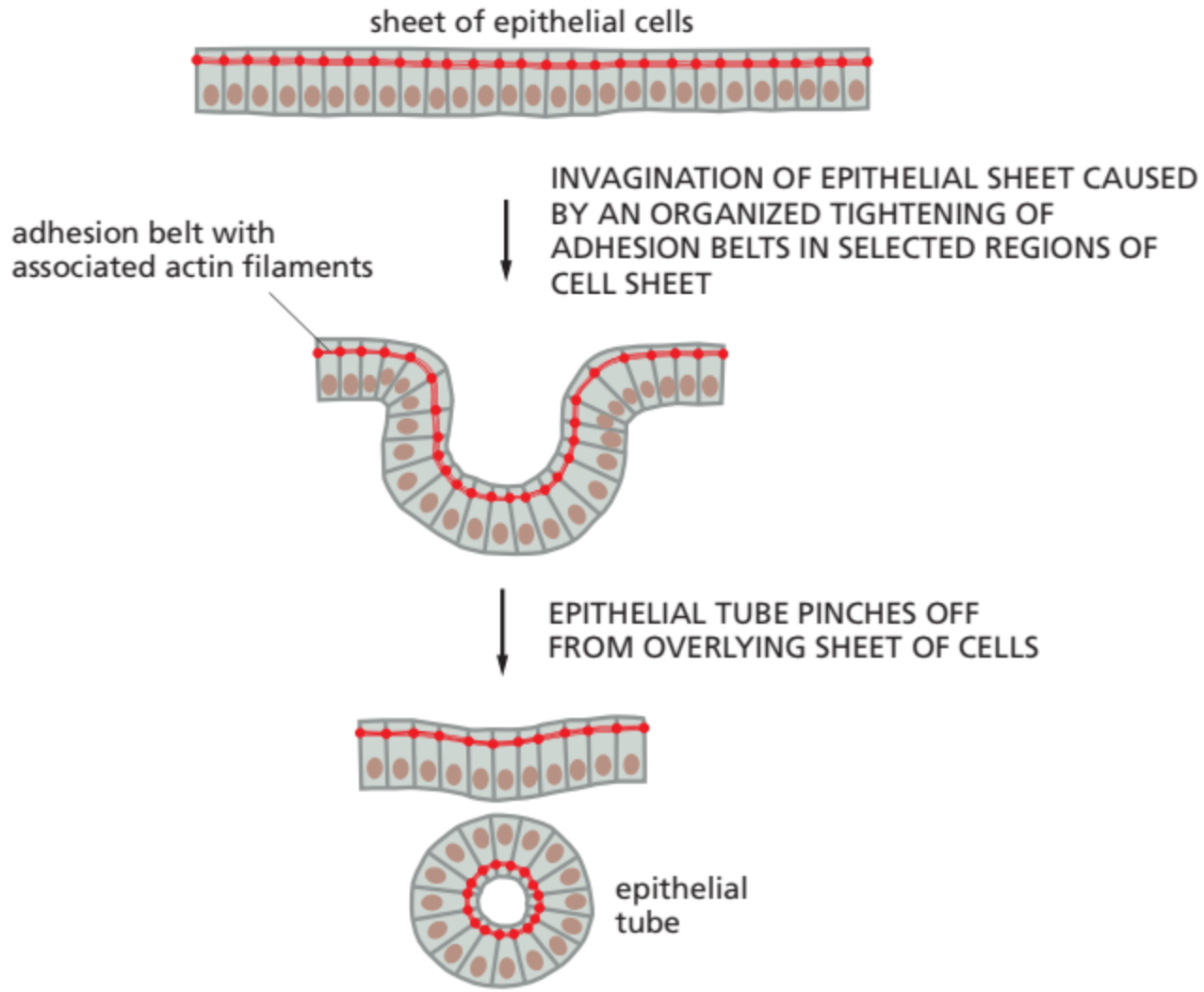


Figure 19–14 The folding of an epithelial sheet to form an epithelial tube. The oriented contraction of the bundles of actin and myosin filaments running along adhesion belts causes the epithelial cells to narrow at their apex and helps the epithelial sheet to roll up into a tube. An example is the formation of the neural tube in early vertebrate development (see Figure 19–8).

Desmosomes - Structure and Function

- **Definition:**
  - Disk-shaped (1 µm diameter) cell-cell junctions
  - Provide mechanical strength in tissues subject to stress
  - Abundant in cardiac muscle, epidermis, uterus
- **Key Features:**
  - **Cadherins Used:** Desmogleins and desmocollins (not classical cadherins)
  - **Cytoplasmic Linkage:** Intermediate filaments (keratin, desmin)
  - **Adaptor Proteins:** Desmoplakin, plakoglobin, plakophilin

Desmosomal Components

- **Transmembrane Cadherins:**
  - **Desmogleins** (Dsg1, Dsg2, Dsg3)
  - **Desmocollins** (Dsc1, Dsc2, Dsc3)
  - Mediate homophilic adhesion across intercellular gap
- **Cytoplasmic Plaque Proteins:**
  - **Plakoglobin** – Links desmogleins/desmocollins to intermediate filaments
  - **Plakophilin** – Additional link protein
  - **Desmoplakin** – Anchors plaque to intermediate filaments
- **Intermediate Filaments:**
  - **Keratin** in epithelial cells
  - **Desmin** in cardiac muscle
  - Create ropelike structural network

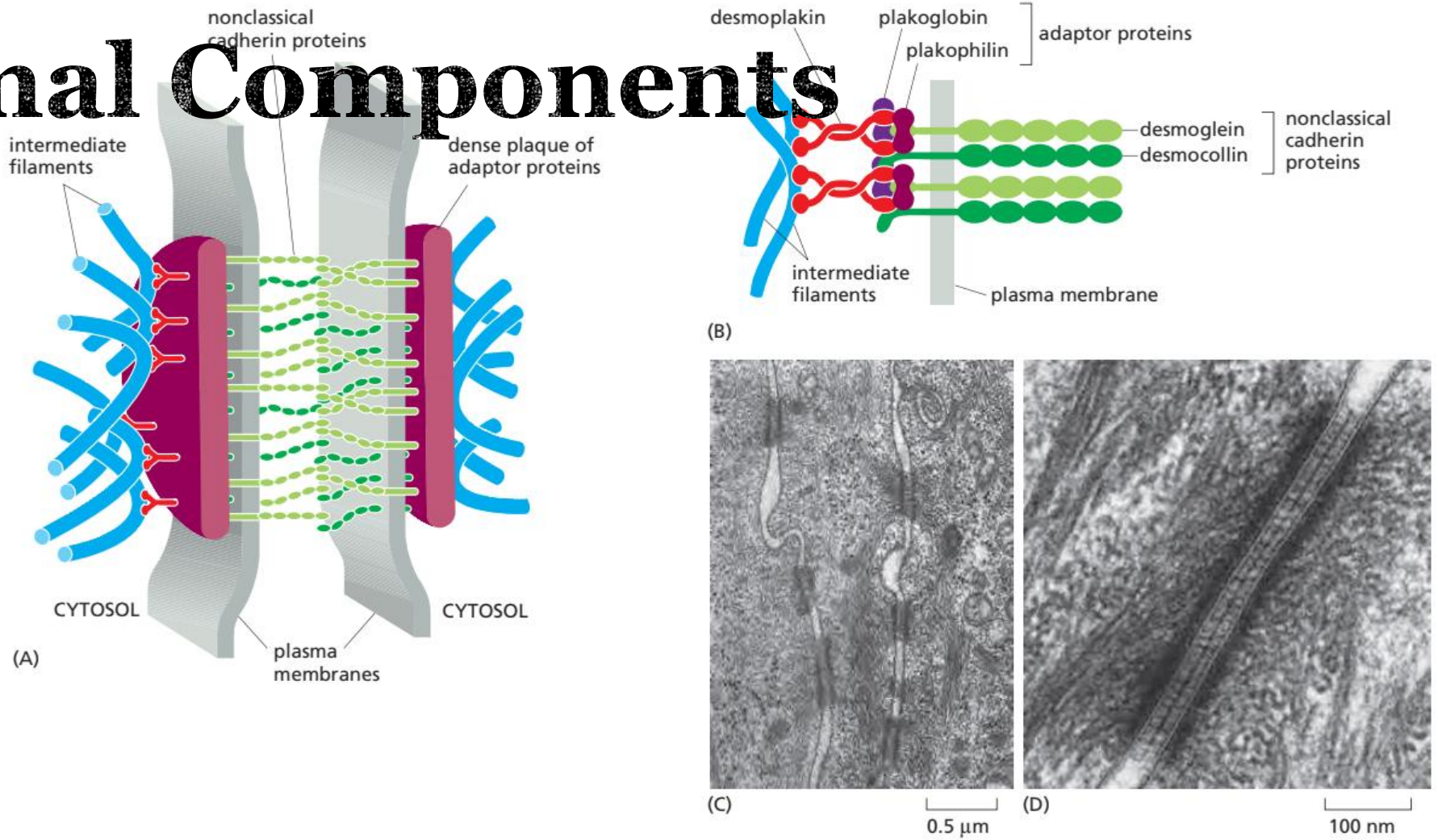
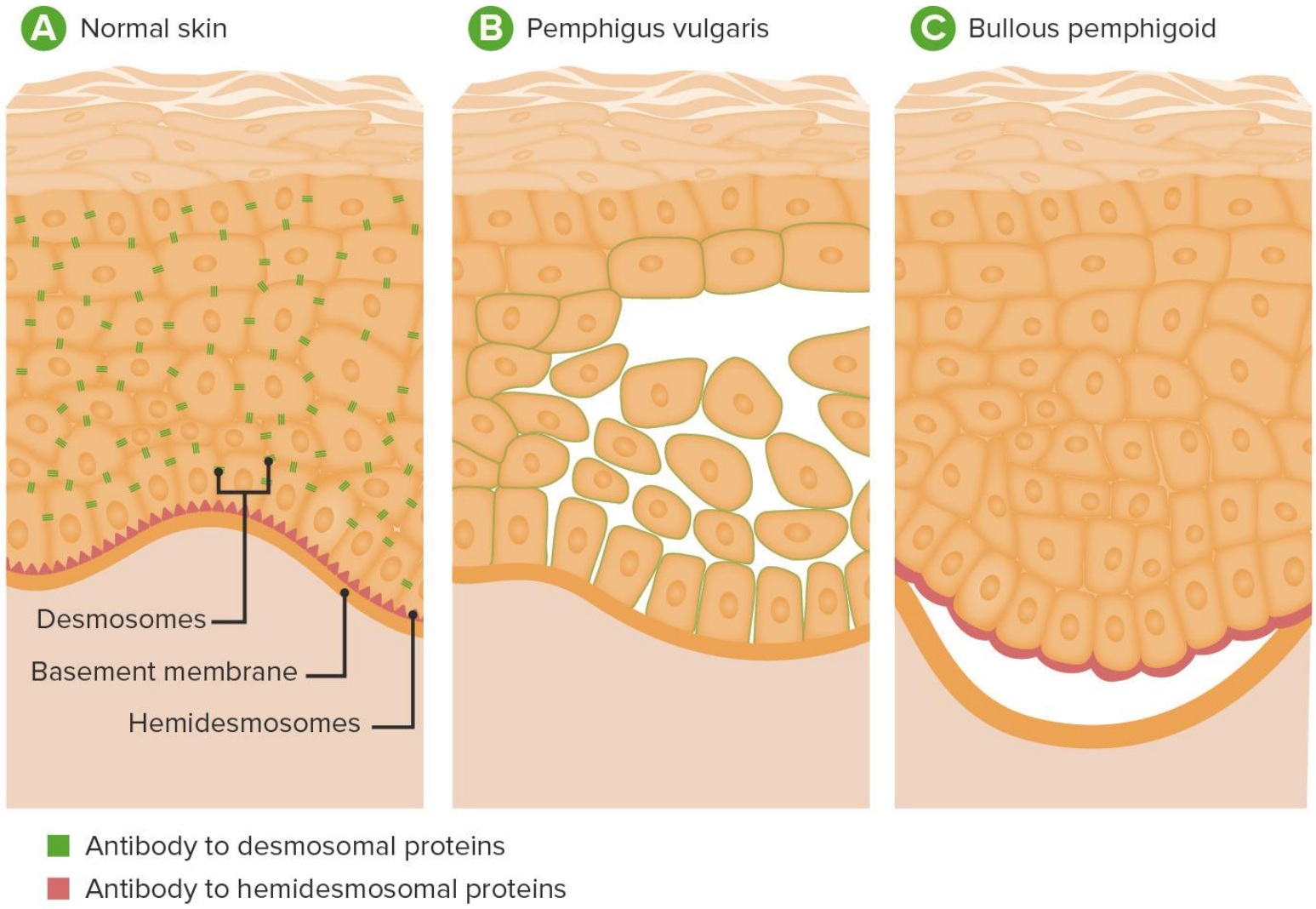


Figure 19–16 Desmosomes. (A) The structural components of a desmosome. On the cytoplasmic surface of each interacting plasma membrane is a dense plaque composed of a mixture of intracellular adaptor proteins. A bundle of keratin intermediate filaments is attached to the surface of each plaque. Transmembrane nonclassical cadherins bind to the plaques and interact through their extracellular domains to hold the adjacent membranes together. (B) Some of the molecular components of a desmosome. Desmoglein and desmocollin are nonclassical cadherins. Their cytoplasmic tails bind *plakoglobin* (γ-catenin) and *plakophilin* (a distant relative of p120-catenin), which in turn bind to *desmoplakin*. Desmoplakin binds to the sides of intermediate filaments, thereby tying the desmosome to these filaments. (C) An electron micrograph of desmosome junctions between three epidermal cells in the skin of a baby mouse. (D) Part of the same tissue at higher magnification, showing a single desmosome, with intermediate filaments attached to it. (C and D, from W. He, P. Cowin and D.L. Stokes, Science 302:109–113, 2003. With permission from AAAS.)

Desmosomal Function and Clinical Disease

- **Mechanical Strength:**
  - Keratin filament networks interconnected through desmosomes
  - Create tissue with great tensile strength
  - Distribute mechanical stress across many attachment points
- **Clinical Disease - Pemphigus Vulgaris:**
  - Autoimmune disease against desmogleins
  - Results in breakdown of desmosomes
  - Severe blistering of skin and mucous membranes
  - Demonstrates importance of desmosomal adhesion



Focal Adhesions - Cell-Matrix Junctions

- **Definition:**
  - Integrin-mediated attachment sites where cells bind to extracellular matrix
  - Link actin cytoskeleton to matrix proteins
- **Structure:**
  - Large protein complexes (>100 proteins)
  - Can be 1-10 micrometers in size
  - Dynamic structures with rapid assembly/disassembly
- **Function:**
  - Transmit mechanical forces between cell and matrix
  - Sense mechanical properties of environment
  - Transduce signals affecting cell behavior

Focal Adhesion Molecular Components

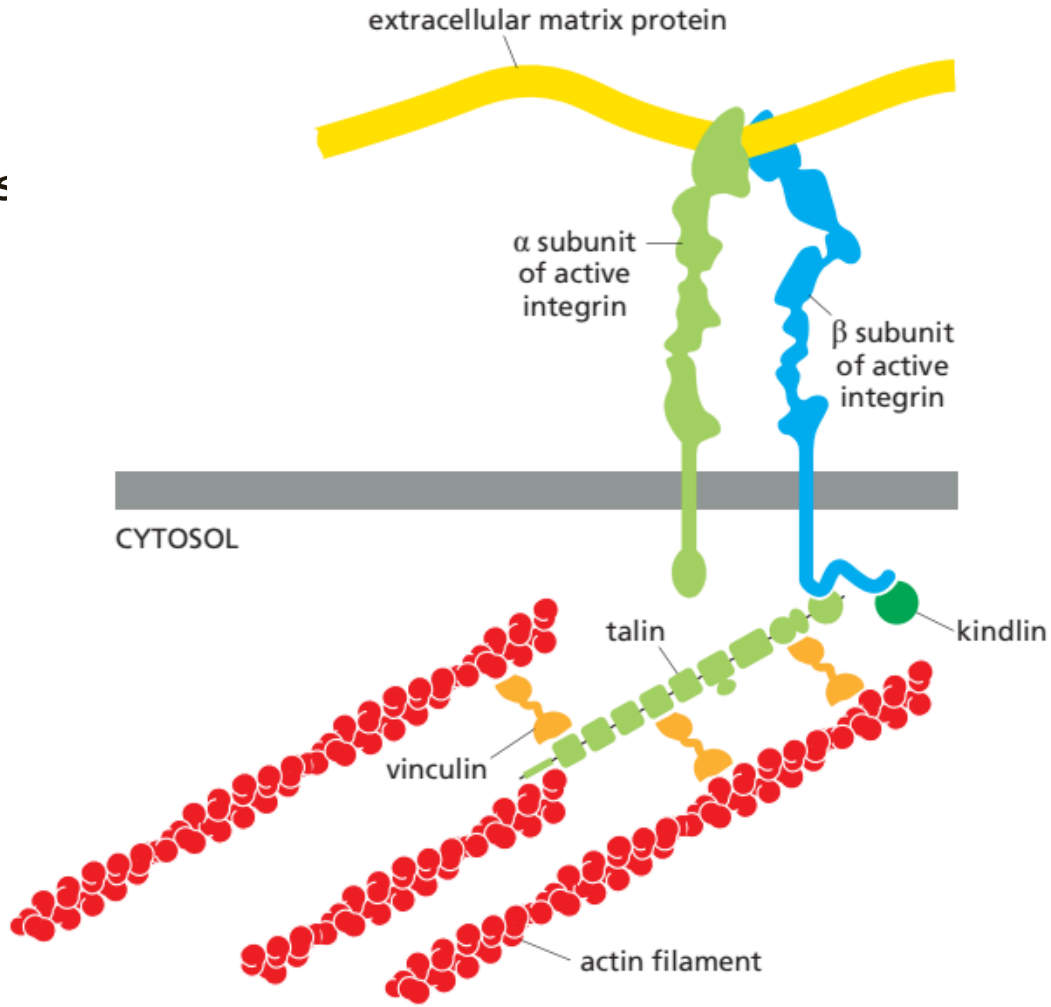
Key Proteins:

Component	Function
Integrins	Transmembrane matrix receptors
Talin	Major adaptor protein; binds integrin tail
Vinculin	Reinforces actin linkage
Kindlin	Regulates integrin activation
Paxillin	Scaffolding protein
FAK	Focal Adhesion Kinase; signaling enzyme

- **Actin Linkage:**
  - Integrin cytoplasmic tails bind talin
  - Talin recruits other proteins
  - Network links to stress fiber actin bundles

Integrin Structure and Function

- **Heterodimeric Structure:**
  - Composed of α and β subunits
  - 18 α subunits × 8 β subunits = 24 different integrins in humans
  - Form different ligand-binding pockets
  - Ca^{2+} and Mg^{2+} affect the integrin and ligand binding
- **Integrin Activation (Inside-Out Signalling):**
  - Resting integrin = low affinity for matrix proteins
  - Cytoplasmic signals → conformational change
  - High-affinity integrin binds matrix proteins (fibronectin, collagen, laminin)
- **Outside-In Signalling:**
  - Matrix binding → conformational change
  - Recruits adaptor proteins
  - Activates signalling kinases
  - Affects cell migration, proliferation, survival



Hemidesmosomes - Basal Cell Anchoring

- **Definition:**
  - Half-desmosomes anchoring epithelial cells to the basement membrane
  - Found on the basal surface of epithelial tissues
  - Link epithelium to the underlying connective tissue
- **Structure:**
  - Integrin-mediated (α6β4 integrin)
  - Anchors intermediate filaments to the basal lamina
  - Electron-dense cytoplasmic plaque visible on the inner membrane surface
- **Components:**
  - **Integrins**: α6β4 (main matrix receptor)
  - **Adaptor Proteins**: Plectin, BP180, BP230
  - **Filaments**: Keratin intermediate filaments
  - **Matrix Binding**: Laminin-5 in basement membrane

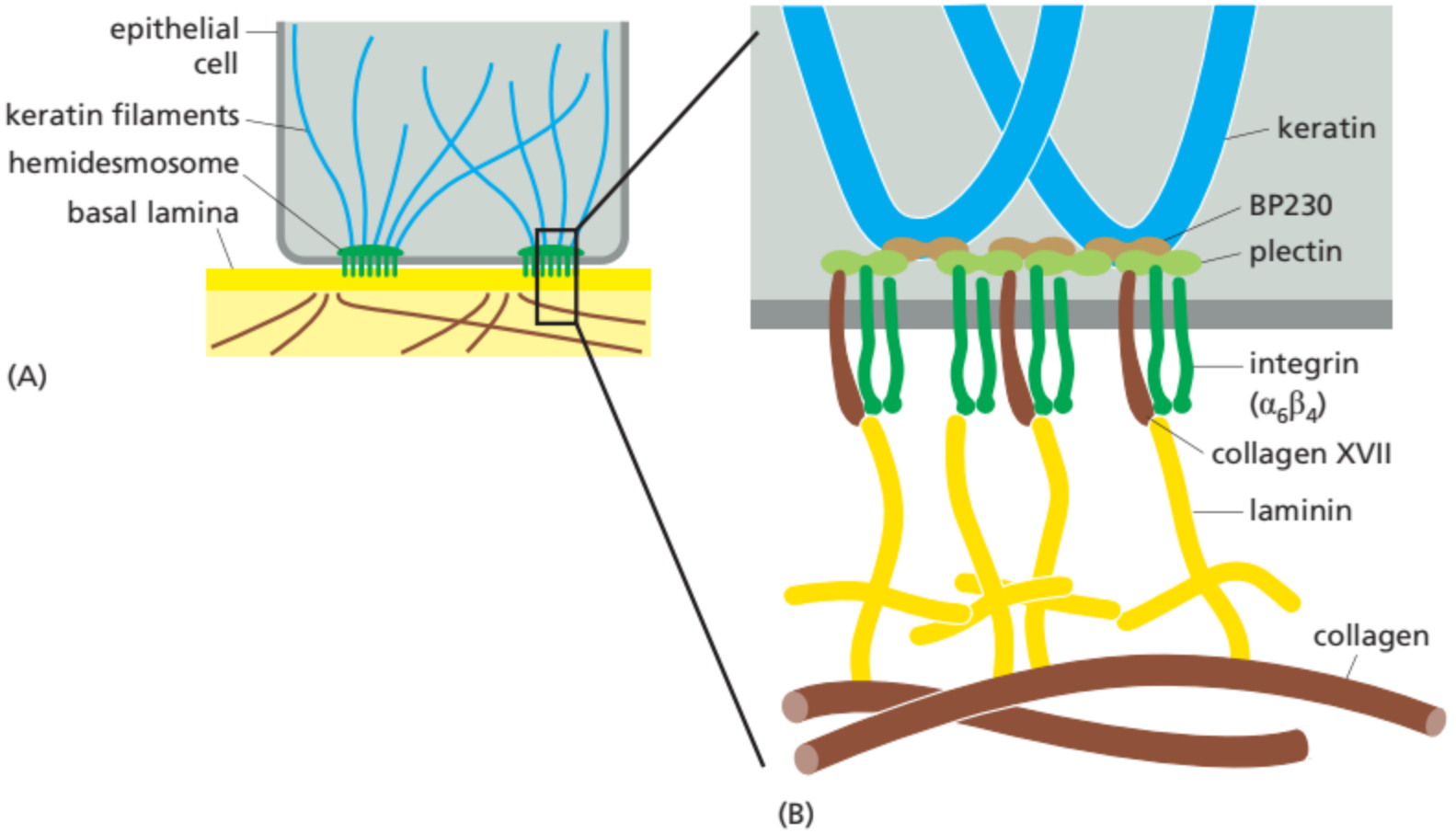


Figure 19–56 Hemidesmosomes. (A) Hemidesmosomes spot-weld epithelial cells to the basal lamina, linking laminin outside the cell to keratin filaments inside it. (B) Molecular components of a hemidesmosome. A specialized integrin ($\alpha_6\beta_4$ integrin) spans the membrane, attaching to keratin filaments intracellularly via adaptor proteins called plectin and BP230, and to laminin extracellularly. The adhesive complex also contains, in parallel with the integrin, an unusual collagen family member known as collagen type XVII; this has a membrane-spanning domain attached to its extracellular collagenous portion. Defects in any of these components can give rise to a blistering disease of the skin. One such disease, called *bullous pemphigoid*, is an autoimmune disease in which the immune system develops antibodies against collagen XVII or BP230.

Hemidesmosomal Diseases

- **Bullous Pemphigoid:**
  - Autoimmune attack on BP180 or BP230
  - Results in blistering at the dermal-epidermal junction
  - Demonstrates the importance of hemidesmosomes in preventing separation
- **Epidermolysis Bullosa:**
  - Genetic mutations in:
    - α6 or β4 integrin genes
    - Collagen VII gene
    - Laminin-5 gene
  - Results in severe blistering and skin fragility
  - Shows critical importance of integrin-matrix connection

Part III

Communicating Junctions

Gap Junctions - Overview

- **Definition:**
  - Specialised intercellular channels connecting the cytoplasm of adjacent cells
  - Allow direct communication via small molecules and ions
  - Present in most animal tissues
- **Key Features:**
  - Aqueous channels spanning the intercellular space
  - 1.5 nm diameter channel
  - Selective permeability: molecules <1000 daltons pass through
- **Location and Tissues:**
  - Epithelial cells, cardiac muscle, smooth muscle
  - Nervous tissue, connective tissue
  - Some immune cells

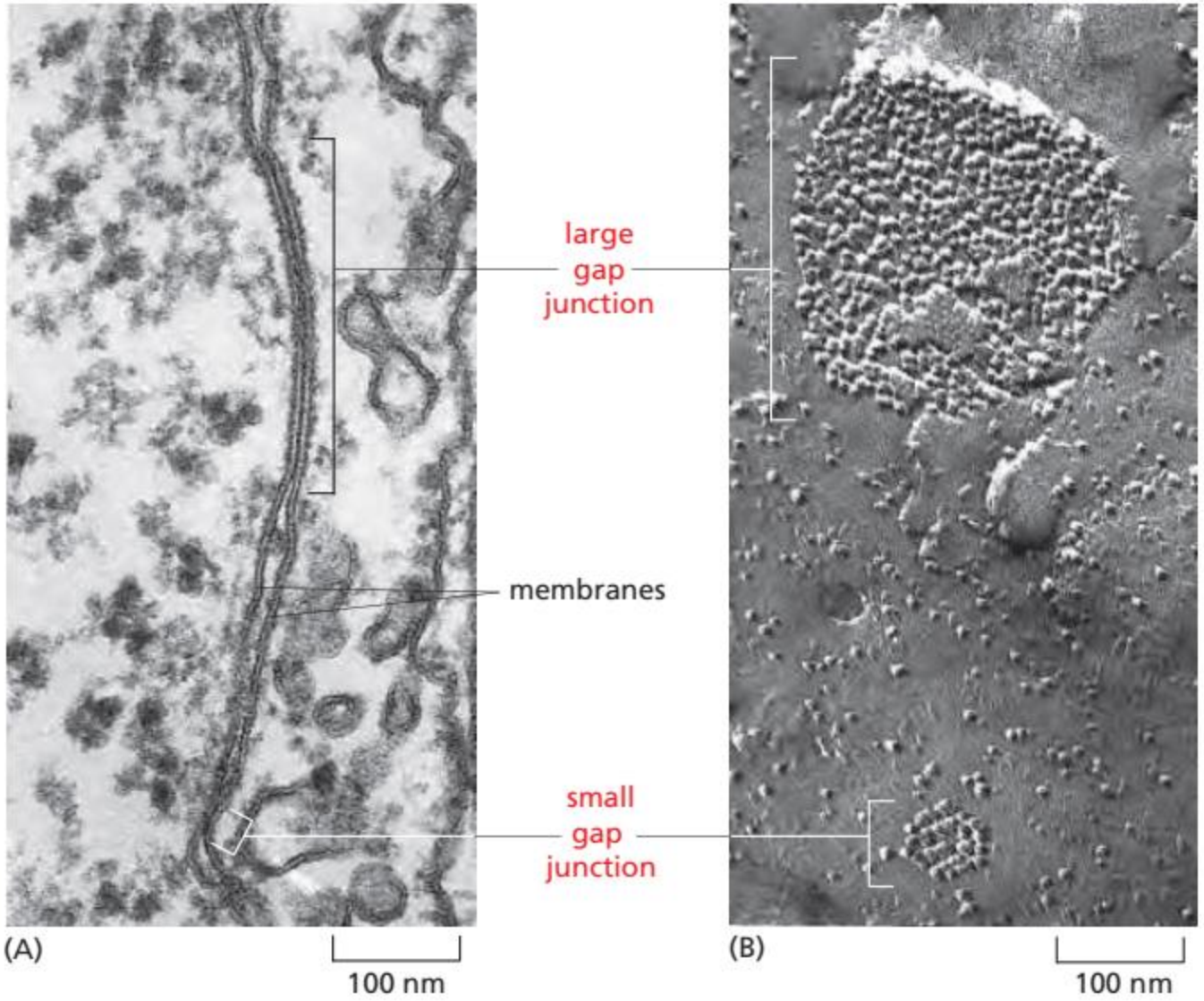


Figure 19–23 Gap junctions as seen in the electron microscope. (A) Thin-section and (B) freeze-fracture electron micrographs of a large and a small gap-junction plaque between fibroblasts in culture. In (B), each gap junction is seen as a cluster of homogeneous intramembrane particles. Each intramembrane particle corresponds to a connexon (see Figure 19–25). (From N.B. Gilula, in Cell Communication [R.P. Cox, ed.], pp. 1–29. New York: Wiley, 1974.)

Gap Junction Molecular Architecture

- **Connexin Proteins:**
  - 21 different human connexins (Cx types)
  - Four transmembrane domains
  - 6 connexins assemble → **connexon** (hemichannel)
  - Two connexons (one from each cell) → complete **channel**
- **Connexon Assembly:**
  - 6 connexin subunits arranged in ring
  - Central aqueous pore approximately 1.5 nm diameter
  - Can be homomeric (all same connexin) or heteromeric (mixed connexins)
- **Channel Alignment:**
  - Connexons on adjacent cell membranes must align precisely
  - Results in complete channel spanning both plasma membranes
  - Forms "gap junction plaque" containing many channels

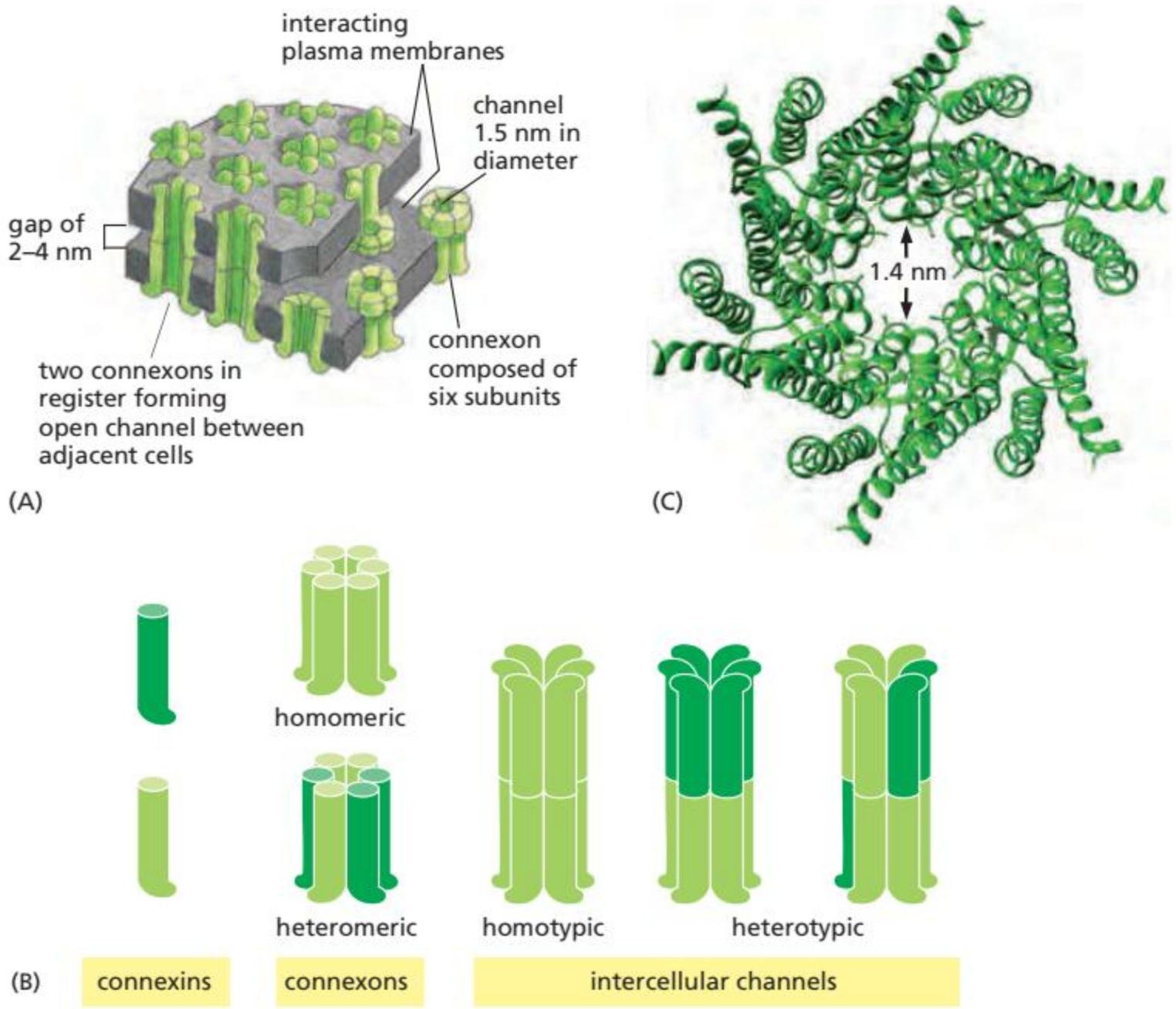


Figure 19–25 Gap junctions. (A) A drawing of the interacting plasma membranes of two adjacent cells connected by gap junctions. Each lipid bilayer is shown as a pair of *red* sheets. Protein assemblies called connexons *(green)*, each of which is formed by six connexin subunits, penetrate the apposed lipid bilayers. Two connexons join across the intercellular gap to form a continuous aqueous channel connecting the two cells. (B) The organization of connexins into connexons, and connexons into intercellular channels. The connexons can be homomeric or heteromeric, and the intercellular channels can be homotypic or heterotypic. (C) The high-resolution structure of a homomeric gap-junction channel, determined by x-ray crystallography of human connexin 26. In this view, we are looking down on the pore, formed from six connexin subunits. The structure illustrates the general features of the channel and suggests a pore size of about 1.4 nm, as predicted from studies of gap-junction permeability with molecules of various sizes (see Figure 19–24). (PDB code: 2ZW3.)

(a)

(b)

(c)

(d)

FIGURE 7.29 Gap junctions. (a) Electron micrograph of a section through a gap junction perpendicular to the plane of the two adjacent membranes. The "pipelines" between the two cells are seen as electron-dense beads on the apposed plasma membranes. (b) Schematic model of a gap junction showing the arrangement of six connexin subunits to form a connexon, which contains half of the channel that connects the cytoplasm of the two adjoining cells. Each connexin subunit is an integral protein with four transmembrane domains. (c) High-resolution images derived from atomic force microscopy of the extracellular surface of a single connexon in the open (left) and closed (right) conformations. Closure of the connexon was induced by exposure to elevated Ca^{2+} ion concentration. (d) Freeze-fracture replica of a gap junction plaque showing the large numbers of connexons and their high concentration. (The crystal structure of a gap junction can be found in *Nature* 458: 597, 2009.)

SOURCE: (a) From Camillo Peracchia and Angela F. Dulhunty, *J. Cell Biol.* 70:419, 1976, Fig. 5. Reproduced with permission of the Rockefeller University Press; (c) Courtesy Gina E. Sosinsky. From *J. Cell Science* 116:4479, 2003; by permission of The Company of Biologists, Ltd. http://jcs.biologists.org/content/116/22/4479.full?sid=43a03f80-6c77-4b57-ad32-7d6e8884a69e; (d) Don W. Fawcett / Science Source Images.

Gap Junction Function

- **Electrical Coupling:**
  - Allows direct passage of ions (Na^+, K^+, Ca^{2+})
  - Synchronizes contractions in cardiac muscle
  - Coordinates peristalsis in smooth muscle
- **Metabolic Coupling:**
  - Passes small metabolites: glucose, amino acids, nucleotides, ATP
  - Coordinates metabolic activities across tissue
  - Allows sharing of coenzymes in avascular tissues (lens)
- **Signaling:**
  - Allows passage of intracellular signals:
    - Cyclic AMP (cAMP)
    - Inositol trisphosphate (IP_3)
    - Ca^{2+} ions
  - Coordinates cellular responses to stimuli

Gap Junction Gating and Regulation

- **Gating Mechanisms:**
  - Channels can open or close in response to stimuli
  - Regulated by:
    - Membrane voltage
    - Intracellular pH
    - Free Ca^{2+} concentration
    - Phosphorylation
- **Physiological Importance:**
  - High Ca^{2+} closes channels (protects cells during injury)
  - pH changes regulate channel function
  - Allows selective communication during development
- **Dynamic Assembly:**
  - Gap junctions are dynamic structures
  - Connexons continuously assembled and removed
  - Half-life of connexin proteins: ~3-5 hours
  - Allows rapid changes in junctional communication

Gap Junction Diseases

Connexin Mutations Cause Multiple Diseases:

Disease	Connexin Affected	Symptoms
Charcot-Marie-Tooth (CMT)	Cx32	Peripheral nerve degeneration
Congenital Cataracts	Cx43, Cx46	Eye lens opacity
Deafness	Cx26, Cx43	Hearing loss
Skin Disorders	Cx26, Cx30	Eczema, erythrokeratoderma

Why Limited Compensation?

- ❖ Not all connexins can form functional channels together
- ❖ Mutant connexins may act as "dominant negative"
- ❖ Trap normal connexins during processing
- ❖ Tissue-specific reliance on particular connexins

Gap Junctions and Cancer

- **Normal Cell Function:**
  - Gap junctional intercellular communication (GJIC) active in normal cells
  - Allows coordination of growth and differentiation
- **Cancer Cell Dysfunction:**
  - Many cancer cells show decreased or absent GJIC
  - Loss of communication may allow uncontrolled growth
  - Blocking GJIC can promote malignant transformation
- **Experimental Evidence:**
  - C6 glioma cells transfected with the Cx43 gene
  - Regain GJIC → dramatically reduced tumour growth
  - Suggest gap junctions have tumour-suppressive role
  - Restoration of gap junctions may be therapeutic

Functional Organization

- Tight junctions → seal epithelium
- Adherens junctions → mechanical coupling of actin
- Desmosomes → mechanical coupling of intermediate filaments
- Gap junctions → intercellular communication
- Hemidesmosomes → anchoring to basement membrane

Tissue-Specific Junction Expression

- **Intestinal Epithelium:**
  - Tight junctions: absorptive barrier
  - Adherens junctions: mechanical integrity
  - Desmosomes: stress distribution
  - Gap junctions: coordinate nutrient uptake
- **Cardiac Muscle:**
  - Gap junctions: electrical coupling (Cx43)
  - Adherens junctions: force transmission
  - Desmosomes: mechanical strength
- **Skin Epidermis:**
  - Tight junctions: barrier (claudin-1)
  - Desmosomes: mechanical strength (keratin network)
  - Hemidesmosomes: basal anchoring
- **Nervous System:**
  - Gap junctions: electrical synapses
  - Tight junctions: blood-brain barrier

References and Further Reading

- Alberts et al. (2015). *Molecular Biology of the Cell* (6th ed.). Garland Science.
- Karp (2016). *Molecular Biology* (8th ed.). Wiley-Blackwell.
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Suggested Reading

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