Epithelium

3

LEARNING OBJECTIVES OUTLINE

I. FEATURES & FUNCTIONS

A. *Composition*
- **1.** Cells
- **2.** ECM (limited)

B. *Classification of epithelia*
- **1.** Surface epithelia
- **2.** Glandular epithelia
- **3.** Special epithelia

C. *Important characteristics*
- **1.** Covers or lines all body surfaces
- **2.** Polarity (epithelial cells have specific apical, lateral & basal domains)
- **3.** Characterized by specific intermediate filaments called cytokeratins
- **4.** Attached to underlying CT via ECM basement membrane
- **5.** Generally avascular
- **6.** Gives rise to majority of glands
- **7.** High regenerative capacity; plasticity
- **8.** Great diversity of function

II. SURFACE EPITHELIA

A. *Simple epithelia*
- **1.** Definition: single layer of cells
- **2.** Types & examples
  - **a.** Simple squamous
    - **i.** Kidney: Bowman's capsule, loop of Henle
    - **ii.** Lung: alveoli
    - **iii.** Endothelium: vasa, heart
    - **iv.** Mesothelium: serosae
  - **b.** Simple cuboidal
    - **i.** Kidney: PCT, DCT, small collecting ducts
    - **ii.** Exocrine glands: small ducts
  - **c.** Simple columnar
    - **i.** Alimentary tract: e.g., stomach, intestines, gallbladder
    - **ii.** Exocrine glands: small ducts

B. *Stratified epithelia*
- **1.** Definition: multiple layers of cells
- **2.** Types & examples
  - **a.** Stratified squamous (SSE)
    - **i.** Wet surfaces (mucosae)
      - "Nonkeratinizing" (=mucous) (="hypokeratinizing") (SSNKE)
      - Parakeratosis (physiologic)
      - Orthokeratosis (physiologic)
    - **ii.** Dry surfaces (skin)
      - "Keratinizing" (=cutaneous); orthokeratosis (SSKE)
      - Parakeratosis (pathologic)
    - **iii.** Keratins: cytoskeletal proteins present in all SSE
  - **b.** Stratified cuboidal
    - **i.** Exocrine glands: larger ducts
    - **ii.** Often mixed with stratified columnar
  - **c.** Stratified columnar
    - **i.** Exocrine glands: larger ducts
    - **ii.** Portion of male urethra

C. *Pseudostratified epithelia*
- **1.** Definition: all cells touch basal lamina, but all cells don't reach free surface
- **2.** Types & examples
  - **a.** Respiratory: pseudostratified ciliated columnar with goblet cells
  - **b.** Urinary: urothelium (=transitional epithelium)
  - **c.** Male genital tract
    - **i.** Ductus epididymidis
    - **ii.** Ductus deferens
    - **iii.** Seminal vesicles
    - **iv.** Prostate

III. GLANDULAR EPITHELIA

A. *Classification*
- **1.** Types of glands
  - **a.** Exocrine
  - **b.** Endocrine (hemocrine)
  - **c.** Paracrine
  - **d.** Autocrine
- **2.** Exocrine gland criteria
  - **a.** Ducts
  - **b.** Secretory components
  - **c.** Types of secretion
  - **d.** Mechanisms of secretion

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- **B.** *Ducts: structure in exocrine glands*
  - **1.** Simple glands (=unbranched ducts)
  - **2.** Compound glands (=branched ducts)
- **C.** *Secretory components*
  - **1.** Number of secretory cells
    - **a.** Unicellular (e.g., goblet cells)
    - **b.** Multicellular glands (majority)
  - **2.** Structure of secretory units
    - **a.** Tubular
    - **b.** Acinar/alveolar
- **D.** *Types of secretion* (secretory product)
  - **1.** Mucous
  - **2.** Serous
  - **3.** Seromucous
    - **a.** Mixed secretions
    - **b.** Serous demilunes (fact or artifact)
    - **c.** Intercellular canaliculi
- **E.** *Mechanisms of secretion* (methods of release)
  - **1.** Merocrine
    - **a.** Exocytosis
    - **b.** Examples
      - **i.** Salivary glands
      - **ii.** Pancreas
  - **2.** Apocrine
    - **a.** Decapitation secretion
    - **b.** Examples
      - **i.** Apocrine sweat glands
      - **ii.** Mammary glands
  - **3.** Holocrine
    - **a.** Secretion of whole disintegrated cells
    - **b.** Sebaceous glands
- **F.** *Myoepithelial cells*
  - **1.** Contractile, branched epithelial cells
  - **2.** Located between glandular epithelial cells and basement membrane
  - **3.** Contain actin filaments; smooth muscle-like
  - **4.** Facilitate glandular secretion

IV. SPECIAL EPITHELIA

- **A.** *Myoepithelium*
- **B.** *Neuroepithelium*
  - **1.** Non-neuronal
    - **a.** Receptor cells of taste buds
    - **b.** Hair cells of inner ear
  - **2.** Neuronal
    - **a.** Sensory cells of olfactory epithelium
    - **b.** Rods and cones of retina
- **C.** *Seminiferous epithelium*
  - **1.** Germinal epithelium of testis
    - **a.** Spermatogenic (germ) cells
    - **b.** Supporting (Sertoli) cells
  - **2.** Sertoli cells: simple epithelium
  - **3.** Spermatogenic cells: stratified

V. EPITHELIAL SPECIALIZATIONS

- **A.** *Definition*: morphologic & functional specializations at, on and/or within membrane surfaces of epithelial cells
- **B.** *Nomenclature of epithelial surfaces*
  - **1.** Apical
  - **2.** Lateral
  - **3.** Basal
- **C.** *Specializations of apical surfaces* (=free cell surfaces facing lumen)
  - **1.** Microvilli [L. *villus* =shaggy hair]
    - **a.** Structure
      - **i.** Evagination of cell membrane
      - **ii.** Core of actin filaments
    - **b.** Important locations
      - **i.** Striated (cuticular) border (gut)
      - **ii.** Brush border (kidney)
      - **iii.** Stereocilia (epididymis)
  - **2.** Cilia and flagella
    - **a.** Structure
      - **i.** Evagination of cell membrane
      - **ii.** Core of microtubules: 9x2+2 (=axoneme)
      - **iii.** Basal bodies: 9x3
    - **b.** Important locations: respiratory, reproductive systems
  - **3.** Glycocalyx
    - **a.** Glycoproteins
    - **b.** Glycolipids
    - **c.** Proteoglycans
- **D.** *Specializations of lateral surfaces* (=surfaces facing adjacent cells)
  - **1.** Junctional (jxnal) complexes
    - **a.** Array of multiple cell-to-cell jxns
    - **b.** Terminal bars of LM
  - **2.** Zonula occludens (=tight junction)
    - **a.** Integral membrane proteins
      - **i.** Claudins
      - **ii.** Occludin
      - **iii.** Homotypic junctions
    - **b.** Peripheral membrane proteins
      - **i.** ZO-1, -2, -3
      - **ii.** Others (cingulin, spectrin)
    - **c.** Cytoskeleton binding (F-actin)
    - **d.** Major functions
      - **i.** Regulate paracellular transport
      - **ii.** Restrict membrane flow
    - **e.** Occurrence: Usually part of junctional complex
  - **3.** Zonula adherens (=adhering band)
    - **a.** Integral membrane proteins
      - **i.** E-cadherins
      - **ii.** Homotypic junctions
    - **b.** Peripheral membrane proteins
      - **i.** Catenins (α β
      - **ii.** Plakoglobin (γ-catenin)

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iii. α-Actinin
iv. Vinculin
c. Cytoskeleton binding: F-actin
d. Major function: adhesion
e. Occurrence: part of jxnal complex

4. Macula adherens (=desmosome; adhering spot)
a. Integral membrane proteins
i. Desmocollins (cadherins)
ii. Desmogleins (cadherins)
iii. Homotypic junctions
b. Peripheral membrane proteins
i. Desmoplakin
ii. Plakoglobin (γ-catenin)
iii. Plakophilin
c. Cytoskeleton binding: cytokeratins
d. Major functions: adhesion; support
e. Occurrence: alone or part of jxn complex

5. Macula communicans (=nexus, gap junction, communicating junction)
a. Integral membrane proteins
i. Connexins (monomers)
ii. Connexons (hexamer channels)
iii. Homotypic or heterotypic jxns
b. Major function: communication
c. Occurrence: widespread in epithelia and other tissues

E. *Specializations of basal surfaces* (=surfaces along basement membrane)
1. Basement membrane
a. Basal lamina (epithelial)
i. Lamina lucida (rara): laminin, perlecan
ii. Lamina densa: type IV collagen
iii. Analogous to external lamina of adipose, muscle, perineurial, and Schwann cells
b. Reticular lamina (CT; not constant)
i. Type III collagen
ii. Ground substance
c. Anchoring fibrils: type VII collagen
2. Hemidesmosome
a. Integral membrane proteins
i. Integrins
ii. Binds to laminin of ECM
iii. Heterotypic junction
b. Peripheral protein (plectin)
c. Cytoskeleton binding (cytokeratins)
d. Major function: adhesion to ECM
3. Basal (basolateral) foldings of plasma membrane
a. Infoldings
i. Transporting epithelia (PCT & DCT: kidneys; striated salivary ducts)
ii. Increased surface area (membrane redundancy) for transport
b. Outfoldings
i. Dermal-epidermal junction
ii. Increased area for attachment

F. *Cytoskeleton and cytoarchitecture*
1. Terminal web
2. Filaments
a. Microfilaments (actin): 6-8 nm diameter
b. Intermediate filaments (tonofibrils; tonofilaments): 9-11 nm
c. Thick filaments (myosin): 15 nm
3. Microtubules (tubulin): 23-25 nm

VI. Light Micrographs TO KNOW

A. *Types of surface epithelia*
1. Simple
2. Stratified
3. Pseudostratified

B. *Types of glandular epithelia*
1. Unicellular glands
2. Mucous, serous, seromucous glands
3. Merocrine, apocrine & holocrine glands
4. Myoepithelial cells

C. *Types of epithelial specializations*
1. Apical
a. Striated/brush borders; stereocilia
b. Glycocalyx
2. Lateral
a. Terminal bars
b. Desmosomes & tonofibrils
3. Basal
a. Basement membrane
b. Basal infoldings
c. Basal outfoldings

VII. Electron Micrographs TO KNOW

A. *Goblet cells; types of secretion*

B. *Apical specializations*
1. Microvilli
2. Cilia
3. Glycocalyx

C. *Lateral specializations*
1. Zonula occludens
2. Zonula adherens
3. Macula adherens
4. Macula communicans

D. *Basal specializations*
1. Basal lamina
2. Reticular lamina (when present)
3. Hemidesmosomes
4. Infoldings for transport
5. Outfoldings for attachment

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OVERVIEW

Definition & properties. An **epithelium** is a **society of cells** in functional association that covers and lines all free body surfaces. Epithelial cells are held together in intimate contact with each other as well as to the underlying connective tissue. These contacts are mediated by small amounts of extracellular components and a number of plasma membrane specializations on the contact surfaces. In most instances, these specializations represent integral membrane proteins that are linked to cytoplasmic proteins via specific peripheral proteins. Thus, an epithelium is a tissue that consists mainly of cells with a relatively small amount of **extracellular matrix** (ECM).

1. Classification. Since epithelia cover the external surface of the body, line all internal cavities and tubular organs, and constitute the **parenchyma** (=specific functional cells of organ or gland) of many glands, they are typically classified into three categories (surface, glandular, special) even though this classification is quite arbitrary since there is considerable overlap between each of them.

a. Surface epithelia are simply defined as those epithelia that cover and line all body surfaces. They are also the varieties that are given specific names based largely on their layers and cell shape (see below).

b. Glandular epithelia represent all the varieties of epithelia that are specialized for **secretion** [L. *secretus* =to separate], which is the process by which cells release specific substances onto their apical surfaces. These cells may be located within the surface epithelium or at some distance, but are still connected to the surface via ducts. In some instances, they may lose these connections (e.g., thyroid epithelium).

c. Special epithelia may also be classified as surface or glandular, but have specialized functions. Examples of these include neuroepithelium (e.g., gustatory, olfactory), reproductive epithelium (e.g., seminiferous epithelium), and myoepithelium (epithelial cells specialized for contraction). The latter is described below in this chapter, whereas the others are discussed in later chapters in the context of their organs and systems.

2. Polarity. All epithelia are polarized and exhibit specific **domains** that are related to one of their surfaces: **apical** (located at the free surface), **lateral** (surfaces facing adjacent members of epithelium), and **basal** (surface adjacent to underlying connective tissue). In some instances, the lateral and basal domains are considered as a unit, i.e., **basolateral** domain.

3. Intermediate filaments* (IFs) are essential components of the cytoskeleton and nucleoskeleton of all cells. IFs are products of the largest family of cytoskeleton protein genes. In humans, at least 65 members of this multigene family are presently known to encode these 10-12 nm filaments (Hermann, H et al. *Int Rev Cytol* 223:83-175, 2003).

Epithelia have been characterized by containing specific types of IF proteins known as **cytokeratins**, which form the largest group of IFs with about 50 genes (Hesse, M et al. *J Cell Sci* 114:2569-2575, 2001).

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*Based on gene structure and sequence homologies at least 5 classes of IFs have been described: **I** =acidic cytokeratins; **II** =basic cytokeratins; **III** =vimentin, desmin, etc; **IV** =neurofilaments; **V**=nuclear lamins (for reviews, see Hermann, H & Foisner, R. *Cell Mol Life Sci* 60:1607-1612, 2003; Strelkov, SV et al. *BioEssays* 25:243-251, 2003; Helfand, BT et al. *J Cell Sci* 117:133-141, 2004). Some authors also include a sixth class. In addition, these filaments can also be placed into at least 3 groups based upon their assembly mechanisms and cytoplasmic or nuclear localization: **assembly groups 1 & 2** =cytoplasmic IFs; **assembly group 3** =nuclear IFs (e.g., Hermann, H & Aebi, U. *Annu Rev Biochem* 73:749-789, 2004).

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a. Organization. In epithelia, cytokeratin IFs have been referred to as **tonofilaments** (~10nm filaments visualized with TEM) and bundles of tonofilaments are called **tonofibrils** (aggregates visualized at LM). It is now known that cytokeratin IFs are linear aggregates of heterodimers of acidic (class I) and basic (class II) keratins in a 1:1 ratio (e.g., Kirfel, J et al. *Cell Mol Life Sci* 60:56-71, 2003). Therefore, a wide variety of epithelial cytokeratins are possible from this 1:1 partnership of an acidic keratin with a basic keratin. Indeed, specific keratins are now known to be associated with specific epithelial types as well as to stages of development (e.g., Fuchs, E & Cleveland, DW. *Science* 279:514-519, 1998).

b. Cytokeratin and IF functions. Although a primary function of tonofilaments, and IFs in general, is structural and supportive (IFs are often referred to as intracellular "ligaments"), a large body of growing evidence also demonstrates their important roles in cell signaling (see Paramio, JM &

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Jorcano, JL *BioEssays* 24:836-844, 2002).

4. Basement membrane. Epithelial cells rest upon a condensation of ECM called the **basement membrane**. As seen in the light microscope, this structural specialization is resolved with the electron microscope as consisting of a narrow **basal lamina** (that includes type IV collagen) just beneath the epithelium, and often (but not always) a subjacent **reticular lamina** (that includes type III collagen) of varying width, which is continuous with the underlying connective tissue. In those areas where a reticular lamina is absent (e.g., kidney glomerulus), the basal lamina is the basement membrane.

5. Regulatory roles of epithelia. Epithelia provide important *interfaces* between the internal and external environments of the body. Since all materials entering or exiting the body must traverse an epithelium, this tissue serves important regulatory functions--not just for nutrients and wastes, but also for microorganisms and other potential pathogens. Thus, epithelia also have a critically important role as part of the innate immune system.

6. Renewal and stem cells. Epithelia have a high regenerative capacity and many turn over in a matter of days. This capacity is not only important for normal maintenance and wound healing of these barrier layers, but it also plays a critical role in innate immunity. The continuous sloughing of cells to which microorganisms may have become attached is an important mechanism in preventing the potential uptake of pathogens into other epithelial cells or underlying tissues. Stems cells may reside within the epithelium proper, within specific areas connected with the epithelium (e.g., glands or ducts), or they may arise from outside of the epithelium (e.g., bone marrow).

7. Blood supply. Epithelial tissue is generally **avascular**, and thus is dependent on the blood vessels in the underlying connective tissue for oxygen and nutrients. In thicker (i.e., multilaminar) epithelia (e.g., epidermis of skin), intercellular channels between adjacent epithelial cells are important for distribution of oxygen and nutrients.

Shapes of epithelial cells vary depending upon whether they are viewed vertically (from basement membrane to free surface) or in surface view. In vertical view, three shapes are typical: squamous, cuboidal, and columnar. In surface view, epithelial cells are almost always polygonal.

1. Squamous cells [L. *squama* =scale] are characterized as being much wider than tall. These very thin, scale-like or flattened "pavement" cells present a minimal barrier to passage of materials through the epithelium. The cytoplasm can be so thin as to be difficult or impossible to see with the light microscope (e.g., gas exchange epithelium of lung alveoli). Nuclei are flattened and elongated in the direction of the long axis of the cell.

2. Cuboidal cells are characterized by having their height approximately equal to their width. Thus, they appear more or less square in vertically-sectioned profiles. Nuclei are generally spherical in cuboidal cells. However, the term "cuboidal", which implies a cube in 3 dimensions, is actually a misnomer due to their polygonal surface profiles.

3. Columnar cells are characterized by being taller than they are wide in vertical section. Nuclei are usually (but not always) more oval in shape and elongated in the long axis of the cell.

4. Surface views. Seen from above, all epithelial cells are usually polygonal (more or less hexagonal) in shape. The strategy of hexagonal packing and arrays in cells and tissues is common.

Important points to remember. Epithelial tissue consists of a wide variety of cell types with a minimal amount of extracellular material/matrix (ECM), which together line and cover virtually all free surfaces of the body. Epithelia are derived from all three germ layers and form sheets composed of groups of cells, in one or more layers, joined by specialized adhesions. The **apical** surfaces of epithelia face the free surface of the body or lumen of an organ or gland; **lateral** surfaces interact with adjacent epithelial cells; and the **basal** surfaces are attached to an underlying basal lamina/basement membrane. Epithelial tissues are avascular so that nutrients and blood gases must diffuse from blood vessels located in the underlying connective tissues to the more superficially located epithelial cells.

SURFACE EPITHELIA

Epithelia that cover and line all surfaces within the body are principally named and identified on the basis of two major characteristics: 1) the *number of cell layers* in the epithelium [i.e., **simple** (one layer) or **stratified** (two or more layers)], and 2) the *shape of the cells in the surface layer* (i.e., **squamous**, **cuboidal**, **columnar**). These conventions apply when the epithelium is viewed in

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vertical section, i.e., a plane of section that extends perpendicularly from the free surface to the basement membrane. As described previously, in surface view all epithelia have a polygonal shape that often appears hexagonal. The exception to the above naming convention is seen in **pseudostratified** epithelium (vide infra)

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2. Lateral [L. *latus* =side] **surface specializations** occur at the surfaces between adjacent epithelial cells. These surfaces are the interfaces between each member of an epithelial society. Lateral specializations include **occluding junctions**, **adhering junctions**, and **communicating junctions**.

3. Basal surface specializations occur at the base/bottom of epithelia. These surfaces are the interfaces between an epithelium and its underlying connective tissue or vasculature. Basal specializations include **basement membranes**, **hemidesmosomes**, and redundant surface membrane increases (**infoldings** and **outfoldings**).

Apical (Free) Surface Specializations

1. Microvilli [L. *villus* =tuft of hair] are plasma membrane evaginations of the apical surface that greatly increase the area available for absorption (or secretion). They contain a core of actin microfilaments and are covered by a coat of surface-bound carbohydrates, called the **glycocalyx** (see below), which gives a PAS-positive appearance under the light microscope.

a. Striated border of the intestines consists of densely packed (~60/μm^2) microvilli that assist and enhance nutrient absorption.

b. Brush border of the kidney proximal tubules also consists of thousands of densely packed microvilli, which facilitate the reabsorption that takes place in this location.

c. Stereocilia are elongated microvilli found at the apices of cells lining the ductus epididymidis and ductus deferens of the male genital tract. Stereocilia also occur on cochlear and vestibular hair cells of the internal ear.

d. Other locations. Microvilli are found on many other cells including mesothelium. In general, their purpose is to increase membrane surface area for absorption or secretion. Typically, they are shorter and less numerous in cells that are not highly specialized for absorption or transport.

2. Cilia are also plasma membrane and cytoplasmic projections from the apical surface. They are specializations for motility and contain a core of microtubules arranged in a specific configuration called the **axoneme**. Cilia are longer and thicker than microvilli, and their core of microtubules are extensions of centriole-like basal bodies that are located in the terminal web.

a. Axoneme is the characteristic array of microtubules that makes up the longitudinal core structure found in all cilia and flagella. As revealed by TEM, it contains a central pair of microtubules encircled by nine doublets (9x2+2). Attached to one end of each doublet and facing the adjacent doublet are two dynein arms that represent molecular motors that run along the adjacent microtubular tracks. These motors are powered by ATP and are responsible for ciliary/flagellar motion.

b. Basal bodies, which can arise from centrioles and have a similar structure, are responsible for giving rise to cilia and for anchoring axonemes into a cell's terminal web. Their characteristic structure is a pinwheel arrangement of nine triplets of microtubules (9x3).

c. Motility. Cilia move back and forth to propel fluid and particles unidirectionally. Movement is brought about by differential sliding of adjacent doublets past each other, which is facilitated by the energy-dependent movement motor proteins along adjacent microtubules.

3. Flagella, which have the same microstructure as cilia, occur singly and are much longer in length. They provide motility for spermatozoa.

4. Glycocalyx [Gr. *glykys* =sweet + *kalyx* =husk, shell] typically refers to a carbohydrate-rich, PAS-positive covering on the apical surface of certain epithelial cells, which can be seen with the LM due to the high density of carbohydrate residues. However, all cell membranes consist of externally-directed glycoproteins and glycolipids, which can be observed with the TEM and comprise the glycocalyx.

Lateral Surface Specializations

1. Junctional complexes in epithelia. Intercellular specializations called *terminal bars* and *desmosomes* have been recognized at the light microscopic level for a century or more. When the terminal bars of many hollow organs and glands were examined with the electron microscope, a characteristic tripartite junctional complex was observed, which consisted of the following components in a luminal to abluminal direction: 1) tight junction (called **zonula occludens**), an intermediate zonary adhering junction (called **zonula adherens**), and a punctate desmosome

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(called **macula adherens**) (Farquhar MG & Palade GE. *J Cell Biol* 17:375-412, 1963).

2. Zonula occludens (occluding junction, tight junction) occurs on the lateral cell surfaces just beneath the apical poles.

a. Structure. Formed by inosculations/interactions of special transmembrane proteins (**claudins**, **occludin**) in the plasma membranes of adjacent cells, these junctions form a network that extends completely around the cell perimeter and represent the closest contacts between cells (see Table 3-1).

b. Functions.

i. Restrict Paracellular Flow. Occluding junctions serve as permeability seals to isolate the underlying intercellular clefts (paracellular compartment) from the outside environment, therefore restricting intercellular movement of materials.

ii. Restrict Membrane Flow. In addition, they separate the apical and basolateral domains in cell membranes, which insures that specific proteins will remain in specific domains.

3. Zonula adherens lies subjacent to the zonula occludens. It is also a band-like junction that extends around the perimeter of cells; it serves in the attachment of adjacent epithelial cells (see Table 3-1).

4. Macula [L. =spot] **adherens (desmosome).** Desmosomes [Gr. *desmos* =bond, ligament + *soma* =body] are adhesive intercellular junctions, which are found in tissues subjected to mechanical strain. They are widespread in epithelia, particularly in stratified squamous varieties, and also occur in cardiac muscle. They not only link the membranes of adjacent cells, but also the intermediate (keratin) filament cytoskeletons across cells (Garrod, DR et al. *Curr Opin Cell Biol* 14:537-545, 2002). Essentially, these junctions are "spot welds" between adjacent cells, which are formed by the juxtaposition and attachment of two symmetrical disk-shaped structures provided by each cell.

a. Structure: light microscopic. At the LM level, desmosomes are difficult to resolve, but can be readily observed in SSE due to their high density between cells. Here, they appear as small punctate bodies, which were once thought to connect areas of cytoplasmic continuity between adjacent cells and thus believed to mediate what was called "cytoplasmic bridges".

b. Structure: electron microscopic. Although EM studies showed that desmosomes are complex junctions morphologically (McNutt, NS & Weinstein, RS. *Prog Biophys Mol Biol* 26:45-101, 1973; Staehelin, LA. *Int Rev Cytol* 39:191-283, 1974), it was clear that cytoplasmic continuity at these structures does not exist. Rather, their ultrastructure revealed that desmosomes are bipartite junctions, which consist of symmetrical, mirror-image-like components provided by each adjacent cell.

i. Intracellular components. Inside each cell, just beneath their lateral plasma membranes, electron dense structures called **attachment plaques** were found to connect the cell membrane on one side with intermediate filaments of the keratin cytoskeleton on the cytoplasmic side.

ii. Extracellular components. Between each cell in the middle of the intercellular space, an intermediate **dense midline** was observed, which appeared to be a region of attachment between adjacent cells.

c. Structure: submicroscopic. At the molecular level, desmosomes are constructed of specialized adhesive proteins (see Table 3-1). The major components are integral membrane glycoproteins that belong to the cadherin superfamily of adhesion molecules (e.g., Angst, BD et al. *J Cell Sci* 114:629-641, 2001). To date, several isoforms of two major desmosomal cadherins have been described and a schema for their nomenclature proposed (Buxton, RS et al. *J Cell Biol* 121:481-483, 1993): **desmocollins** (Dsc1a,b; Dsc2a,b; Dsc3a,b) and **desmogleins** (Dsg1, Dsg2, Dsg3). Region-specific expression for various isoforms of these proteins has also been shown to occur in SSE: e.g., Dsg1 is normally located in upper layers of oral mucosa but throughout entire epidermis (especially in upper layers), while Dsg3 is located in basal layers of epidermis but throughout oral mucosa (Arnemann, J et al. *J Cell Sci* 104:741-750, 1993; Amagai, M et al. *J Invest Dermatol* 106:351-355, 1996; Amagai, M et al. J Am Acad Dermatol 40:167-170, 1999; Mahoney, MG et al. J Clin Invest 103:461-468, 1999). This localization has proved to be important for understanding certain diseases (see below).

i. Extracellular components. The integral transmembrane desmocollins and desmogleins have extracellular, intramembrane, and intracellular (cytoplasmic) domains. Their extracellular domains include the following. 1) **Cell adhesion recognition sites** at the distal ends, which mediate the intercellular binding of these cadherins between adjacent cells. These binding domains appear to be the molecular basis of the dense midline seen at the EM level. 2) **Calcium-**

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binding repeats, which occur at various sites along the extracellular domains. These sites are important for the cadherin-cadherin binding because removal of calcium results in disassociation of the desmosomal junction.

ii. Intracellular components. On the cytoplasmic sides of adjacent cell membranes, the intracellular domains are associated with specialized cytoplasmic proteins (**desmoplakins**, **plakogobin**, and **plakophilins**), which together are components of the disk-shaped, dense attachment plaques seen with EM. Keratin tonofilaments of the cytoskeleton are securely anchored into these plaques via desmoplakin (Ruhrberg, C & Watt, FM. *Curr Opin Genet Dev* 7:392-397, 1997).

b. Function. Most abundant in lining membranes subject to wear and tear, but present in all epithelia, desmosomes are important cellular spot welds that hold cells together by a calcium-dependent adhesion mechanism. They represent an important means of resistance to lateral shearing forces between cells by coupling external attachment of adjacent cells to internal linkage of their keratin cytoskeletons across the epithelium.

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HistoCAPS®: Capsules of *C*linical *A*nd *P*athologic *S*ignificance

Pemphigus [Gr. *pemphix* =a blister] is a potentially fatal autoimmune disorder that affects cell adhesion at desmosomes. Recent advances in basic and clinical research have shown that this condition is actually a group of bullous [L. *bulla* =bubble] or blistering disorders of skin and mucous membranes, which are characterized by disruption of intercellular adhesion and caused by antibodies against various desmosomal proteins (e.g., Hashimoto, T *Arch Dermatol Res* 295:S2-S11, 2003). Although about a dozen variants have been described worldwide, pathology textbooks (e.g., Kumar, V et al. *Robbins and Cotran Pathologic Basis of Disease*, Elsevier Saunders, Philadelphia, 2005) describe four classic types of pemphigus: 1) *pemphigus vulgaris*, 2) *p. vegetans*, 3) *p. foliaceus*, and 4) *p. erythematosus*. However, based on the similarity of autoantigens, it now appears that p. vegetans is a subtype of p. vulgaris, and p. erythematosus is a subtype of p. foliaceus (see Hashimoto, 2003). From this work, the following important features of blister formation in two classic variants can be summarized. If blisters form in the deep layers, they are classified as "suprabasal"; if blisters occur higher up in the more superficial layers, they are classified as "subcorneal" (=superficial). In this regard, it is important to recall the distribution of Dsg isoforms in SSE (see above).

Pemphigus vulgaris can be divided into two types based upon which antigens are reactive. In the *mucosal dominant type*, the pathomechanism of blister formation is due to autoantibodies against Dsg3. Thus, blisters occur suprabasally in the oral mucosa since Dsg1 provides some compensation for the epidermis of skin. In the mucocutaneous type, pathology is due to autoantibodies against both Dsg1 and Dsg3. Thus, no compensation occurs and suprabasal blisters form in both oral mucosa and epidermis. P. vegetans pathology appears to have a similar mechanism to the mucocutaneous type.

Pemphigus foliaceus is characterized by antibodies against Dsg1 only. Thus, blisters occur subcorneally due to the higher concentration of Dsg1 more superficially. P. erythematosus pathology appears to have a similar mechanism.

Impetigo [L. =a scabby eruption] is a common childhood disease of the skin, which is mainly caused at the present time by the bacteria *Staphylococcus aureus*. It is characterized by superficial bullous pustules in the epidermis that form as a result of exfoliative toxins (ETs) produced and released by the bacteria. Recent studies (Amagai, M et al. *Nat Med* 6:1275-1277, 2000; Amagai, M et al. *J Invest Dermatol* 118:845-850, 2002; Hanakawa Y et al. *J Clin Invest* 110:53-60, 2002) have shown that ETs act by attacking Dsg1 proteins of desmosomes. Genes for three toxins have been cloned and amino acid sequences of the toxins show homology to chymotrypsin-like proteases. Thus, impetigo, like pemphigus foliaceus, is a superficial blistering disease of skin affecting the integrity of desmosomes.

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5. Macula communicans (communicating junction, gap junction, nexus) is a junctional area of between adjacent cells that facilitates intercellular communication by allowing the passage of small molecules and ions across the narrow intercellular gap through a multitude of junctional pores (see Table 3-1). Although these structures have been given a variety of names and described in many tissues and species by many investigators, it was George Palade and coworkers (Simionescu M et al. *J Cell Biol* 67:863-885, 1975) who proposed the term communicating junction (macula communicans, maculae communicantes) based upon its principal function.

a. Structure. The junction consists of a hexagonal lattice of **connexin** protein subunits called **connexons**, which form intramembrane hydrophilic channels connecting the cytoplasm of adjacent cells.

b. Function. The low resistance

communicating channels through the gap junction permit intercellular signaling and electrical coupling by allowing the regulated passage of ions and small molecules between cells. These junctions are perhaps an important cellular strategy for approaching the efficiency of a syncytium.

c. Distribution. Gap junctions are not only found between epithelial cells, but also in all primary tissues. They occur between cells of other tissues that require direct communication, e.g., osteocytes in bone matrix. In addition, impulses for cardiac and smooth muscle contraction pass from one cell to the next through gap junctions.

Basal Surface Specializations

1. Basement membrane is a sheet-like layer that underlies virtually all epithelia, and isolates them from the subjacent CT. (Exceptions are found in lymphatic capillaries and certain blood capillaries where the basement membrane may be poorly developed or discontinuous.) At LM level, visualization usually requires special stains such as PAS reaction, silver, and CT trichromes, except in some locations such as the trachea where it is exceptionally thick. TEM revealed that it consists of a basal lamina and a variably-present reticular lamina.

a. Basal lamina is a product of the epithelium and consists of an electron-lucent zone called the **lamina lucida** (rara), located next to the basal plasmalemma, and an electron-dense layer called the **lamina densa**, located next to the CT.

i. Composition is complex and may vary in different locations, but consists primarily of **type IV collagen**, glycoproteins [mainly **laminin**; also nidogen (=entactin)], and the large heparan sulfate proteoglycan called **perlecan**.

ii. External lamina is the basal lamina that surrounds muscle cells, peripheral glial cells (e.g., Schwann cells), and adipocytes. It serves both anchoring and separating functions in relation to the surrounding CT compartment.

b. Reticular lamina is a product of the CT and is composed of delicate reticular (**type III collagen**) and type I collagen fibers.

c. Anchoring fibrils, which are composed of **type VII collagen**, form an important linkage between the basal and reticular laminae.

2. Hemidesmosomes have the appearance of half-desmosomes and are found at sites where epithelial cells are attached to underlying extracellular matrix. However, in hemidesmosomes, **integrins** are the integral membrane proteins and not cadherins as with desmosomes (see Table 3-1).

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Bullous [L. *bulla* =bubble] **pemphigoid** is a blistering autoimmune disease, which is caused by antibodies that react with proteins at the basal lamina area of stratified squamous epithelium in skin and oral mucosa. These proteins, referred to as bullous pemphigus antigens 1 and 2, are associated with hemidesmosomes. The attack at this location results in the formation of subepithelial blisters that cause the epithelium to separate away from the underlying basement membrane and CT. Since the entire epithelium covers these blisters, they do not rupture as easily as those occurring in pemphigus (see above).

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3. Basolateral infoldings of plasma membrane. As microvilli provide increases in surface area on the apical surface, these infoldings increase the surface area of the basolateral surfaces. They are found in transporting epithelia and are associated with numerous mitochondria, which provide energy for the ionic pumps. Important examples include the proximal and distal kidney tubules, and the striated ducts of salivary glands.

4. Basal outfoldings of plasma membrane. Another specialization of the plasma membrane is seen as elaborate basal protrusions in certain epithelia. These outfoldings occur along the basement membrane and serve the purpose of increasing surface area for attachment of the epithelial cells to the underlying CT. An important example of this specialization is found at the dermal-epidermal junction in the skin. **|Ω|**

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Table 3-1. Cellular Junctions: Description and Components.

	Junction Type	Principal Function	Extracellular Binding	Intracellular Binding	
			IMP*	PMP*	CP*
Cell-Cell Jxns (*homotypic* interactions**)	*Zonula occludens* (tight jxn)	Seal intercellular space; restrict movement within cell membrane; regulate paracellular transport	Claudin-Claudin; Occludin-Occludin	ZO-1, -2, -3, cingulin, spectrin	Actin filaments
	Zonula adherens	Cell-cell adhesion	Cadherin-Cadherin (E-cadherin)	Catenins, plakoglobin, α-actinin, vinculin	Actin filaments
	Macula adherens (desmosome)	Cell-cell adhesion	Cadherin-Cadherin (desmocollins; demogleins)	Desmoplakin, plakoglobin, plakophilins	Keratin (intermediate) filaments
	Macula communicans (communicating jxn; gap jxn; nexus	Cell-cell communication	Connexin-Connexin Connexon-Connexon (channels may be homo- or heterotypic)		
Cell-ECM Jxns (*heterotypic* interaction***)	*Hemidesmosome*	Cell-ECM adhesion	Integrin-Laminin	Plectin	Keratin (intermediate) filaments

***IMP** =Integral Membrane Proteins; **PMP** =Peripheral Membrane Proteins; **CP** = Cytoplasmic (intracellular; cytoskeletal) Proteins. Cell junction proteins consist of IMPs that are transmembrane proteins with extracellular, transmembrane, and intracellular domains: extracellular domains interact with their counterparts on adjacent cells; transmembrane domains are generally hydrophobic and may have multiple spans; intracellular domains are generally attached to cytoskeleton (CPs) via PMPs.
**Homotypic interactions =association between like receptors
***Heterotypic interactions =association between unlike receptors

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