I. General Principles:
- Cell junctions mediate cell adhesion and communication
- Junctions are important for normal development and differentiation
- Cell adhesion molecules play roles in desquamation, wound healing, and tumorigenesis
- Adhesion molecules are often mutated in genetic skin diseases
- Adhesion molecules are targets of autoantibodies

II. What are the major cell junctions?

A. Cell-Cell junctions

1. Gap junctions: Communicating junctions that allow passage of ions and small molecules between neighboring cells. Major transmembrane membrane component: connexins. Connexin mutations give rise to Vohwinkel syndrome (Cx26), erythrokeratoderma variabilis (EKV)(Cx31/30), and hidrotic ectodermal dysplasia (Cx 30).

2. Tight junctions: Provide barrier to ion movement between tissue compartments. Major membrane components: occludin and the claudins. Emerging data indicate role for claudins and tight junctions in epidermal barrier and prevention of water loss.

3. Adherens junctions: Anchor actin to the plasma membrane at points of cell-cell adhesion; important signaling functions. Major transmembrane components are the classic cadherins (E- and P-cadherin).

4. Desmosomes: Anchor keratin intermediate filaments to cell membranes at cell-cell borders; desmosomes are critical to epidermal integrity. Major transmembrane components are the desmosomal cadherins (desmogleins and desmocollins). Desmogleins are major targets in pemphigus, inherited disease, and bullous impetigo.
B. Cell-Extracellular Matrix junctions

1. Focal contacts: Anchor actin to plasma membranes at the cell-basement membrane interface; important for signaling and motility. Major transmembrane components are integrins.

2. Hemidesmosomes: Anchor keratin intermediate filaments to plasma membranes at the cell-basement membrane interface; important for adhesion, signaling and keratinocyte motility. Major transmembrane components: $\alpha_6\beta_4$ integrin and BP180 (BPAG2), both of which are targets in human disease (see below).

III. Protein Components Present in Adhesive Junctions:

A. Transmembrane components of Junctions

1. Cell-cell junctions

   a. Classic cadherins: E-, N- and P-cadherin mediate homophilic adhesion in actin associated cell-cell adherens junctions

   b. Desmosomal Cadherins: Desmogleins and desmocollins mediate adhesion in intermediate filament associated desmosomes

2. Cell-substrate junctions

   Integrins: Each composed of an $\alpha$ and $\beta$ integrin subunit, this is a large family of heterodimeric receptors whose ligands are primarily extracellular matrix components including collagen, laminin and fibronectin. $\alpha 6\beta 4$ is known primarily as the hemidesmosomal integrin receptor for laminin 5, whereas focal contacts are composed of a wide variety of integrins.
B. Cytoplasmic Plaque Components of Cell-Cell Junctions

1. The Armadillo Gene Family: This family of proteins is characterized by a central domain constructed of tandem “armadillo” motifs (named after a protein found in Drosophila). Armadillo domains tend to mediate protein-protein interactions. Members of this gene family are found in cell-cell adherens junctions, desmosomes and sometimes in the nucleus where they can serve important gene regulatory and possibly other nuclear functions.

   Armadillo family members in Adherens Junctions

   a. \( \beta \)-catenin: along with its Drosophila counterpart, armadillo, this is the most heavily studied armadillo family member. It is important for adherens junction structure and function and also plays an important role in a signaling pathway (the wnt/wingless pathway) that drives embryonic axis formation and cell growth.

   b. p120-catenin: This cadherin binding protein is required for cadherin stability. p120 functions to prevent cadherin endocytosis and degradation, and plays other roles in cadherin clustering and in the regulation of actin cytoskeletal organization.

   Armadillo family members in Desmosomes

   a. Plakoglobin: closest vertebrate relative to \( \beta \)-catenin. Plakoglobin binds to desmogleins and desmocollins and is important for desmosomal integrity

   b. Plakophilins 1, 2, and 3: These proteins are more closely related to p120-catenin than to plakoglobin. Plakophilin 1 is important for integrity of the upper epidermis; plakophilin 2 is required for normal cardiac function, while plakophilin 3 plays important roles in the hair follicle.

2. \( \alpha \)-catenin and vinculin: \( \alpha \)-catenin is located in adherens junctions. \( \alpha \)-catenin binds to \( \beta \)-catenin and also associates with actin and regulates actin branching. Vinculin is also present at adherens junctions but is probably more important in focal contacts at the cell-matrix interface.
3. Plakin Family of Plaque Proteins: These proteins are characterized structurally by a carboxyl terminal intermediate filament binding site, a central $\alpha$-helical coiled coil rod domain, and an amino-terminal domain that targets to cell junctions.

   a. Cell-cell junctions

      Desmoplakin: The most abundant desmosomal plaque molecule and an obligate constituent of desmosomes. Mice lacking desmoplakin die early in embryogenesis.

      Envoplakin and Periplakin: Newer family members that participate in cornified envelope assembly and also found in desmosomes, but are not required for desmosome assembly.

   b. Cell-substrate junctions

      BP230 (BPAG1): This plakin family member is present in hemidesmosomes and is thought to be involved in keratin linkage to the hemidesmosomal plaque.

      Plectin: Plectin is the most promiscuous family member, interacting with intermediate filaments, actin, microtubules and cell junctions. It is a prominent component of hemidesmosomes and may also be found in desmosomes.
Table 1: Desmosomal targets in disease

<table>
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<tr>
<th>Protein</th>
<th>Tissue Distribution</th>
<th>Disease Type</th>
<th>Autoimmune</th>
<th>Infection</th>
<th>Inherited</th>
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<tr>
<td>Dsg1</td>
<td>stratified epithelia</td>
<td>pemphigus foliaceus</td>
<td>mc pemphigus vulgaris</td>
<td>paraneoplastic pemphigus</td>
<td>pemphigus erythematousus</td>
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<td>Dsg2</td>
<td>simple and stratified epithelia, myocardium</td>
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<td>ad 3,7,11 &amp; 14 respiratory</td>
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<td>IgA pemphigus</td>
<td>pemphigus vulgaris</td>
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<tr>
<td>Dsc2</td>
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<tr>
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<td>Desmoplakin</td>
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<td>Plakophilins 1-3</td>
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</table>

Abbreviations: mc, mucocutaneous; md, mucosal dominant; SSSS, staphylococcal scalded skin syndrome; ad, adenovirus serotypes; BA-LT, Bacillus anthracis lethal toxin; PPK, palmoplantar keratoderma; ARVC, arrhythmogenic right ventricular cardiomyopathy; DC, dilated cardiomyopathy; LAEB, lethal acantholytic epidermolysis bullosa; EDSF, ectodermal dysplasia-skin fragility
Functional Classification of Junctions

1) Occluding Junctions (Tight Junctions)

2. Communicating Junctions
   A) Gap Junctions
   B) Chemical Synapses

3) Anchoring Junctions
   A) Actin Attachment sites
      i. Cell-Cell Adherens junctions (Adhesion Belt)
      ii. Cell-Matrix Adherens junctions (Focal Contact)
   B) Intermediate Filament Attachment Sites
      i. Cell-Cell (Desmosome)
      ii. Cell-Matrix (Hemidesmosome)
Protein Components of the Tight Junction

Gap Junctions Permit Flux of Small Molecules Between Adjacent Cells

Connexins Assemble into Connexons

- MW
- 100
- 1000
- 5000
- 20,000

- channel 1.5 nm in diameter
- two connexons in register forming an open channel between adjacent cells
- connexon composed of six subunits
- interacting plasma membranes
Three Gene Families Contribute to the Formation of Adhesive Junctions

Filament Binding Families:
- IF: Plakins
- Actin: α-catenin/vinculin

Armadillo Family of Linkers (Catenins)
- β-catenin & Plakoglobin
- p120-catenin

Cytoskeletal Linking Proteins
- α-catenin
- Vinculin

Armadillo Proteins
- Plakoglobin
- PKP 1-3 etc.

Cadherins
- Classical Cadherins
  - E-cadherin, P-cadherin
- Desmosomal Cadherins
  - Desmogleins 1-4
  - Desmocollins 1-3

Adherens Junction

Desmosome
Cadherins are Calcium-Dependent Transmembrane Adhesion Molecules

Classical Cadherins
E-cadherin and P-cadherin

Desmosomal Cadherins
Desmogleins and Desmocollins

>100 Cadherin genes in humans
Cytoskeletal Linkage of Cadherin in Adherens Junctions

Actin Binding Proteins

α-actinin

β-catenin

α-catenin

Actin

Cytoplasmic

E-cadherin or P-cadherin

Ca^{2+} Dependent Homophilic Adhesion

p120

Extracellular
1) Classical Cadherins play key roles in epidermal differentiation and tissue patterning

2) Loss of E-cadherin expression is associated with epithelial tumor progression and metastasis

3) P-cadherin mutations cause:
   - Hypotrichosis with juvenile macular dystrophy
   - Ectodermal dysplasia, ectrodactyly and macular dystrophy syndrome (EEM)
Desmosomes are Adhesive Spot Welds Associated with Keratin Intermediate Filaments

Desmoglein: Green
Keratin: Red
The Desmosome

Plakoglobin

Desmoglein

Desmocollin

Intermediate Filaments

Desmoplakin

Plakoglobin

Plakoglobin

Desmocollin

Envoplakin

Periplakin

Plakophilins

Plakins

Armadillo Proteins

Cadherins

Cytoplasmic Plaque

Extracellular Adhesive Core
Autoimmune Disorders of the Desmosome

Intermediate Filaments

- Plakoglobin
- Desmoglein
- Desmocollin

Plakophilsins

Plakoglobin

Pemphigus Vulgaris
Pemphigus Foliaceus
Paraneoplastic Pemphigus
Keratins: K5/K14

Plakins: BPAG1/BP230

Cytoplasm

BPAG2/BP180 COL XVII

α6 β4

Laminin-5

Dermis

COL VII

Dermis

Basal Keratinocyte

Courtesy of JCR Jones
Genetic Disorders of the Hemidesmosome: Epidermolysis Bullosa

EB Simplex
- K5/K14
- EB-MD: Plectin

Junctional EB
- EB-PA: Integrin α6, β4
- GABEB: COLXVII
- Laminin

Dystrophic EB
- COL VII

Cytoplasm
- BPAG2 COL XVII
- α6 β4

Laminin-5
- Dermis COL VII
Autoimmune Disorders of the Hemidesmosome

Bullous Pemphigoid:
BPAG1

Bullous Pemphigoid:
BPAG2/Col XVII

Mucous Membrane/
Cicatricial Pemphigoid

EBA

Cytoplasm

Dermis

BPAG1

Plectin

α6 β4

BPAG2 COL XVII

Laminin-5

Laminin-5, BPAG2

COL VII

COL VII