

Cell–cell interactions

Junctions, epithelial polarity, biosynthesis and secretion

Foundations of cellular pathology

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Learning objectives

- Distinguish occluding, anchoring and communicating junctions.
- Relate junctional proteins to the cytoskeleton and epithelial polarity.
- Explain clinically relevant failures of cell adhesion.
- Trace protein maturation through ER and Golgi.
- Contrast classical secretion, unconventional release and extracellular vesicles.

What junctional complexes accomplish

Seal

Restrict movement through spaces between epithelial cells.

Anchor

Couple neighboring cells or the extracellular matrix to the cytoskeleton.

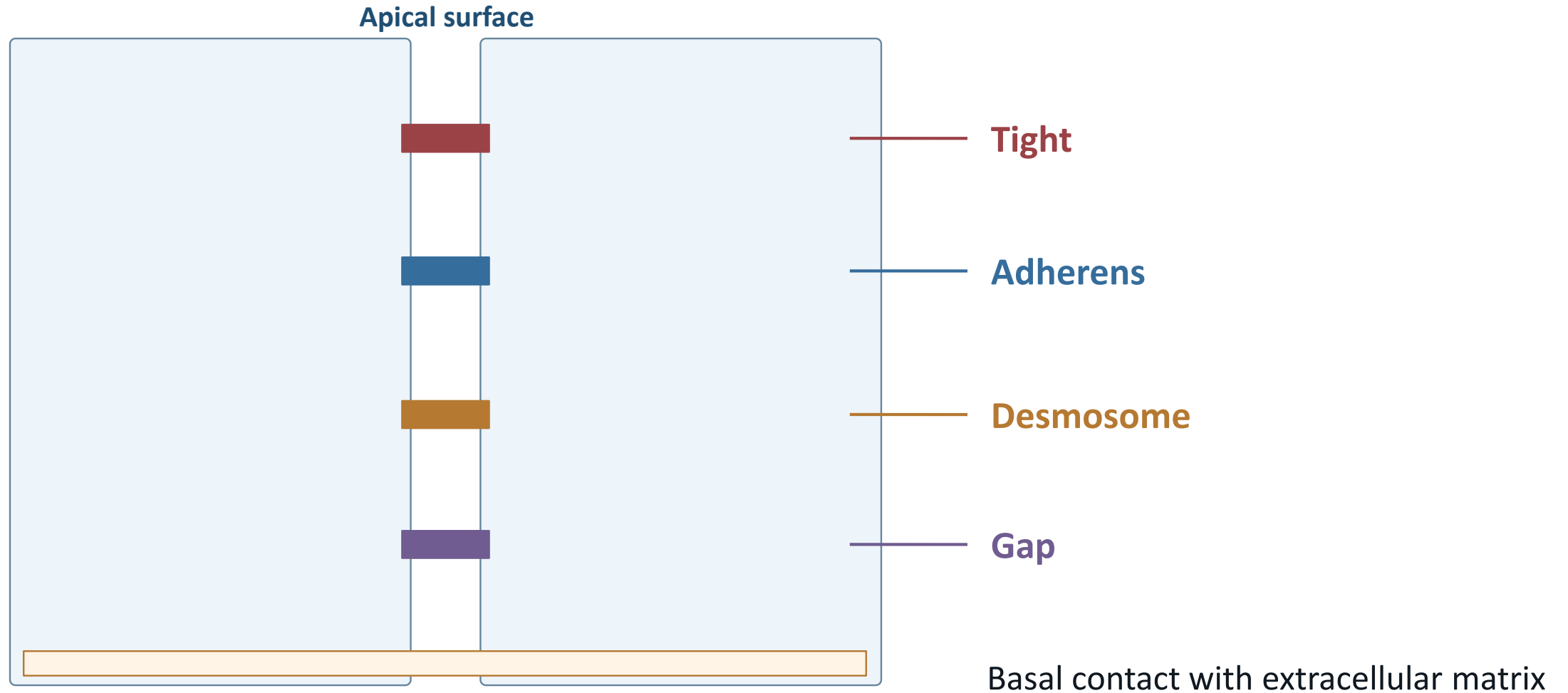
Communicate

Transfer chemical or electrical information between adjacent cells.

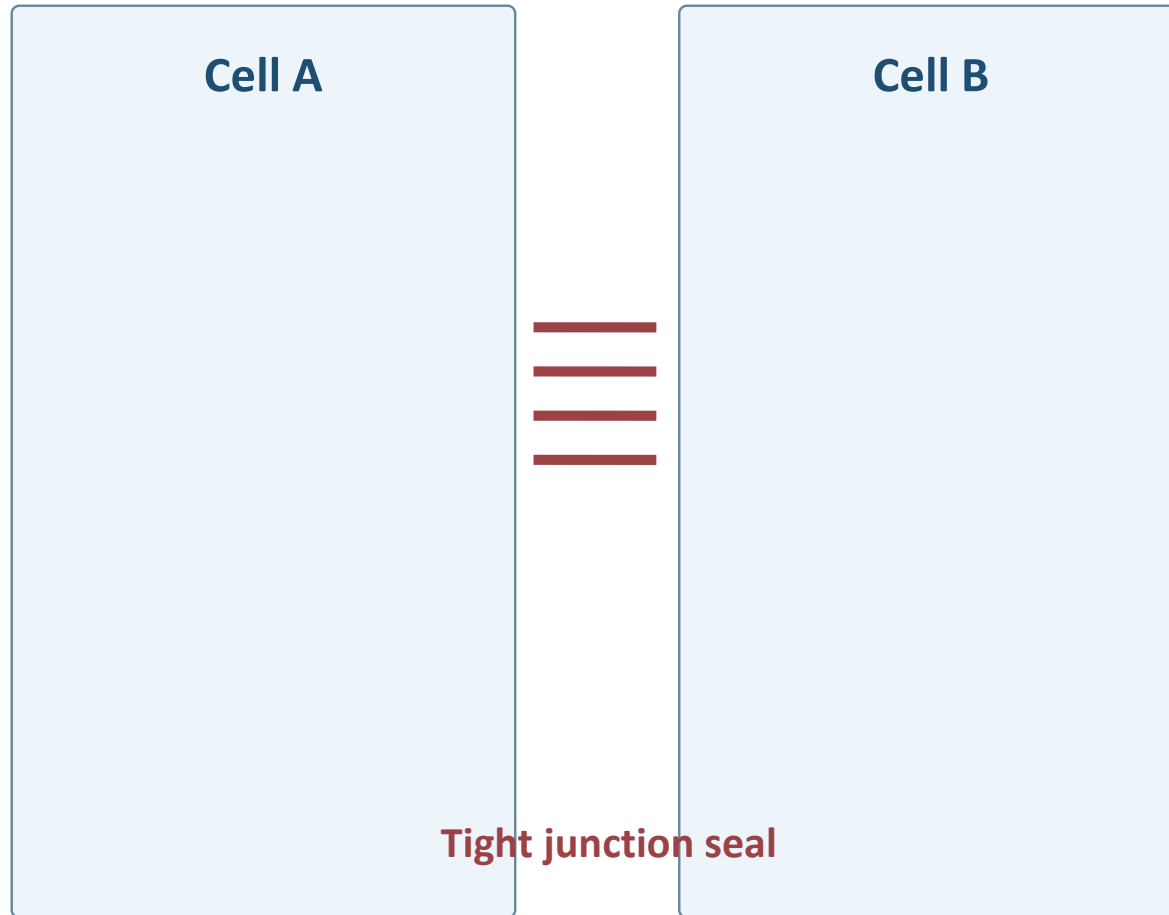
Three major classes of cell–cell junction

Class	Main role	Examples
Occluding	Paracellular barrier; Polarity boundary	Tight junctions
Anchoring	Mechanical continuity and force transfer	Adherens junctions; Desmosomes
Communicating	Chemical / electrical cell-to-cell signals	Gap junctions

A polarized epithelium organizes several junction types



Tight junctions create an epithelial barrier



- Neighboring epithelial cells form an apical seal.
- The seal limits paracellular passage of ions and other molecules.
- Barrier permeability is selective, not absolute.

Two routes across an epithelial sheet

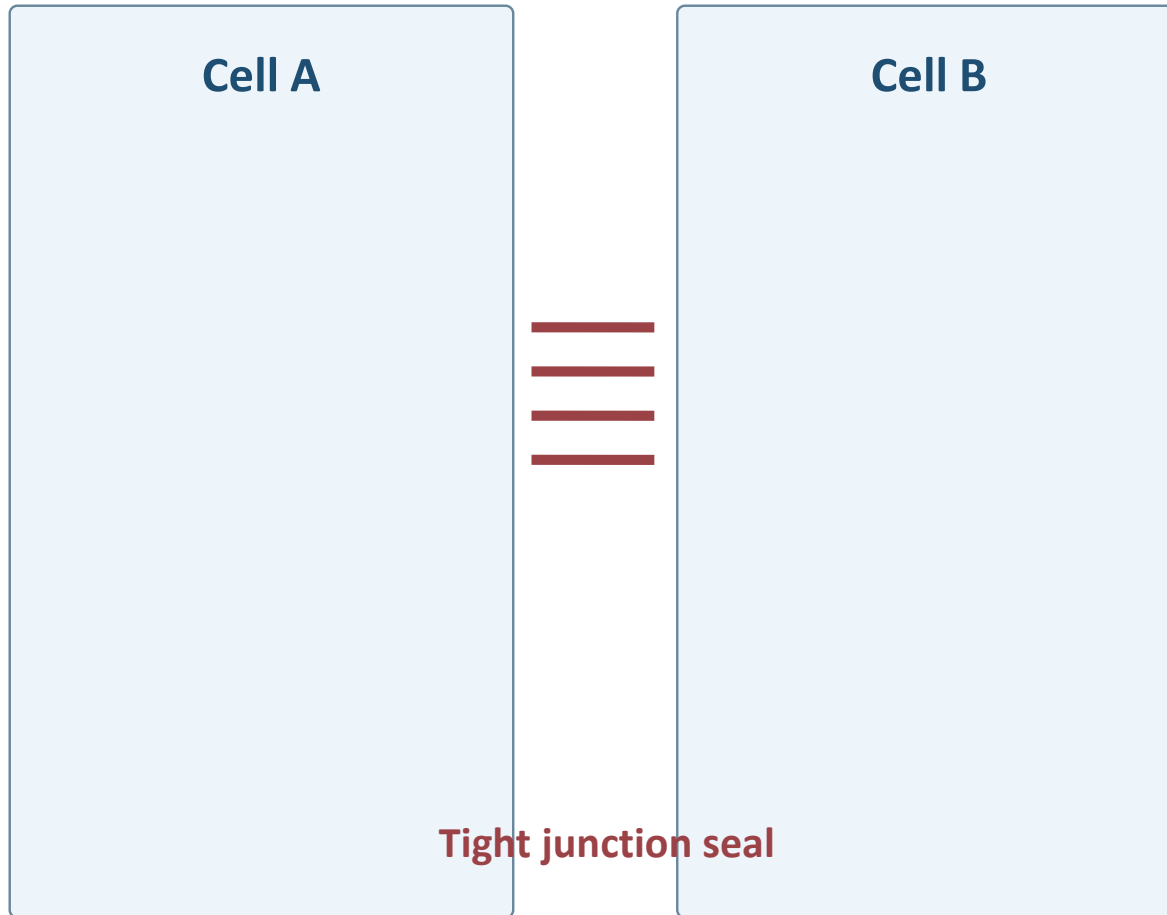
Transcellular route

A substance crosses the plasma membranes and cytoplasm of a cell.

Paracellular route

A substance passes between cells; Tight junctions restrict this path.

Tight junctions form a mesh of contacts



- Multiple molecular contacts create a continuous belt.
- Freeze-fracture views show a tight mesh-like network.
- The network is situated near the apical margin.

Transmembrane components of tight junctions

- Claudin family proteins contribute to the intercellular seal.
- Tight junction–associated MARVEL proteins (TAMPs) are also present.
- Protein complexes span adjacent plasma membranes.
- The extracellular contacts act together as a barrier.

Tight-junction cytoplasmic scaffold

ZO-1, ZO-2, ZO-3

Zonula occludens adaptor/scaffolding proteins.

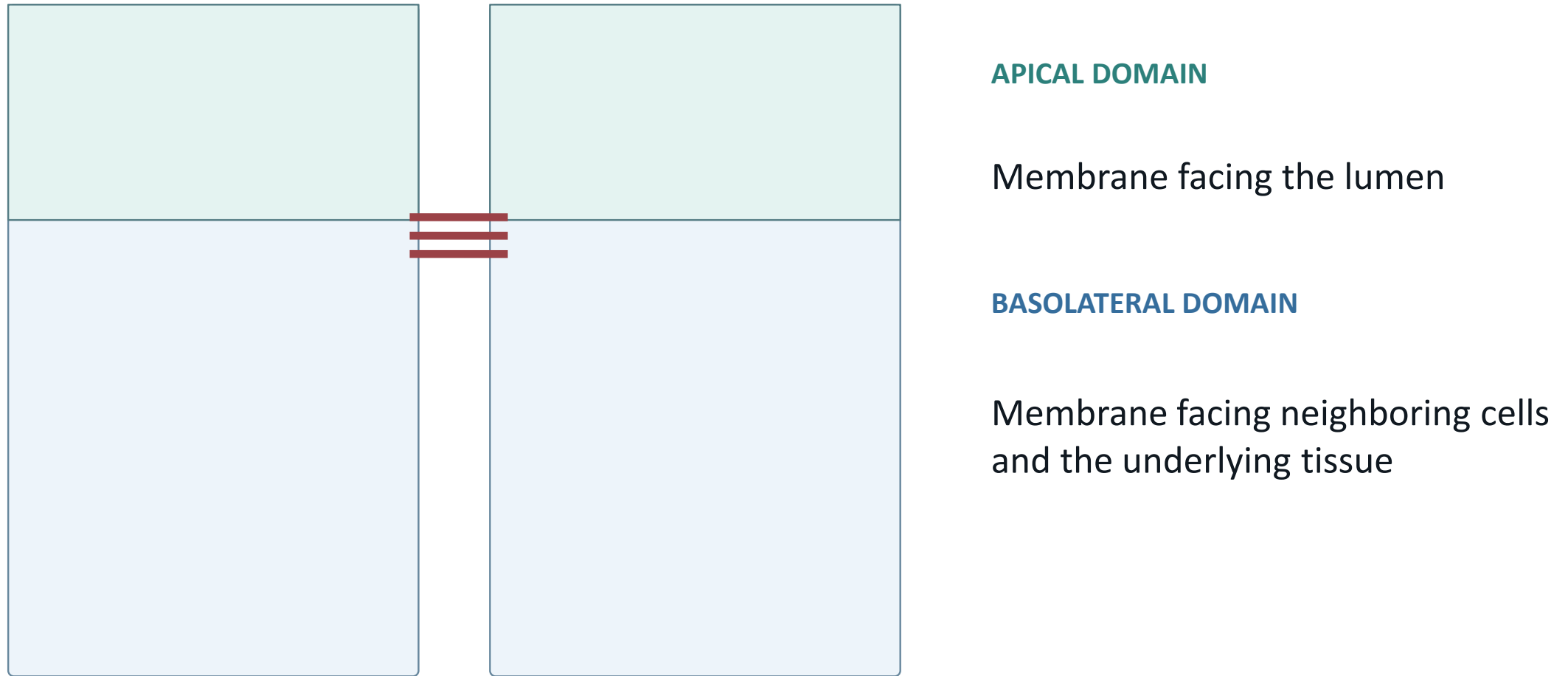
Cingulin

Intracellular component of the tight-junction complex.

Functional assembly

Transmembrane components connect with cytoplasmic scaffolds.

Tight junctions delineate membrane domains



The junctional belt helps maintain polarity.

Barrier function and polarity are linked

- The apical and basolateral membrane regions remain distinct.
- Tight junctions define the boundary between these domains.
- The junction therefore has both transport and organizational functions.

Tight junctions are dynamically regulated

Baseline

Stable epithelial barrier and polarity.



Modification

Contacts change as the tissue responds.



Outcome

Controlled restructuring during repair or migration.

Physiologic contexts for barrier remodeling

Epithelial repair

A dynamic junction allows the epithelium to reorganize while healing.

Inflammatory cell passage

Regulated changes permit inflammatory cells to cross epithelial-lined mucosal surfaces.

Anchoring junctions are mechanically specialized

Adherens junction

Cadherin adhesion couples to actin microfilaments.

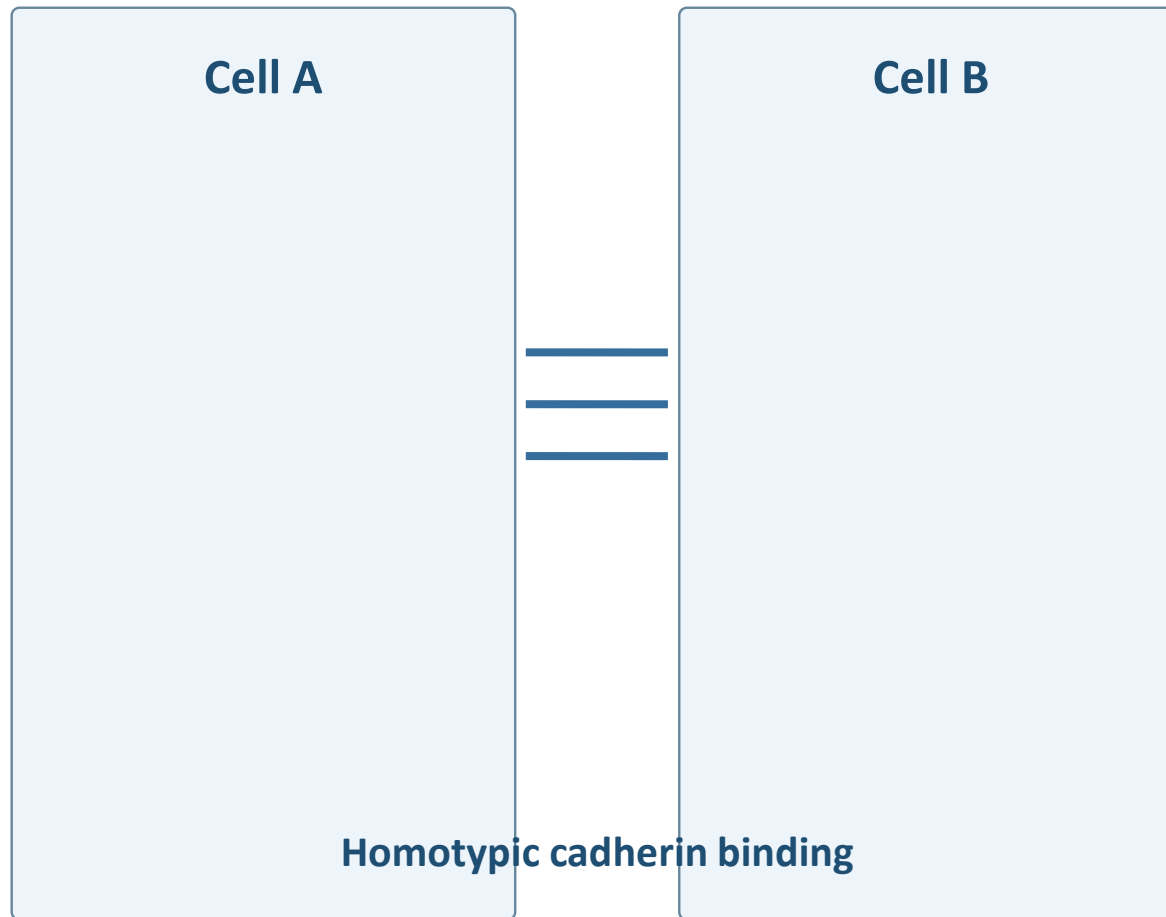
Desmosome

Cadherin adhesion couples to intermediate filaments.

Hemidesmosome

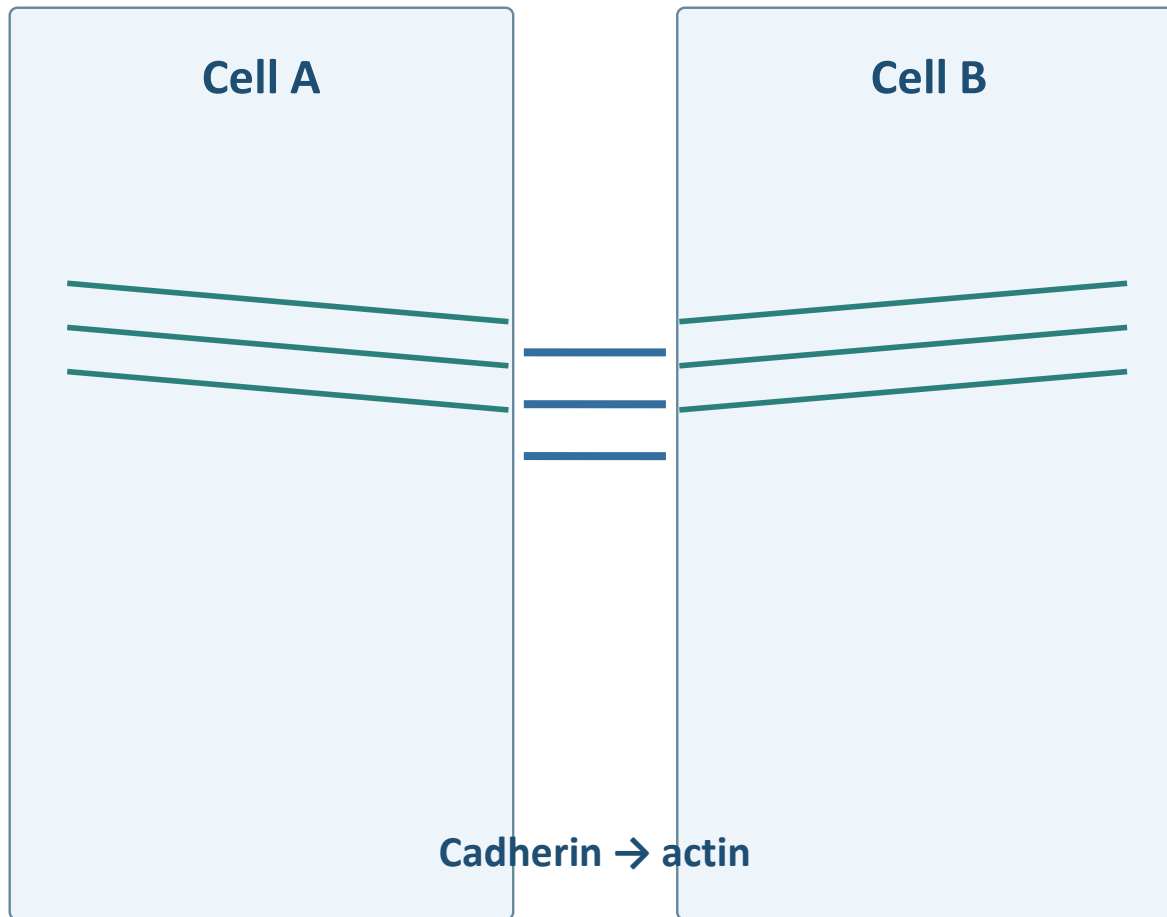
Integrins couple intermediate filaments to extracellular matrix.

Cadherins support cell–cell adhesion



- Transmembrane glycoproteins bridge adjacent cells.
- Homotypic cadherin interactions occur across the intercellular space.
- Intracellular connections determine mechanical behavior.

Adherens junctions couple to actin



- Located commonly beneath tight junctions.
- Adhesion proteins connect with actin microfilaments.
- Actin coupling links adhesion to shape and motility.

From adhesion to epithelial organization

E-cadherin

Cell–cell adhesive contact.



Actin linkage

Mechanical integration with cytoskeleton.



Cell behavior

Influence on cell shape and movement.

E-cadherin loss can produce discohesive invasion

Reduced epithelial cohesion permits cells to infiltrate without remaining in cohesive groups.

Gastric carcinoma and lobular carcinoma of the breast as important examples.

Discohesion: Two classic cancer examples

Gastric carcinoma

Some gastric cancers display a discohesive invasive pattern associated with E-cadherin loss.

Breast lobular carcinoma

Loss of epithelial E-cadherin explains the characteristic discohesive growth pattern.

Application: Loss of epithelial cohesion

An infiltrative carcinoma is composed of poorly cohesive cells. Which junctional protein best accounts for this pattern?

A. E-cadherin

B. Connexin

C. Claudin

D. Cingulin

Application: E-cadherin

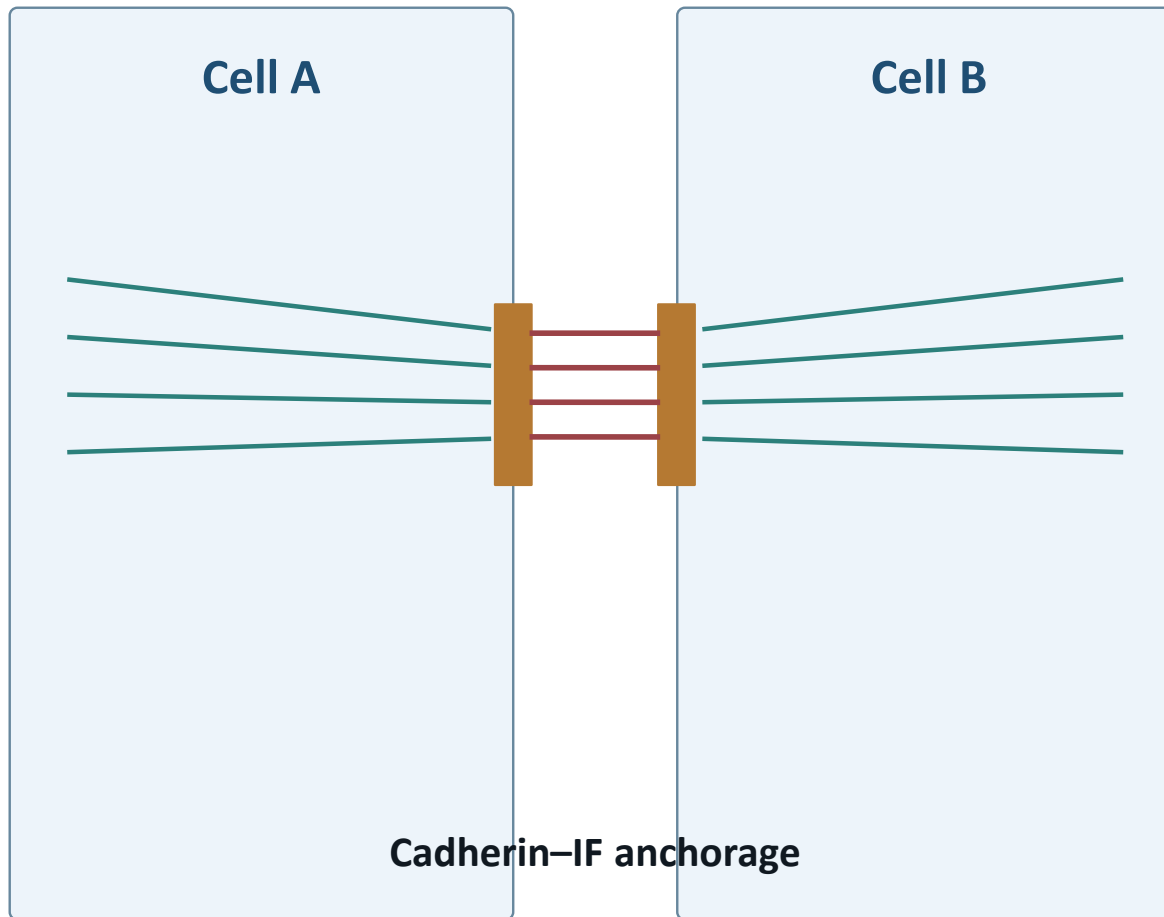
Most consistent answer

E-cadherin

Mechanistic explanation

E-cadherin is an epithelial adherens-junction protein. Reduced adhesion can generate a discohesive invasion pattern.

Desmosomes connect intermediate filaments



- Desmosomal cadherins bridge adjoining cells.
- Intracellular plaques connect to intermediate filaments.
- This architecture resists and distributes mechanical stress.

Desmosomes dissipate mechanical force

Force applied

Stress reaches one epithelial cell.



Desmosomal links

Anchorage joins neighboring cytoskeletons.



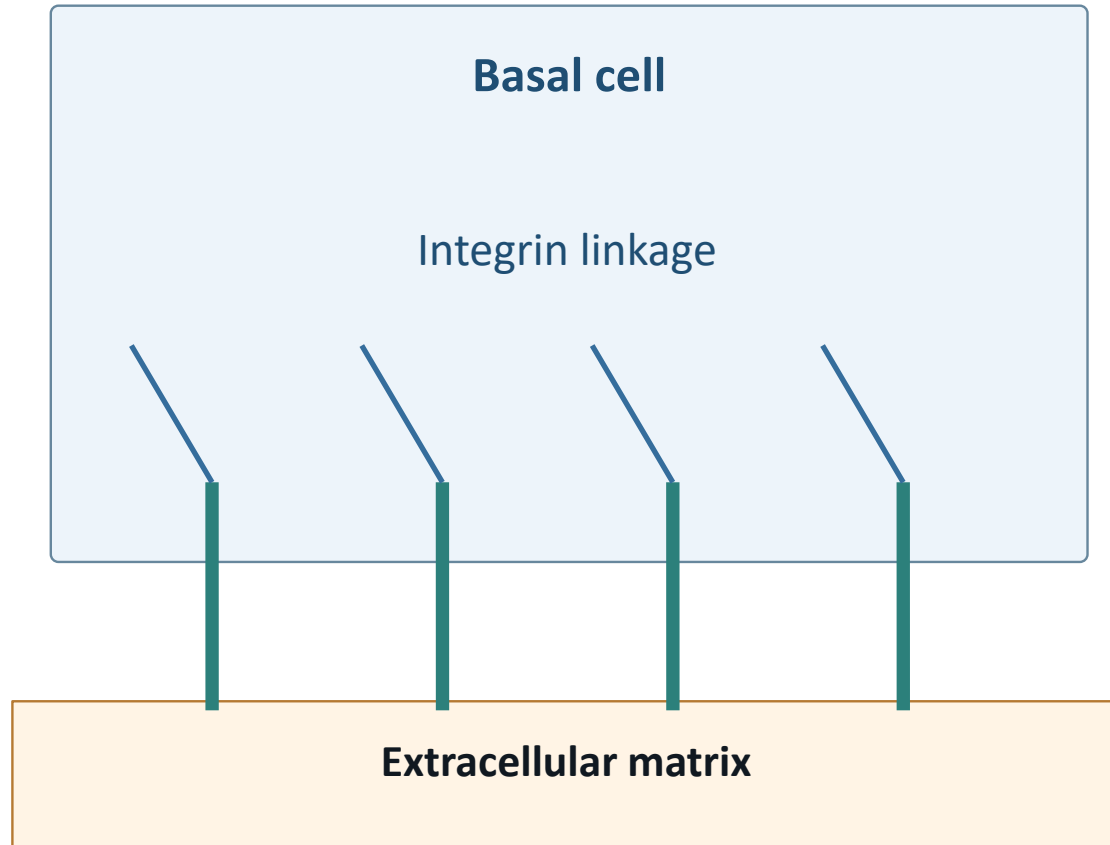
Distributed load

Forces spread across several cells.

Adherens junctions versus desmosomes

Property	Adherens junction	Desmosome
Intercellular adhesion	Cadherins	Cadherins
Intracellular linkage	Actin microfilaments	Intermediate filaments
Prominent function	Shape and motility	Resistance to tissue stress
Relative location	Near/below tight junction	Generally more basal

Hemidesmosomes anchor cells to matrix



- The opposing structure is extracellular matrix, not another cell.
- Integrins act as transmembrane connectors.
- Intermediate filaments couple the cell to its basal substrate.

Desmosome versus hemidesmosome

Property	Desmosome	Hemidesmosome
Attachment	Cell to cell	Cell to extracellular matrix
Transmembrane link	Cadherins	Integrins
Cytoskeletal partner	Intermediate filaments	Intermediate filaments
Mechanical role	Distributes cell-to-cell forces	Anchors the cell to its substrate

Cell adhesion also senses mechanical load

Multiprotein assemblies

Focal adhesion complexes incorporate many interacting proteins.

Mechanical stimulus

Cells may experience shear or other loading forces.

Signal response

Adhesion-associated proteins can initiate intracellular signals.

Two contexts for mechanotransduction

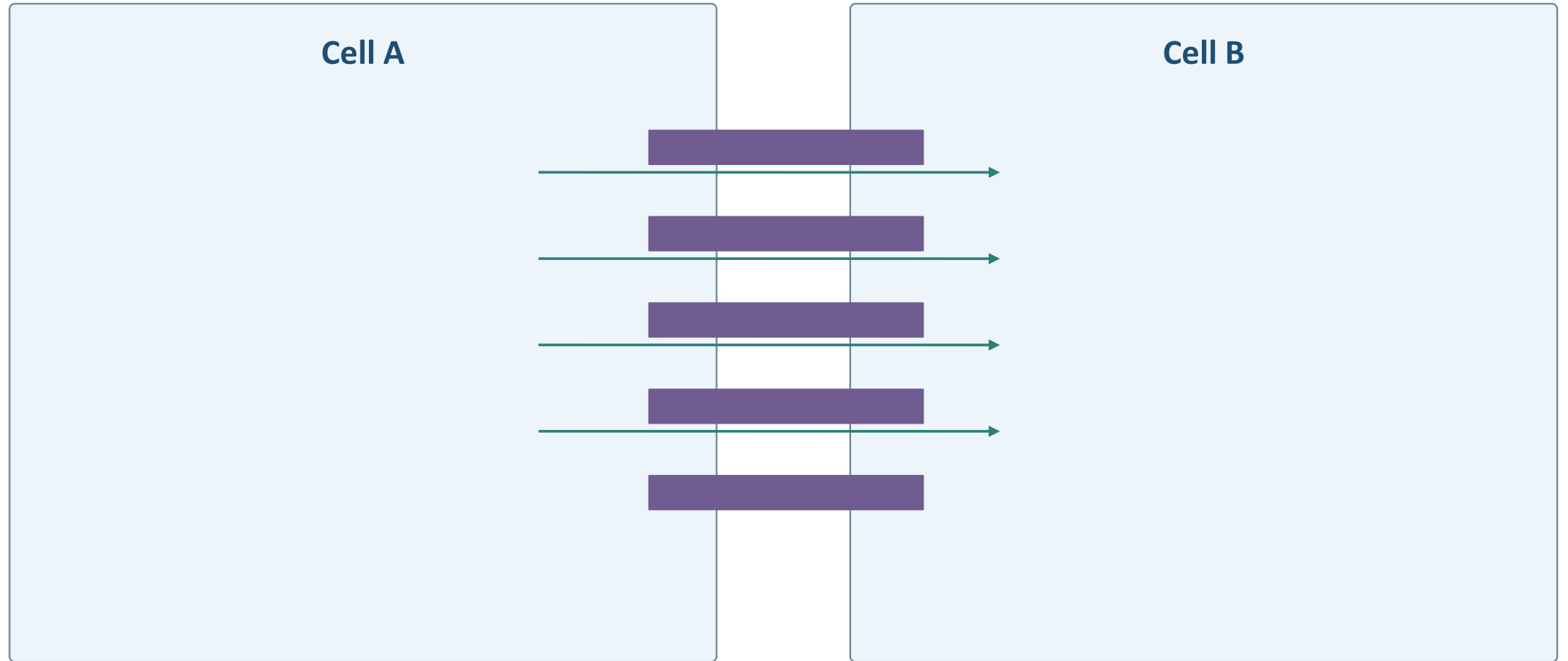
Vascular endothelium

Blood flow exposes endothelial cells to shear stress.

Cardiac myocytes

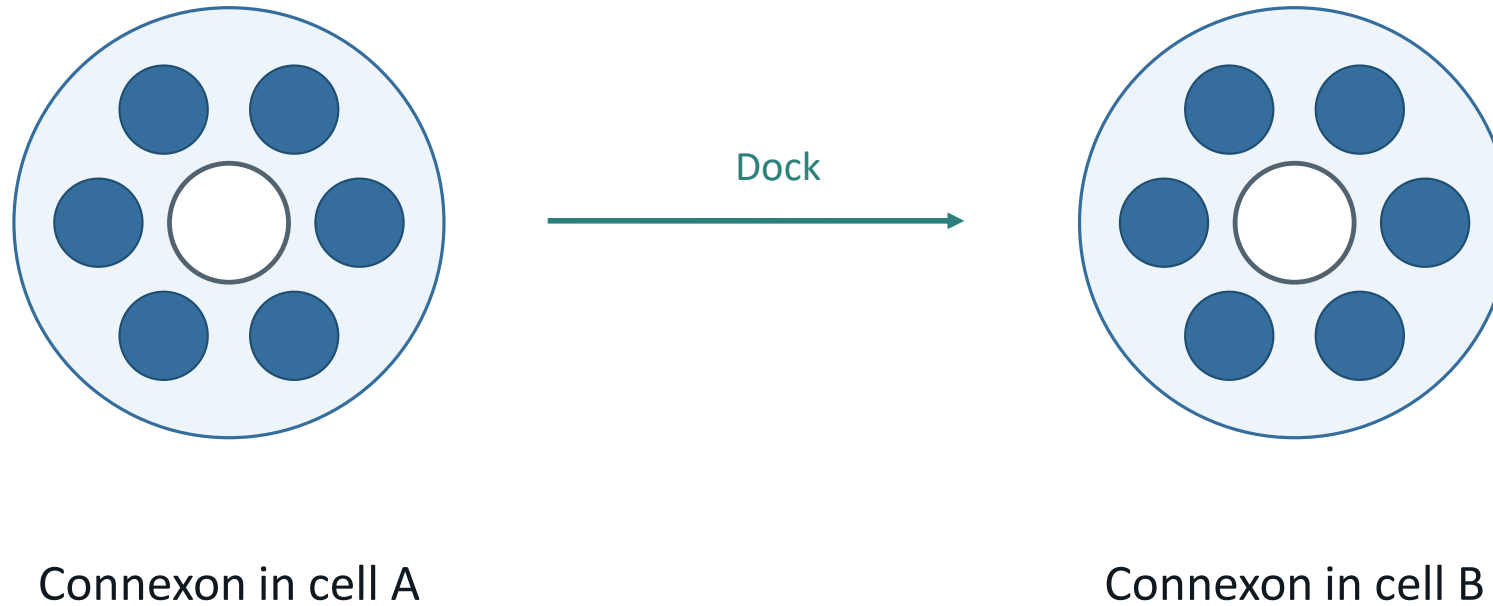
Mechanical loading in a failing heart provides an example of stress-linked signaling.

Gap junctions connect two cytoplasms



Paired connexons form intercellular pores

Connexon architecture: Paired connexin hexamers



One hexamer per cell; The aligned pair forms a pore.

What can pass through a gap junction?

- Ions and small metabolites.
- Nucleotides and sugars.
- Amino acids and vitamins.
- Signals that coordinate neighboring cell activity.

Gap junction permeability is regulated

Intracellular acidification

Lowered cytoplasmic pH rapidly reduces permeability.

Intracellular calcium elevation

Increased intracellular Ca^{2+} also reduces gap-junction permeability.

Cardiac myocytes behave as a functional syncytium

Gap channels

Direct passage of small signaling substances.



Cell coordination

Intercellular calcium and electrical signaling.



Myocardial response

Waves of contraction across coupled cells.

Junctional defects: Identify the lost function

Affected structure	Primary disrupted process	Relevant context
Tight junction	Epithelial barrier / polarity	Mucosal and epithelial surfaces
Adherens junction	Epithelial cell cohesion	Discohesive carcinomas
Desmosome	Force distribution	Mechanically stressed tissues
Gap junction	Intercellular signaling	Coordinated cardiac contraction

Biosynthesis and secretion

Endoplasmic reticulum • Golgi apparatus • Secretory routes

Cellular constituents undergo continual renewal

The cell continuously balances synthesis and degradation.

Structural proteins, enzymes, transcription factors and membranes all participate in ongoing turnover.

The ER has three central synthetic roles

Membrane proteins

Production of proteins destined for cellular membranes.

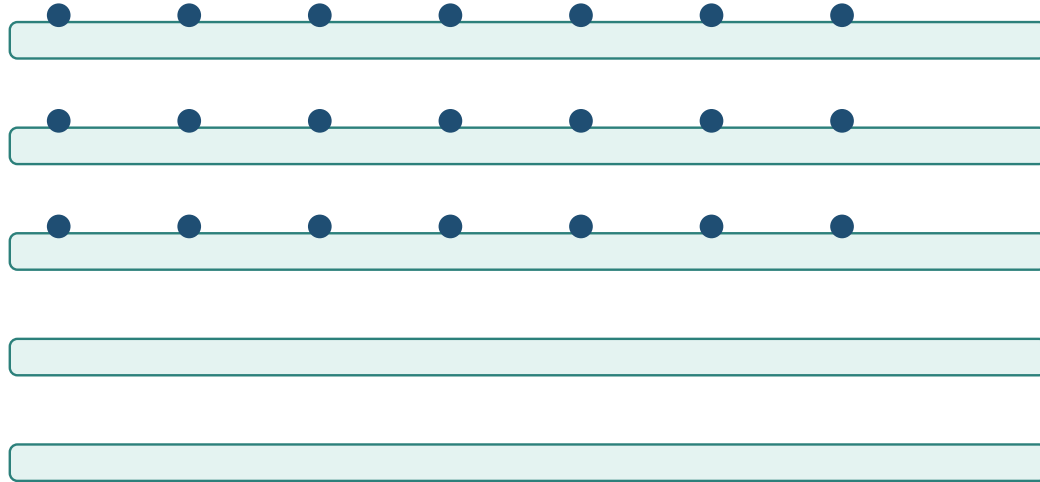
Membrane lipids

Synthesis of lipid components for cellular organelles and surface.

Secreted proteins

Initial protein synthesis and processing before export.

The ER is a continuous membrane system



Rough ER

CONTINUOUS LUMEN

RER: Ribosome-studded surface

Rough versus smooth endoplasmic reticulum

Property	Rough ER (RER)	Smooth ER (SER)
Ribosomes	Attached to cytosolic face	Absent
Major emphasis	Protein synthesis and maturation	Lipid/steroid metabolism and Ca ²⁺ storage
Specialization	Prominent in secretory protein cells	Prominent in steroidogenic cells and hepatocytes

An ER signal sequence determines protein routing

Start

Ribosomes initially translate in cytosol.



Signal

N-terminal sequence directs nascent product to ER.



Insertion

Protein enters the ER lumen or membrane.

Proteins with and without an ER signal peptide

With signal peptide

Translation is directed to the ER; Products are inserted into the membrane or conveyed into its lumen.

Without signal peptide

Translation remains on free cytosolic ribosomes; The proteins remain within the cytoplasm.

RER establishes a pathway to the cell surface

Nascent peptide

Signal-directed ribosome recruitment to ER.



ER compartment

Membrane insertion or luminal delivery.



Downstream traffic

Transport toward Golgi for maturation and sorting.

Proteins mature within the ER

Folding

Polypeptides acquire a functional conformation.

Oligomerization

Multiple protein chains may form complexes.

Chemical changes

Disulfide bond formation and N-linked glycosylation.

N-linked glycosylation begins in the ER

- Oligosaccharides are added to asparagine residues.
- This modification begins before arrival in the Golgi.
- The sugar chains undergo further modification during Golgi transit.

ER chaperones participate in quality control

New proteins

Fold and assemble within the ER.



Chaperones

Assist maturation and retention.



Disposition

Correctly folded: Progress;
Defective: Retain/degrade.

Two outcomes of ER protein surveillance

Correctly folded cargo

Proteins complete modifications and proceed through secretory traffic.

Persistently misfolded cargo

Protein is retained within the ER and subjected to degradation.

CFTR Phe508 deletion: A proteostasis example

Deletion

Loss of phenylalanine at position 508.



ER handling

Abnormal folding triggers retention/degradation.



Functional result

Reduced CFTR expression at cell surface.

Unfolded protein response is activated by ER overload

Misfolded proteins accumulating beyond ER quality-control capacity trigger the unfolded protein response (UPR).

The response aims to restore folding homeostasis.

The unfolded protein response: Three outcomes

Reduce input

Overall cellular protein synthesis is reduced.

Increase capacity

Chaperone protein production rises.

If unresolved

Persistent stress can trigger apoptosis.

Escalation from ER stress to apoptosis

Protein overload

Misfolded proteins accumulate.



UPR activation

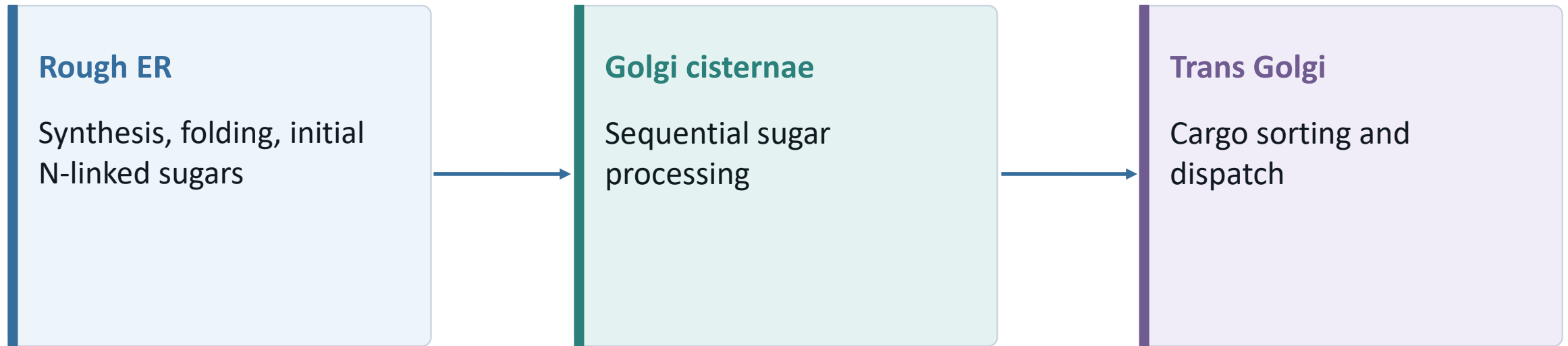
Adaptation attempts to control the burden.



Failure

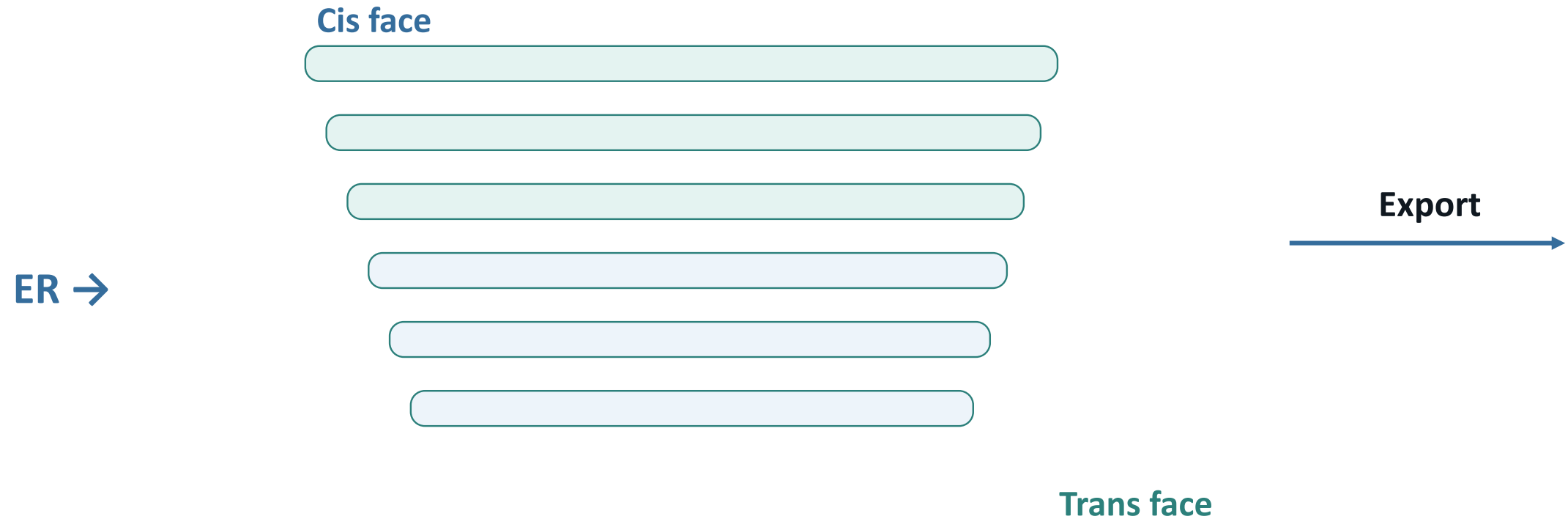
Uncorrected stress can lead to programmed cell death.

ER-to-Golgi transport and cargo maturation



Vesicle-mediated transfer; Ordered processing

Golgi traffic progresses from cis to trans



Ordered cisternal processing and sorting

Cisternal progression supports ordered processing

Cis side

Receives newly transported ER cargo.



Maturation

Golgi cisternae progress toward the trans side.



Recycling

Vesicles return resident enzymes to earlier regions.

N-linked and O-linked glycosylation

Feature	N-linked	O-linked
Amino acid	Asparagine	Serine or threonine
ER step	Initial oligosaccharide addition	—
Golgi step	Stepwise pruning and extension	Oligosaccharide addition

Mannose-6-phosphate directs lysosomal enzymes

Cargo

Selected enzymes acquire mannose-6-phosphate labeling.



Recognition

M6P receptor recognizes modified cargo.



Destination

Transport into the lysosomal pathway.

Glycosylation affects more than protein structure

Lysosome delivery

Selected sugar marks enable intracellular sorting.

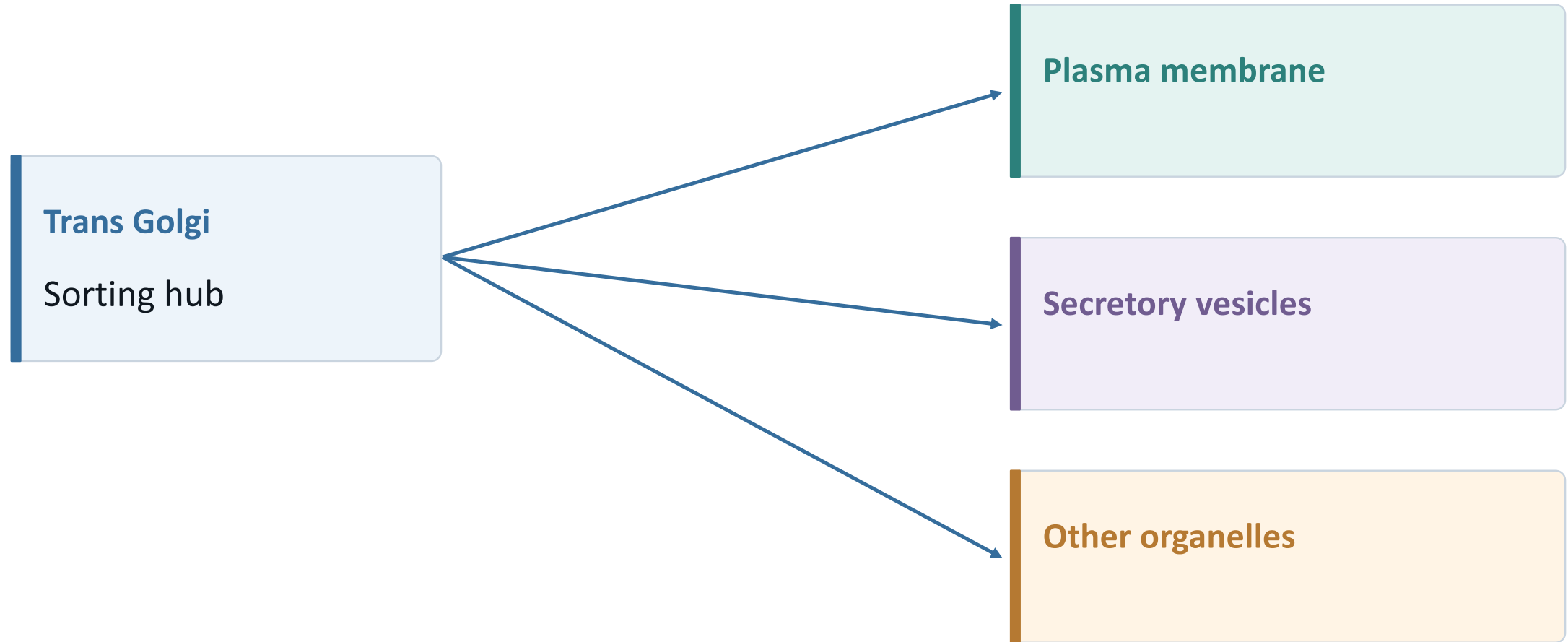
Adhesive interactions

Glycosylation influences cell–cell and cell–matrix contacts.

Clearance

Sugar-related changes participate in removal of senescent blood cells.

The trans Golgi network directs cellular cargo



Secretory cell morphology reflects Golgi activity

Goblet cell

Prominent Golgi activity supports high-volume secretion of polysaccharide-rich mucus.

Plasma cell

The Golgi appears as a perinuclear hof on H&E sections in antibody-producing cells.

Smooth ER performs distinct cellular tasks

Transport interface

A transition zone can generate ER-to-Golgi vesicles.

Metabolism

Prominent in steroidogenic and xenobiotic-processing cells.

Calcium homeostasis

Sequesters intracellular calcium for signaling.

Smooth ER is enlarged in selected cell types

Gonadal and adrenal cells

Specialized for steroid-hormone biosynthesis.

Hepatocytes

Contain SER supporting metabolism of lipid-soluble molecules.

Xenobiotic exposure can induce smooth ER

Repeated exposure

Compound processed by SER enzymes.



Enzymatic demand

Cytochrome P450 systems catabolize the compound.

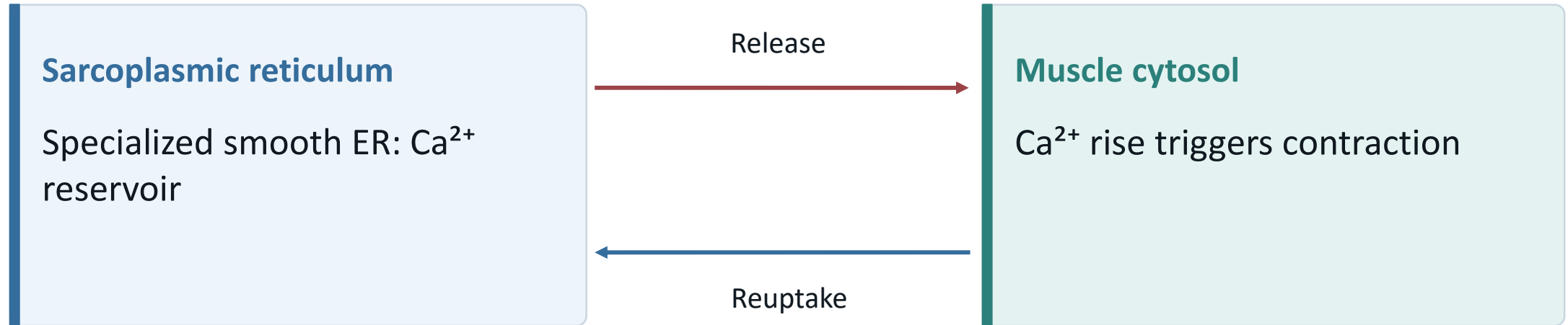


Adaptive response

Smooth ER hyperplasia may develop.

Phenobarbital is a source example of an inducing exposure.

Sarcoplasmic reticulum governs calcium cycling



Release → contraction | sequestration → relaxation

Classical versus unconventional secretion

Feature	Classical pathway	Unconventional release
Core route	ER → Golgi → secretory or surface destination	Release without the classical ER–Golgi route
Illustrations	Secretory proteins and membrane cargo	IL-1 β ; α -synuclein; Extracellular vesicles
Teaching focus	Ordered maturation and sorting	Alternative mechanisms of export

Examples of unconventional secretion

- Interleukin-1 β (IL-1 β): A major proinflammatory cytokine.
- α -Synuclein: A protein implicated in Parkinson disease.
- Extracellular vesicles: Membrane-bound particles released into extracellular space.

Extracellular vesicles export molecular cargo

Forms

Exosomes and microvesicles are examples.

Contents

May contain proteins, lipids and nucleic acids.

Destination

Released to extracellular fluid and can enter biofluids.

Extracellular vesicles have biomarker potential

Vesicles in blood and other biofluids can be investigated as sources of tissue-derived biomarkers.

This is a rationale for liquid-biopsy research; The source does not give clinical sensitivity or specificity.

Transport processes at a glance

Process	Principal components	Consequence
Junction assembly	Transmembrane proteins + scaffolds	Adhesion, polarity and intercellular signaling
Classical secretion	ER + Golgi + transport vesicles	Mature cargo reaches targeted location
Unconventional export	Alternative release routes / vesicles	Cell-derived molecules enter extracellular space

Application: A protein fails to reach the surface

A mutant membrane protein is retained and degraded in the ER because it cannot fold properly. Which mechanism is most directly implicated?

A. ER protein quality control

B. Loss of connexon docking

C. Desmosomal cadherin binding

D. Paracellular ion transport

Application: ER quality control

Most consistent answer

ER retention and degradation

Mechanistic explanation

The Phe508 deletion in CFTR is the source example: Abnormal folding reduces delivery to the plasma membrane.

Principal teaching points

- Tight junctions regulate paracellular movement and epithelial polarity.
- Cadherin-based junctions connect cells to actin or intermediate filaments.
- Integrin-based hemidesmosomes anchor cells to extracellular matrix.
- Gap junctions coordinate adjacent cells through direct communication.
- ER and Golgi produce, mature, surveil and route cellular cargo.

Primary reading

Core textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 1: The Cell as a Unit of Health and Disease; Cell–Cell Interactions and Biosynthesis and Secretion, pp. 11–13.

Illustrations in this lecture are original editable schematics based on the supplied text.