

Cell Biology

for

M.Sc. Semester II
(Paper 2)

Author

Dr. Subhash Kumar

Assistant Professor & HOD

Dept. of Botany, CCR (PG) College, Muzzaffarnagar (UP)

Dr. Chandra Bali Patel

Assistant Professor

Dept. of Botany, Rastriya Kisan PG College, Shamli (UP)



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CONTENTS

UNIT 1. Cell Interactions and Membrane Structure

1-34

Cell interactions: Extra cellular matrix, Cell adhesion molecules; cadherins, integrins, selectins, fibronectins, laminin and Immunoglobulin superfamily. Cell-cell adhesions (Junctional and non junctional adhesive mechanisms; occluding junctions, anchoring junctions, communicating junctions (Connexons) and plasmodesmata).

Membrane structure: Plasma membrane: the lipid bilayer, fluidity of the lipid bilayer, phospholipids, sphingolipids, cholesterol, glycolipids, rafts, Membrane proteins, and membrane transport (Active & Passive)

UNIT 2. Protein Targeting, Post Transcriptional Modification and Vesicular Transport

35-76

Protein Targeting: Protein secretion, synthesis and targeting of mitochondria, chloroplasts, Nucleus, & Peroxisomes.

Posttranslational Modification of protein: Glycosylation in the Rough Endoplasmic Reticulum and Golgi Complex. Vesicular Transport: Transport From the ER to the Golgi Complex; Transport of Materials through the Golgi Complex; Mechanism of transport to Lysosomes.

Types of Vesicle Transport and Their Functions: COPII-Coated Vesicles: COPII-Coated Vesicles & Clathrin coated vesicles.

Targeting Vesicles to a Particular Compartment: Movement, Tethering, Docking & Fusion of Vesicles with target membrane.

UNIT 3. Cell Cycle Regulation and Protein Degradation in Cell Cycle Control

77-103

Cell Cycle: Overview of Cell Cycle Phases; Cell Cycle Checkpoints; Regulation of cell cycle:

Positive regulation (Cyclin, Cdk Phosphorylation/dephosphorylation; Activation of cyclin-dependent kinases, Mechanism of Cdk regulation; DNA replication licensing; CDK inhibitors, Maturation promoting factor (MPF) Regulation).

Negative regulation (Retinoblastoma protein (pRb); p53, (Mechanism of p53)

Protein Degradation in Cell-Cycle Control SCF (Skp1-Cullin-F-box protein complex) and the APC (Anaphase-Promoting Complex),

Structural maintenance of Chromosomes (SMC); Spindle formation and its disintegration, mechanism of chromosome movement and separation during anaphase, Spindle Assembly Checkpoint and Progression to Anaphase

UNIT 4. Cell Signaling and Cell Surface Receptors

104-136

Cell Signalling General principle, ligands and receptors, types of cell signaling, Component of cell signaling. Features of signal-transducing systems, Types of signal transducers,

Molecular switch Kinase/Phosphatase Molecular Switch, GTPase Molecular Switch

G Protein G Cycle, G Protein-Coupled Receptors and Second Messengers

Cell surface receptors cAMP/PKA Signal transduction, The Phospholipase C/Calcium Signal Transduction Pathway, Receptor Tyrosine Kinases (RTKs), The MAP Kinase Signaling Cascade

Intracellular Receptors Nitric Oxide Cell Signaling, Calmodulin signaling pathway, Role of Ca ion as an intracellular messenger in the stomatal movement.

UNIT 1

Cell Interactions and Membrane Structure

CELL INTERACTIONS

Cell interactions via the ECM and CAMs are fundamental to multicellular life. They provide the physical architecture of tissues and organs while also serving as sophisticated signaling platforms that integrate mechanical and chemical cues. The dynamic interplay between different CAM families—from the strong, stable bonds of cadherins to the transient tethering of selectins—orchestrates complex processes like development, immunity, and tissue repair. Dysregulation of these interactions

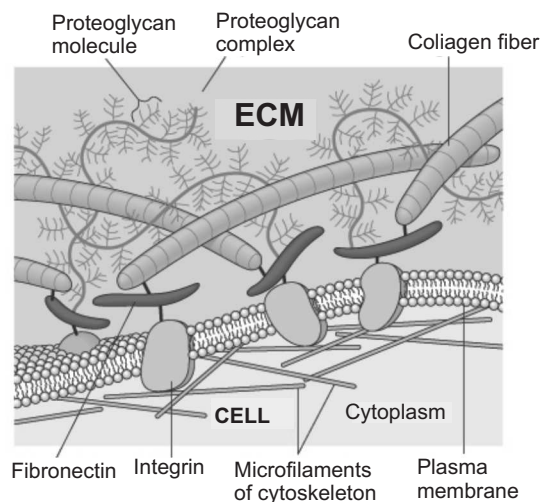
underpins numerous diseases, including cancer, autoimmune disorders, and chronic inflammatory conditions, highlighting their critical importance in biology and medicine.

Multicellular organisms require precise cell-cell and cell-matrix interactions for tissue organization, morphogenesis, immune function, and homeostasis. These interactions are mediated by specialized cell adhesion molecules (CAMs) and the extracellular matrix (ECM), forming a dynamic communication network.

EXTRA CELLULAR MATRIX (ECM)

Definition and Functions

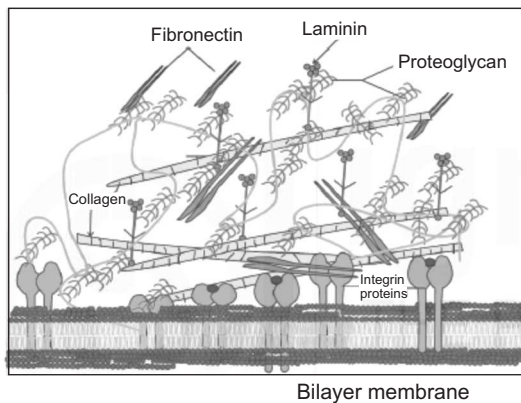
- **Definition:** A complex, non-cellular, three-dimensional network of macromolecules secreted by cells into their local environment. It is the "biological glue" that holds tissues together.
- **Major Functions:**
 1. **Structural Support & Scaffolding:** Determines tissue architecture and mechanical properties (rigidity in bone, elasticity in skin).



2. **Cell Adhesion & Migration:** Provides anchorage sites via specific ligands for cell surface receptors (integrins).
3. **Signaling Hub:** Regulates cell behavior (proliferation, differentiation, survival) via mechanotransduction and presentation of growth factors/cytokines.
4. **Tissue Barrier & Filtration:** e.g., Basement membranes regulate molecular passage.
5. **Wound Healing & Regeneration:** Scaffold for tissue repair.

Major Components

The ECM composition varies greatly between tissues (e.g., bone vs. cartilage vs. connective tissue).

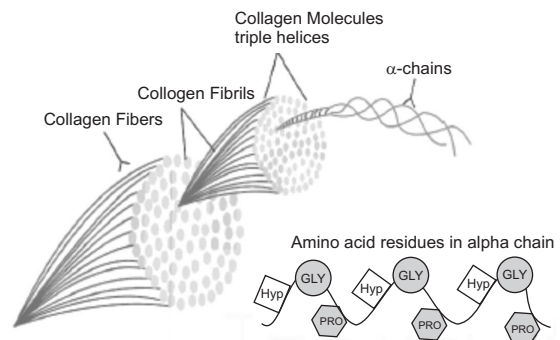


An Overview of the Organization of the ECM

Fibrous Structural Proteins

- **Collagens:** The most abundant protein in animals (~25% of body protein). Provide tensile strength.

- **Structure:** Triple helix of α -chains. Types I, II, III form fibrils; Type IV forms meshworks in basement membranes.



The Assembly of Collagen Fibers

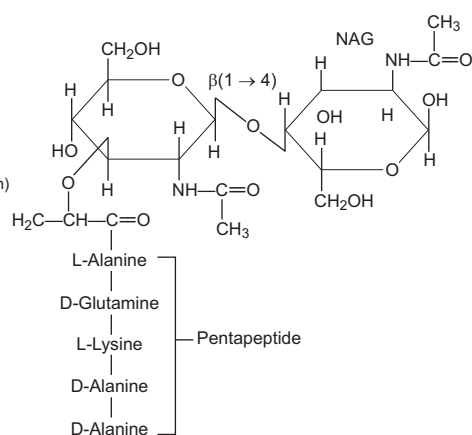
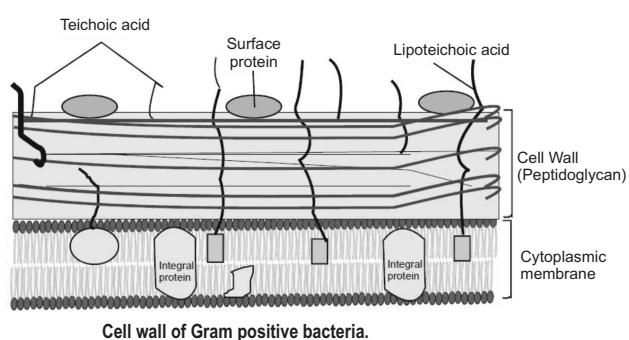
- **Elastins:** Provide elasticity (e.g., skin, lungs, blood vessels). Form cross-linked networks that can stretch and recoil.

Adhesive Glycoproteins

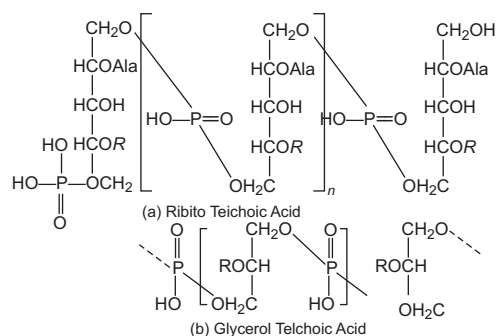
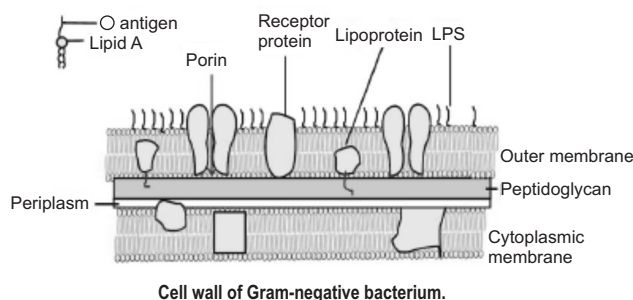
- **Fibronectin:** A large, multi-domain dimer that binds integrins, collagen, fibrin, and heparan sulfate.
 - **Functions:** Cell adhesion, migration (during embryogenesis, wound healing), and hemostasis.
- **Laminin:** A major component of basement membranes. Large cross-shaped glycoprotein.
 - **Functions:** Key organizer of basement membrane assembly; binds integrins, dystroglycan, and other ECM components.

👉 Proteoglycans (PGs) & Glycosaminoglycans (GAGs)

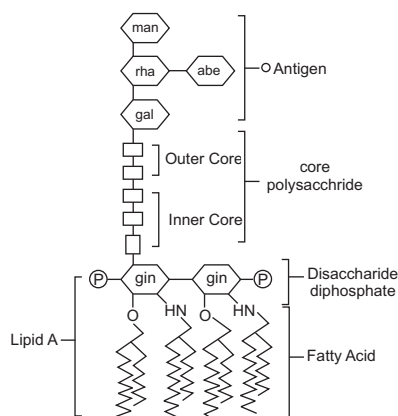
- **GAGs:** Long, unbranched polysaccharide chains of repeating disaccharide units. Highly negatively charged (attract cations, trap water → form hydrated gels). Examples: Hyaluronan, chondroitin sulfate, heparan sulfate.
- **Proteoglycans:** Core protein with one or more covalently attached GAG chains.
- **Functions:** Hydration, resistance to compression (e.g., aggrecan in cartilage), growth factor binding/ reservoir, signaling.



The Repeating Unit of Peptidoglycan.



Teichoic acid polymers



Structure of Lipopolysaccharide (LPS).

Major ECM Components

Component	Primary Structure	Key Functions	Location/Example
Collagen	Triple helix fibrils	Tensile strength, structural integrity	Skin, bone, tendons (Type I); Cartilage (Type II); Basement membrane (Type IV)
Elastin	Cross-linked network	Elasticity, recoil	Lungs, arteries, skin
Fibronectin	Dimeric glycoprotein	Cell adhesion, migration, wound healing	Plasma (soluble), connective tissue (insoluble)
Laminin	Cross-shaped glycoprotein	Basement membrane assembly, cell adhesion	All basement membranes
Proteoglycans	Core protein + GAGs	Hydration, compression resistance, signaling	Aggrecan (cartilage), Perlecan (basement membranes)

CELL ADHESION MOLECULES (CAMs)

CAMs are transmembrane glycoproteins that mediate specific, often calcium-dependent, binding between cells or between cells and the ECM. They link the extracellular environment to the intracellular cytoskeleton via adaptor proteins.

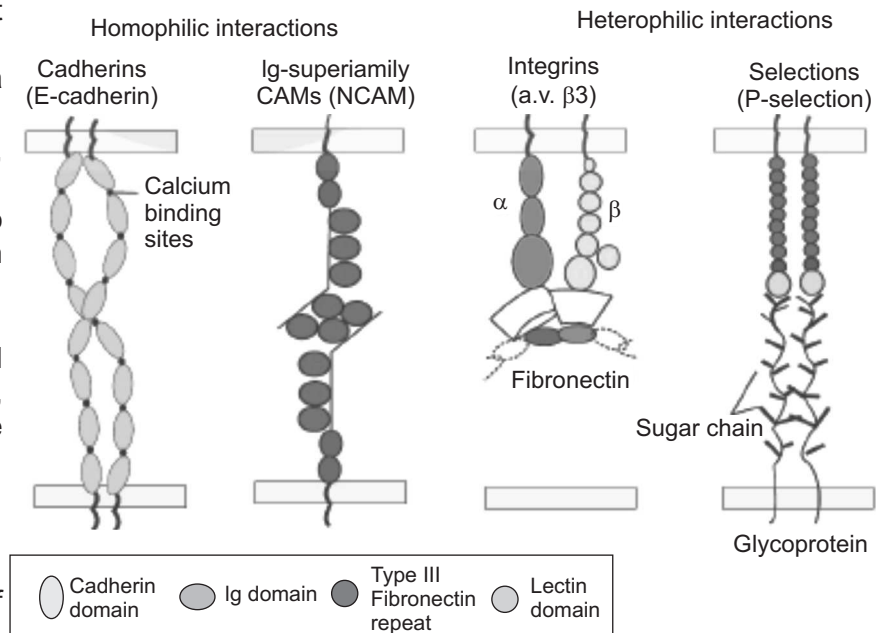
The Four Major Families

👉 Cadherins

- **Structure:** Single-pass transmembrane proteins with extracellular cadherin (EC) repeats that mediate homophilic, Ca^{2+} -dependent binding (e.g., E-cadherin binds to E-cadherin on adjacent cell).

- **Intracellular Linkage:** Bind via catenins (α , β , p120) to the actin cytoskeleton.

- **Functions:**
 - Major mediators of adherens



Major Families of Cell Adhesion Molecules (CAMs) and their Receptors

junctions in epithelial tissues.

- Tissue morphogenesis and integrity (loss of E-cadherin is a hallmark of epithelial-mesenchymal transition (EMT) in cancer metastasis).
- Provide cell sorting during development (differential adhesion hypothesis).
- **Types:** E-cadherin (epithelial), N-cadherin (neuronal, muscle), P-cadherin (placental).

Integrins

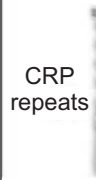
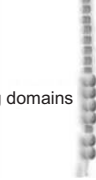
- **Structure:** Heterodimers of non-covalently linked α and β subunits. 24 different combinations in mammals, each with specific ligand preferences.
- **Binding:** Mediate heterophilic adhesion between cell and ECM ligands (fibronectin, laminin, collagen) or other CAMs on adjacent cells.
- **Key Feature:** Bidirectional Signaling.
 - **Outside-In Signaling:** Ligand binding induces conformational change $\rightarrow$ clustering $\rightarrow$ recruitment of adaptor proteins (talin, vinculin) to form focal adhesions linked to actin. Activates intracellular pathways (FAK, Src).

- **Inside-Out Signaling:** Intracellular signals alter integrin conformation, increasing its affinity for ligand (activation).

- **Functions:** Cell-ECM adhesion, migration, immune cell trafficking, platelet aggregation.

Selectins

- **Structure:** Single-pass transmembrane proteins with an N-terminal lectin domain that binds specific carbohydrate moieties (e.g., sialyl-Lewis X).
- **Binding:** Heterophilic, Ca^{2+} -dependent, but weak and transient. Facilitate rolling adhesion of leukocytes on endothelial cells.
- **Types:**
 - **E-selectin:** Endothelial cells (induced by inflammation).
 - **P-selectin:** Platelets and endothelial cells (stored in granules).
 - **L-selectin:** Leukocytes.
- **Function:** Critical first step in the leukocyte adhesion cascade during inflammation.

Cell Adhesion Molecules (CAMs)			
			
Cadherins	Integrins	Selectins	IgSFs
calcium dependent transmembrane cell-cell adhesion protein composed of a single-span transmembrane protein five extracellular calcium-binding repeats from homodimers through cadherin repeat.	signal across the plasma membrane in both directions cell-matrix proteins composed of two type of noncovalently associated transmembrane glycoproteins (α - and β -subunits)	first of adhesion composed of an N-terminal lectin domain, epidermal growth factor domain, complement regulatory proteins, transmembrane and cytoplasmic domains	cell surface receptors and cell adhesions composed of N-terminal signal peptide, immunoglobulin and fibronectin domains, cytoplasmic tail.

👉 Immunoglobulin Superfamily (IgSF) CAMs

- **Structure:** Contain one or more immunoglobulin-like (Ig) domains in their extracellular region. Most are single-pass transmembrane proteins.
- **Binding:** Can be homophilic (NCAM-NCAM) or heterophilic (NCAM-integrin, VCAM-1-integrin).
- **Functions:** Diverse roles in the immune system and nervous system.
- **Key Members:**
 - **Neural CAM (NCAM):** Important in neuron-neuron adhesion, synaptic plasticity, axon guidance.
 - **Intercellular CAM-1 (ICAM-1):** On endothelial cells; binds LFA-1 integrin on leukocytes, stabilizing adhesion after rolling.
 - **Vascular CAM-1 (VCAM-1):** Binds VLA-4 integrin, important in lymphocyte homing.
 - **Carcinoembryonic Antigen (CEA):** Cell adhesion in cancer; often overexpressed.

Comparison of Major CAM Families

Feature	Cadherins	Integrins	Selectins	IgSF CAMs
Binding Type	Homophilic (like-like)	Heterophilic (to ECM or other CAMs)	Heterophilic (to carbohydrates)	Homophilic or Heterophilic
Dependence	Ca ²⁺ -dependent	Divalent cation-dependent (Mg ²⁺ , Mn ²⁺)	Ca ²⁺ -dependent	Ca ²⁺ -independent
Cytoskeletal Link	Actin (via catenins)	Actin (focal adhesions) or Intermediate filaments (hemidesmosomes)	Actin (weak)	Variable (often actin)
Primary Role	Strong, stable adhesion (adherens junctions)	Cell-ECM adhesion, signaling, migration	Weak, transient adhesion (leukocyte rolling)	Immune & neural cell adhesion, signaling
Key Example	E-cadherin (epithelia)	α5β1 (fibronectin receptor)	E-selectin (inflamed endothelium)	NCAM (neurons), ICAM-1 (immune)
Binding Strength	High	High (when clustered)	Low	Moderate to High

Specialized Adhesive Structures (Junctions)

CAMs and ECM receptors organize into specific structures for specialized functions.

👉 Cell-Cell Junctions

1. **Adherens Junctions:** Cadherin-based, linked to actin belt. Provide strong mechanical attachment.
2. **Desmosomes:** Desmosomal cadherins (desmoglein, desmocollin) linked to intermediate filaments (keratin). Provide mechanical resilience in tissues under stress (skin, heart).

3. **Tight Junctions (Zonula Occludens):** Claudins & Occludins, form a seal that prevents paracellular leakage (barrier function).
4. **Gap Junctions:** Connexin proteins forming channels for direct cytoplasmic exchange of ions/small molecules (electrical/chemical coupling).

👉 Cell-ECM Junctions

1. **Focal Adhesions:** Integrin-based, linked to actin stress fibers. Dynamic structures for migration and force sensing.
2. **Hemidesmosomes:** Integrin $\alpha 6\beta 4$ linked to keratin intermediate filaments. Anchor epithelial cells to basement membrane.
3. **Fibrillar Adhesions:** Involved in fibronectin matrix assembly.

Biological Processes Mediated by CAMs and ECM

👉 Morphogenesis and Development

- **Selective Cell Adhesion:** Differential expression of cadherins guides tissue layer formation and cell sorting (e.g., ectoderm vs. mesoderm).
- **Cell Migration:** Integrin-ECM interactions guide neural crest cell migration, primordial germ cells.

👉 Immune Response

The Leukocyte Adhesion Cascade is a textbook example of sequential CAM use:

1. **Rolling:** Selectins (P- and E-) on endothelium bind carbohydrate ligands on leukocyte → weak, transient adhesion slows leukocytes.
2. **Activation:** Chemokines on endothelium activate leukocyte integrins (inside-out signaling).

3. **Arrest & Adhesion:** Activated integrins (LFA-1, VLA-4) bind IgSF CAMs (ICAM-1, VCAM-1) → firm adhesion.

4. **Transmigration (Diapedesis):** Leukocyte migrates between endothelial cells via PECAM-1 (IgSF) interactions.

👉 Cancer Metastasis

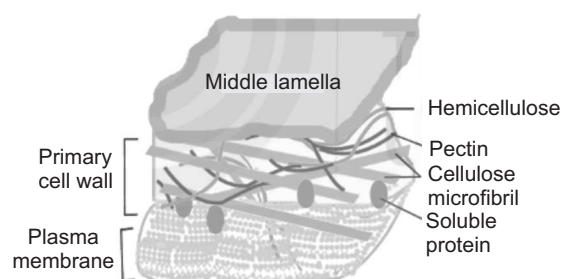
- Loss of E-cadherin promotes dissociation of epithelial cancer cells (EMT).
- Altered integrin expression allows cancer cells to adhere to and migrate through new ECM environments (e.g., bone, liver).
- Selectin-mediated adhesion facilitates cancer cell arrest in blood vessels (hematogenous spread).

👉 Wound Healing

- Platelet aggregation via integrin $\alpha IIb\beta 3$ binding fibrinogen.
- Keratinocyte migration over provisional ECM (fibronectin, vitronectin) via integrins to re-epithelialize the wound.

The Cell Wall as ECM

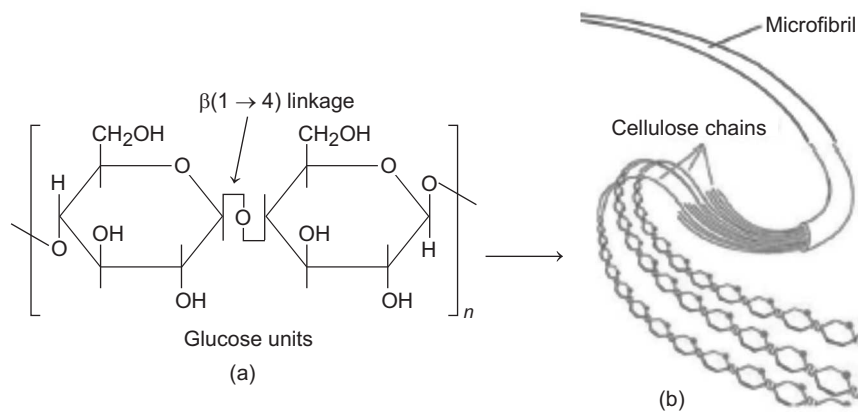
- Plant cells are surrounded by a rigid cell wall, their primary ECM.
- **Major Components:** Cellulose microfibrils (tensile strength), hemicellulose, pectin (gel matrix, adhesion), and structural proteins (e.g., extensins).



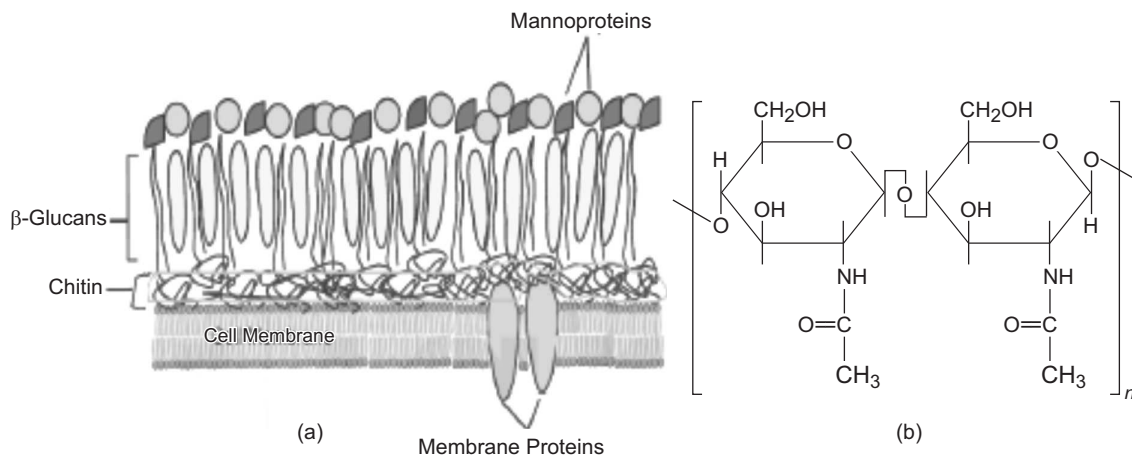
The Structure of Primary Cell Wall

- **Adhesion:** Middle lamella is a pectin-rich layer that cements adjacent cell walls together. Plasmodesmata are channels connecting plant cell cytoplasms (analogous to gap junctions).

Signaling: Cell wall fragments (oligosaccharins) can act as signaling molecules in defense responses.



(a) Building Block of Cellulose (b) Cellulose Microfibrils.



(a) The structure of fungal cell wall (b) Chitin Structure

CELL-CELL ADHESIONS - JUNCTIONAL AND NON-JUNCTIONAL MECHANISMS



Cell-cell adhesions are not merely static glue. They are dynamic, multifunctional complexes that integrate mechanical, barrier, and signaling roles. The specialized

organization of occluding, anchoring, and communicating junctions allows tissues to form regulated barriers, withstand mechanical forces, and coordinate behavior across many cells. Understanding these structures is fundamental to cell biology, developmental biology, and pathophysiology, with defects in junctions leading to a wide array of diseases, from blistering skin disorders to heart failure and cancer metastasis. The parallel evolution of gap junctions in animals and plasmodesmata in plants underscores the universal need for intercellular communication in multicellular life.

The Architecture of Tissue Integrity

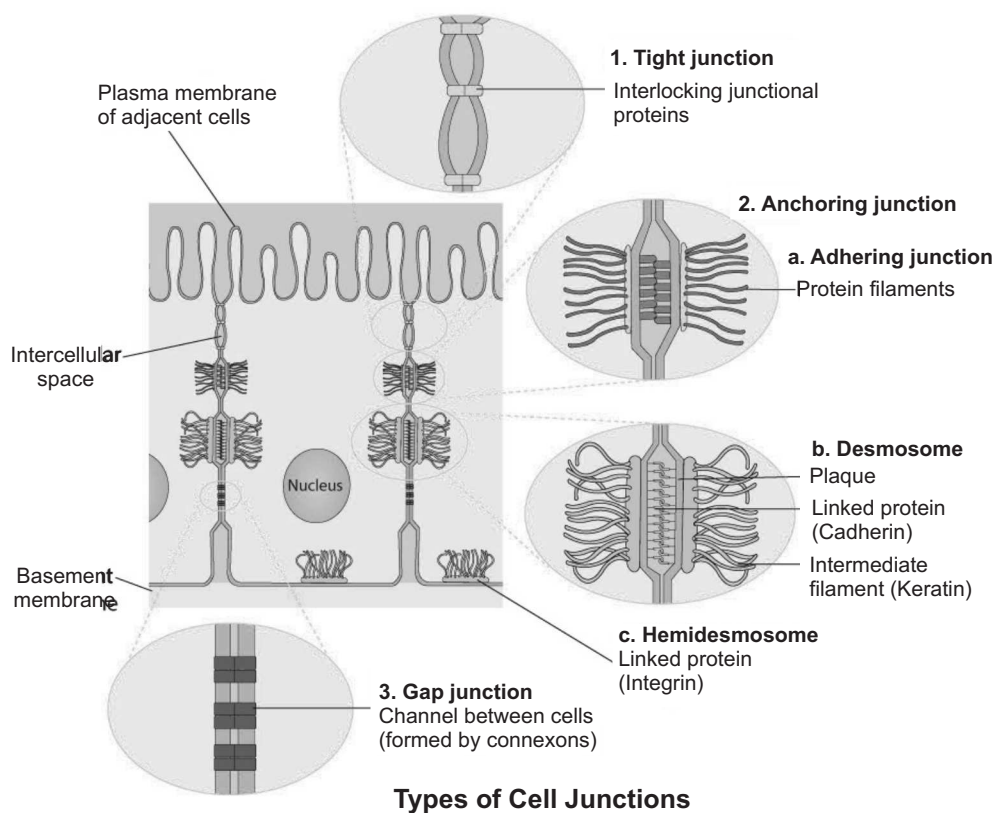
For multicellular organisms to function as coherent tissues and organs, cells must be

precisely and functionally connected. Cell-cell adhesions are specialized structures that mediate these connections, performing critical roles in barrier formation, mechanical strength, and intercellular communication. These adhesions are categorized into junctional (highly organized, ultrastructurally defined) and non-junctional (more diffuse) mechanisms.

Non-Junctional Adhesive Mechanisms

Before examining specialized junctions, it's important to recognize that diffuse, non-specialized adhesions also occur.

- **Definition:** Adhesive interactions that are not localized to a specific plaque or membrane domain. They often involve the same CAM families (cadherins,



IgSF CAMs) but in a less organized manner.

- **Function:** Provide generalized cell-cell recognition, initial contact, and weaker adhesion, often preceding the formation of more stable junctions. Important in dynamic tissues and during development.
- **Example:** The initial, calcium-dependent contacts mediated by E-cadherin prior to the assembly of mature adherens junctions.

Junctional Adhesive Mechanisms

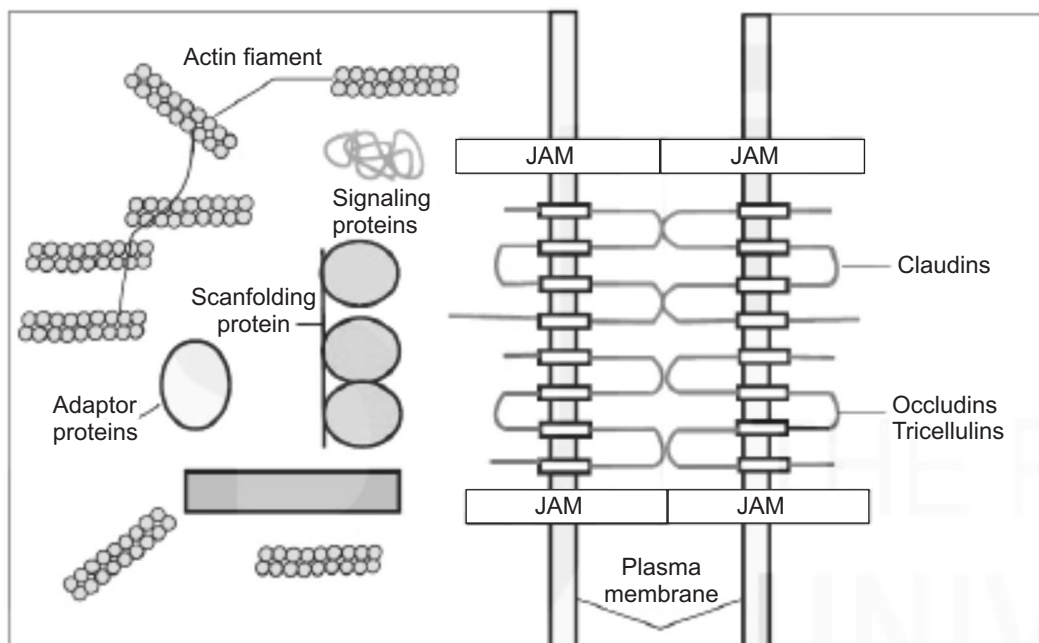
Junctions are highly organized, multi-protein complexes visible by electron microscopy. They are classified into three major functional types based on their primary role:

1. Occluding Junctions (Tight Junctions)
2. Anchoring Junctions (Adherens Junctions, Desmosomes)
3. Communicating Junctions (Gap Junctions, Plasmodesmata)

OCCUDING JUNCTIONS

Primary Function: Create a selective permeability barrier and maintain cell polarity.

Location: Apical region of epithelial and endothelial cells, forming a continuous belt around the cell (zonula).



Tight Junction Proteins Interact with Zonula Occludens (Zo) Family that Links them to Actin Cytoskeleton.

- **Structure:** A branching network of transmembrane sealing strands that fuse the outer leaflets of adjacent plasma membranes.
- **Key Molecular Components:**
- **Transmembrane Proteins:**
 - **Claudins:** Primary sealing proteins. A multigene family (~24 in humans) whose specific combination determines the size and charge selectivity of the paracellular pore.
 - **Occludin:** Regulates tight junction dynamics and barrier function; its phosphorylation state controls permeability.
- **Junctional Adhesion Molecules (JAMs):** IgSF members that initiate cell-cell contacts and recruit signaling proteins.
- **Cytoplasmic Plaque Proteins:**
 - **ZO proteins (Zonula Occludens-1, -2, -3):** Scaffolding proteins that link claudins/occludin to the actin cytoskeleton and recruit signaling molecules.
- **Key Functions:**
 1. **Barrier Function ("Gate"):** Seal the paracellular space, preventing uncontrolled leakage of molecules between cells. Creates separate compartments (e.g., gut lumen from blood).
 2. **Fence Function:** Restricts lateral diffusion of lipids and proteins between apical and basolateral membrane domains, maintaining cell polarity.
- **Dysfunction:** Leads to increased permeability ("leaky" gut/barrier), implicated in inflammatory bowel disease, celiac disease, and asthma.

Comparison: Vertebrate Tight Junctions vs. Invertebrate Septate Junctions

- **Septate Junctions:** Found in invertebrates (e.g., *Drosophila*). Perform a similar barrier function but are located more basally and have a characteristic ladder-like appearance in EM. Involve different proteins (e.g., Neurexin IV, Coracle).

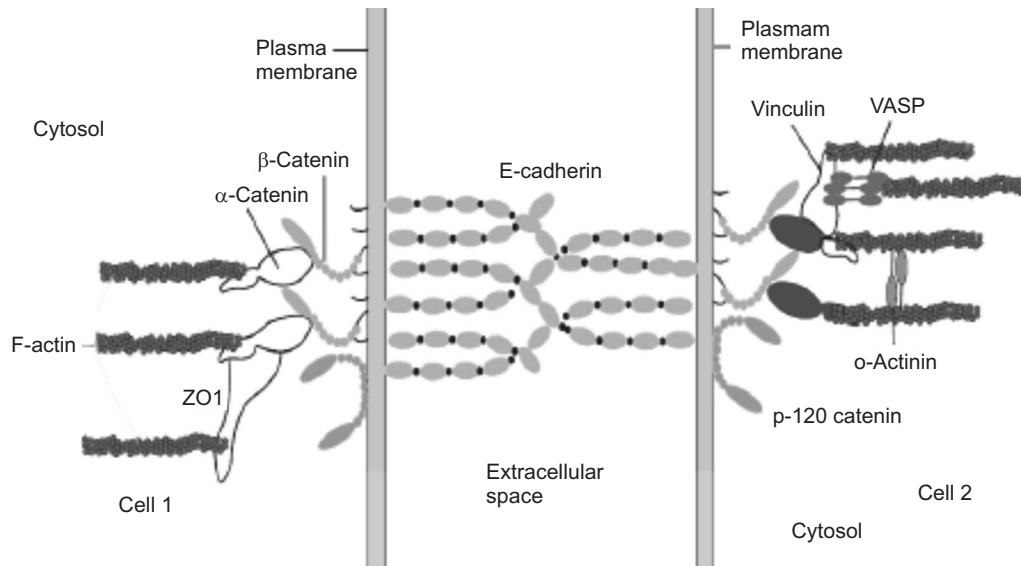
ANCHORING JUNCTIONS

Primary Function: Provide mechanical strength by linking the cytoskeletons of adjacent cells. Two main types, distinguished by their cytoskeletal attachment.

Adherens Junctions (AJs)

- **Cytoskeletal Linkage:** Actin filaments.
- **Core Transmembrane Protein:** Classical Cadherins (E-cadherin in epithelia, N-cadherin in neurons).
- **Molecular Architecture:**

- **Extracellular:** Cadherins from adjacent cells engage in homophilic, Ca^{2+} -dependent binding.
- **Intracellular:** Cadherin tail binds β -catenin or γ -catenin (plakoglobin), which in turn binds α -catenin. α -catenin links the complex to the actin cytoskeleton, though this linkage is dynamic and regulated.
- **p120-catenin:** Binds the cadherin juxtamembrane domain, stabilizing



Protein Interactions at an Adherens Junction.

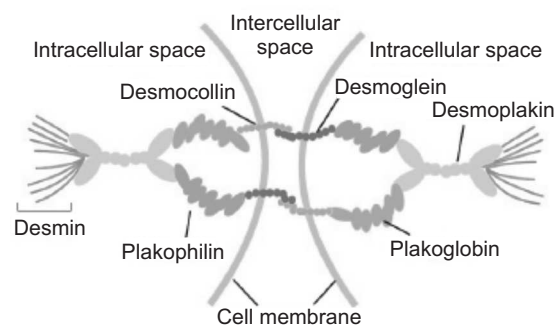
cadherin at the membrane and regulating its turnover.

- **Structure:** Can form a continuous adhesion belt (zonula adherens) just below tight junctions in epithelia, or smaller punctate adhesions.
- **Key Functions:**
 - Initiate and stabilize cell-cell contacts.
 - Transduce mechanical forces via the actin cytoskeleton.
 - Critical for tissue morphogenesis (e.g., during gastrulation, neural tube closure).
 - **Signaling Hub:** β -catenin is a dual-function protein; when released from cadherins, it acts as a transcriptional co-activator in the Wnt pathway.

Desmosomes (Macula Adherens)

- **Cytoskeletal Linkage:** Intermediate filaments (keratins in epithelia, desmin in muscle).

- **Core Transmembrane Proteins:** Desmosomal Cadherins - Desmogleins and Desmocollins.



Schematic Model of a Desmosome.

- **Molecular Architecture:**
 - **Extracellular:** Desmosomal cadherins mediate homophilic (and some heterophilic) adhesion.
 - **Intracellular Plaque:** Dense plaque contains plakoglobin (γ -catenin) and plakophilins, which link cadherins to desmoplakin.

Desmoplakin directly binds and organizes keratin intermediate filaments.

- **Structure:** Discrete, button-like spots (maculae) providing strong, spot-welded adhesion.
- **Key Functions:**
 - Provide tensile strength to tissues subjected to mechanical stress (skin, heart muscle, uterine cervix).
 - Tissue integrity and wound healing.
- **Dysfunction:** Autoantibodies against desmogleins cause pemphigus vulgaris (blistering skin disease). Mutations in desmosomal proteins cause cardiomyopathies (e.g., Arrhythmogenic Right Ventricular Dysplasia) and skin disorders.

Comparison of Major Anchoring Junctions

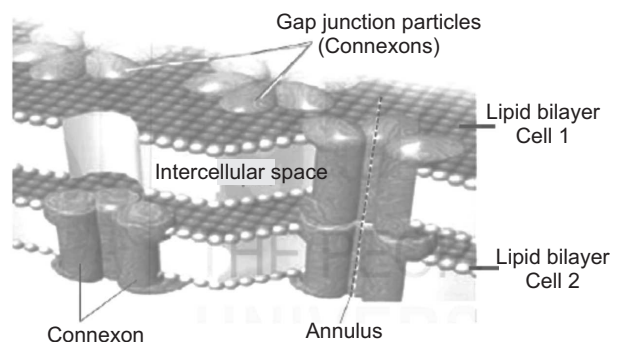
Feature	Adherens Junctions	Desmosomes
Transmembrane Adhesor	Classical Cadherins (E-, N-cadherin)	Desmosomal Cadherins (Desmoglein, Desmocollin)
Cytoskeletal Linkage	Actin Filaments (via α/β -catenin)	Intermediate Filaments (Keratin/Desmin, via desmoplakin)
Key Cytoplasmic Adaptors	β -catenin, α -catenin, p120-catenin	Plakoglobin, Plakophilins, Desmoplakin
Typical Morphology	Continuous belt (Zonula) or punctate	Discrete spot (Macula)
Primary Tissue	Epithelia, also in other tissues	Tissues under mechanical stress (skin, heart)
Major Function	Initiate adhesion, morphogenesis, force transduction	Mechanical integrity, resistance to shear stress

COMMUNICATING JUNCTIONS

Primary Function: Allow direct passage of ions and small molecules between adjacent cells, enabling rapid metabolic and electrical coupling.

Gap Junctions (Connexons in Animals)

- **Structure:** Composed of connexons (or hemichannels), which are hexameric assemblies of transmembrane proteins called connexins.
- **Formation:** A connexon in one cell membrane aligns with a connexon in the adjacent cell membrane, forming a continuous aqueous pore (diameter ~1.5-2 nm).

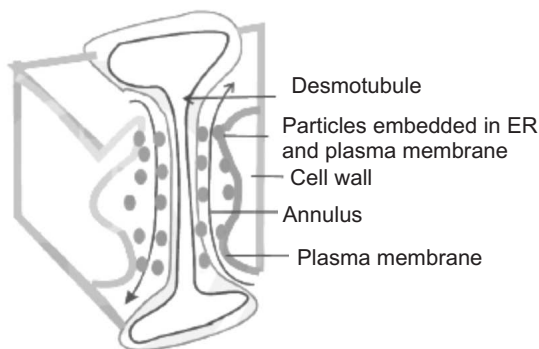


A Gap Junction (Connexons)

- **Regulation:** The channel is gated by intracellular Ca^{2+} , pH, voltage, and phosphorylation.
- **Permeability:** Allows passage of ions (K^+ , Ca^{2+}), second messengers (cAMP, IP_3), and small metabolites (<1 kDa), but not proteins or nucleic acids.
- **Functions:**
 - **Electrical Synapses:** Rapid transmission of action potentials in cardiac muscle, smooth muscle, and some neurons.
 - **Metabolic Cooperation:** Sharing of nutrients and signaling molecules (e.g., glucose in liver).
 - **Coordinated Activity:** Synchronization of contraction, secretion, and developmental signaling.
- **Diversity:** Multiple connexin genes; different combinations confer specific permeability properties.
- **Dysfunction:** Mutations in connexins cause Charcot-Marie-Tooth disease (peripheral neuropathy), cataracts, and deafness.

PLASMODESMATA

- **Structure:** Cytoplasmic channels that traverse the plant cell wall, connecting the cytoplasm of adjacent plant cells. They are lined by the plasma membrane and contain a central tubule called the desmotubule (derived from the endoplasmic reticulum).
- **Regulation:** Can dilate or constrict in response to physiological signals, calcium, or pathogen attack.
- **Functions:**
 - **Symplasmic Transport:** Movement of water, ions, sugars, amino acids, and hormones.
 - **Signaling:** Trafficking of transcription factors (e.g., KNOTTED1) and small RNAs for systemic gene silencing, crucial for plant development and defense.
 - **Viral Movement:** Many plant viruses exploit plasmodesmata to spread between cells using movement proteins.



Structure of Plasmodesmata. The Arrows Indicate the Movement

- **Size Exclusion Limit (SEL):** The size of molecules that can passively diffuse through. Can be dynamically regulated.

The Functional Synergy of Junctions in an Epithelial Cell

A polarized epithelial cell (e.g., in the intestinal lining) showcases the integrated function of all junction types, from apex to base:

1. **Apical Surface:** Tight Junctions form the seal and fence.
2. **Sub-apical Region:** Adherens Junction belt provides contractile support and adhesion.
3. **Lateral Membrane:** Desmosomes are scattered, providing spot-welded strength.
4. **Lateral Membrane:** Gap Junctions facilitate communication.
5. **Basal Surface:** Integrin-based adhesions (hemidesmosomes, focal adhesions) attach the cell to the basal lamina.

This integrated complex is often called the "Apical Junctional Complex."

Major Cell-Cell Junction Types

Junction Type	Main Function	Key Transmembrane Proteins	Cytoskeletal Linkage	Primary Location
Tight Junction (Occluding)	Barrier & Polarity	Claudins, Occludin, JAMs	Actin (via ZO proteins)	Apical, epithelial/endothelial
Adherens Junction (Anchoring)	Adhesion, Morphogenesis	Classical Cadherins	Actin (via catenins)	Sub-apical belt, many tissues
Desmosome (Anchoring)	Mechanical Integrity	Desmosomal Cadherins	Intermediate Filaments (via desmoplakin)	Spot welds, stress-bearing tissues
Gap Junction (Communicating)	Metabolic/Ionic Coupling	Connexins (form connexons)	None (channel)	Lateral, excitable & epithelial tissues
Plasmodesmata (Communicating)	Symplasmic Transport	Not a single protein (membrane-lined channel)	Cytosolic continuity	Plant cell walls

MEMBRANE STRUCTURE



The plasma membrane is a sophisticated, dynamic composite of lipids and proteins. The fluid lipid bilayer provides the fundamental barrier and matrix, whose properties are finely tuned by lipid composition and cholesterol. Membrane proteins, strategically oriented and often organized within microdomains like rafts, execute the vast majority of cellular functions-transport, signaling, and adhesion. The asymmetric and dynamic nature of this structure is not static but is actively maintained and remodeled, making it a central coordinator of cellular life and a key target for therapeutic intervention.

The plasma membrane is the defining boundary of the cell, a selectively permeable barrier that maintains cellular integrity. The Fluid Mosaic Model (Singer & Nicolson, 1972) describes it as a two-dimensional fluid in which lipids form a bilayer and proteins are embedded or attached, free to diffuse laterally. This dynamic structure is fundamental to all cellular functions.

The Lipid Bilayer

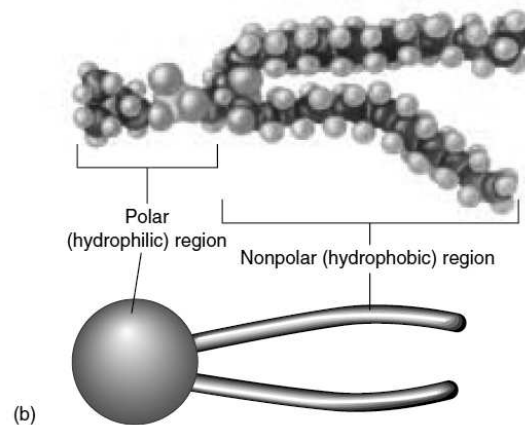
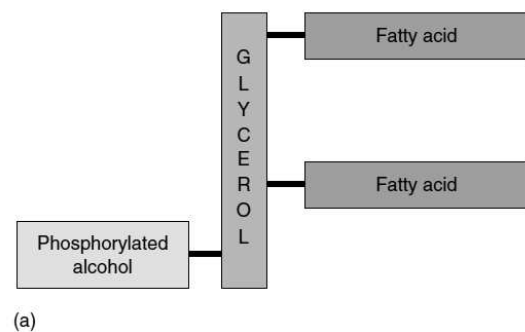
☞ General Structure and Properties

- **Structure:** A 5-10 nm thick double layer of amphipathic lipids (hydrophilic head, hydrophobic tail).
- **Core Properties:**
 - **Selective Permeability:** Impermeable to ions and most polar molecules; permeable to small nonpolar molecules (O_2 , CO_2) and small uncharged polar molecules (H_2O , ethanol).
 - **Fluidity:** Allows lateral movement of lipids and proteins.
 - **Asymmetry:** Different lipid compositions in the inner and outer leaflets.
 - **Self-sealing:** Spontaneously reseals due to hydrophobic effect.

☞ Major Lipid Classes

1. Phospholipids

- Most abundant membrane lipids.
- **Structure:** Glycerol backbone + two fatty acid chains (tails) + phosphate group + polar head group.
 - Fatty acid chains vary in length (14-24 carbons) and saturation (saturated = no double bonds, straight; unsaturated = one or more cis double bonds, kinked).
- **Major Types (by head group):**
 - **Phosphatidylcholine (PC):** Most common; neutral charge.
 - **Phosphatidylethanolamine (PE):** Common in inner leaflet; small head, promotes curvature.
 - **Phosphatidylserine (PS):** Negatively charged; exclusively in inner leaflet in healthy cells. Externalization is a signal for apoptosis.



Phospholipid structure. (a) A phospholipid is a composite molecule similar to a triacylglycerol, except that only two fatty acids are bound to the glycerol backbone; a phosphorylated alcohol occupies the third position on the backbone. (b) Because the phosphorylated alcohol usually extends from one end of the molecule and the two fatty acid chains extend from the other, phospholipids are often diagrammed as a polar head with two nonpolar hydrophobic tails.

- **Phosphatidylinositol (PI):** Can be phosphorylated (e.g., PIP_2) for cell signaling.

2. Sphingolipids

- **Structure:** Based on sphingosine backbone (an amino alcohol) + one fatty acid chain (forming ceramide) + polar head group.
- **Major Types:**
 - **Sphingomyelin:** Head group is phosphocholine. Major component of myelin sheaths.
 - **Glycosphingolipids:** Head group is one or more sugar residues (e.g., cerebroside, ganglioside). Abundant in nervous tissue; involved in cell recognition.

3. Cholesterol

- **Structure:** A rigid, planar sterol molecule with a small -OH group (hydrophilic) and a hydrophobic hydrocarbon tail.
- **Location:** Predominantly in animal cell membranes (absent in most plant cell membranes, bacteria).
- **Key Functions:**
 - **Modulates Fluidity:** At high temps, rigid steroid ring restrains phospholipid movement, decreasing fluidity. At low temps, prevents close packing, increases fluidity (prevents membrane from freezing).
 - **Mechanical Stability:** Fills spaces between phospholipid tails, thickens and strengthens membrane.
 - **Forms Lipid Rafts:** With saturated phospholipids and sphingolipids.

4. Glycolipids

- **Definition:** Lipids with carbohydrate groups attached.
- **Types:** Include glycosphingolipids and less common glycosphingolipids.
- **Location:** Exclusively in the non-cytosolic (outer) leaflet.

Functions: Cell recognition, adhesion, immune response, and as receptors.

Major Membrane Lipid Classes

Lipid Class	Backbone	Key Features	Primary Location/Function
Phosphatidylcholine (PC)	Glycerol	Neutral, most abundant	Both leaflets, structural
Phosphatidylethanolamine (PE)	Glycerol	Small head, conical shape	Inner leaflet, promotes curvature
Phosphatidylserine (PS)	Glycerol	Negatively charged	Inner leaflet (apoptosis signal if flipped)
Sphingomyelin	Sphingosine	Phosphocholine head	Outer leaflet, myelin, rafts
Glycosphingolipids	Sphingosine	Sugar head groups	Outer leaflet, cell recognition
Cholesterol	Sterol	Modulates fluidity & stability	Both leaflets (animal cells), rafts

Membrane Fluidity and Its Regulation

Fluidity is the measure of how easily lipids and proteins move laterally within the bilayer.

1. Factors Affecting Fluidity:

- **Fatty Acid Chain Length:** Shorter chains decrease hydrophobic interactions, increase fluidity.
- **Degree of Saturation:** Unsaturated (cis) fatty acids (with kinks) prevent tight packing, increase fluidity. Saturated chains pack tightly, decreasing fluidity.
- **Cholesterol Content:** As described, a fluidity buffer.
- **Temperature:** Fluidity increases with temperature.

2. Biological Regulation:

- **Homeoviscous Adaptation:** Organisms (e.g., bacteria, fish) adjust lipid composition (increase

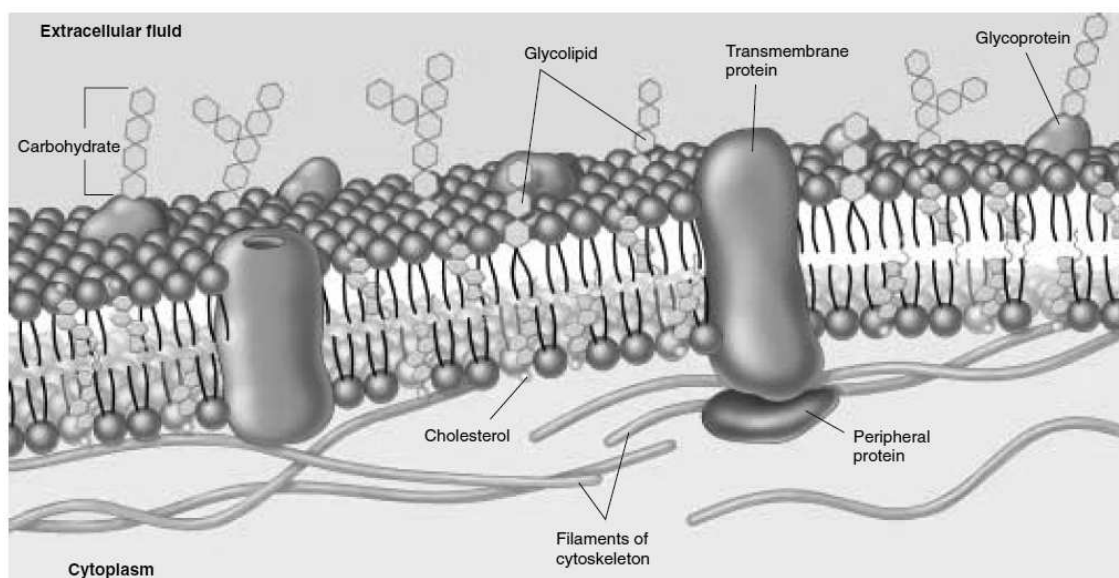
unsaturation in cold) to maintain optimal fluidity.

- **Asymmetry Maintenance:** Flippases (ATP-dependent) move PS/PE to inner leaflet; Floppases move lipids outward; Scramblases (ATP-independent) randomize lipids during apoptosis.

Membrane Microdomains: Lipid Rafts

☞ Concept and Controversy

- **Definition:** Small (10-200 nm), dynamic, heterogeneous assemblies in the membrane enriched in cholesterol, sphingolipids (with saturated tails), and specific proteins.
- **Properties:** More ordered and packed ("liquid-ordered phase") than the surrounding "liquid-disordered" bilayer. Thicker due to longer, saturated tails.
- **Controversy:** Their size, stability, and even existence in vivo are debated due to imaging limitations.



The fluid mosaic model of the plasma membrane.

👉 Proposed Functions

1. **Protein Sorting & Trafficking:** Platforms for assembling signaling complexes and sorting proteins in the Golgi.
2. **Signal Transduction:** Concentrate receptors (e.g., GPI-anchored proteins) and signaling molecules (e.g., Src-family kinases) for efficient signal initiation.
3. **Pathogen Entry:** Used as portals by viruses (e.g., HIV, influenza) and bacteria for cell entry.
4. Cell Adhesion & Polarity.

Membrane Proteins

Proteins confer most of the membrane's specific functions. They constitute ~50% of membrane mass.

👉 Classification by Mode of Association

1. **Integral (Intrinsic) Membrane Proteins:**
 - **Definition:** Permanently embedded in the lipid bilayer via hydrophobic interactions.
 - **Types:**
 - **Transmembrane Proteins:** Span the entire bilayer one or more times. Have transmembrane domains (TMDs) typically as α -helices (sometimes β -barrels in outer bacterial membranes).
 - **Monotopic Proteins:** Insert into but do not span the bilayer (e.g., prostaglandin synthase).
 - **Extraction:** Require detergents or organic solvents to disrupt the bilayer.

2. **Peripheral (Extrinsic) Membrane Proteins:**

- **Definition:** Temporarily associated with the membrane surface, often via electrostatic interactions or hydrogen bonds with lipid head groups or integral proteins.
- **Extraction:** Released by mild treatments (salt washes, pH change).

3. **Lipid-Anchored Proteins:**

- **Definition:** Covalently attached to lipid molecules embedded in the bilayer.
- **Types of Anchor:**
 - **GPI-anchor:** Glycosylphosphatidylinositol. Attached to C-terminus; targets proteins to outer leaflet and lipid rafts.
- **Myristoylation:** N-terminal attachment of myristate (C14).
- **Palmitoylation:** S-acylation of cysteine with palmitate (C16); reversible, regulates localization.
- **Farnesylation/Geranylgeranylation:** Prenylation of C-terminus (e.g., Ras GTPases).

👉 Functions of Membrane Proteins

- **Transporters/Channels:** Selective permeability (e.g., Na^+/K^+ ATPase, aquaporin).
- **Receptors:** Signal transduction (e.g., G-protein coupled receptors, receptor tyrosine kinases).
- **Enzymes:** Catalysis at membrane surface (e.g., adenylate cyclase).
- **Structural/Linker Proteins:** Attach cytoskeleton to ECM (e.g., integrins).
- **Cell Recognition:** Glycoproteins (e.g., MHC molecules).

Membrane Asymmetry and Dynamics

☞ Asymmetry

- **Lipid Asymmetry:**
 - **Outer Leaflet:** Enriched in PC, sphingomyelin, glycolipids.
 - **Inner Leaflet:** Enriched in PE, PS, PI, and signaling lipids (PIP₂).
- **Protein Asymmetry:** Proteins have defined orientation (e.g., receptors face outward, signaling domains face inward).

☞ Dynamics

1. **Lateral Diffusion:** Rapid movement within the plane of the membrane. Measured by FRAP (Fluorescence Recovery After Photobleaching). Proteins diffuse slower than lipids.
2. **Rotational Diffusion:** Spinning around an axis perpendicular to the membrane.
3. **Transverse Diffusion ("Flip-Flop"):** Movement between leaflets. Extremely slow for lipids without enzymes (flippases); negligible for proteins.

Plant Cell-Specific Considerations

- **Lipid Composition:** Plant membranes contain phytosterols (e.g., sitosterol) instead of cholesterol, and unique galactolipids (in chloroplast membranes).
- **Plasmodesmata:** Specialized membrane-lined channels that traverse the cell wall, connecting plant cell cytoplasms.
- **Tonoplast:** The membrane of the large central vacuole, with specific transporters (e.g., H⁺-ATPase, aquaporins).

MEMBRANE TRANSPORT - ACTIVE & PASSIVE



Membrane transport is not merely about crossing a barrier; it is a sophisticated, energy-coupled system that establishes gradients, powers nutrient uptake, generates signals, and maintains cellular integrity. The interplay between passive channels/ carriers and active pumps-often using one gradient to build another-illustrates the economy and integration of cellular design. From the generation of a neuron's action potential to a plant cell's turgor pressure, the principles

of membrane transport underpin the fundamental processes of life.

The plasma membrane's selective permeability is essential for maintaining cellular homeostasis. Membrane transport is the controlled movement of ions and molecules across this barrier, categorized by energy requirement: Passive (no cellular energy) and Active (requires cellular energy).

Transport Types

Classification Based on Energy Requirement

Transport Type	Energy Source	Direction	Examples
Passive Transport	Concentration/Electrochemical Gradient	Downhill (High → Low)	Simple Diffusion, Facilitated Diffusion, Osmosis
Active Transport	ATP or other energy currency	Uphill (Low → High)	Primary Active Transport, Secondary Active Transport
Bulk Transport	ATP (for cytoskeleton/membrane fusion)	Variable	Endocytosis, Exocytosis

PASSIVE TRANSPORT

Molecules move down their electrochemical gradient (combination of concentration gradient and electrical potential). No direct cellular energy expenditure.

Simple Diffusion

- **Definition:** Spontaneous, net movement of substances directly through the lipid bilayer without aid of transport proteins.
- **What Diffuses?** Small, nonpolar molecules (O_2 , CO_2 , N_2 , benzene) and small uncharged polar molecules (H_2O , ethanol, glycerol). Ions and large polar molecules cannot diffuse.
- **Rate Factors:** Governed by Fick's Law. $Rate \propto (Concentration\ Gradient \times Permeability\ Coefficient \times Surface\ Area) / Membrane\ Thickness$.
- **Permeability Coefficient:** Depends on size and hydrophobicity (oil-water partition coefficient).

Osmosis

- **Definition:** Diffusion of water across a selectively permeable membrane from a region of higher water concentration (lower solute concentration) to lower water concentration (higher solute concentration).
- **Tonicity:** Describes how extracellular solute concentration affects cell volume.
 - **Isotonic:** Equal solute concentration. No net water movement (animal cell normal).
 - **Hypotonic:** Lower solute outside. Water enters cell. Animal cells lyse; plant cells become turgid (normal state).
 - **Hypertonic:** Higher solute outside. Water leaves cell. Animal cells crenate; plant cells undergo plasmolysis.
- **Aquaporins:** Specialized channel proteins that greatly increase water permeability in many cells.

Facilitated Diffusion

- **Definition:** Protein-mediated passive transport down a gradient. Provides a polar pathway for ions and polar molecules that cannot diffuse through the bilayer.
- **Key Features:** Stereospecific, saturable (follows Michaelis-Menten kinetics), and subject to competitive inhibition.
- **Two Main Classes of Transport Proteins:**
 - Channels
 - Carriers (Permeases/Transporters)

Channels

- **Structure:** Form hydrophilic pores across the membrane. Usually composed of multiple transmembrane subunits.
- **Mechanism:** Gated diffusion. Ions/water move through an open pore at very high rates (10^6 - 10^8 ions/sec).
- **Selectivity:** Based on size, charge, and hydration energy.
- **Types of Gating:** Controlled by specific stimuli.
 - **Voltage-Gated Channels:** Open/close in response to change in membrane potential (e.g., Na^+ , K^+ , Ca^{2+} channels in neurons).
 - **Ligand-Gated Channels:** Open upon binding of a chemical messenger (neurotransmitter) - extracellular or intracellular (e.g., nicotinic ACh receptor, IP_3 -gated Ca^{2+} channel).
 - **Mechanically-Gated Channels:** Open in response to physical force (e.g., touch receptors, sound receptors in ear).
- **Example:** The K^+ Channel

- High selectivity for K^+ over Na^+ due to the selectivity filter lined with carbonyl oxygens that perfectly substitute for water, allowing K^+ to shed its hydration shell.

Carriers (Transporters)

- **Mechanism:** Undergo conformational change to shuttle molecules across. Much slower than channels (10^2 - 10^4 molecules/sec).
- **Types:**
 - **Uniporters:** Transport one molecule down its gradient (e.g., GLUT1 glucose transporter).
 - **Symporters (Cotransporters):** Transport two molecules in the same direction.
 - **Antiporters (Exchangers):** Transport two molecules in opposite directions.
- **Example:** GLUT Family Uniporters: Mediate passive uptake of glucose into erythrocytes and other cells.

Channels vs. Carriers (Facilitated Diffusion)

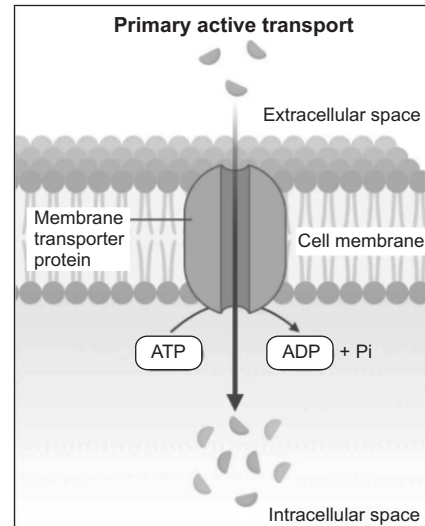
Feature	Channels	Carriers (Transporters)
Mechanism	Pore-mediated diffusion	Conformational change (binding-flipping-release)
Rate	Very high (ion conduction)	Slower (transport limited by conformational change)
Saturation	No (rate limited by diffusion to pore)	Yes (follows Michaelis-Menten kinetics)
Specificity	Based on pore size & charge	High specificity for binding site
Gating	Yes (voltage, ligand, mechanical)	Continuous conformational cycle
Example	Voltage-gated Na^+ channel	GLUT1 glucose uniporter

ACTIVE TRANSPORT

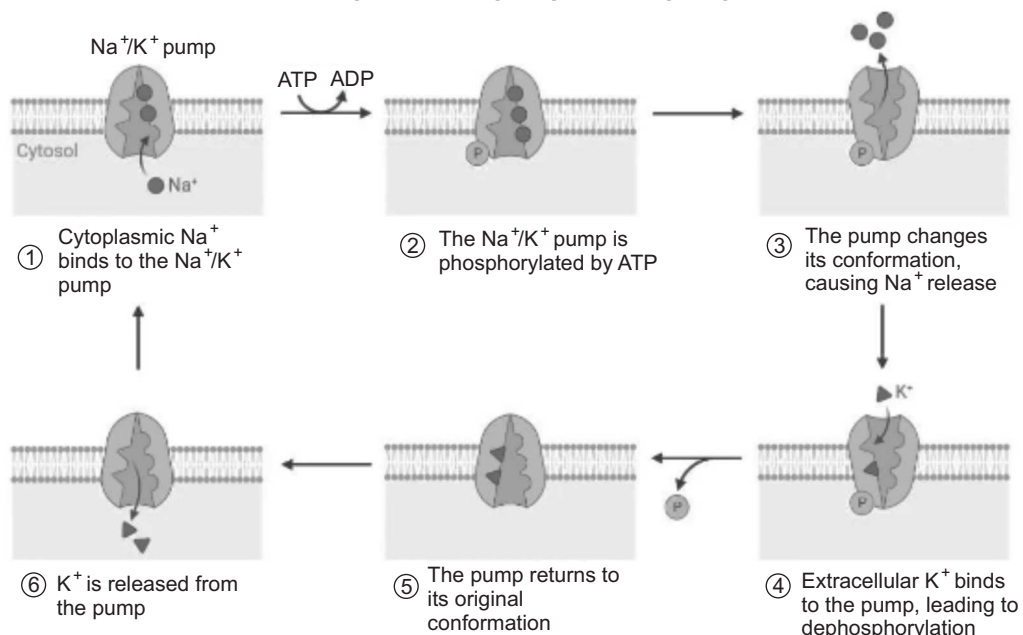
Movement of molecules against their electrochemical gradient (uphill). Requires direct input of cellular energy.

Primary Active Transport

- **Definition:** Uses ATP hydrolysis directly to pump ions/molecules uphill.
- **Key Player:** P-type ATPase pumps.
 - Form a phosphorylated intermediate (Asp residue) during transport cycle.
- **Examples:**
- **Na^+/K^+ ATPase (The Sodium-Potassium Pump):** Crucial for animal cells. Pumps 3 Na^+ out and 2 K^+ in per ATP. Establishes and maintains the resting membrane potential and Na^+ gradient used for secondary transport. Ouabain inhibits it.
- **H^+/K^+ ATPase:** In stomach parietal cells (acid secretion).
- **Ca^{2+} ATPase (SERCA):** Pumps Ca^{2+} from cytosol into SR/ER.
 - **Other ATPases:** V-type (vacuolar, e.g., lysosomal H^+ pump), F-type (ATP synthases, work in reverse).

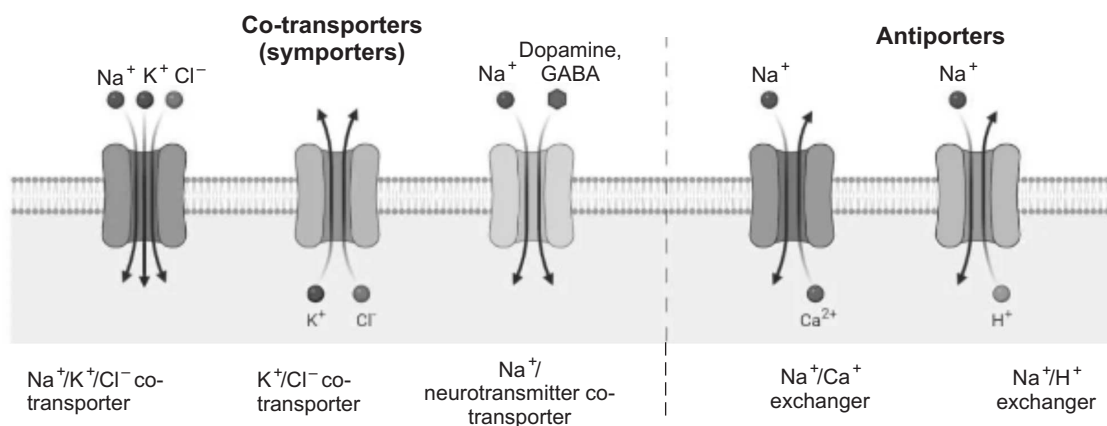


Sodium-potassium pump Na^+/K^+ pump



Secondary Active Transport (Coupled Transport)

- **Definition:** Uses the energy stored in an ion gradient (created by primary active transport) to drive the uphill transport of another molecule. No direct ATP use for the transporter itself.
- The "Ion Gradient Battery": The Na^+ gradient (high outside, low inside) established by the Na^+/K^+ pump is the most common energy source in animal cells. In plants, fungi, and bacteria, it is often an H^+ gradient.



Examples of Secondary Active Transporters

- **Types:**
 - **Symport (Cotransport):** The driving ion and the co-transported solute move in the same direction.
- **Example:** $\text{Na}^+/\text{Glucose}$ Symporter (SGLT1) in intestinal/renal epithelia. Na^+ moving in down its gradient provides energy to pull glucose in against its gradient.
- **Antiport (Exchange):** The driving ion and the co-transported solute move in opposite directions.
- **Example:** Na^+/H^+ Antiporter: Regulates intracellular pH (exports H^+ using Na^+ gradient).

Comparison of Transport Mechanisms

Feature	Simple Diffusion	Facilitated Diffusion	Primary Active Transport	Secondary Active Transport
Energy Source	Gradient	Gradient	ATP hydrolysis	Ion electrochemical gradient
Direction	Downhill	Downhill	Uphill	Uphill (for the solute)
Requires Protein?	No	Yes (Channel or Carrier)	Yes (Pump)	Yes (Symporter/Antiporter)
Saturable?	No	Yes (Carriers)	Yes	Yes
Example	O_2 , CO_2	Glucose via GLUTs, K^+ via channel	Na^+/K^+ ATPase, Ca^{2+} ATPase	Glucose via SGLT, Amino acid uptake

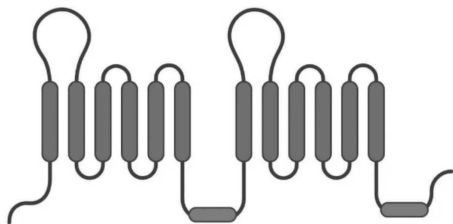
Specialized Transport Systems

☞ Transport Across Epithelia

- **Transcellular Transport:** Combined action of different transporters on apical and basolateral membranes to move substances across a cell layer.
- Example: Intestinal Glucose Absorption:
 1. **Apical membrane:** SGLT1 (Na^+ -glucose symporter, secondary active) imports glucose from lumen.
 2. **Basolateral membrane:** GLUT2 (uniporter, facilitated diffusion) exports glucose to blood.
 3. Na^+/K^+ ATPase on basolateral side maintains Na^+ gradient.

☞ Plant-Specific Transport

- **H^+ -ATPase (P-type):** In the plasma membrane, pumps H^+ out of the cell, creating a large H^+ gradient (low pH outside, inside alkaline). This proton-motive force drives secondary active transport of nutrients (sucrose, amino acids, NO_3^-) via H^+ symporters.



ATP Binding Cassette (ABC) Transporters

- **Tonoplast Transport:** Vacuolar membrane contains V-type H^+ -ATPase and H^+ -pyrophosphatase that pump H^+ into the vacuole, driving secondary transport of ions/metabolites for storage.

Biological Significance

- **Resting Membrane Potential:** Established by Na^+/K^+ ATPase and K^+ leak channels. Fundamental for nerve impulse transmission and muscle contraction.
- **Nutrient Uptake:** Secondary active transporters are key for intestinal absorption and renal reabsorption.
- **Drug Targets & Disease:**
 - **Cardiac Glycosides (digoxin):** Inhibit Na^+/K^+ ATPase $\rightarrow$ increase intracellular Ca^{2+} $\rightarrow$ strengthen heart contraction (treat heart failure).
 - **Proton Pump Inhibitors (omeprazole):** Inhibit H^+/K^+ ATPase $\rightarrow$ treat gastric ulcers.
 - **Cystic Fibrosis:** Defect in CFTR Cl^- channel (an ATP-gated channel, ABC transporter family) leads to thick mucus.
 - **Diabetes:** SGLT2 inhibitors (canagliflozin) block renal glucose reabsorption, lowering blood sugar.

QUESTIONS



Section A: Very Short Answer Type Questions

1. Define the extracellular matrix (ECM).

Ans. The extracellular matrix (ECM) is a complex, three-dimensional network of proteins (e.g., collagen, fibronectin) and polysaccharides (e.g., glycosaminoglycans) secreted by cells, providing structural and biochemical support to surrounding cells.

2. Which class of cell adhesion molecules is Ca^{2+} -dependent and mediates homophilic adhesion?

Ans. Cadherins.

3. Name the transmembrane proteins that form channels for direct cytoplasmic communication between adjacent animal cells.

Ans. Connexins (which assemble to form connexons/gap junctions).

4. What is the main function of tight junctions (occluding junctions)?

Ans. To form a selective permeability barrier that seals the space between adjacent epithelial/endothelial cells, preventing the paracellular passage of molecules and maintaining apical-basal polarity.

5. Which lipid, abundant in the plasma membrane, regulates membrane fluidity and stability in animal cells?

Ans. Cholesterol.

6. What are lipid rafts?

Ans. Lipid rafts are dynamic, sterol- and sphingolipid-enriched microdomains within the plasma membrane that serve as organizing centers for signal transduction and membrane trafficking.

7. Name the glycoprotein that serves as a major linker between cells and the ECM by binding to integrins.

Ans. Fibronectin.

8. What type of anchoring junction connects the actin cytoskeleton of adjacent cells?

Ans. Adherens junctions.

9. Which membrane protein family facilitates the transport of ions and small molecules down their concentration gradient?

Ans. Channel proteins (e.g., ion channels, aquaporins).

10. How do plasmodesmata differ from gap junctions?

Ans. Plasmodesmata are plant-specific channels traversing the cell wall, connecting the cytoplasm of adjacent plant cells and allowing transport of molecules up to ~1 kDa. Gap junctions are animal-specific channels formed by connexins, connecting adjacent animal cells.

Section B: Short Answer Type Questions

11. Explain the role of integrins in cell-ECM adhesion.

Ans. Integrins are transmembrane heterodimeric receptors (α and β subunits) that bind to specific ligands in the ECM (e.g., fibronectin, laminin). They form a physical link between the ECM and the intracellular actin cytoskeleton via adaptor proteins (e.g., talin, vinculin). This connection mediates bidirectional signaling ("outside-in" and "inside-out"), regulating cell adhesion, migration, proliferation, and survival.

12. Differentiate between passive and active transport across the plasma membrane.

Ans. Passive transport moves molecules down their concentration or electrochemical gradient without energy input (e.g., simple diffusion, facilitated diffusion via channels/carriers). Active transport moves molecules against their gradient, requiring energy (usually ATP hydrolysis). It can be primary (directly uses ATP, e.g., Na^+/K^+ ATPase) or secondary (uses an ion gradient established by primary transport, e.g., Na^+ /glucose symport).

13. Describe the structure and function of a connexon.

Ans. A connexon (or hemichannel) is an assembly of six transmembrane protein subunits called connexins. Two connexons from adjacent cells dock in the extracellular space to form a complete gap junction channel. These aqueous pores allow the direct passage of ions, second messengers (cAMP, Ca^{2+}), and small metabolites (<1 kDa) between the cytoplasm of neighboring cells, enabling electrical coupling and metabolic cooperation.

14. List the four major types of anchoring junctions and their cytoskeletal associations.

Ans.

1. **Adherens Junctions:** Connect actin filaments (via cadherins, catenins).
2. **Desmosomes:** Connect intermediate filaments (via desmogleins/desmocollins, desmoplakin).
3. **Focal Adhesions:** Connect actin filaments to the ECM (via integrins).
4. **Hemidesmosomes:** Connect intermediate filaments to the ECM (via integrin $\alpha 6\beta 4$).

15. What is the significance of membrane fluidity? How do cholesterol and fatty acid chain saturation affect it?

Ans. Membrane fluidity is crucial for protein function, membrane trafficking, and cell signaling. Cholesterol modulates fluidity: at high temps, it restricts phospholipid movement, decreasing fluidity; at low temps, it prevents tight packing, increasing fluidity. Saturated fatty acids (straight chains) pack tightly, decreasing fluidity. Unsaturated fatty acids (kinks from double bonds) prevent tight packing, increasing fluidity.

16. Explain the concept of "outside-in" and "inside-out" signaling in the context of integrin activation.

Ans. Outside-in signaling: ECM ligand binding to integrin induces a conformational change, leading to clustering of integrins and recruitment of cytoskeletal/signaling proteins (e.g., FAK, Src), initiating intracellular signaling cascades. **Inside-out signaling:** Intracellular signals (e.g., from chemokines) alter the conformation of integrin cytoplasmic domains, increasing their

affinity for ECM ligands ("activation"), allowing dynamic regulation of adhesion during processes like immune cell trafficking.

17. How do glycolipids contribute to cell surface identity?

Ans. Glycolipids (e.g., cerebrosides, gangliosides) are lipids with carbohydrate head groups exposed on the extracellular leaflet. They contribute to the glycocalyx, providing a unique cellular "fingerprint." They are involved in cell recognition, immune response (as antigens, e.g., ABO blood groups), and serve as receptors for toxins and viruses.

18. What are the key structural differences between a desmosome and a hemidesmosome?

Ans. Desmosomes are cell-cell junctions linking the intermediate filament networks of two adjacent cells via cadherin-family proteins (desmogleins/desmocollins). Hemidesmosomes are cell-ECM junctions linking the intermediate filaments of a single cell to the basal lamina via integrin $\alpha 6\beta 4$ and other proteins (e.g., plectin, BP180). They resemble "half" a desmosome.

19. Describe the role of fibronectin in the ECM.

Ans. Fibronectin is a large, dimeric glycoprotein. It acts as a multifunctional adapter, possessing binding sites for integrins, collagen, heparin, and fibrin. It plays key roles in: Cell adhesion and migration (during embryogenesis, wound healing), ECM assembly (organizing other components), and signaling (influencing cell shape, proliferation, and differentiation).

20. What distinguishes peripheral membrane proteins from integral membrane proteins?

Ans. Integral membrane proteins are embedded in the lipid bilayer, often traversing it (transmembrane proteins) via hydrophobic α -helices or β -barrels. They can only be removed by detergents. Peripheral membrane proteins are attached to the membrane surface via electrostatic/hydrogen bonding to lipid head groups or integral proteins. They can be removed by changes in pH, ionic strength, or chelating agents.

Section C: Long Answer Type Questions

21. Compare and contrast the structure, composition, and functions of the three major types of cell junctions: occluding, anchoring, and communicating. Use specific examples in your answer.

Ans.

Junction Type	Primary Function	Key Structural Components	Cytoskeletal Linkage	Example & Specific Role
Occluding Junctions (Tight Junctions)	Barrier Function & Polarity. Seal the paracellular space, creating a selectively permeable barrier that regulates the passage of ions and molecules. Also maintain apical-basal polarity by preventing diffusion of membrane proteins between domains.	Transmembrane proteins: Claudins (form the sealing strands), Occludin, JAMs (Junctional Adhesion Molecules). Cytoplasmic plaque: ZO proteins (Zonula Occludens).	Indirectly linked to the actin cytoskeleton via ZO proteins.	In intestinal epithelium: Tight junctions prevent gut lumen contents from leaking into the bloodstream (barrier) and keep digestive enzymes on the apical surface (polarity).

Anchoring Junctions	Mechanical Strength & Adhesion. Physically tether cells to each other or to the ECM, providing structural integrity and resisting mechanical stress.	Cell-Cell: Adherens junctions: Cadherins (E-cadherin), Catenins (α , β , p120). Desmosomes: Desmogleins/Desmocollins, Desmoplakin, Plakoglobin. Cell-ECM: Focal adhesions: Integrins, Talin, Vinculin. Hemidesmosomes: Integrin $\alpha 6 \beta 4$, Plectin.	Adherens junctions & Focal adhesions: Actin filaments. Desmosomes & Hemidesmosomes: Intermediate filaments (keratins in epithelia).	Desmosomes in skin epidermis: Provide strong intercellular adhesion, enabling the epidermis to withstand shearing forces. Focal adhesions in fibroblasts: Anchor the cell to the underlying collagen matrix during migration.
Communicating Junctions (Gap Junctions)	Direct Intercellular Communication. Allow the direct passage of small molecules, ions, and electrical signals between the cytoplasm of adjacent cells.	Connexons: Each composed of six connexin subunits. Two connexons from adjacent cells dock to form a complete channel.	None. The channel itself spans the membrane and connects cytoplasm.	In cardiac muscle: Gap junctions (composed of connexin 43) enable rapid propagation of action potentials, ensuring synchronous contraction of the heart. In plants: Plasmodesmata perform a similar function, connecting plant cell cytoplasm.

Integration: These junctions often work together in a functional unit. For instance, in an epithelial sheet, tight junctions form the apical seal, adherens junctions provide a belt of actin-linked adhesion just below, and desmosomes spot-weld the cells together, with gap junctions allowing metabolic coordination. This integrated junctional complex is crucial for tissue integrity, compartmentalization, and coordinated function.

22. Describe the fluid mosaic model of the plasma membrane. Discuss in detail how the composition of lipids (phospholipids, cholesterol, glycolipids) and the asymmetry of the lipid bilayer contribute to membrane structure and function.

Ans. The Fluid Mosaic Model (Singer & Nicolson, 1972):

This model describes the plasma membrane as a two-dimensional fluid in which lipids and proteins are able to diffuse laterally. The membrane is a mosaic of lipids, proteins, and carbohydrates. Key tenets: 1) Lipid bilayer forms the structural foundation. 2) Proteins are embedded (integral) or attached (peripheral). 3) Components are asymmetrically distributed. 4) The bilayer is fluid, allowing lateral movement.

Lipid Composition and Its Impact:

1. **Phospholipids:** The most abundant lipids. They are amphipathic (hydrophilic head, hydrophobic tails) and form a stable bilayer in aqueous environments. The specific head groups (e.g., phosphatidylcholine - outer leaflet, phosphatidylethanolamine, phosphatidylserine - inner leaflet) contribute to charge and signaling.
2. **Cholesterol:** A sterol intercalated between phospholipids. Its rigid steroid ring interacts with fatty acid chains, modulating membrane fluidity and stability. It acts as a fluidity buffer: at high temperatures, it restrains phospholipid movement; at low temperatures, it prevents crystallization. It also increases mechanical strength and reduces permeability to small water-soluble molecules.
3. **Glycolipids:** Lipids with carbohydrate head groups (e.g., galactocerebroside, gangliosides). They are found almost exclusively in the outer leaflet. They contribute to the glycocalyx, are involved in cell recognition (e.g., blood group antigens), and form part of lipid rafts.

Lipid Bilayer Asymmetry and Its Functional Significance:

The two leaflets of the bilayer have different lipid compositions, actively maintained by flippases, floppases, and scramblases.

- **Outer Leaflet:** Enriched in phosphatidylcholine, sphingomyelin, and glycolipids. This makes it neutrally charged and resistant to hydrolysis.
- **Inner Leaflet:** Enriched in phosphatidylethanolamine, phosphatidylserine (PS), and phosphatidylinositol (PI).

Functional Consequences of Asymmetry:

1. **Cell Signaling:** PS and PI are involved in intracellular signaling. PS exposure on the outer leaflet is a key "eat-me" signal for apoptosis.
2. **Membrane Curvature:** Cone-shaped lipids (like PE) in the inner leaflet promote curvature, important for vesicle formation.
3. **Charge Differential:** The inner leaflet is more negatively charged due to PS, influencing the localization of peripheral proteins with polybasic domains.
4. **Barrier Function:** Asymmetry contributes to the impermeability of the bilayer to ions and polar molecules.

Conclusion: The fluid mosaic model, updated with concepts of asymmetry, lipid rafts, and controlled dynamics, explains the plasma membrane as a complex, dynamic, and functional interface. The specific lipid composition and its asymmetric distribution are not random but are critically tuned to regulate fluidity, permeability, signaling, and cell identity.

23. Explain the various mechanisms of membrane transport, categorizing them based on energy requirement and the nature of the transported solute. Include specific examples of channel proteins, carriers, pumps, and transporters.

Ans. Membrane transport mechanisms can be categorized based on energy requirement (Passive vs. Active) and the nature of the solute and transporter.

I. Passive Transport (Down the Gradient, No Energy):

- A. Simple Diffusion:** Small, nonpolar molecules (O_2 , CO_2 , steroid hormones) and small uncharged polar molecules (H_2O , ethanol) diffuse directly through the lipid bilayer. Rate depends on concentration gradient and lipid solubility.

B. Facilitated Diffusion: Mediated by membrane proteins for ions and polar molecules.

1. **Channel Proteins:** Form aqueous pores. They are usually ion-selective and gated (voltage-, ligand-, or mechanically-gated).

Example: Voltage-gated Na^+ channel in neurons (opens upon depolarization, allowing Na^+ influx for action potential).

Example: Aquaporins facilitate rapid water transport.

2. **Carrier Proteins (Uniporters):** Bind specific solutes and undergo conformational change to transport across.

Example: GLUT1 glucose transporter in erythrocytes moves glucose down its concentration gradient.

II Active Transport (Against the Gradient, Requires Energy):

A. **Primary Active Transport:** Directly uses energy (ATP hydrolysis, light, redox).

- **P-type ATPases:** Undergo phosphorylation during cycle. Example: Na^+/K^+ ATPase pumps 3 Na^+ out and 2 K^+ in per ATP, establishing crucial ion gradients.
- **V-type & F-type ATPases:** Proton pumps (lysosomes, mitochondria, chloroplasts).
- **ABC Transporters:** Use ATP to export a wide variety of molecules (drugs, toxins, lipids).

B. **Secondary Active Transport (Cotransport):** Uses the energy stored in an ion electrochemical gradient (usually Na^+ or H^+) established by primary transport.

- **Symport (Cotransport):** Solute and ion move in the same direction.
- **Example:** SGLT1 ($\text{Na}^+/\text{glucose}$ symporter) in intestinal epithelium uses the Na^+ gradient to import glucose against its gradient.
- **Antiport (Exchange):** Solute and ion move in opposite directions.
- **Example:** Na^+/H^+ exchanger regulates intracellular pH.

III. Transport of Macromolecules (Not strictly across the lipid bilayer):

- **Endocytosis & Exocytosis:** Vesicle-mediated transport for large particles, macromolecules, and fluids.

Summary: The cell employs a sophisticated toolkit of transport proteins. Channels provide rapid, gated pores for ions and water. Carriers (uniporters) facilitate diffusion of specific solutes. Pumps are primary active transporters that establish gradients. Cotransporters harness these gradients to power the movement of other solutes. This integrated system maintains cellular homeostasis, signaling, and nutrient acquisition.

24. Discuss the role of the extracellular matrix (ECM) in cell behavior. Detail the structure and function of its major components: collagen, proteoglycans, and adhesive glycoproteins like fibronectin and laminin.

Ans. The ECM is not merely a static scaffold; it is a dynamic, information-rich environment that profoundly influences cell behavior, including adhesion, migration, proliferation, differentiation, and survival. It provides structural support, tensile strength, and elasticity, and acts as a reservoir for growth factors.

Major Components and Their Functions:**1. Collagen:**

- **Structure:** The most abundant protein in the ECM. A family of fibrous proteins, with Type I being most common. Each molecule is a triple helix of α -chains. These molecules assemble into fibrils, which bundle into strong, cross-linked fibers.
- **Function:** Provides tensile strength and mechanical integrity to tissues (e.g., skin, bone, tendons, cartilage). It also influences cell adhesion and migration.

2. Proteoglycans:

- **Structure:** Consist of a core protein covalently attached to one or more glycosaminoglycan (GAG) chains (e.g., chondroitin sulfate, heparan sulfate). GAGs are long, unbranched polysaccharides with high negative charge. Many proteoglycans (e.g., aggrecan) form huge aggregates with hyaluronan.
- **Function:**
 - **Hydration & Compression Resistance:** The negatively charged GAGs attract cations and water, forming a hydrated gel that resists compressive forces (e.g., in cartilage).
 - **Molecular Sieve:** The gel acts as a barrier to pathogen movement.
 - **Growth Factor Reservoir:** Heparan sulfate proteoglycans bind and sequester growth factors (e.g., FGF), regulating their bioavailability and signaling.

3. Adhesive Glycoproteins:**A. Fibronectin:**

- **Structure:** A large, dimeric glycoprotein with multiple functional domains.
- **Function:** A multifunctional adaptor. Binds to integrins (cell surface), collagen, heparin, and fibrin. It is crucial for cell adhesion, spreading, and migration (especially during embryogenesis and wound healing). It guides ECM assembly by cross-linking other components.

B. Laminin:

- **Structure:** A large, cross-shaped heterotrimeric glycoprotein (α , β , γ chains).
- **Function:** A major component of the basal lamina. It binds to integrins (e.g., $\alpha 6 \beta 4$ in hemidesmosomes), other ECM components (e.g., nidogen, perlecan), and cell surface receptors. It is essential for basement membrane assembly, cell polarization, differentiation, and survival. It provides crucial signals for epithelial and neuronal cells.

Integration and Cell Signaling: Cells sense the ECM primarily through integrins. The clustering of integrin-ECM bonds leads to the assembly of focal adhesions, which not only provide anchorage but also initiate intricate signaling cascades (e.g., via FAK, Src) that regulate the cytoskeleton, gene expression, and cell fate—a process known as mechanotransduction.

Conclusion: The ECM is a master regulator of cellular form and function. Its components work in concert to create tissue-specific microenvironments. The mechanical and biochemical signals from the ECM are integrated by cells to orchestrate development, maintain tissue homeostasis, and respond to injury.

25. "Cell adhesion molecules are crucial for tissue morphogenesis and immune function." Justify this statement by discussing the roles of cadherins, selectins, and the immunoglobulin superfamily in specific biological processes.

Ans. Justification: Tissue morphogenesis requires precise cell sorting, aggregation, and migration, all governed by adhesion molecules. Immune function relies on highly dynamic and specific cell-cell interactions for leukocyte trafficking, antigen presentation, and effector functions. Different CAM families are specialized for these distinct tasks.

1. Cadherins in Tissue Morphogenesis:

- **Role:** Cadherins are Ca^{2+} -dependent, homophilic adhesion molecules. They mediate strong, stable adhesion between similar cell types.
- **Specific Process:** Embryonic Development & Tissue Sorting.
- **Example:** E-cadherin is expressed on early embryonic cells (blastomeres) and later on epithelial cells. Its homophilic binding is crucial for compaction of the morula and maintenance of epithelial integrity.
- **Classic Experiment:** Cells from different tissues (e.g., liver and retina) dissociated and mixed will sort out and aggregate separately based on their cadherin expression levels and types ("differential adhesion hypothesis"). Cells expressing higher levels of a particular cadherin cluster together, driving tissue boundary formation.
- **Significance:** Cadherins establish and maintain tissue architecture by regulating homotypic adhesion, ensuring that liver cells stick to liver cells and retinal cells to retinal cells.

2. Selectins in Immune Function (Leukocyte Trafficking):

- **Role:** Selectins are Ca^{2+} -dependent, lectin-type adhesion molecules that bind to specific carbohydrate ligands (e.g., sialyl Lewis X). They mediate transient, low-affinity adhesion under shear flow.
- **Specific Process:** Leukocyte Rolling on Vascular Endothelium.
- **Sequence:** During inflammation, endothelial cells upregulate P-selectin and E-selectin. Circulating leukocytes express ligands (e.g., PSGL-1). This interaction causes leukocytes to roll slowly along the vessel wall.
- **Significance:** Rolling is the first critical step in the leukocyte adhesion cascade. It slows down leukocytes, allowing them to sense chemokines presented on the endothelium, which then trigger integrin activation and firm arrest—a prerequisite for transmigration into tissues. Without selectins, immune surveillance and inflammatory responses are severely impaired.

3. Immunoglobulin Superfamily (IgSF) in Both Morphogenesis and Immunity: IgSF CAMs (e.g., NCAM, ICAM-1, VCAM-1) have immunoglobulin-like domains and often mediate Ca^{2+} -independent, homophilic or heterophilic adhesion.

In Morphogenesis (Nervous System):

- **Example:** NCAM (Neural Cell Adhesion Molecule). Promotes homophilic adhesion between neurons and between neurons and glia. It is crucial for axon guidance, fasciculation (bundling of axons), synapse formation, and plasticity. Different NCAM

isoforms (e.g., polysialylated NCAM) modulate adhesion strength, allowing for dynamic rearrangements during neural development.

- **In Immune Function:**

- **Example:** ICAM-1 (Intercellular Adhesion Molecule-1) & VCAM-1 (Vascular Cell Adhesion Molecule-1). These are expressed on activated endothelium. They serve as counter-receptors for integrins on leukocytes (e.g., LFA-1 binds ICAM-1, VLA-4 binds VCAM-1). After selectin-mediated rolling, chemokine signaling activates leukocyte integrins to bind tightly to ICAM-1/VCAM-1, leading to firm adhesion and arrest. This step is essential for leukocyte extravasation.

Conclusion: Cadherins provide the "glue" for building stable tissues, selectins act as the "first responders" to capture immune cells from circulation, and IgSF molecules serve versatile roles as both builders of neural architecture and critical partners in the immune synapse. The diversity and regulated expression of these CAM families underpin the exquisite precision of tissue formation and the adaptive agility of the immune system.