Cell functions

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Objectives

• Can describe types of membrane transport
  • Diffusion (passive) transport
    • Simple diffusion
    • Facilitated diffusion
  • Active transport
    • Primary active transport
    • Secondary active transport

• Can describe ionic conductance

• Can describe molecular trafficking
  • Protein traffic
  • Vesicular traffic
  • Secretion and endocytosis

• Can apply knowledge to medicine
Physical structures of the cell

Eukaryotic cells
Cell membrane

Consists of

1. **Lipids:** phospholipids
   - 1. Phosphate head
   - 2. Fatty acid end

2. **Proteins:**
   - Peripheral proteins
   - Integral proteins

3. **Carbohydrate**
Cell membranes

Phospholipid

- Phosphatidylcholine
- Sphingomyelin

Outer
- Protein 55%
- Phospholipids 25%
- Cholesterol 13%
- Other lipids 4%
- Carbohydrate 3%

Inner
- Phosphatidylethanolamine
- Phosphatidylserine
- Phosphatidylinositol
Integral and peripheral cell membrane proteins

- Glycolipid
- Oligosaccharide
- Integral protein
- Hydrophobic α helix
- Peripheral protein
- Phospholipid
- Cholesterol
- Lipid-linked protein

Figure 9-26  Fundamentals of Biochemistry, 2/e
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Integral and peripheral cell membrane protein

: glycoproteins

- **Integral proteins:**
  - **pores or channels:** water and water soluble substances diffuse between ICF and ECF
  - **carrier proteins:** lipid insoluble substances
  - **receptors:** water soluble chemicals eg. Peptide hormones

- **Peripheral proteins:**
  - enzymes
  - controller of substance transport
Membrane carbohydrate

- Glycoproteins: most of integral proteins
  - varyably protrude outside the cell

- Glycolipids: 1/10 of membrane lipids

Proteoglycans: mainly carbohydrate substances bound to protein cores

“Glycocalyx”
Lipid component:
- High permeability to lipid-soluble substances: $\text{CO}_2$, $\text{O}_2$, fatty acid and steroid hormones

Protein component:
- Low permeability to water-soluble substances: ions, glucose and amino acids
- Consists of transporters, enzymes, hormone receptors, cell-surface antigens and ion & water channels
## Major classes of plasma membrane transports

<table>
<thead>
<tr>
<th>Class</th>
<th>Transport mode</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water channels</strong></td>
<td></td>
</tr>
<tr>
<td>• Aquaporins (AQP)</td>
<td>Gated</td>
</tr>
<tr>
<td>• Aquaglyceroporins</td>
<td></td>
</tr>
<tr>
<td><strong>Ion channels</strong></td>
<td></td>
</tr>
<tr>
<td>• Uniporters</td>
<td>Gated</td>
</tr>
<tr>
<td>• Symporters (co-transporter)</td>
<td></td>
</tr>
<tr>
<td>• Antiporters (counter transporter or exchangers)</td>
<td></td>
</tr>
<tr>
<td><strong>Solute carriers</strong></td>
<td></td>
</tr>
<tr>
<td>• Uniporters</td>
<td>Cycle</td>
</tr>
<tr>
<td>• Symporters (co-transporter)</td>
<td></td>
</tr>
<tr>
<td>• Antiporters (counter transporter or exchangers)</td>
<td></td>
</tr>
<tr>
<td><strong>ATP dependent</strong></td>
<td></td>
</tr>
<tr>
<td>• ATPase ion transporters</td>
<td>Cycle</td>
</tr>
<tr>
<td>• ATP-binding cassette (ABC) transporters</td>
<td></td>
</tr>
</tbody>
</table>
Transport of substances through cell membrane

- Directly through the lipid bilayer or through the proteins

- **Diffusion transport (passive)**

- **Active transport**
Differences between diffusion and active transport

**Electrochemical gradient**
- High concentration of Na⁺
- Low concentration of Na⁺

**Metabolic energy**
- ATP
- ADP
1. Simple diffusion

- Diffusion through cell membrane
  - Lipid bilayers: Lipid soluble substances
- Diffusion through protein pores/channels: Lipid insoluble substances

2. Facilitated diffusion
Aquaporins or water channels at least 13 different types found in human

Simple diffusion “through cell membrane”

1. Through interstices of lipid bilayers
2. Through watery channels

Lipid soluble substances
eg. Oxygen, Nitrogen, Carbon dioxide and alcohol

Lipid insoluble substances
eg. Urea

Lipid soluble substances

Lipid insoluble substances

Aquaporins or water channels at least 13 different types found in human
Water channels

Aquaporins (AQPs)

- 13 AQPs are identified in human
Diffusion of nonelectrolytes

“Random thermal motion of molecules”

Membrane (permeate to the solute)

“Net diffusion of the solute from A to B”
Net diffusion “flux or flow”

1. Concentration gradient
2. Partition coefficient (K): the solubility of a solute in oil relative to its solubility in water

\[ K = \frac{\text{Concentration in olive oil}}{\text{Concentration in water}} \]

Nonpolar solutes: are soluble in oil → High partition coefficient

Polar solutes: are insoluble in oil → Low partition coefficient
3. Diffusion coefficient (D)

Diffusion coefficient inversely correlates size of solute molecules and viscosity of the medium.
4. Thickness of the membrane ($\Delta X$)

- Thick membrane
- Thin membrane

“The greater the distance the solute must diffuse and the lower the rate of diffusion”
5. Surface area

“The greater the surface area of membrane available, the higher the rate of diffusion”
Permeability ($P$) is given by the equation:

$$P = \frac{KD}{\Delta X}$$

where:
- $K$ is the partition coefficient,
- $D$ is the diffusion coefficient,
- $\Delta X$ is the membrane thickness.
Diffusion of electrolytes

There are 2 additional consequences of the presence of charge on the solute:

1. Potential difference: will alter the net rate of charged solutes but does not alter nonelectrolytes.
2. Diffusion potential: is the potential difference generated across a membrane when a charged solute (an ion) diffuses down its concentration gradient.

1. caused by diffusion of ions
2. membrane is permeate to that ions
3. magnitude measured in mV
4. sign depends on the charge of diffusing ions
Inside of cell becomes (-)

Electrical force opposes outflow of $K^+$ and favors inflow of $Na^+$

Chemical force for $K^+$

Electrical force for $Na^+$

Semipermeable Membrane

Cytoplasm | Extracellular Fluid
Facilitated diffusion (carrier-mediated diffusion)

- occur down electrochemical gradient
- no input of metabolic energy
- use a membrane carrier
Carrier-mediated transport

- transports that involve integral membrane proteins
- facilitated diffusion, primary active transport and secondary active transport

Saturation

Transport rate

Carrier-mediated transport

Simple diffusion

Concentration
Stereospecificity

D-glucose
D-galactose

Transporter

Competition
Transport of D-glucose by GLUT4
Active transport:

A cell membrane moves molecules or ions “uphill” against a concentration/electrical/pressure gradient.

1. Primary active transport
2. Secondary active transport

(divided by the source of energy used to cause the transport)
Primary active transport

Energy is derived directly from the breakdown of ATP or some other high-energy phosphate compound,

*eg. sodium, potassium, calcium, hydrogen, chloride and a few other ions*

**Na⁺ - K⁺ pump**

1. **3 receptor sites for binding sodium ions**
2. **2 receptor sites for binding potassium ions**
3. **Near the sodium binding sites has ATPase activity**
Na\(^+\)-K\(^+\) ATPase

1. Na\(^+\) binding site
2. K\(^+\) binding site
3. Ouabain binding site
4. Phosphorylation site
5. ATP-binding site

Cardiac glycoside; used like digitalis
Ca\textsuperscript{2+} ATPase

"Plasma-membrane Ca\textsuperscript{2+} ATPase (PMCA)"

: to extrude Ca\textsuperscript{2+} from the cell against an electrochemical gradient, one Ca\textsuperscript{2+} ion is extruded for each ATP hydrolyzed
: found in sarcoplasmic reticulum of muscle cells and endoplasmic reticulum
**H^+-K^+ ATPase**

- pumps H^+ from the ICF of the parietal cells into the lumen of the stomach, where it acidifies the gastric contents
- found in the parietal cells of the gastric mucosa and in the α-intercalated cells of renal collecting duct
Peptic ulcer

- **Proton pump inhibitor**
- e.g. Omeprazole (Miracid)
- decrease $H^+$ secretion into lumen
Proton pump inhibitor
Secondary active transport

: energy is derived secondarily from energy stored in the form of ionic concentration differences of secondary molecular or ionic substances between the 2 sides of a cell membrane

1. Co-transport (Symports)

2. Counter-transport (Antiports)

Uniports: transport only one substance
Co-transport: required coupling mechanism

Sodium-Glucose co-transport

Important mechanism in transporting glucose across renal and intestinal epithelial cells.
Na\textsuperscript{+}-glucose co-transport in an intestinal epithelial cell
**Na/Glucose cotransporter (SGLT1-3)**

**Na/K/Cl cotransporter (NKCC)**

**Na/HCO₃ cotransporter** (NBCe1, e2)

**H/Oligopeptide cotransporter** (Pep T)

**Na/Amino acid cotransporter**

**Na/Cl cotransporter (NCC)**

**Na/HCO₃ cotransporter** (NBCe1, e2)

**H/Monocarboxylate cotransporter** (MCT)

**Na/Phosphate cotransporter (NaPi)**

**K/Cl cotransporter (KCC)**

**Na/HCO₃ cotransporter** (NBCe1, e2)

**H/Divalent metal ion cotransporter** (DMT)
Counter-transport

: required opposite transport direction of substances

**Sodium-Calcium counter-transport**

**Sodium-Hydrogen counter-transport**

The proximal tubules of the kidneys
Ca\textsuperscript{2+}-Na\textsuperscript{+} countertransport

to maintain the intracellular Ca\textsuperscript{2+} concentration at very low levels
# Summary of membrane transport

<table>
<thead>
<tr>
<th>Type of Transport</th>
<th>Active or Passive</th>
<th>Carrier-Mediated</th>
<th>Uses Metabolic Energy</th>
<th>Dependent on Na⁺ Gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple diffusion</td>
<td>Passive; downhill</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Facilitated diffusion</td>
<td>Passive; downhill</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Primary active transport</td>
<td>Active; uphill</td>
<td>Yes</td>
<td>Yes; direct</td>
<td>No</td>
</tr>
<tr>
<td>Cotransport</td>
<td>Secondary active</td>
<td>Yes</td>
<td>Yes; indirect</td>
<td>Yes (sloutes move in same direction as Na⁺ across cell membrane)</td>
</tr>
<tr>
<td>Countertransport</td>
<td>Secondary active</td>
<td>Yes</td>
<td>Yes; indirect</td>
<td>Yes (sloutes move in opposite direction as Na⁺ across cell membrane)</td>
</tr>
</tbody>
</table>
Osmosis

“the process of net movement of water caused by a concentration difference of water”
Osmosis

Solute concentration: 0.3 M (300 mOsm) 0 M
Water concentration: 55.2 M 55.5 M
Osmosis

Solute concentration: 300 mOsm 1000 mOsm
Water concentration: 55.2 M 54.5 M

Water flow
(1 molar sucrose)
Osmotic pressure

"the exact amount of pressure required to stop osmosis"
The concentration of a solution in terms of numbers of particles

"osmole"

\[
mole = \frac{\text{grams}}{\text{molecular weight}}
\]

Non-dissociated solute: 1 mole = 1 osmole

180 grams of glucose = 1 gram molecular weight = 1 osmole

Dissociated solute: 1 mole > 1 osmole

58.5 grams of NaCl = 1 gram molecular weight = 2 osmole
Osmolarity = 1 osmole of solute dissolved in each liter of water (1 liter or 1,000 ml)

Osmolality = 1 osmole of solute dissolved in each kilogram of water (1 kg or 1,000 mg)

1 osmole/kilogram or liter or 1,000 ml
\[
\frac{1}{1,000} \text{ Osm/L} = 1 \text{ mOsm/L}
\]

Normal osmolarity of ICF and ECF
= 282 mOsm/L or ~300 mOsm/L
Types of solutions

- Hypotonic solution
- Isotonic solution
- Hypertonic solution

Depends on **tonicity** of solution (solute conc. & solute permeability) (effect of solution on cell volume)

- Hypoosmotic solution
- Isosmotic solution
- Hyperosmotic solution

Depends on **osmotic pressure** and **osmolarity** of solution
Tonic solutions

Hypertonic | Isotonic | Hypotonic
---|---|---

Hypertonic solution causes cells to shrink.
Isotonic solution maintains normal cell volume.
Hypotonic solution causes cells to swell.

Ion concentration in extracellular space:
Hypertonic | Isotonic | Hypotonic
Osmotic solutions

Concentration of solutes

Inside cell

Concentration of solutes

Outside cell

osmotic concentration
Solute concentration: 300 mOsm (0.3 M) 500 mOsm (0.5 M)
Water concentration: 55.2 M 55.0 M
Osmotic pressure: 7.4 atm 12.3 atm
Osmotic pressure gradient (Δπ): 12.3 atm − 7.4 atm = 4.9 atm
Ion conductance

Small, nonpolar molecules (e.g. O\(_2\) and N\(_2\)) and small uncharged polar molecules (CO\(_2\))

Ion channels: ion channels specific for K\(^+\), Na\(^+\), Ca\(^{2+}\) and Cl\(^-\)

: important for the function of excitable cells e.g. neurons and muscle cells

: can be classified by
  - Selectivity
  - Mechanism of gating
  - Conductance
Ion channels: are integral membrane proteins, when open, permit the passage of certain ions.

1. Selectivity: allow ions with specific characteristics to move through them, based on both the size of the channel and the charges lining it.

- Channel lined with negative charges: permit the passage of cations.
- Channel lined with positive charges: permit the passage of anions.
2. Gate

Ion channels are **controlled by gates** depending on the position of gates: when the channel is open, the selective ions can flow through it, **down the existing electrochemical gradient**.
3. Conductance

: depends on the probability that it is open
: the higher the probability that the channel is open, the higher its conductance or permeability
Different forms of ion channels

- **Tetramers**
  - 5 identical subunits (A)
  - CIC family (B)
  - Tetramers with intracellular channels (D)

- **K⁺ channels**
- **Acetylcholine receptor**
- **Cl⁻ channels**
- **Aquaporin water channels**
Two types of gates control of ion channels

1. Voltage-gated channels: open or close in response to changes in membrane potential

2. Ligand-gated channels: open or close in response to binding of ligands such as hormones, neurotransmitters, or second messengers
Voltage-gated ion channels

Nerve action potential

“depolarization”

Terminating action potential

“repolarization”
Interesting characteristic of voltage-gated channels

“all or none” response
Ligand-gated ion channels

“Chemical-gated channels”

- are controlled by hormones, neurotransmitters and second messengers

Nicotinic receptor on the motor end plate

- when open, it is permeable to Na$^+$ and K$^+$ ions
Gates of protein channels

- Voltage-gated channels
- Ligand (chemical)-gated channels
- Phosphorelation-gated channels
- Stretch or pressure-gated channels
Regulation of gating in ion channels

- **Ligand-gated**
  - Closed
  - Open
  - Bind ligand

- **Phosphorylation-gated**
  - Closed
  - Open
  - Phosphorylate
  - Dephosphorylate

- **Voltage-gated**
  - Closed
  - Open
  - Change membrane potential

- **Stretch or pressure-gated**
  - Closed
  - Open
  - Stretch
  - Cytoskeleton
Molecular trafficking

How to transport?

Rough ER → Protein molecules

Smooth ER → Lipid substances
Golgi apparatus functions with association with ER

- **Golgi vesicles**
- **Synthesising certain carbohydrates**
- **cis site**
- **trans site**

**ER vesicles** (Transport vesicles)

**ER vesicles**

**Golgi apparatus**

**Endoplasmic reticulum**
Lysosomes

“Breaking off from Golgi apparatus”

Intracellular digestive system

1. Damaged cellular structures
2. Ingested food particles
3. Unwanted matter: bacteria

“Hydrolase (digestive) enzymes”
Bactericidal agents in lysosome

1. **Lysozyme**: dissolve bacterial cell membrane

2. **Lysoferrin**: bind iron and other substances before promotion of bacterial growth

3. **Acid (pH 5.0)**: activate hydrolase and inactivate bacterial metabolic systems
Regression of tissues

Uterus

Muscle

Mammary glands
**Lysosomal storage diseases**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Accumulated material</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucopolysaccharidosis</td>
<td>Glycosaminoglycans (GAGs) in many tissues and organs</td>
<td>- Presence of GAGs in urine</td>
</tr>
<tr>
<td></td>
<td>- Other manifestation depend on which GAGs accumulate</td>
<td></td>
</tr>
<tr>
<td>I-cell disease</td>
<td>Many compounds normally degraded in lysosomes (inability to phosphorylate mannose residues that target proteins to lysosomes)</td>
<td>- Absence of lysosomal enzymes in lysosomes</td>
</tr>
<tr>
<td></td>
<td>- Severe growth impairment, extreme mental and motor retardation, clear corneas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Fibroblasts contain many dark inclusions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Onset in young children; fatal</td>
<td></td>
</tr>
<tr>
<td>Pompe’s disease (type II glycogen storage disease)</td>
<td>Glycogen (deficiency of α-1, 4-glycosidase)</td>
<td>- Enlarged liver and heart, hypotonia, mental and motor retardation</td>
</tr>
<tr>
<td></td>
<td>- Usually fatal in infants and children</td>
<td>- In adults, muscle weakness and respiratory problems but usually not fatal</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Ganglioside in nervous tissue</td>
<td>- Doll-like facies, cherry-red macular spot, seizures, hypotonia, early blindness</td>
</tr>
<tr>
<td></td>
<td>- Onset in infancy; death by age 5 years</td>
<td></td>
</tr>
</tbody>
</table>

* An inherited deficiency of one or more lysosomal enzymes causes accumulation of materials that normally would be degraded. Clinical manifestations can involve multiple tissues and organs.
Assembly protein 1 (AP-1) clathrin coats

Coat protein I and II (COPI & COPII)

ER | Golgi apparatus | Secretory granules

Regulated secretion

Constitutive secretion

Recycling

Endocytosis

Nucleus | Lysosome | Late endosome | Early endosome

Cis | Trans

AP-2 clathrin coats

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Regulation of vesicular traffic

- is regulated by a combination of common mechanisms along with special mechanisms

- **GTP or GDP binding** (small G proteins)
- **SNAREs** (for soluble N-ethylmaleimide-sensitive factor attachment receptor): v-(for vesicle) SNAREs interact in a lock-and-key fashion with t- (target) SNAREs

v-SNARE/t-SNARE arrangement
Quality control

- The process involved in protein synthesis, folding and migration to the various parts of the cells are so complex.
- No more errors and abnormalities occurred in protein synthesis to provide normal body function.

Defective protein structures are degraded in Lysosomes and proteosomes in ER and Golgi apparatus.
Endocytosis

- Ingestion by the cell

- Nutrients
- Other substances

- Diffusion
- Active transport
Endocytosis

- Pinocytosis
- Phagocytosis
- Clathrin-mediated endocytosis
- Caveolae-dependent uptake
- Nonclathrin/noncaveolae endocytosis
Pinocytosis consists of the nonspecific uptake of small molecules and water into the cell.
Phagocytosis allows the internalization of large particles (bacteria, cell debris), important for immune system.
Clathrin-mediated endocytosis

- **Clathrin**
- **Coated pit**
- **Proteins**
- **Receptors**
- **Actin and myosin**
- **Dissolving clathrin**

**Triskelions**
Late endosome

Early endosome
(a) Phagocytosis

“Food” or other particle

Pseudopod

CYTOPLASM

(b) Pinocytosis

Plasma membrane

Vesicle

(c) Receptor-mediated endocytosis

Receptor

Coated pit

Coat protein

Coated vesicle
Exocytosis

Leave the contents of the vesicle outside

Bound to the cell membrane via v-SNARE/t-SNARE arrangement

$Ca^{2+}$ dependent process
Transcytosis

Lysosomes

Pinocytotic or phagocytic vesicle

Digestive vesicle

Residual body

Excretion
Autolysis of cells

- Slight damage
  - Remove damaged part
  - Repaired cells

- Severe damage
  - Autolysis

- Damage phase
Apoptosis or programmed cell death

- Unneeded or threaten cells
- activate
- Specific proteolytic cascade
- Caspases (cysteine proteases)
- digest
- Phagocytic cells: macrophage

“cell suicide”
Necrosis

Cells

Acute injury

Swelling and burst

Inflammation and injury

Neighboring cells

Necrosis

“cell murder”
Cancers

Normal cells

Mutation

Activation

Oncogenes

Cancer cells

antioncogenes

Suppress activation of specific Oncogenes

Tumor suppressor gene: p53 gene on human chromosome 17 found up to 50% of human cancers
Dyslipidemia

**Normal**: cholesterol is an important component of the cells

- **Most cells**: Can’t synthesize cholesterol
- **Uptake cholesterol via LDL from blood**

**Defect of LDL receptor**

- **Elevate of LDL & Cholesterol in blood**
- **Atherosclerosis**

**Endocytosis**
References


