Cell Membranes Function as Integrative Systems

Understanding how cell membrane's molecules cross-talk in assuring the membrane functioning

1. Cell Membranes Allow Exchanges of Substances

Cell membrane in transport phenomena

&

2. Cell Membranes Allow Exchanges of Information

Cell membrane in cell signaling

Cell Membrane in Transport Phenomena

- Transport through membrane

  ions and small molecules (ϕ<10Å, M<800Da)

- Transport with membrane

  large molecules, macromolecules (solubilized, in volumes of atto-liter order) and particles (insolubilized materials even in significantly larger volumes)

Transport through membrane

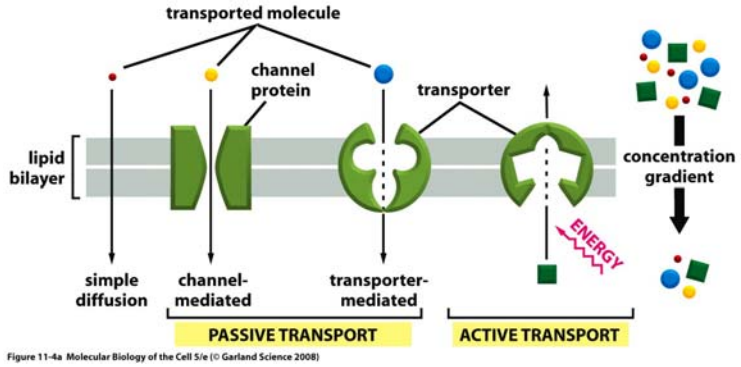


Figure 11-4a Molecular Biology of the Cell 5/e (© Garland Science 2008)

- **Passive** (entropic, dissipative)– without energy consuming ("downhill transport ")
  - through bilayer, (among lipids) – nonpolar molecules, small uncharged polar molecules (<100Da) – this is ***simple diffusion***
  - through proteins – ions, large polar molecules – this is ***facilitated diffusion***
    - channels (for ions)
    - carriers (transporters)
- **Active** (anti-entropic) – energy consuming ("uphill transport")
  - **Primary active** – simultaneous energy consuming
  - **Secondary active** – (coupled transport) combines uphill transport (one solute) with downhill transport (another solute) – previous energy consuming

Simple Diffusion

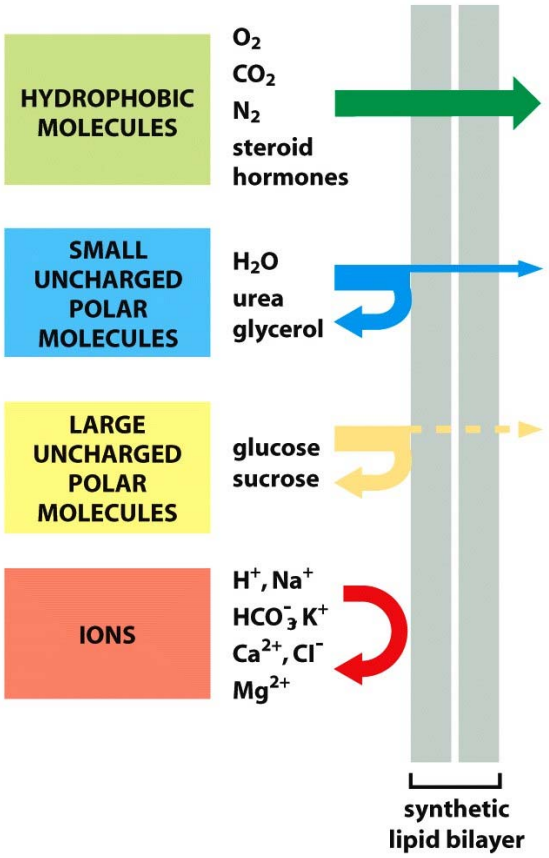


Figure 11-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Facilitated Diffusion

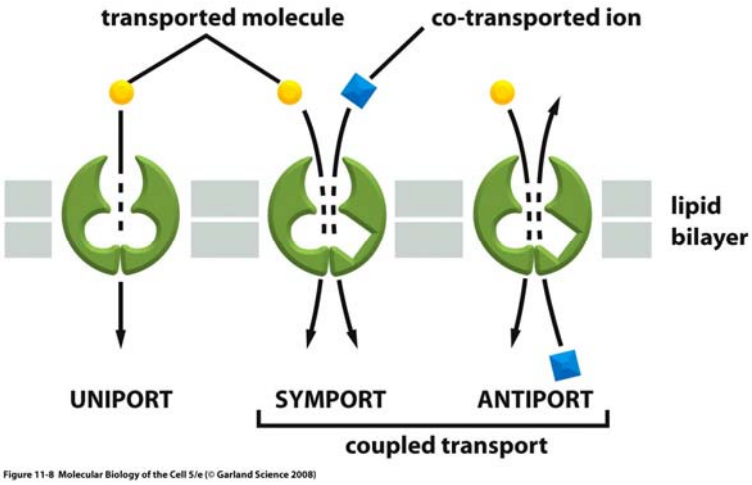


Figure 11-8 Molecular Biology of the Cell 5/e (© Garland Science 2008)

1. Uniport transport – one ion (molecule) transported;

2. Coupled transport (co-transport) – several ions (molecules) simultaneously transported

   - symport – ions (molecules) all transported in the same direction

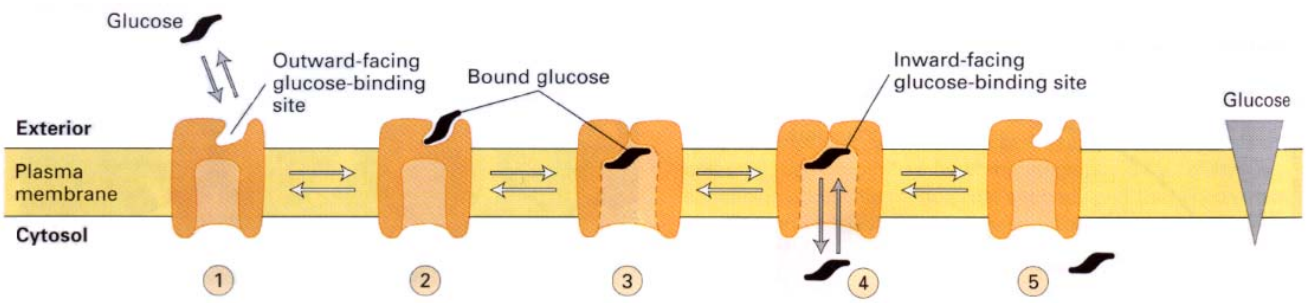
   - antiport – at least one ion (molecule) transported in opposite direction

N.B. ***These forms of transport through the membrane are also applicable to the active transport.***

GLUT1, example for uniport transport

found in erythrocyte membrane and most of animal cells

Erythrocyte GLUT1: ~45 kDa; 12 α-helixes containing hydrophobic amino acids, and some Ser, Thr, Asn, Gln; both N- and C- termini of the protein facing the cytosol



From: Lodish et al., Molecular Cell Biology. 4th Edition. WH Freeman & Comp. (Fig. 15-7)

N.B. 14 members of GLUT family were discovered (GLUT1-12 + HMIT)

(Ion) Channels

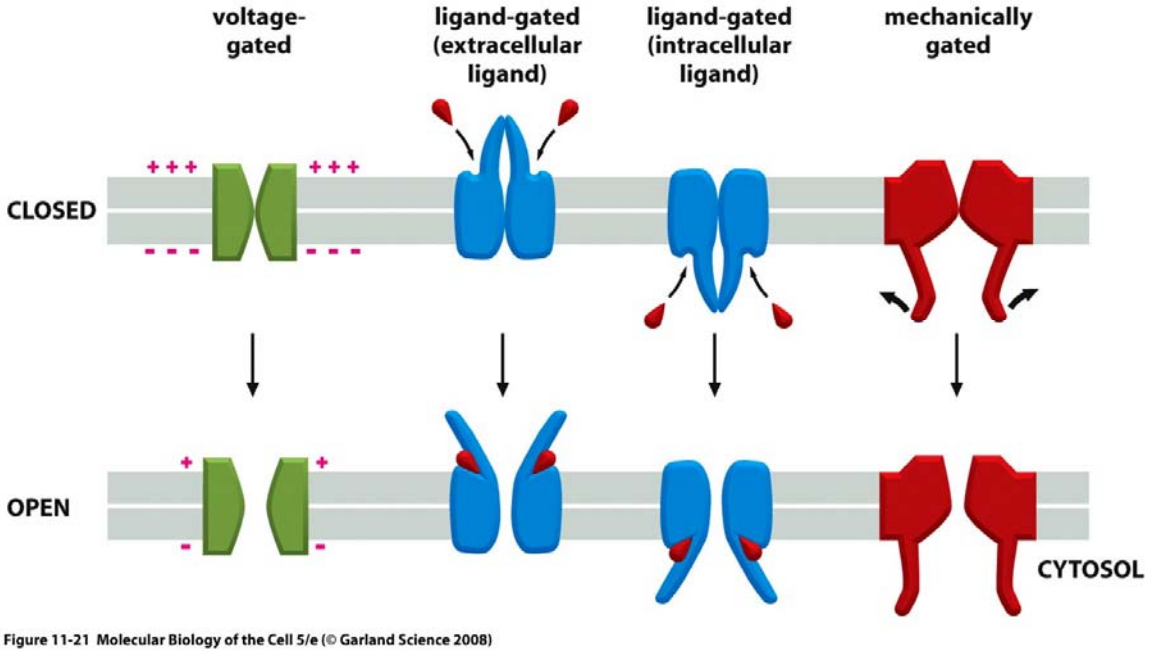
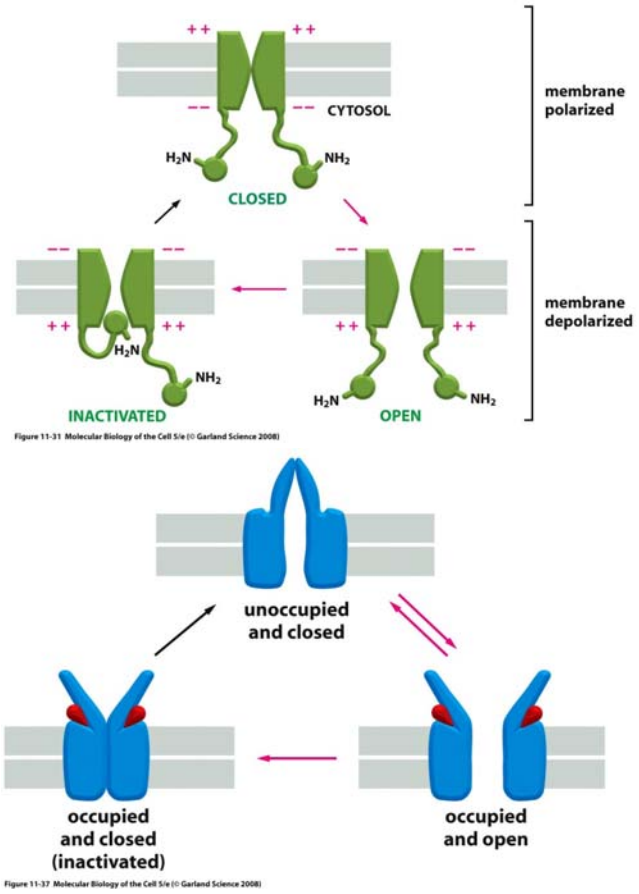


Figure 11-21 Molecular Biology of the Cell 5/e (© Garland Science 2008)

- Voltage-gated (voltage-operated)
- Ligand-gated (ligand-operated)
- Mechanically gated (mechanically operated)

Cyclical conformations of channels



Cross-talk of various channels at neuromuscular junction level

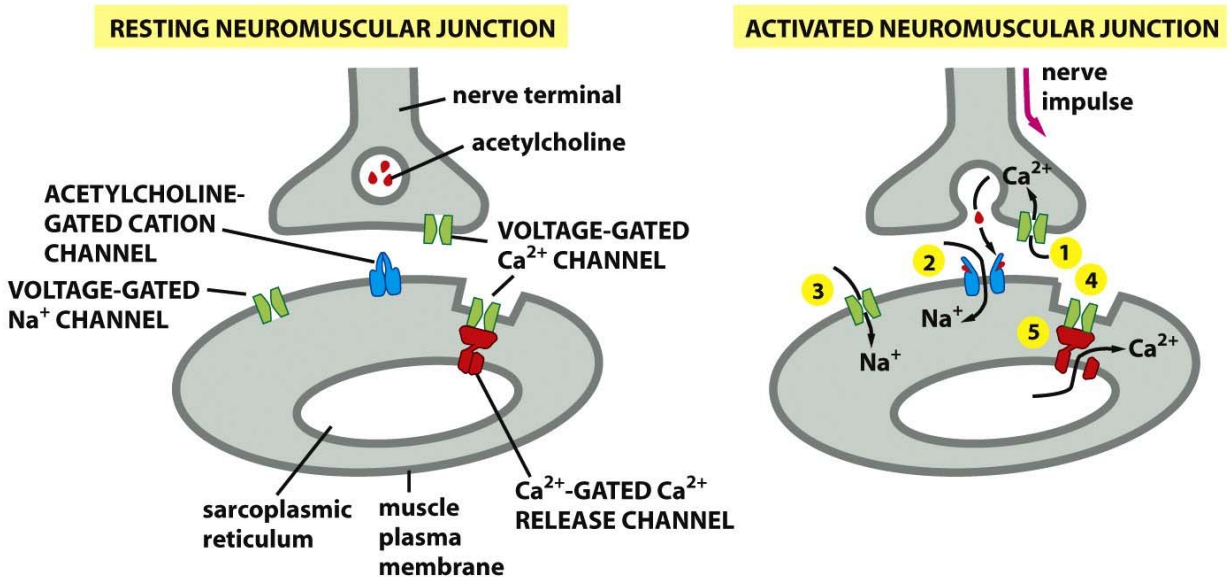
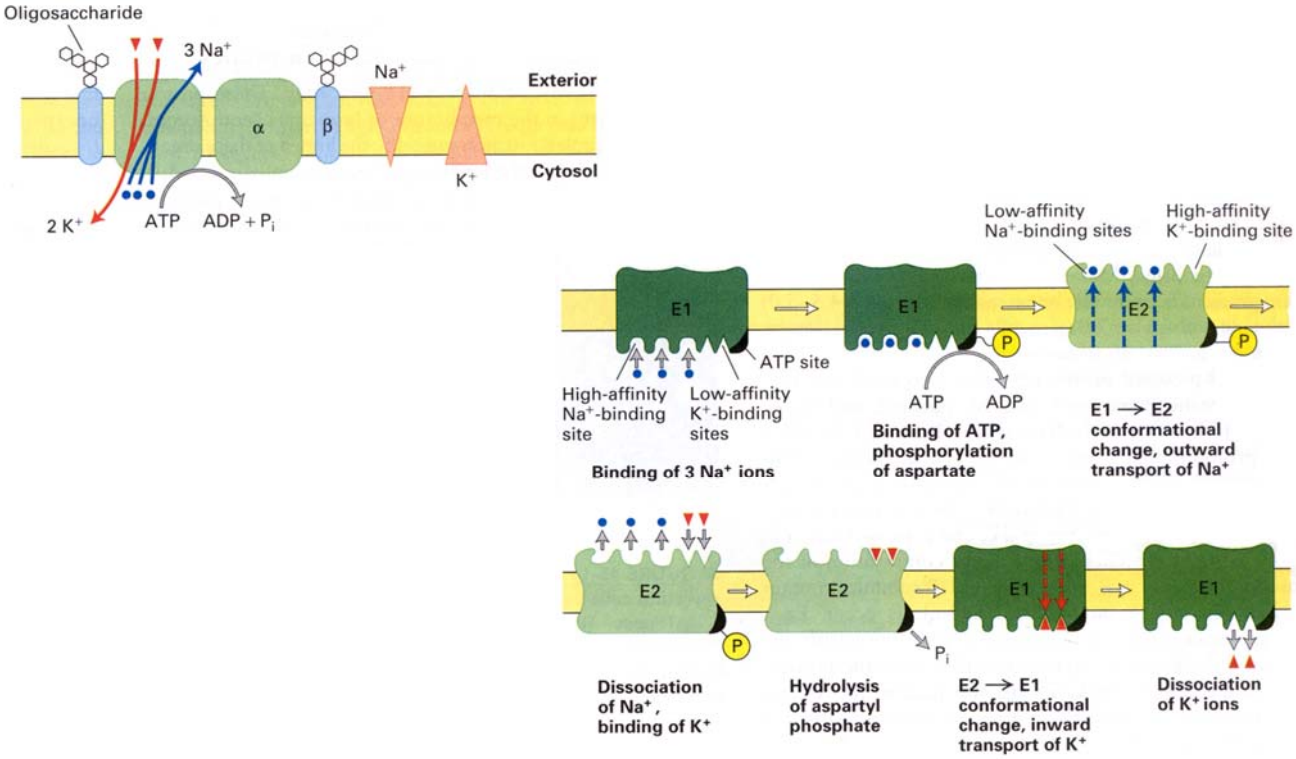


Figure 11-39 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Na^+/K^+ ATPase (Na^+/K^+ pump)

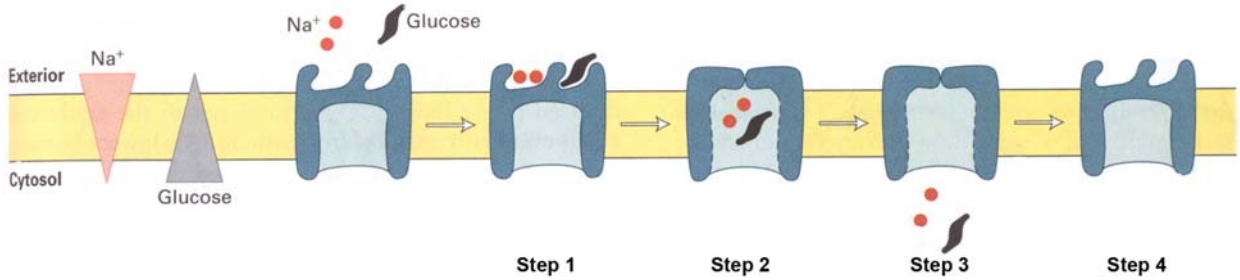
example of active transport



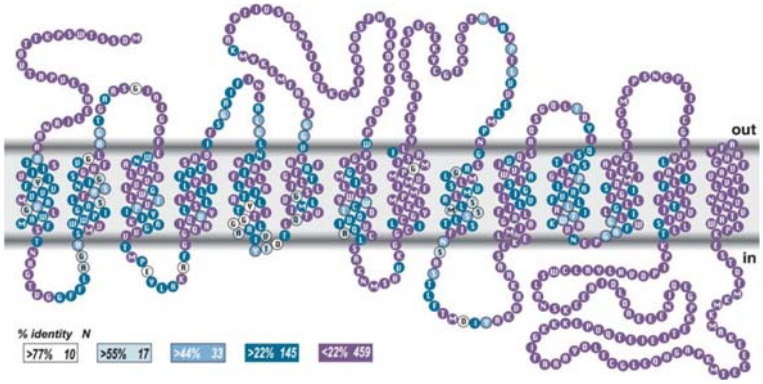
From: Lodish et al., Molecular Cell Biology. 4th Edition. WH Freeman & Comp. (Fig. 15-13)

SGLT1 (glucose transporter in enterocytes)

example of symport transport



From: Lodish et al., Molecular Cell Biology. 4th Edition. WH Freeman & Comp.



From: Wright EM, Turk E. (2004) The sodium/glucose cotransport family SLC5. *Pflugers Arch – Eur J Physiol*. **447**: 510-518.

Example of secondary active transport

Secondary active transport

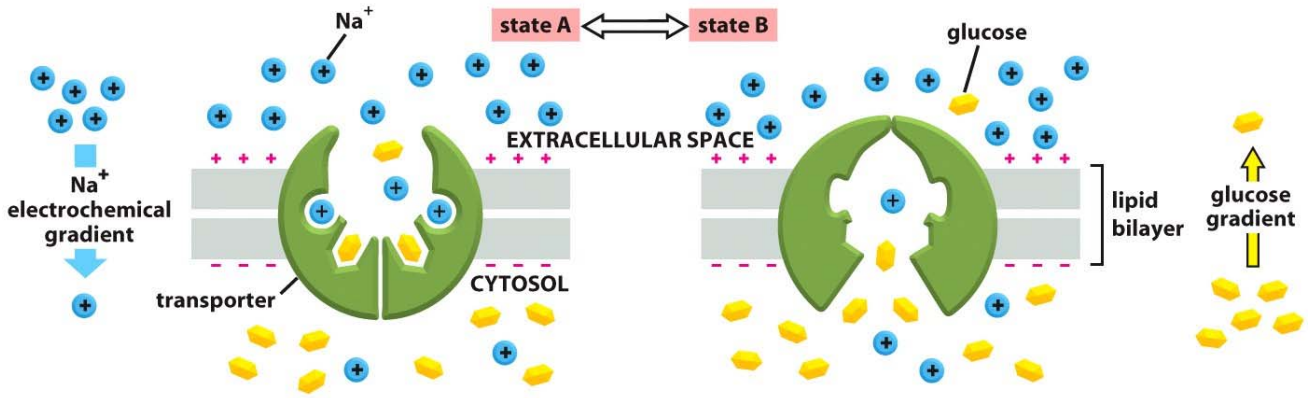


Figure 11-9 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cross-talk of membrane transport proteins, in enterocytes

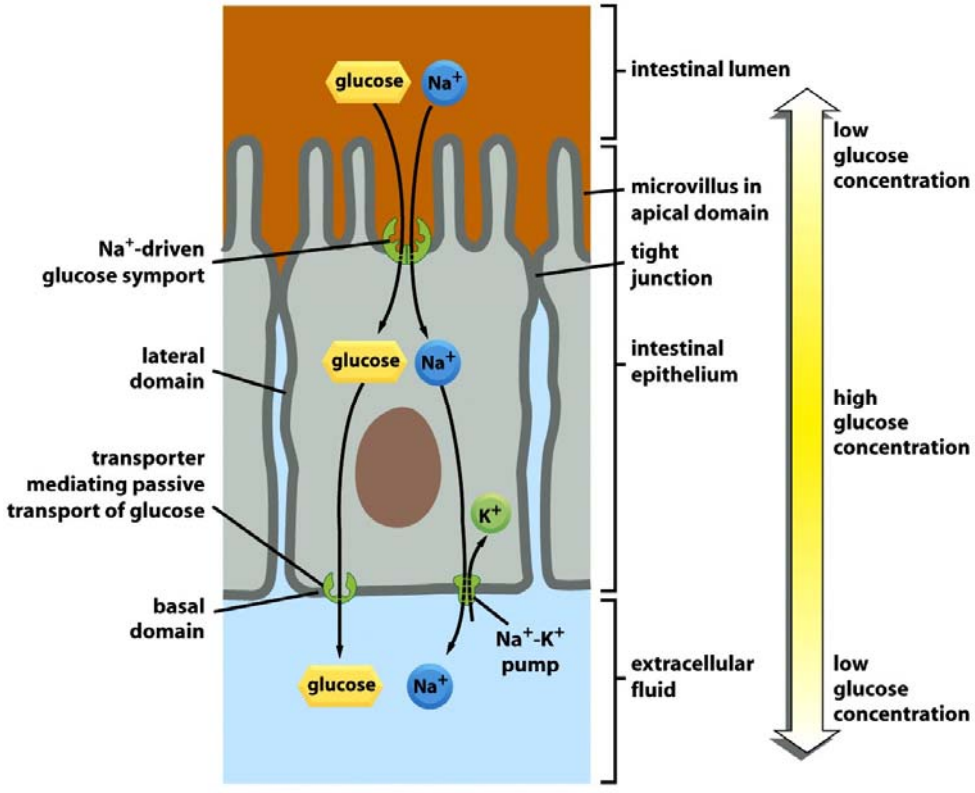


Figure 11-11 Molecular Biology of the Cell 5/e (© Garland Science 2008)

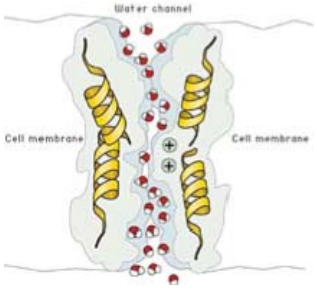
Water transport through the cell membrane

- Osmosis (nothing about the mechanism)
- Water pass through the cell membrane by a double mechanism: simple diffusion + facilitated diffusion (aquaporins)
- Clinical significance
  - Hypertonic – low water, many (high concentration) solutes
  - Hypotonic – more water, few (low concentration) solutes
  - Isotonic – equal concentration for solutes, equal concentration of water (on both faces of the cell membrane)

Aquaporins

- Fast water (facilitated) transport (in both directions, according to the colloid-osmotic pressure)

2003, Nobel Prize in chemistry: "for discoveries concerning channels in cell membranes"



Peter Agre
John Hopkins
"for the discovery of water channels"

Roderick MacKinnon
Rockefeller
"for structural and mechanistic studies of ion channels"

Transport with membrane

1. Endocytosis:
   - Phagocytosis
   - Pinocytosis:
     - Constitutive
     - Receptor mediated (clathrin mediated)
     - Potocytosis
2. Exocytosis
3. Transcytosis

Phagocytosis

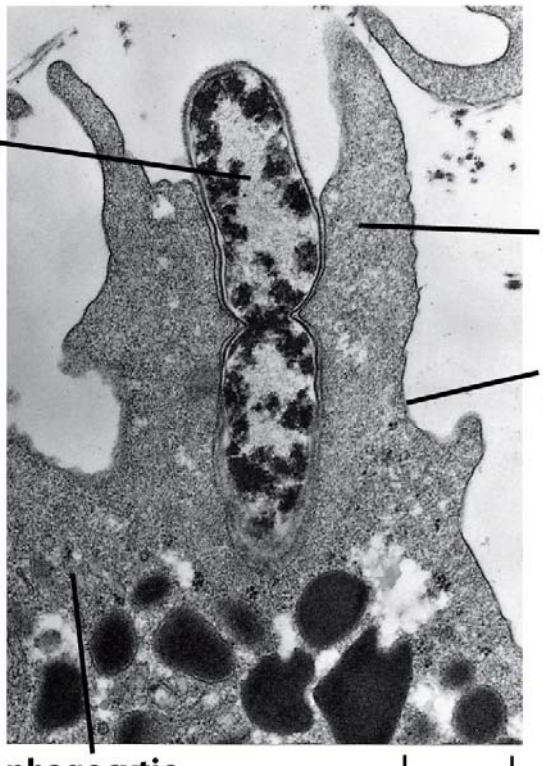


Figure 13-47a Molecular Biology of the Cell 5/e (© Garland Science 2008)

Endocytosed material particle (insoluble)

Material directed to the lysosome

Pinocytosis: constitutive / potocytosis

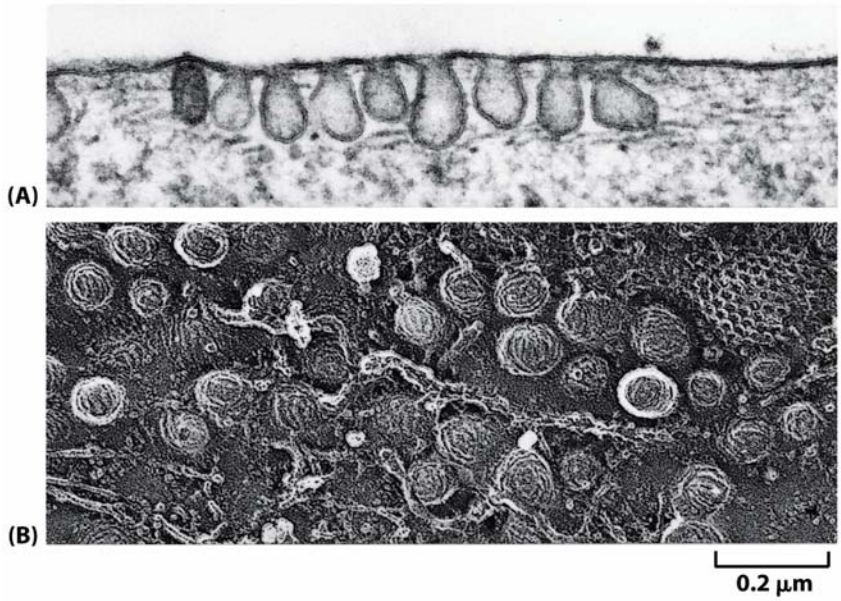


Figure 13-49 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Endocytosed material: soluble macromolecules

Directed to lysosome for constitutive pinocytosis

For potocytosis, directed to:
- cytosol (e.g. folic acid)
- other final intracellular locations (e.g. direct transport to ER)

Receptor-mediated Endocytosis

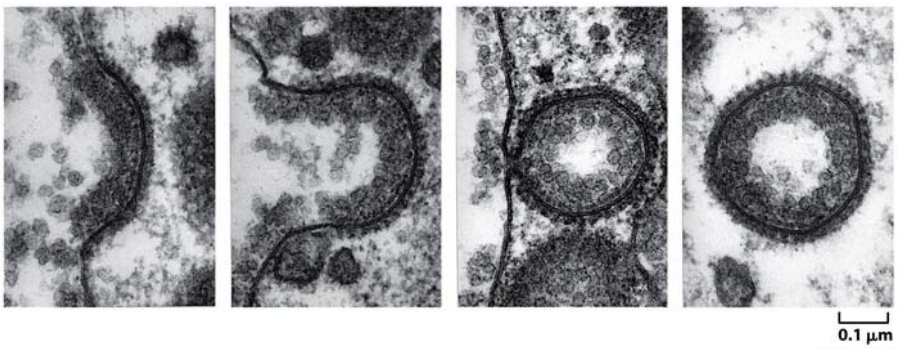


Figure 13-48 Molecular Biology of the Cell 5/e (© Garland Science 2008)

The mechanism:

1. Receptors bind ligands
2. Receptor-ligand complexes accumulated in coated pits, by adaptor protein (AP) and clathrin
3. Formation of coated vesicles and their detachment from the cell membrane
4. Release of the clathrin coat and leading of the endosome to the final destination inside the cell

Endocytosed material: soluble macromolecules ligands for cell surface receptors (e.g. LDL, transferrin, growth factors – EGF) – intracellular destiny is various

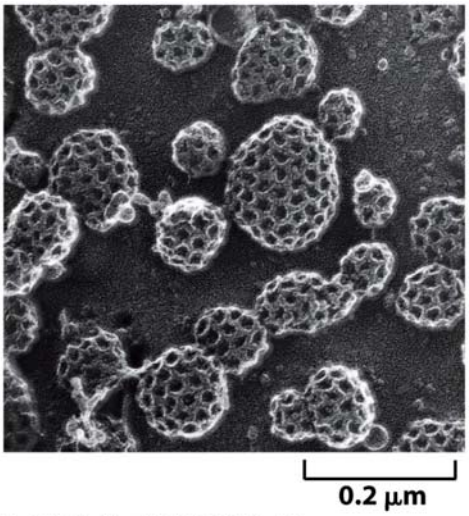


Figure 13-6 Molecular Biology of the Cell 5/e (© Garland Science 2008)

The structure of clathrin coat

Clathrin organizes triskelion structures
Triskelion contains three large and three small polypeptide chains
Triskelions assemble in a basketlike framework as a convex cage

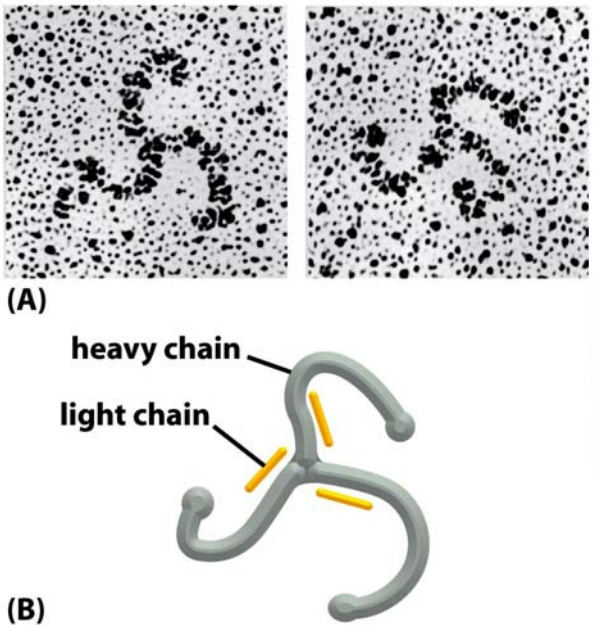


Figure 13-7ab Molecular Biology of the Cell 5/e (© Garland Science 2008)

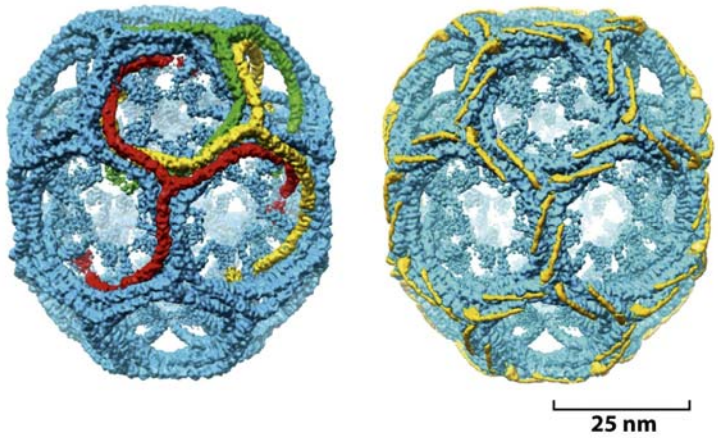


Figure 13-7cd Molecular Biology of the Cell 5/e (© Garland Science 2008)

Transport with membrane

- Exocytosis
  - needs membrane fusion (secretory vesicle membrane with cell membrane)
  - details at cell secretion section of the lecture about Golgi apparatus
- Transcytosis
  - described for epithelial cells organizing monolayers (endothelial cells, hepatocytes, enterocytes)
  - macromolecules are transported from the organ cavity toward interstitial space or *vice versa*

SUMMARY

- Cell membrane acts as an integrative system by cross-talking of all molecular components in order to allow exchanges with the environmental
- Substance exchanges are done by membrane transport (through or with membrane):
  - Simple diffusion (nonpolar molecules, small polar molecules);
  - Facilitated diffusion (ions, larger polar molecules);
  - Active transport
  - Vesicular transport (macromolecules and particulate materials).