IBO
細胞學講義

台灣大學
生命科學系/動物學研究所
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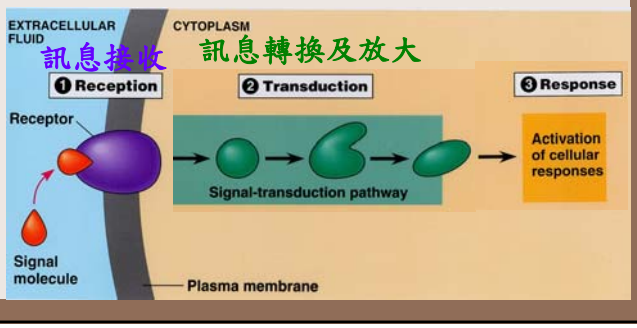
現代細胞學六大議題

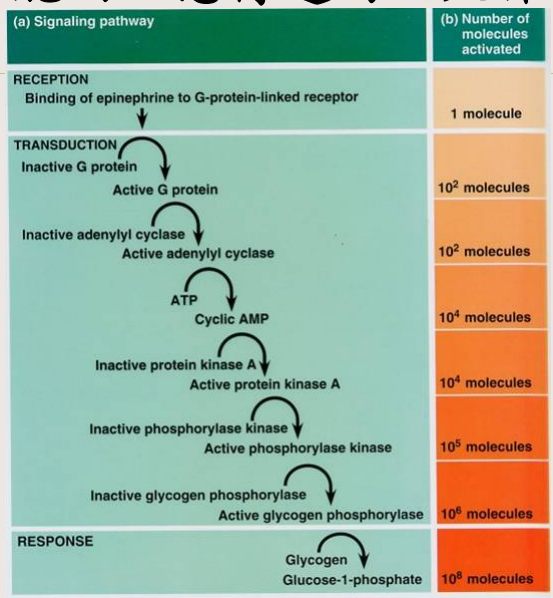
- 細胞內調控：訊息傳遞
- 細胞附著：
- 細胞骨架：
- 細胞膜調控、蛋白質分項及運輸：
- ~~基因表現~~：
- 細胞週期與細胞凋亡：

細胞內訊息傳遞
(Intracellular Signaling Transduction)

- History of studies on intracellular signal transduction
  - Dr. Earl W. Sutherland: The Nobel Prize in Physiology and Medicine 1971; epinephrine/glycogen metabolism



細胞內訊息傳遞的放大作用



細胞內訊息傳遞
(Intracellular Signaling Transduction)

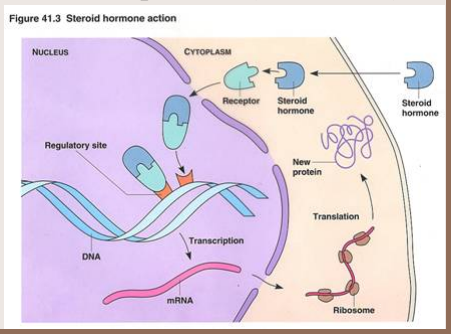
Chemical signals for intercellular communication

- Endocrine, paracrine, and autocrine
- Water-soluble or lipid-soluble messengers
- Interactions between messengers (**ligand**) and **receptor**:

細胞內訊息傳遞
(Intracellular Signaling Transduction)

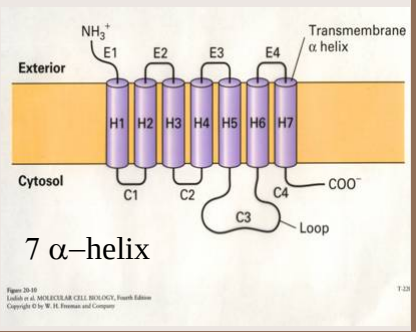
• Characteristics and functions of receptors

1. Intracellular receptors: most in nucleus
   - ligand (lipid-soluble; pass plasma membrane by diffusion)+ receptor = transcription factor: recognize specific DNA sequence (enhancer)



細胞內訊息傳遞
(Intracellular Signaling Transduction)

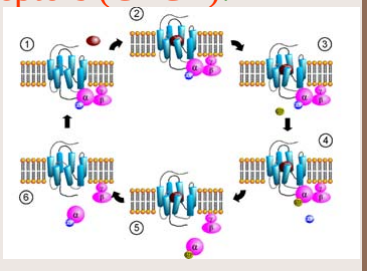
- Characteristics and functions of receptors
  1. Intracellular receptors: most in nucleus
  2. Plasma membrane receptors:
     A.G protein (guanine-binding protein) -coupled receptors:
     - Receptors contain seven membrane-spanning regions:



7 α–helix

細胞內訊息傳遞
(Intracellular Signaling Transduction)

- Characteristics and functions of receptors
  1. Intracellular receptors: most in nucleus
  2. Plasma membrane receptors:
     A. G protein-coupled receptors (GPCR):
     – Receptors
     – G protein
       » large heterotrimeric: Gα (binding with GTP or GDP, and hydrolizing GTP), Gβ, and Gγ



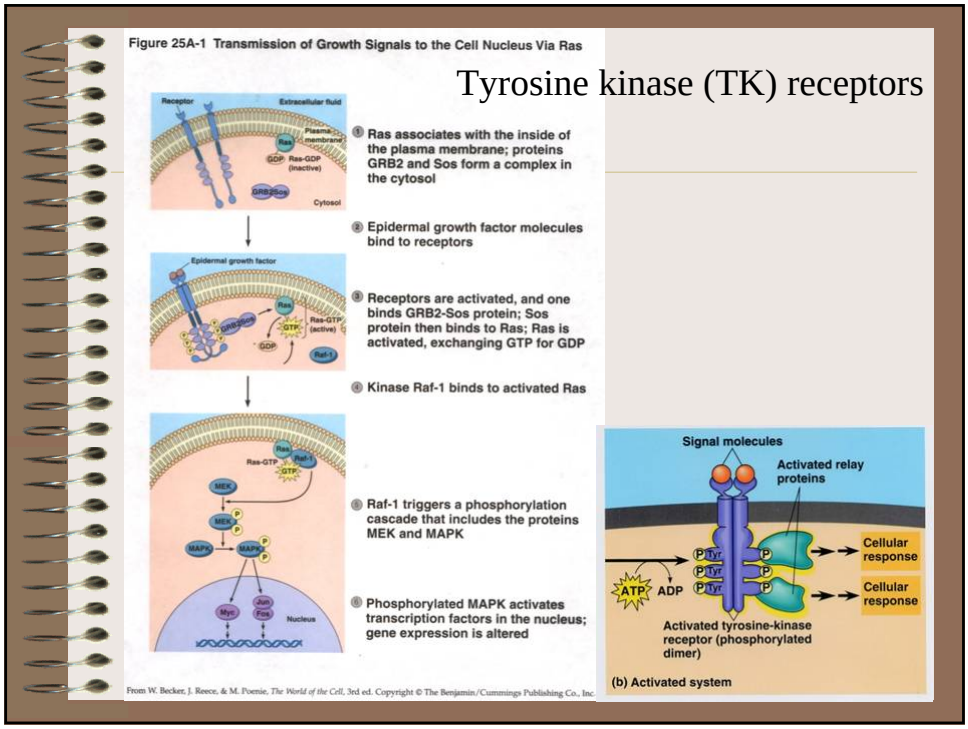
細胞內訊息傳遞
(Intracellular Signaling Transduction)

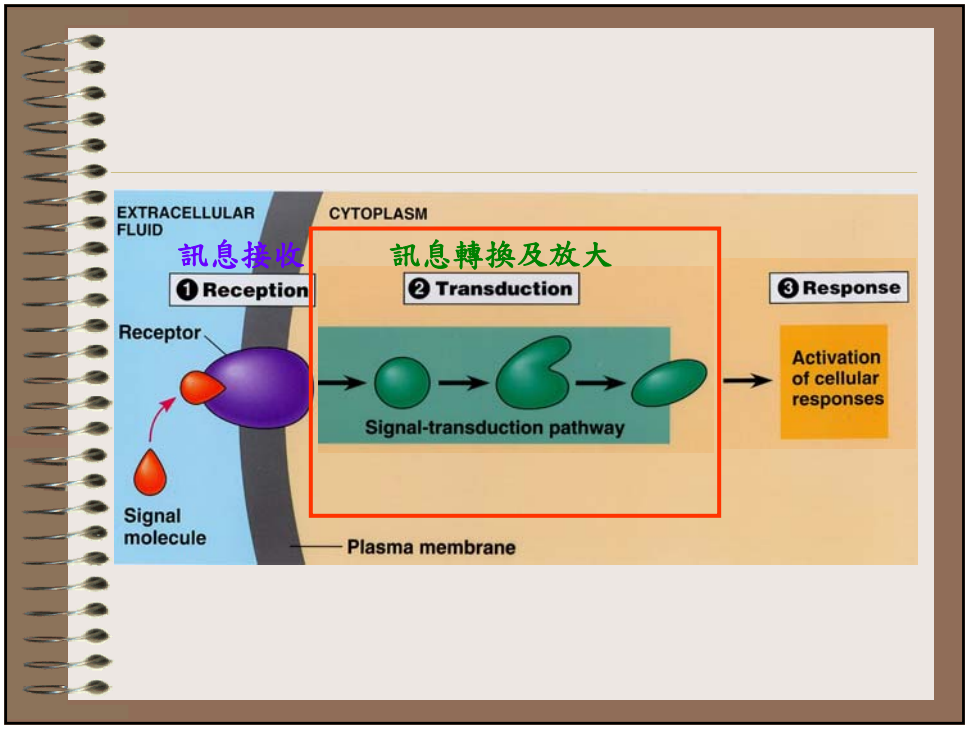
- Characteristics and functions of receptors
  1. Intracellular receptors: most in nucleus
  2. Plasma membrane receptors:
     A. G protein-coupled receptors (GPCR):
        – Receptors:
        – G protein
          » large heterotrimeric:
          » small monomeric: Rho, Ras, etc.
        – **Dr. Martin Rodbell** and **Dr. Alfred Gilman**: **Nobel Prize in Medicine and Physiology 1994** on **G protein study.**

細胞內訊息傳遞
(Intracellular Signaling Transduction)

- Characteristics and functions of receptors
  1. Intracellular receptors: most in nucleus
  2. Plasma membrane receptors:
     A. G protein-coupled receptors:
     B. Tyrosine kinase (TK) receptors:
        - Cytoplasmic portion contains tyrosine kinase and tyrosine residue: receptor aggregation and auto-phosphorylation
        - Recruited cytosolic proteins: having SH2 (Src Homology) domain to bind with phosphorylated tyrosine
        - Activated PLCγ to initiate IP_3 pathway: PLCγ also have SH2 domain

Tyrosine kinase (TK) receptors

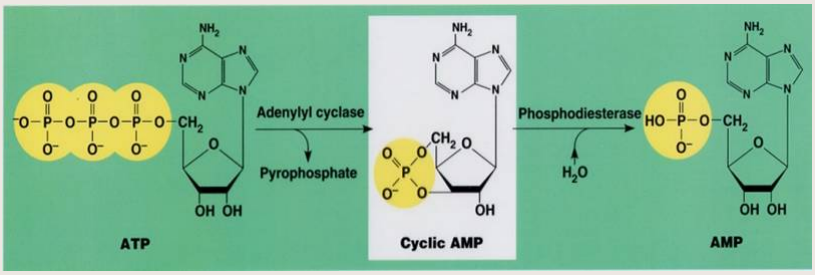




細胞內訊息傳遞
(Intracellular Signaling Transduction)

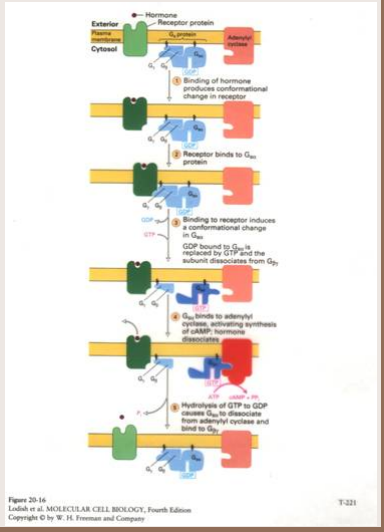
- Signal transduction by second messengers:
  - water-soluble signals can not pass the plasma membrane

1. Cyclic AMP (cAMP):



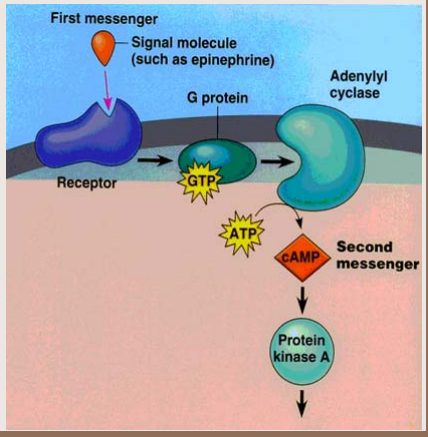
細胞內訊息傳遞
(Intracellular Signaling Transduction)

- Signal transduction by second messengers:
  1. Cyclic AMP (cAMP):
     - Adenylate (adenylyl) cyclase activated by Gsα can convert ATP to cAMP:



細胞內訊息傳遞
(Intracellular Signaling Transduction)

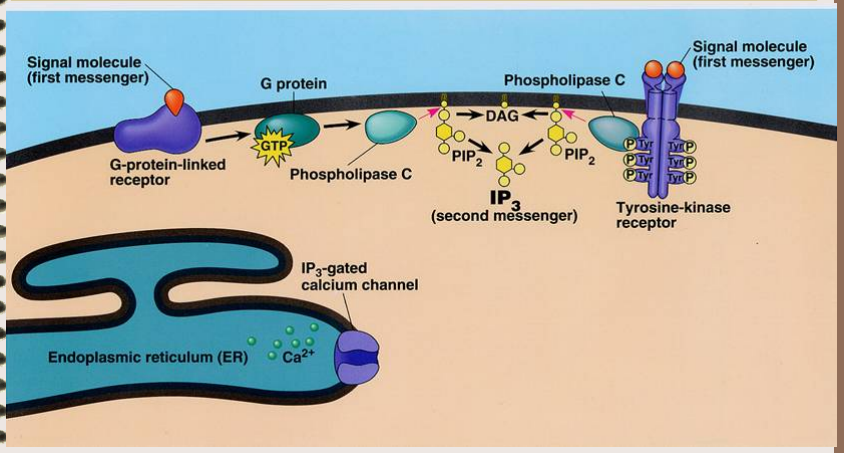
- Signal transduction by second messengers:
  1. Cyclic AMP (cAMP):
     - Adenylate cyclase converts ATP to cAMP:
     - Protein kinase A (PKA): cAMP-dependent protein kinase.
     - cAMP-specific phosphodiesterase: cAMP → AMP



細胞內訊息傳遞
(Intracellular Signaling Transduction)

- Signal transduction by second messengers:
  1. Cyclic AMP (cAMP):
  2. Inositol-1,4,5-trisphosphate ($InsP_3$; IP_3) and diacylglycerol (DAG): inositol-phospholipid-calcium pathway
     - Phospholipase C (PLC): PLCβ activated by G protein
     - Phosphatidylinositol-4,5-bisphosphoate (PIP_2) → IP_3 + DAG
       - IP_3: bind to calcium channel on ER or mitochondria to release Ca^{+2}

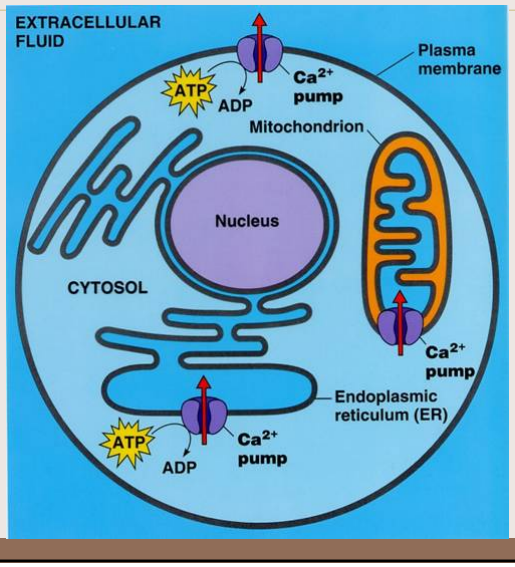
Inositol-phospholipid-calcium pathway



細胞內訊息傳遞
(Intracellular Signaling Transduction)

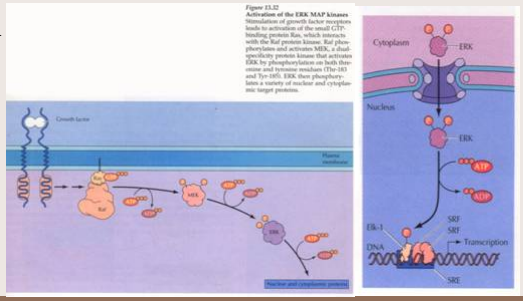
- Signal transduction by second messengers:
  1. Cyclic AMP (cAMP):
  2. Inositol-1,4,5-trisphosphate and diacylglycerol:
     - Phospholipase C (PLC):
     - $PIP_2 \rightarrow IP_3 + DAG$
     - Protein kinase C (calcium-dependent protein kinase; PKC): activation by DAG
     - Calmodulin: Ca^{+2}-binding protein
     - Calcium ions: $[Ca^{+2}]i$ in resting cells is around $10^{-6} \sim 10^{-7}M$
       - calcium channel or calcium pump on plasma membrane, ER or mitochondria

calcium channel or **calcium pump** on plasma membrane, ER or mitochondria



細胞內訊息傳遞
(Intracellular Signaling Transduction)

- Signal transduction by second messengers:
  1. Cyclic AMP (cAMP):
  2. Inositol-1,4,5-trisphosphate and diacylglycerol :
  3. Other messengers in other pathways:
     - Apoptosis
     - Cell migration
     - Cell division



細胞內訊息傳遞
(Intracellular Signaling Transduction)

- Protein activation: phosphorylation by protein kinase and dephosphorylation by phosphotase

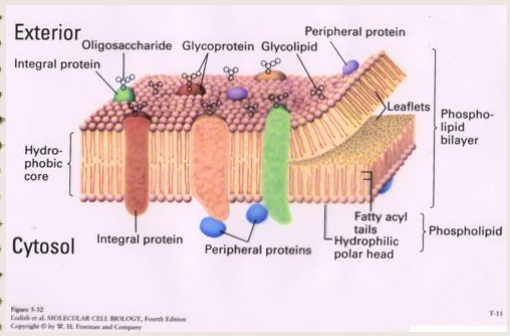
- Signaling regulation
  - Adrenergic receptor
    - epinephrine → β adrenergic receptor → cAMP → glycogen degradation
    - norepinephrine → α adrenergic receptor → IP_3/Ca^{+2} → muscle contraction

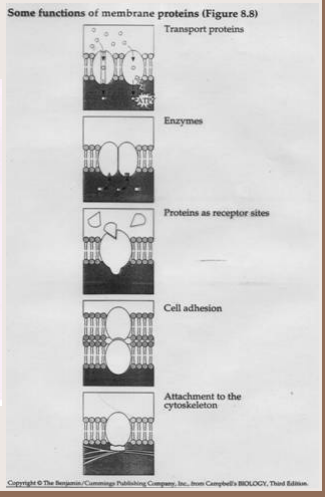
細胞內訊息傳遞
(Intracellular Signaling Transduction)

- Signaling regulation
  - Adrenergic receptor
  - Platelet activation
    - Exposed collagen on wound tissue → collagen receptor on platelets → G protein → phospholipase A2 → arachidonic acid → cyclooxygenase → thromboxane A2 (prostaglandin)→ thromboxane A2 receptor on platelet → G protein
    - Aspirin can reduce heart attack by inhibiting cyclooxygenase: slow platelet activation and recruitment

細胞膜
(Plasma Membrane)

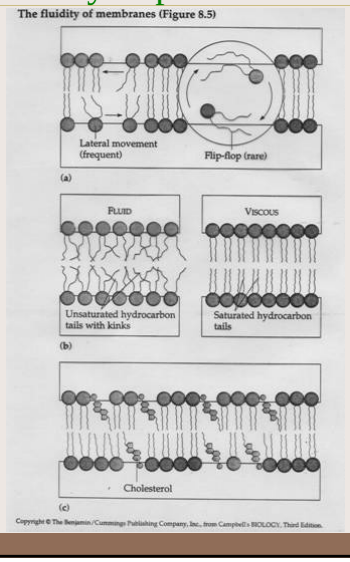
- Structure of plasma membrane:
- Functions of plasma membrane:

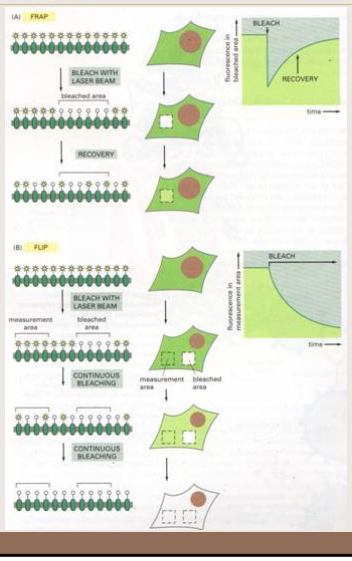




細胞膜
(Plasma Membrane)

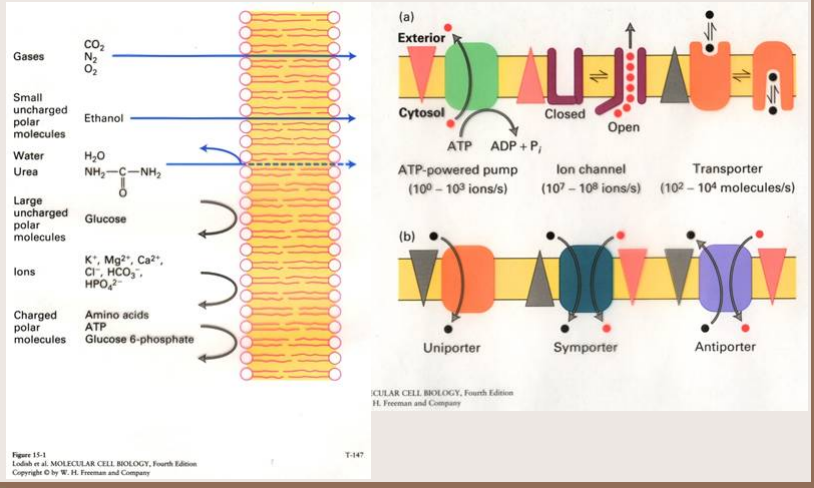
- Fluidity of plasma membrane:





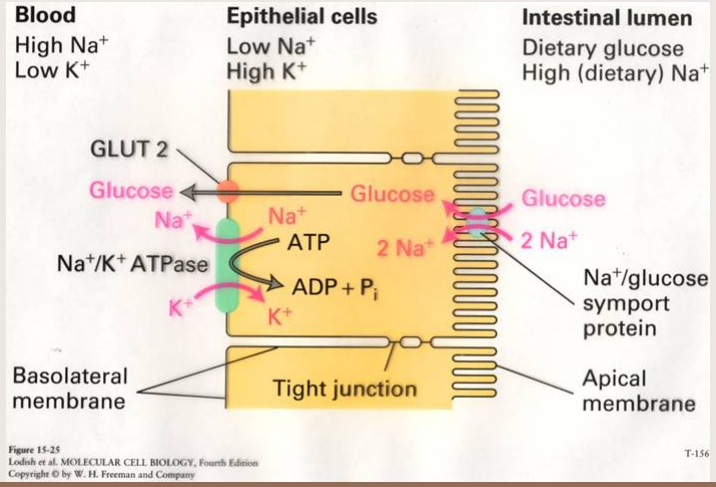
細胞膜調控
(Membrane Regulation)

- Transportation cross the plasma membrane:



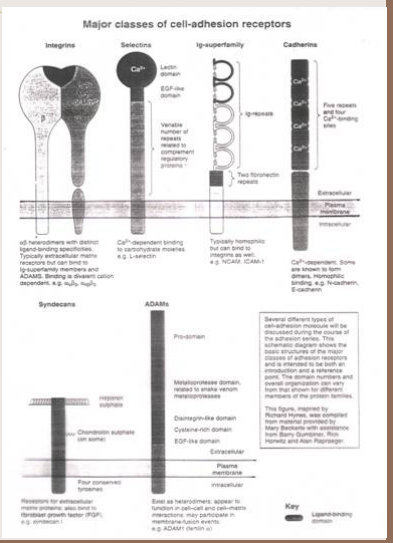
細胞膜調控
(Membrane Regulation)

- Transportation cross the plasma membrane:



細胞附著 (Cell Adhesion)

- Cell-to-cell and cell-to-matrix are the most important phenomena of a multi-cellular life form.

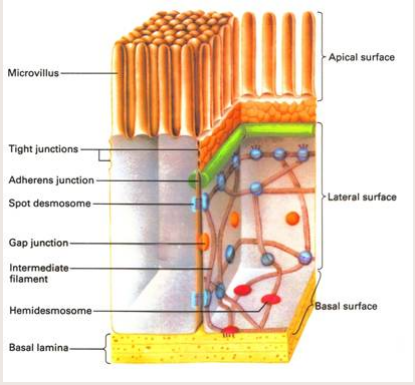


細胞附著 (Cell Adhesion)

- Cell-cell adhesion: for intercellular communication and transportation
  - Fertilization: sperm-egg, yeast mating, etc.
  - Embryogenesis: induction, morphogenesis, etc
  - Metastasis of cancer cells and NK cell killing
  - Neural-neural and neural-muscular junction
  - Immune responses: lymphocyte homing, Ab formation, phagocytosis, etc.
  - Pathogen (bacteria, viruses, and fungi, etc.) infection

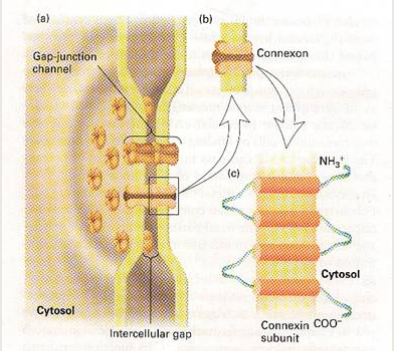
細胞附著 (Cell Adhesion)

- Molecules involved cell-cell adhesion
  - Cell junctions: permanent structures
    - A. Tight junction: Continuous belts around epithelia to prevent leaking of molecules or microbial invasion.
    - B. Desmosome: intermediate filament (tonofilament):



細胞附著 (Cell Adhesion)

- Molecules involved cell-cell adhesion
  - Cell junctions:
    - A. Tight junction:
    - B. Desmosome:
    - C. Gap junction: a direct chemical or electrical communication



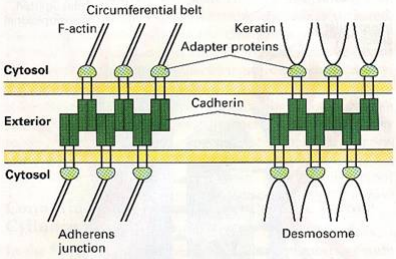
▲ **FIGURE 22-8 Structure of gap junctions.** (a) In this model, a gap junction is a cluster of channels between two plasma membranes that are separated by a gap of about 2–3 nm. (b) Both membranes contain connexon hemichannels, cylinders of six dumbbell-shaped connexin subunits. (c) Each connexin subunit has four transmembrane α helices. Two connexons join in the gap between the cells to form a gap-junction channel, 1.5–2.0 nm in diameter, that connects the cytoplasm of the two cells.

細胞附著 (Cell Adhesion)

- Molecules involved cell-cell adhesion
  - Cell junctions: permanent structures
    - A. Tight junction:
    - B. Desmosome:
    - C. Gap junction:
      - Connexon forms a 1.5 nm diameter channel: <1200 daltons
      - The fastest cell communication: in nerve (electrical coupling), smooth muscle and heart muscle

細胞附著 (Cell Adhesion)

- Molecules involved cell-cell adhesion
  - Cell junctions: permanent structures
  - Cell adhesion molecules (CAMs): dynamic structures
    - Cadherin: Ca^{+2}-dependent binding, cadherin - catenin (α, β, γ) - actin.
      - Adhesion belt:

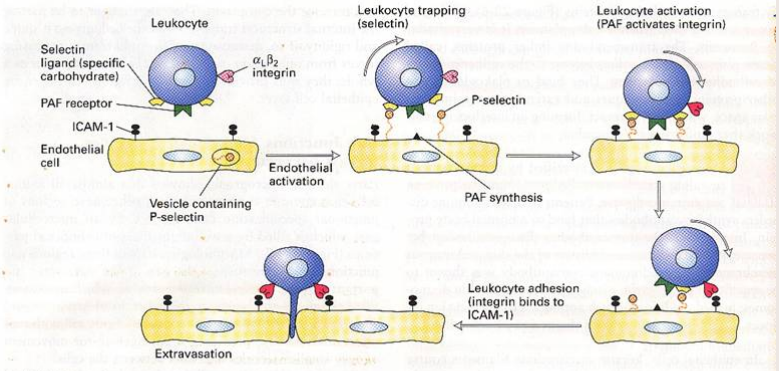


▲ FIGURE 22-5 Adhesion molecules in junctions involved in cell-cell adhesion. Adherens junctions and desmosomes are specialized cell-cell junctions that consist of clustered-cadherin dimers. Cadherin is connected to either the circumferential belt of actin filaments or bundles of keratin filaments in the cyto-skeleton through the catenin adapter proteins.

細胞附著 (Cell Adhesion)

- Molecules involved cell-cell adhesion
  - Cell junctions: permanent structures
  - Cell adhesion molecules (CAMs): dynamic structures
    - A. Cadherin:
    - B. Immunoglobulin superfamily: Ca^{+2}-independent, single-passed transmembrane domain.
      - TCR (T cell receptor), MHC, CD4, CD8, etc.
    - C. Selectin: lectin-like domain (binding with specific CHO), Ca^{+2}-dependent.

Extravasation of leukocytes



▲ **FIGURE 22-4 Interactions between cell-adhesion molecules during the initial binding and tight binding of T cells, a kind of leukocyte, to activation endothelial cells.** Once a T cell has firmly adhered to the endothelium, it can move (extravasate) into the underlying tissue. Activation of the endothelium requires signals, such as platelet-activating factor (PAF), that are released in areas of infection or inflammation; thus extravasation occurs only in such areas. See text for discussion. [Adapted from R. O. Hynes and A. Lander, 1992, *Cell* **68**:303.]

細胞附著 (Cell Adhesion)

- Molecules involved cell-cell adhesion
  - Cell junctions: permanent structures
  - Cell adhesion molecules (CAMs):
    - A. Cadherin:
    - B. Immunoglobulin superfamily:
    - C. Selectin:
    - D. Integrin: transmembrane heterodimer - α (binding site) and β subunit
      - Some recognize RGD (arginine-glycine-aspartate)-peptide, Ca^{+2}/Mg^{+2}-dependent
      - Focal adhesion: integrin - vinculin - talin - actin

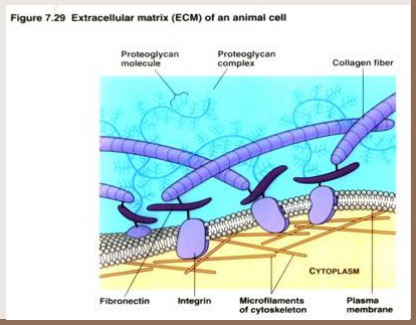
細胞附著 (Cell Adhesion)

Cell-matrix adhesion:

- Extracellular matrix (ECM) is constituted by variety of versatile polysaccharides and proteins.
  - Spermatogenesis and oogenesis:
  - Embryogenesis:
  - Epithelial cell differentiation:
  - Wound healing:
  - Decellularization and recellularization of tissues and organs
  - Settle-down of marine invertebrate larva:

細胞附著 (Cell Adhesion)

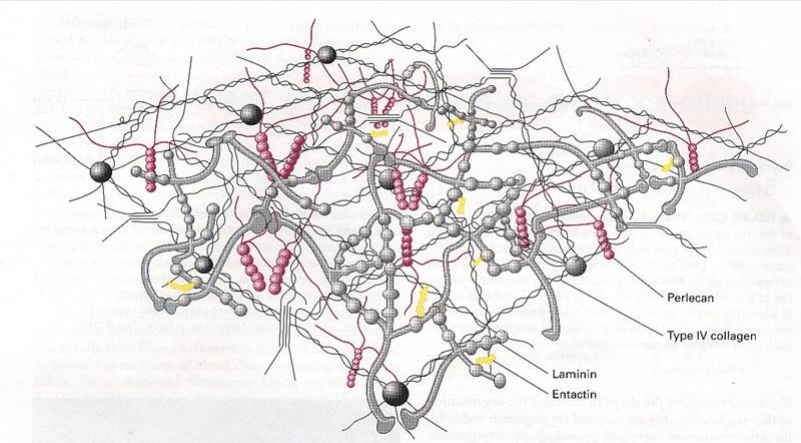
- Molecules involved into cell-matrix interactions:
  - Collagen: most abundant protein in your body to provide tensile strength
    - Connective tissues: type I (in skin, bones and tendons), type II (in cartilage), type III (in skin, and tendons), and type IV in basal laminae
    - Aging: collagen becomes increasingly cross-linked and inflexible.



細胞附著 (Cell Adhesion)

- Molecules involved into cell-matrix interactions:
  - Collagen:
  - Proteoglycan (PG): hydrophilic, gel-like network
    - Glycosaminoglycans (GAGs): unbranched polysaccharide chains composed of repeating disaccharide units)
  - Fibronectin (from fibroblast): RGDS sequence
  - Laminin: the basal lamina specific protein
    - YIGSR (tyrosine-isoleucine-glycine-serine-arginine) sequence for laminin receptor

Model of the Basal Lamina

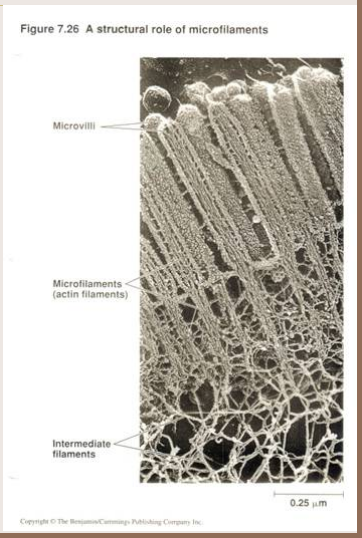


▲ FIGURE 22-20 Model of the basal lamina. [Adapted from B. Alberts et al., 1994, *Molecular Biology of the Cell*, 3d ed, Garland, p. 991.]

細胞骨架 (Cytoskeleton)

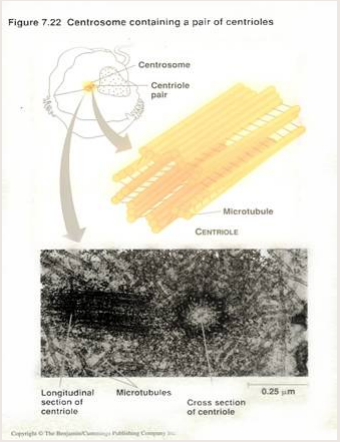
- The general functions of cytoskeletons:

1. Protection and shape maintenance:
2. Spatial distribution: compartmentation
3. Transportation of membrane-bound organelles, mRNA, etc.:
4. Cell motility and contraction:



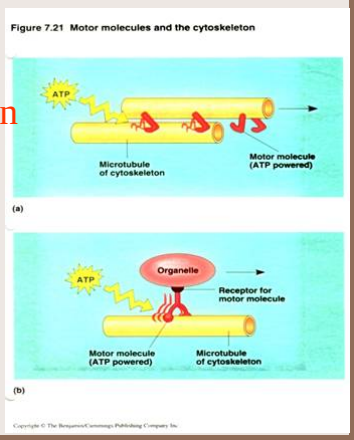
細胞骨架 (Cytoskeleton)

- Structural elements of the cytoskeleton
  - Microtubule: α-tubulin and β-tubulin → protofilament → hollow tube
    - Microtubule organization center (MTOC): initiate MT assembly
      - in centrosome: MTs form mitotic spindle
      - in basal body: MTs form axon, cilia and flagella



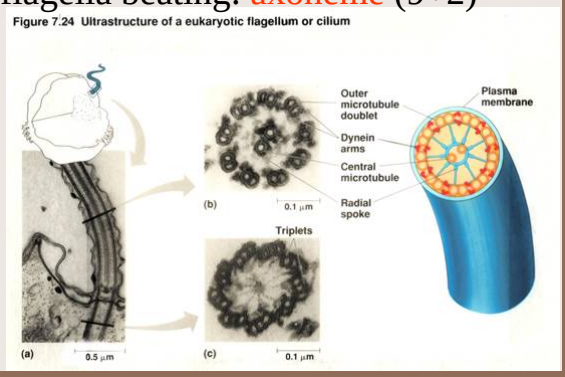
細胞骨架 (Cytoskeleton)

- Structural elements of the cytoskeleton
  - Microtubule: tubulin
    - Microtubule organization center (MTOC):
    - Microtubule-associated protein (MAPs):
      - Motor MAPs: kinesin (to "+" end) and dynein (to "-" end).



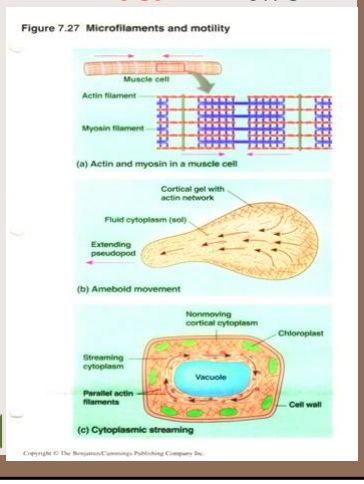
細胞骨架 (Cytoskeleton)

- Structural elements of the cytoskeleton
  - Microtubule:
    - Microtubule organization center (MTOC):
    - Microtubule-associated protein (MAPs):
    - Cilia and flagella beating: axoneme (9+2)



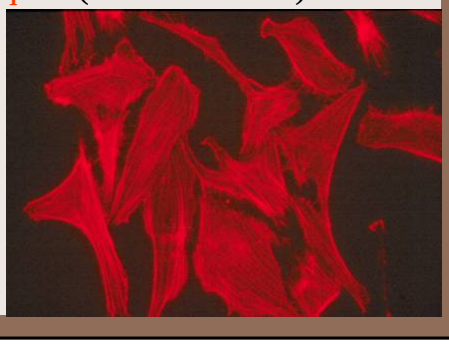
細胞骨架 (Cytoskeleton)

- Structural elements of the cytoskeleton
  - Microtubule:
  - Microfilament **(MF)**: G-actin → F-actin → two interwined chains
    - α-actin (in muscle cells: sliding-filament model) as well as β-actin and γ-actin (in nonmuscle cells)



細胞骨架 (Cytoskeleton)

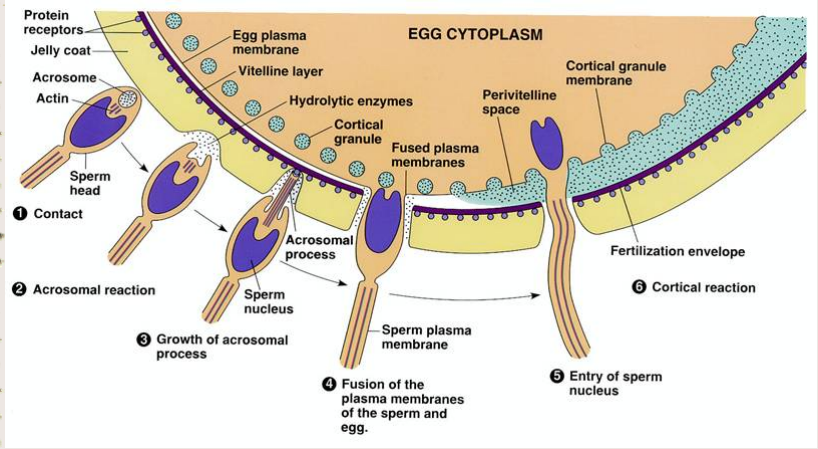
- Structural elements of the cytoskeleton
  - – Microtubule:
  - – Microfilament (MF): actin
    - A. Cell cortex: in dense networks located beneath the plasma membrane
    - B. Focal adhesion plaques (focal contacts): stress fiber



細胞骨架 (Cytoskeleton)

- Structural elements of the cytoskeleton
  - – Microtubule:
  - – Microfilament (MF): actin
    - A. Cell cortex:
    - B. Focal adhesion plaques (focal contacts):
    - C. Cytoplasmic streaming or amoeboid movement:
      - Gel-to-sol transition and filopodia formation:
    - D. Cytokinesis: contractile ring (actin and myosin II)
    - E. Sperm-egg fertilization: acrosome reaction

Sperm-egg fertilization: acrosome reaction



細胞骨架 (Cytoskeleton)

- Structural elements of the cytoskeleton
  - Microtubule:
  - Microfilament (MF):
  - Intermediate filament (IF): real cytoskeleton
    - Tissue specificity: IF typing - differentiate marker and cancer diagnosis

蛋白質分項及運輸
(Protein Sorting and Transportation)

- The proteins secretory pathway: RER → Golgi → secretory vesicles → plasma membrane → cell exterior

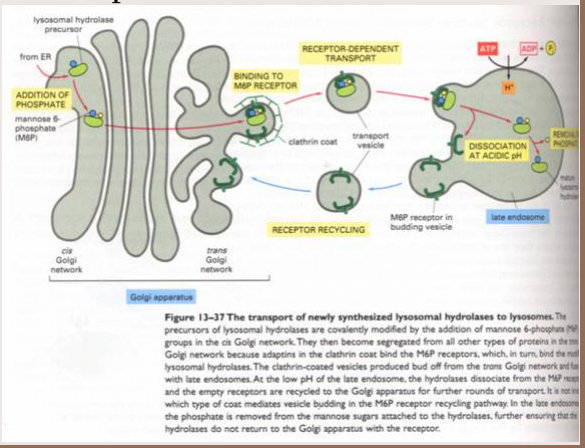


Figure 13–37 The transport of newly synthesized lysosomal hydrolases to lysosomes. The precursors of lysosomal hydrolases are covalently modified by the addition of mannose 6-phosphate (M6P) groups in the *cis* Golgi network. They then become segregated from all other types of proteins in the *trans* Golgi network because adaptins in the clathrin coat bind the M6P receptors, which, in turn, bind the newly lysosomal hydrolases. The clathrin-coated vesicles produced bud off from the *trans* Golgi network and fuse with late endosomes. At the low pH of the late endosome, the hydrolases dissociate from the M6P receptors and the empty receptors are recycled to the Golgi apparatus for further rounds of transport. It is not known which type of coat mediates vesicle budding in the M6P receptor recycling pathway. In the late endosome the phosphate is removed from the mannose sugars attached to the hydrolases, further ensuring that the hydrolases do not return to the Golgi apparatus with the receptor.

蛋白質分項及運輸
(Protein Sorting and Transportation)

- Signal hypothesis by Blobel and Dobberstein in 1975: All mRNA initially bind with free ribosomes in cytoplasm
  1. The N-terminus of the growing polypeptide without signal sequence (contain a stretch hydrophobic a.a.): the synthesized proteins are transported to nucleus, mitochondria, chloroplasts, and peroxisomes.
  2. The N-terminus of the growing polypeptide with signal sequence: The associated ribosomes are targeted to the ER, and the synthesized proteins are transported to plasma membrane, lysosomes and secretory vesicles.

蛋白質分項及運輸
(Protein Sorting and Transportation)

- Translation in ER:
  1. Signal sequence bind to signal recognition particle (SRP): Translation pauses.
  2. The complex (SRP, ribosome, and growing peptide) adheres to the ER membrane (SRP binds to SRP receptor).
  3. Ribosome binds with protein translocation channel (Sec61) causing channel open.
  4. Signal sequence insert into the channel and translation resumes.
  5. Signal sequence cleaved by signal peptidase.

Protein Transportation to ER

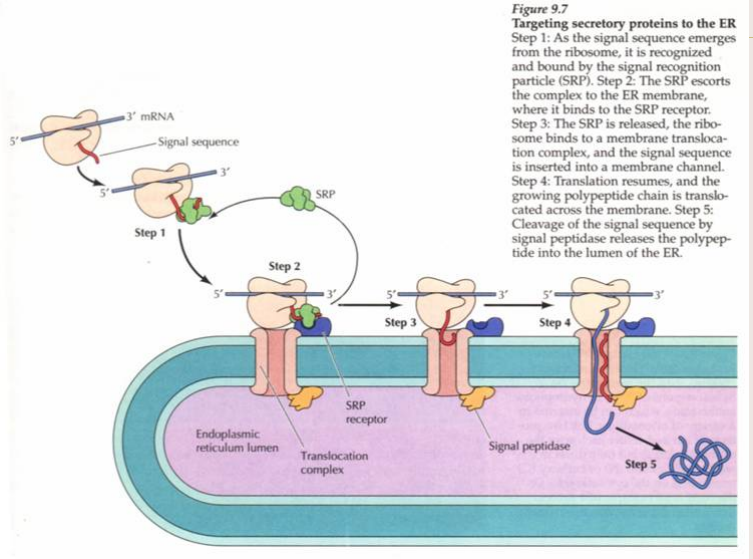


Figure 9.7
Targeting secretory proteins to the ER
Step 1: As the signal sequence emerges from the ribosome, it is recognized and bound by the signal recognition particle (SRP). Step 2: The SRP escorts the complex to the ER membrane, where it binds to the SRP receptor. Step 3: The SRP is released, the ribosome binds to a membrane translocation complex, and the signal sequence is inserted into a membrane channel. Step 4: Translation resumes, and the growing polypeptide chain is translocated across the membrane. Step 5: Cleavage of the signal sequence by signal peptidase releases the polypeptide into the lumen of the ER.

蛋白質分項及運輸
(Protein Sorting and Transportation)

- Translation in ER:
  - Multiple membrane-spanning protein: an alternating series of internal signal sequences and stop-transfer sequences.

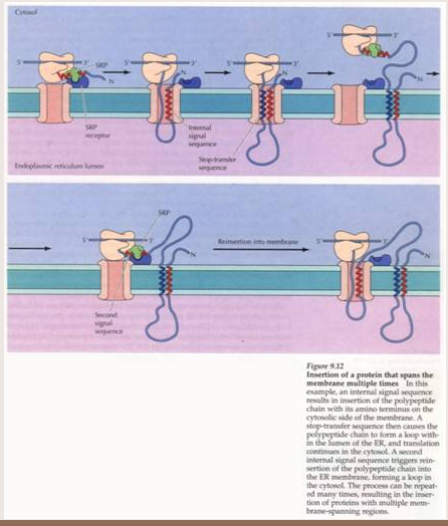


Figure 9.12
Insertion of a protein that spans the membrane multiple times In this example, an internal signal sequence results in insertion of the polypeptide chain with its amino terminus on the cytosolic side of the membrane. A stop-transfer sequence then causes the polypeptide chain to form a loop within the lumen of the ER, and translation continues in the cytosol. A second internal signal sequence triggers reinsertion of the polypeptide chain into the ER membrane, forming a loop in the cytosol. The process can be repeated many times, resulting in the insertion of proteins with multiple membrane-spanning regions.

蛋白質分項及運輸
(Protein Sorting and Transportation)

- Translation in ER:
  - Multiple membrane-spanning protein:
  - Protein can be anchored in the ER membrane by internal signal sequences that are not cleaved by signal peptidase:

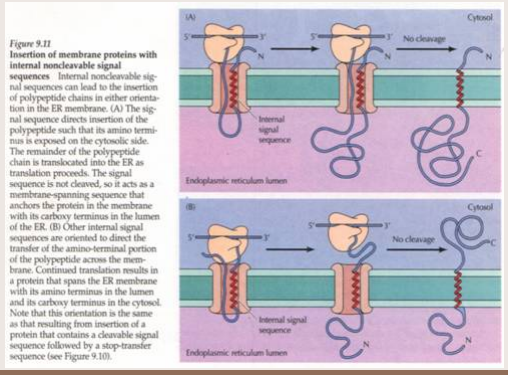


Figure 9.11
Insertion of membrane proteins with internal noncleavable signal sequences Internal noncleavable signal sequences can lead to the insertion of polypeptide chains in either orientation in the ER membrane. (A) The signal sequence directs insertion of the polypeptide such that its amino terminus is exposed on the cytosolic side. The remainder of the polypeptide chain is translocated into the ER as translation proceeds. The signal sequence is not cleaved, so it acts as a membrane-spanning sequence that anchors the protein in the membrane with its carboxy terminus in the lumen of the ER. (B) Other internal signal sequences are oriented to direct the transfer of the amino-terminal portion of the polypeptide across the membrane. Continued translation results in a protein that spans the ER membrane with its amino terminus in the lumen and its carboxy terminus in the cytosol. Note that this orientation is the same as that resulting from insertion of a protein that contains a cleavable signal sequence followed by a stop-transfer sequence (see Figure 9.10).

蛋白質分項及運輸
(Protein Sorting and Transportation)

- Translation in ER:
  - Multiple membrane-spanning protein:
  - Protein can be anchored in the ER membrane by internal signal sequences that are not cleaved by signal peptidase:
  - Protein glycosylation: N-linked glycosylation in ER -14 sugars are added to the growing polypeptide.
  - Glycosylphosphatidylinositol (GPI) anchors contain two fatty acid chains, inositol, oligosaccharide, and ethanolamine:

N-linked glycosylation in ER

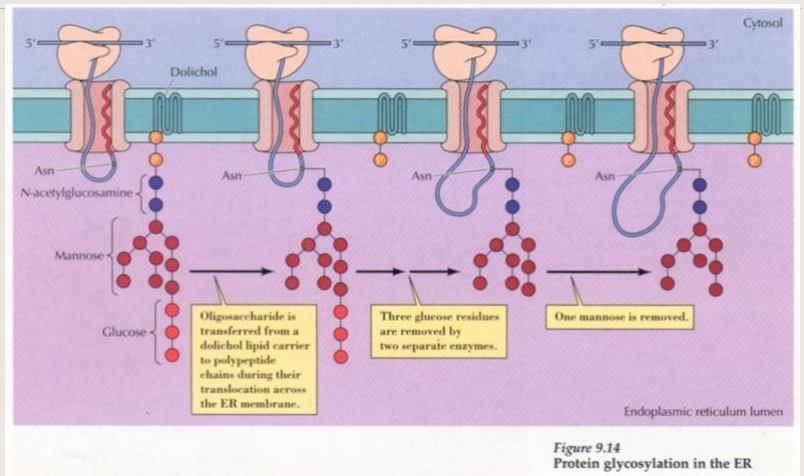


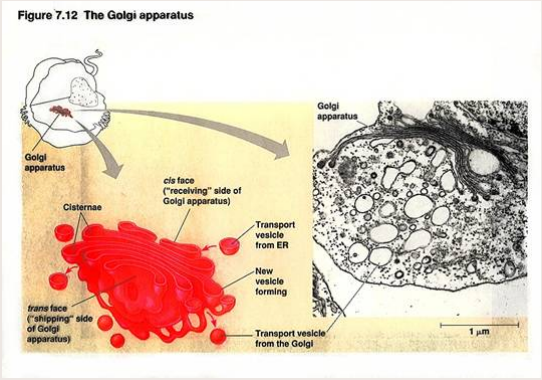
Figure 9.14
Protein glycosylation in the ER

蛋白質分項及運輸
(Protein Sorting and Transportation)

- Export of proteins and lipids from the ER
  - KDEL (Lys-Asp-Glu-Leu) sequence at C-terminus: retain in ER lumen
  - KKXX (Lys-Lys-X-X) sequence at C-terminus: retention on ER membrane

蛋白質分項及運輸
(Protein Sorting and Transportation)

- Organization of the Golgi
  - Golgi: The *cis* (entry) face is convex and the *trans* (exit) face is concave.



蛋白質分項及運輸
(Protein Sorting and Transportation)

- Organization of the Golgi
  - Golgi:
  - Protein glycosylation within the Golgi
    1. Modification for secretion or plasma membrane N-linked glycoprotein:
       - Membrane protein: adding sialic acid
       - Secretion (lysosomal) protein: adding mannose-6-phosphate (M-6-P).
    2. O-linked glycoprotein:

Protein glycosylation within the Golgi

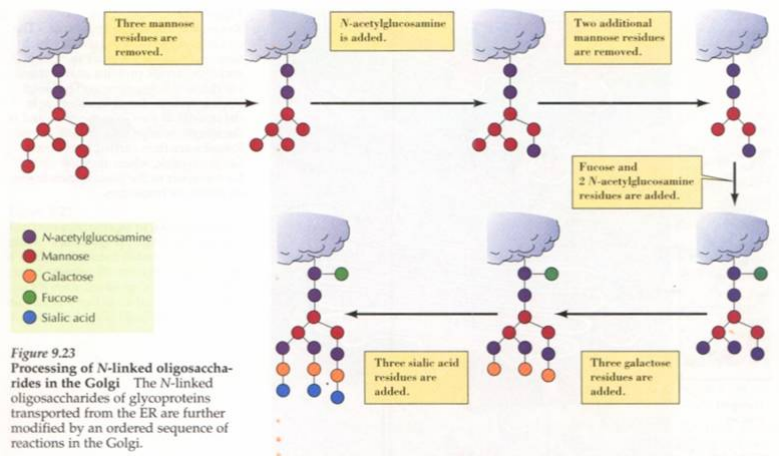


Figure 9.23
Processing of *N*-linked oligosaccharides in the Golgi The *N*-linked oligosaccharides of glycoproteins transported from the ER are further modified by an ordered sequence of reactions in the Golgi.

細胞週期及凋亡
(Cell cycle and apoptosis)

- Phase of the cell cycle:
  - G (gap)$_1$ → S (synthesis) → G_2 → M (mitosis)
    ↘ G_0 ↗

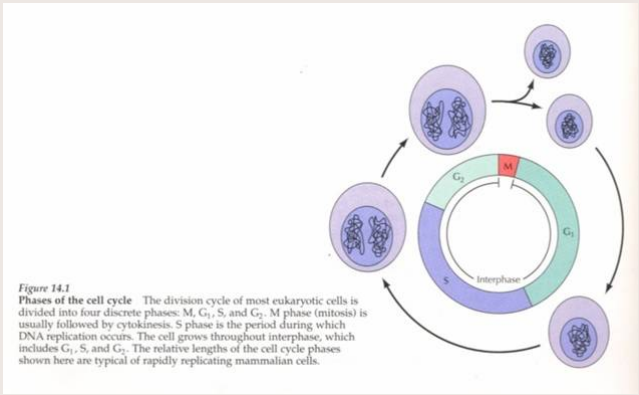
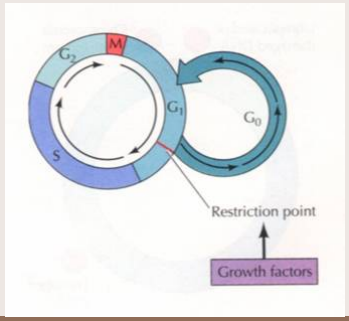


Figure 14.1
Phases of the cell cycle The division cycle of most eukaryotic cells is divided into four discrete phases: M, G_1, S, and G_2. M phase (mitosis) is usually followed by cytokinesis. S phase is the period during which DNA replication occurs. The cell grows throughout interphase, which includes G_1, S, and G_2. The relative lengths of the cell cycle phases shown here are typical of rapidly replicating mammalian cells.

細胞週期及凋亡
(Cell cycle and apoptosis)

- Regulation of the cell cycle:
  - A cell cycle regulatory points in many types of cells occurs late in G_1:
    - Restriction point (regulation by growth factors in animal cells) and START (regulation by nutrients in yeasts)



細胞週期及凋亡
(Cell cycle and apoptosis)

- Regulation of the cell cycle:
  - A cell cycle regulatory points in many types of cells occurs late in G_1:
  - Cell cycle checkpoints
    - At G_1: damaged DNA increases the level of p53.
    - p53: the gene of p53 frequently mutated in human cancers

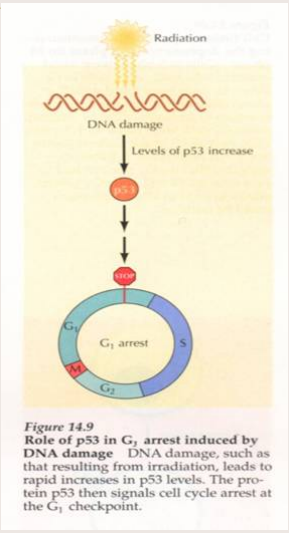
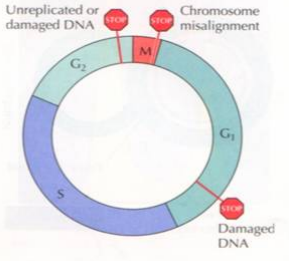


Figure 14.9
Role of p53 in G_1 arrest induced by DNA damage DNA damage, such as that resulting from irradiation, leads to rapid increases in p53 levels. The protein p53 then signals cell cycle arrest at the G_1 checkpoint.

細胞週期及凋亡
(Cell cycle and apoptosis)

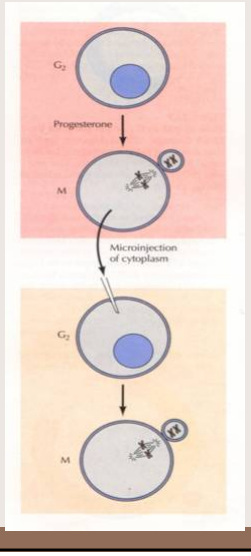
- Regulation of the cell cycle:
  - A cell cycle regulatory points in many types of cells occurs late in G_1:
  - Cell cycle checkpoints
    - At G_1: damaged DNA increases the level of p53.
    - At G_2: damaged or unreplicated DNA
    - At M phase: chromosome mis-alignment

Figure 14.8
Cell cycle checkpoints Several checkpoints function to ensure that complete genomes are transmitted to daughter cells. One major checkpoint arrests cells in G_2 in response to damaged or unreplicated DNA. The presence of damaged DNA also leads to cell cycle arrest at a checkpoint in G_1. Another checkpoint, in M phase, arrests mitosis if the daughter chromosomes are not properly aligned on the mitotic spindle.



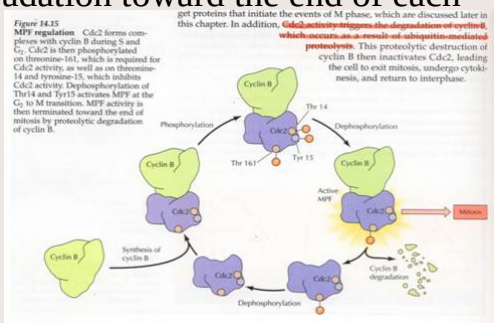
細胞週期及凋亡
(Cell cycle and apoptosis)

- Regulators of cell cycle progression
  - MPF (maturation promoting factor): A dimmer of cdc2 and cyclin B
    - cdc (cell division cycle)2: protein kinase
    - cdc25: protein phosphotase



細胞週期及凋亡
(Cell cycle and apoptosis)

- Regulators of cell cycle progression
  - MPF (maturation promoting factor):
    - cdc2:
    - cdc25:
    - cyclin: accumulation throughout interphase and then rapid degradation toward the end of each mitosis



細胞週期及凋亡
(Cell cycle and apoptosis)

- Regulators of cell cycle progression
  - MPF (maturation promoting factor):
    - cdc (cell division cycle)2:
    - cdc25:
    - cyclin:
  - Families of cyclins and cyclin-dependent kinase
    - cyclin B, cyclin D, G_1cyclin (Cln) cdk (cyclin-dependent kinase), CAK (cdk-activating kinase), CKI (cdk inhibitor), …

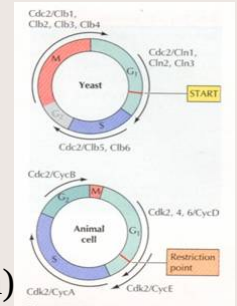
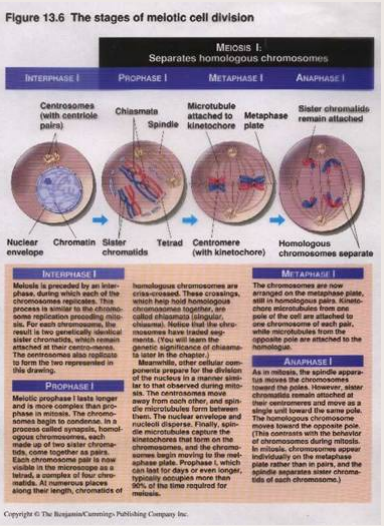


Figure 14.16
Complexes of cyclins and cyclin-dependent kinases In yeast, passage through START is controlled by Cdc2 in association with G_1 cyclins (Cln1, Cln2, and Cln3). Complexes of Cdc2 with distinct B-type cyclins (Clb's) then regulate progression through S phase and entry into mitosis. In animal cells, progression through the G_1 restriction point is controlled by complexes of Cdk2, Cdk4, and Cdk6 with D-type cyclins. Cdk2/cyclin E complexes function later in G_1 and are required for the G_1 to S transition. Cdk2/cyclin A complexes are then required for progression through S phase, and Cdc2/cyclin B complexes drive the G_2 to M transition.

細胞週期及凋亡
(Cell cycle and apoptosis)

- The events of M phase
  - Stages of mitosis: prophase → metaphase → anaphase → telophase



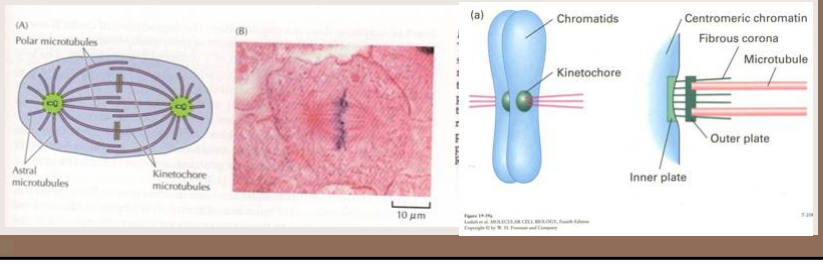
細胞週期及凋亡
(Cell cycle and apoptosis)

- The events of M phase
  - Stages of mitosis:
  - MPF and progression to metaphase:
    - chromatin condensation: phosphorylation of histone H1
    - nuclear envelope breakdown: phosphorylation of lamin

    fragmentation of Golgi and ER

細胞週期及凋亡
(Cell cycle and apoptosis)

- The events of M phase
  - Stages of mitosis:
  - MPF and progression to metaphase:
    - chromatin condensation:
    - nuclear envelope breakdown:
    - fragmentation of Golgi and ER
    - spindle formation: centromere-kinetochore-mtotic spindle (microtubule)



細胞週期及凋亡
(Cell cycle and apoptosis)

- Apoptosis: DNA fragmentation, cytoplasm shrinkage, and membrane change

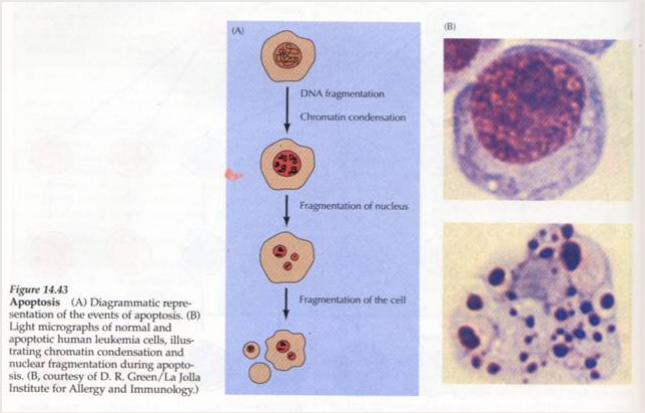


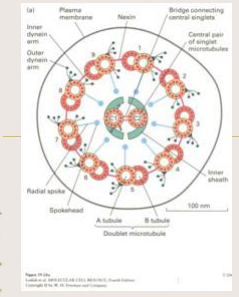
Figure 14.43
Apoptosis (A) Diagrammatic representation of the events of apoptosis. (B) Light micrographs of normal and apoptotic human leukemia cells, illustrating chromatin condensation and nuclear fragmentation during apoptosis. (B, courtesy of D. R. Green/La Jolla Institute for Allergy and Immunology.)

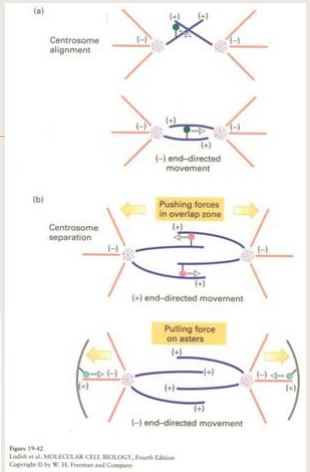
細胞週期及凋亡
(Cell cycle and apoptosis)

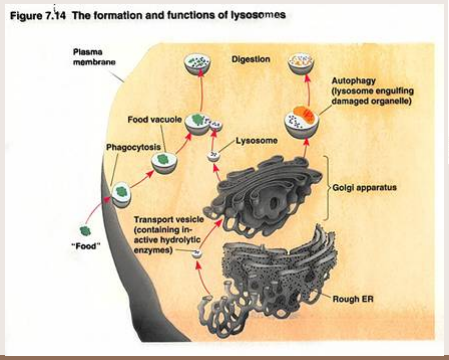
- Apoptosis:
  - Programmed cell death: a normal physiological form of cell death that plays a key role in the maintenance of adult tissues and in embryonic development.
    - maintenance of adult tissues: blood cells
    - maintenance in embryonic development: metamorphosis, nervous system, immune system
    - Death signal →→ Bcl-2 (Ced-9) →→ ICE (Ecd-3) →→ apoptosis

細胞週期及凋亡
(Cell cycle and apoptosis)

- Apoptosis:
  - Programmed cell death:
  - Damaged cells without lysis or damage to neighboring cells
    - Virus-infected cells:
    - DNA damaged cells: UV, heavy metal, etc.







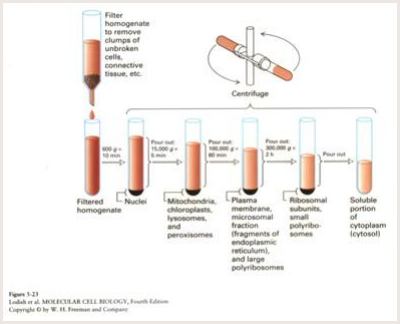


Figure 5-23
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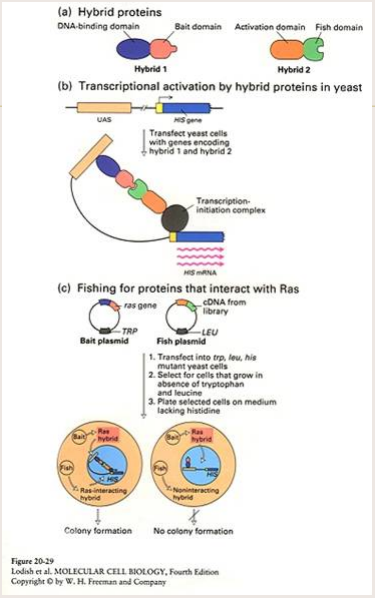

Figure 20-29
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