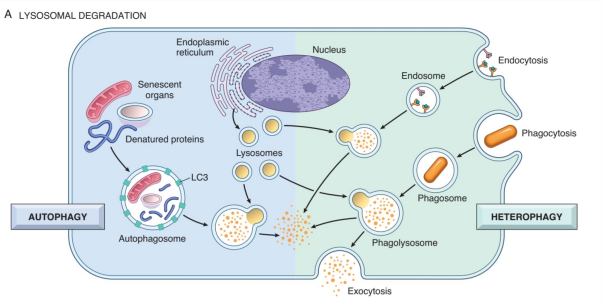
ULTRA LARP Cell II Disease

What to expect

1) Genome
   - Noncoding DNA
   - Histone organization
   - Micro RNA
   - Gene editing
2) Cellular Housekeeping
   - Plasma membrane
   - Cytoskeleton
   - Cell - cell interaction
   - Biosynthetic Machinery
   - Waste Disposal
3) Cellular metabolism & mitochondrial function
   - Energy generation
   - Intermediate metabolism (eg. warburg effect)
   - Cell death signal
4) Cellular activation
   - Cell signalling + Receptor
     - Auto, para, Endo, synaptic
   - Signal transduction pathway
     - G protein coupled receptor, RTKs
   - Transcription factor
   - Growth factor and receptor
   - Extracellular matrix
5) Maintaining cell population
   - Proliferation : Cell cycle
   - Stem cell



! ข้อควรระวัง

เนื้อหาเกิดมาจากการสร้างความบันเทิงให้เข้ากับครีปเพราะแม่งเป็นโรคจิตชอบดูครีปตัวเอง

∴
- ห้ามหน้าไปใช้ประกอบการตัดสินใจ
- Double check because online แม่งโง่

Pathology

pathos : ทุกข์ทรมาน

logos : การศึกษา

virchow

ทุกอย่างมาจากความผิดปกติของ cell

Molecule

Patho แบ่งเยอะ: ดูสรุปทั้งหมด Clip เดี่ยวต่อๆ.

Genome

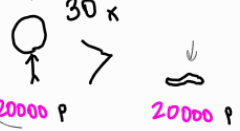
DNA Sequencing

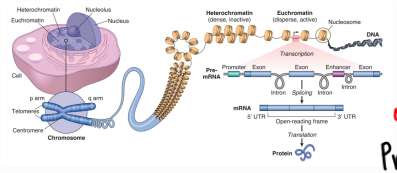
Researchers can exploit the principle of complementary base pairing to determine the complete nucleotide sequence of a DNA molecule, a process called **DNA sequencing**. The first automated procedure, called dideoxy sequencing, was developed in the 1970s by biochemist Frederick Sanger, who received the Nobel Prize in 1980 for this accomplishment. Dideoxy sequencing is still used for routine small-scale sequencing jobs.

- whole genome sequencing 21st century
- first automated DNA sequencing 1970 [Frederick Sanger]

↓ Therapeutic discovery

↓ disease pathologenesis





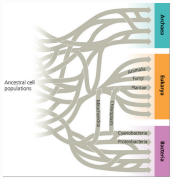
Whole genome. 3.2 b bp

↓

only 1.5 %. account for Protein synthesis (20,000 protein)

Non coding DNA "Dark Matter"

- 1.5% → Protein $ over 85 % transcribe → RNA
- 80% → Gene regulation
- Class of Non coding DNA
  1) Promoter
  2) Binding site
  3) Non coding regulatory RNA → miRNA, lncRNA
  4) Mobile genetic element (es transposon)
  5) Special structural region → telomere, Satellite DNA



SNP (single nucleotide polymorphism)

A T C G A T
A T C A A T

- Biallelic
- ทั้ง Genome % . population
- linkage disequilibrium (อยู่ใกล้กัน gene ก็ไม่ค่อยแยก)

↓ Cross look on

. little to no effect to susceptibility

CNVs

- Deletion / Duplication of 1k - M bp
- Biallelic
- สาเหตุความแตกต่าง
- คร่อม Gene coding sequence
- สร้าง Phenotypic diversity

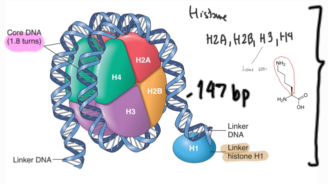
! DNA

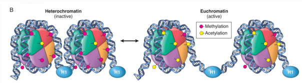
อย่างเดียวไม่สามารถอธิบายความแตกต่างของมนุษย์ได้

ต้องมองเพราะ epigenetic regulation เช่น

Monozygotic twin

Histone organization





- DNA methylation
  - Transcriptional silencing
  - Methyltransferase, Demethylating Enz

Histone Modifying Factor

└ ของ Nucleosome ปรับแต่งทางเคมีได้ > 70 ตำแหน่ง เรียกตัวแต่งปรับแต่งว่า "Mark" มีกลุ่มโปรตีน 4 กลุ่มที่ควบคุม Mark นี้

- Chromatin Remodeling Complex
  - └ ขยับ Nucleosome เพื่อปิดเปิด Promoters
- Chromatin writter
  - └ Enz ที่ติดป้าย Mark ของ Amino ของ Histone แบ่งเป็น 3 แบบ
  - 1) Histone methylation
    - └ Lysine / Arginine → ขึ้นอยู่กับตำแหน่ง if [Activate / repress]
  - 2) Histone acetylation
    - └ Lysine → activate Histone acetylase
  - 3) Histone phosphorylation
    - └ Serine Ⓟ → if [Active / Repress]
- Chromatin eraser
  - ลบ Mark เช่น Histone deacetylase [HDAC]
- Chromatin reader
  - จับ Histone ที่มี Mark
  - [Activate / Repress] — กำหนดการแสดงออกของ gene

H3k4 me3

└ Marker for RNA polymerase II → Promoter → mRNA (lncRNA, miRNA, snRNA)

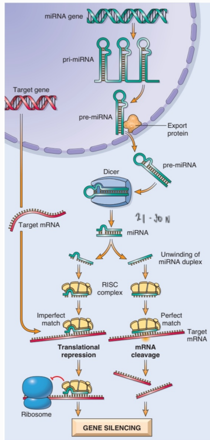
H3k9 me3 / H27 k27 me3

└ HP1 3 / Polycomb complex activation → Heterochromatin

↓

Gene silencing

miRNA (micro RNA)

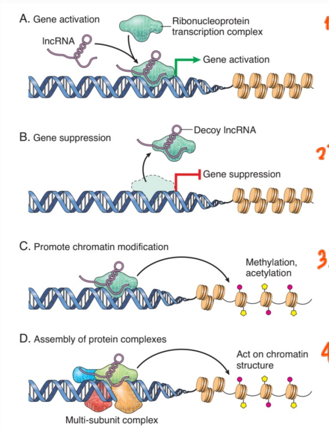


1) ถอด → pri - miRNA มี Hairpin loop
2) ออก Cytoplasm
3) Dicer ตัด Hairpin loop
4) RISC

siRNA → สร้างขึ้นในห้องทดลอง ...

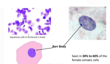
5) จับ target
   - Perfect match ↓ Cleavage
   - Imperfect match ↓ translational repression

LncRNA (Long non coding RNA)



1) Gene activation
   - └ จับ Transcription factor ↓ ไปจับที่ Promoter
2) Gene Decoy
   - └ แย่งจับ TF
3) ↑ Chromatin mod
   - └ กับ Writter / eraser ฯลฯ
4) ↑ Protein Complex
   - Scaffold for replication

ex. XIST Gene



CRISPR-Cas9+gene function determination

1) in vitro mitagenesis → knock out a phenotype

2) RNA i gene knock down

1 Cas 9 nuclease → ตัดสาย DNA ตรงที่

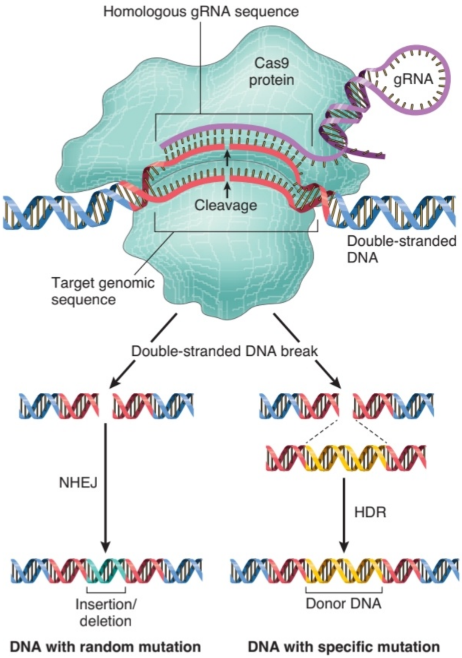
→ 2 guide rna → จำเพาะต่อ DNA ที่อยากตัด

→ 3 ปล่อยให้ cell ซ่อม

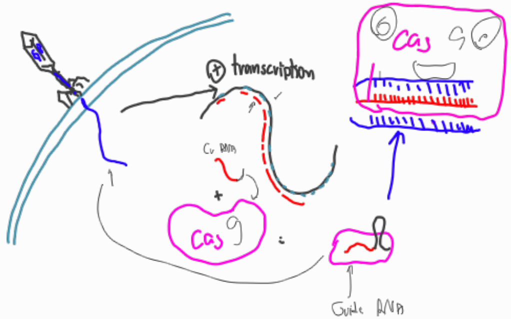
→ non Homologus end (knock out

[redacted]

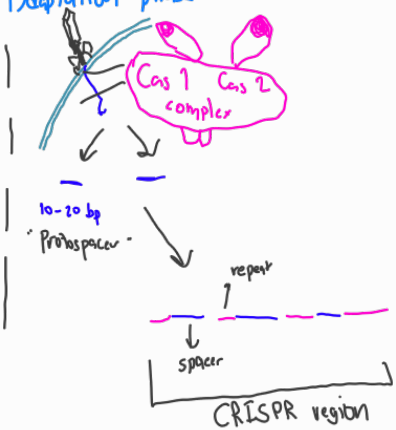
→ Homologus Direct repair



Mechanism



Adaptation phase

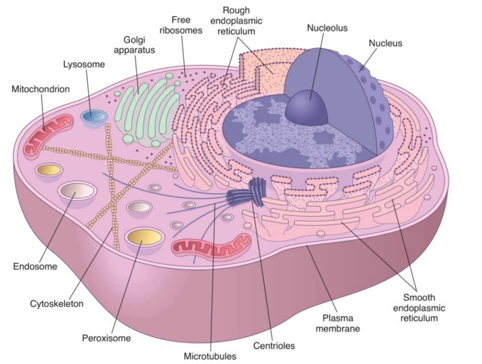


— Genome end —

Cellular Housekeeping

Relative volumes of intracellular organelles (hepatocyte)

Compartment	% total volume	number/cell	role in the cell
Cytosol	54%	1	metabolism, transport, protein translation
Mitochondria	22%	1700	energy generation, apoptosis
Rough ER	9%	1	synthesis of membrane and export protein
Smooth ER, Golgi	6%	1	protein modification, sorting, catabolism
Nucleus	6%	1	cell regulation, proliferation, DNA transcription
Endosomes	1%	200	intracellular transport and export
Lysosomes	1%	300	cellular catabolism
Peroxisomes	1%	400	very long-chain fatty acid metabolism

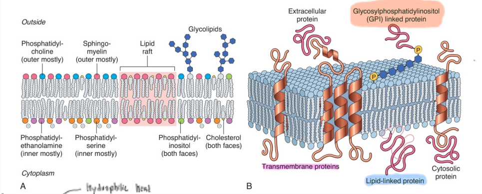


- What to expect

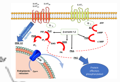
1) Plasmamembrane
   └ Asymmetry, Lipid raft, Lipid bilayer, fluid [illegible]
2) Cytoplasm
   └ Actin microfilaments, Intermidiate filament, Microtubules
3) Cell - cell Interaction
   └ Tight Junction, Desmosome, Gap Junction
4) Biosynthetic Machinery
   └ [illegible] R.E.R. [illegible], ER stress, Unfolded Protein respond [illegible] Golgi
5) Waste Disposal : Lysosome and Proteasomes
   └ Autophagy [illegible] Phagocytosis

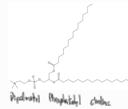
Plasmamembrane

Structure & Asymmetry

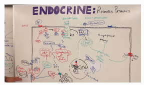


1) เป็น Phospholipid bilayer ⌐ Hydrophilic head / Hydrophobic tail [illegible]
2) Asymmetric partitioning [illegible]
   - Phosphatidylcholine, Sphingomyelin → Outer leaflet → [illegible] Surfactant ในปอด
   - Phosphatidylinositol — [illegible] Phosphate → [illegible] / Phospholipase C — [IP3, DAG] Second messenger
   - Phosphatidyl serine - [illegible] cell [illegible] Macrophage [illegible] / - Cofactor of blood Clotting in plentlet
   - Glycolipid, Ganglioside & Sphingomyelin - sugar w/ Sialic acid terminal support charge base interaction / - Inflammatory cell recruitment / - Sperm - egg fusion
3) Lipid Rafts
   └ [illegible] Sphingomyelin, cholesterol [illegible]
   └ Receptor





↳ [illegible] Pineal

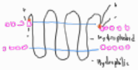


[illegible] Gq [illegible]
- Histamine (H1 receptor)
  └ Inflammation, Vasopressin, bronchodilation
- ADH (V1 receptor)
  └ vasoconstriction
- Angiotensin II (AT1 receptor)

[illegible] Phospholipase C [illegible]:
- Gq / Tyrosine receptor
- Acetylcholine (M1 [illegible] Muscarinic receptor)
- Nore(epinephrine) (α1 - Adrenergic receptor)
- TRH
- GnRH
- Oxytocin

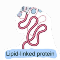
Type of membrane protein

1) Transmembrane protein (Integral)



- α-helix structure
- ปลาย [illegible] + [illegible] bind กับ - [illegible] phosphate
- เป็น channels, receptor
- [illegible] membrane [illegible]

2) Fattyacid linked protein / Prenylated (cytolic side)



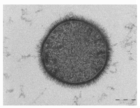
- Protein [illegible] Cytoplasm [illegible]
- [illegible] Cell [illegible] Prenyl (Protein), Farnesyl ([illegible])
- [illegible] RAS, Src-family kinases

3) GPI linked protein

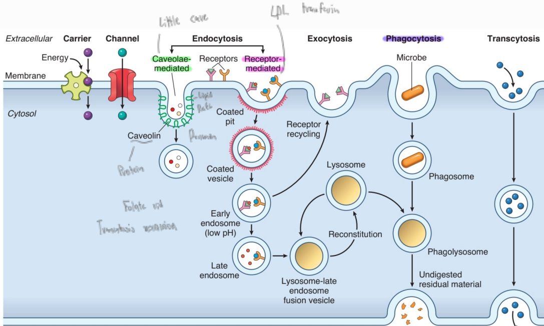
- [illegible]
- [illegible] GPI
- เป็น enzyme และ Receptor [illegible] Cell
- Alkaline phosphatase, Folate receptor

4) Non covalent assiated Protein
   └ [illegible]
   └ [illegible] Non covalent กับ integral Protein [illegible]

→ Glycocalyx



Little cave
LDL
Fe
transferrin



Caveolin
Protein
Folate [illegible]
Transcytosis [illegible]

Passive diffusion

- non polar [illegible]
- non polar [illegible] [illegible]
- polar small → [illegible] → H_2O

Channels

- [illegible] polar
- [illegible]: Voltage gate, ligand-gated, Machanically gated

Carrier

- Bind conformation change release
- [illegible]
- [illegible] Saturation point [illegible] [[ ]]
- Facilitated diffusion ! → Glut
- Active transport ↓ → Na^+/K^+ pump
  [illegible] Gradient

Vessicular transport

1) Phagocytosis
   - [illegible] Pseudopodia [illegible] Phagosome ↓ [illegible] Lysosome
   - Macrophage, neutrophils
2) Receptor-mediated endocytosis
   - [illegible] └ Transferin, LDL receptor
   1) Ligand = receptor
   2) "Clathrin coated pit"

   3)

   4)

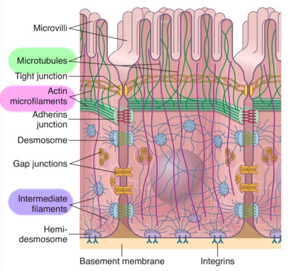
+ Exocytosis

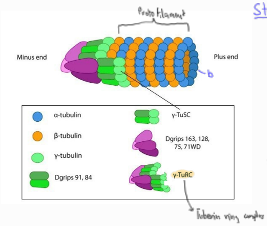
3) Caveolae mediated endocytosis

[illegible] Lipid Raft
↳ [illegible]

Cytoskeleton

microtubule ~ 25 nm





Structure

Subunit

α tubulin β tubulin

Protofilament

Ø, 25 nm

Polarity

• Plus end

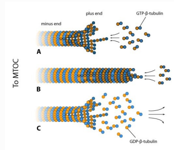
• Minus end

MTOC (microtubule organizing center)

. Centrosome

. γ tubulin Nucleation site

Dynamic Instability

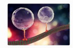


GTP cap

GTP → GTP CAP

GDP → protofilament

Intracellular transport



MTOC (−) (+ end)

kinesin

dynein

Chromosome segregation

1)

2) kinetochore

3) depolymerization

Anaphase

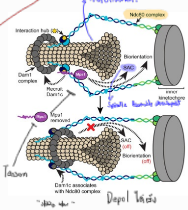
SAC

APC

↓ SAC

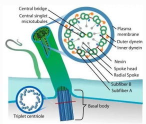
cohesin → depol

Protofilament



Depol

Motility



Central singlet microtubule

Central bridge

Doublet microtubule

Nexin

Dynein arm → A = B

Radial spoke

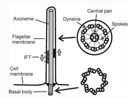
1) Dynein

2) Nexin

3) Intraflagella transport

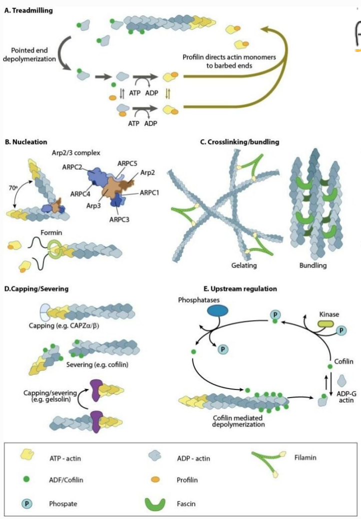
IFT up · kinesin

IFT down · dynein



Dynein Arm

Actin microfilaments 6-8 nm



· สร้างตาข่ายคุมรูปร่าง cell

· ช่วยในการเคลื่อนที่

· ทำงานร่วมกับ Myosin ในการหดตัวกล้ามเนื้อ

Actin dynamic

Cc , [ATP · actin]

1) Actin treadmilling

→ G actin มี 2 แบบ ADP / ATP → (+) barbed end

→ ATP → ADP actin (−) end

→ ADP actin [actin] Cc (−) end

• ADP ATP Profilin

2) Nucleation

1) Arp2/3 complex

→ (−) end 70°

2) Formin

• G actin F actin (filopodia , stress fiber)

3) Crosslinking

1) Gelating

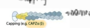
filamin

2) Bundling

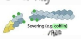
Fascin

4) Capping and Severing

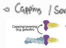
◦ Capping



◦ Severing



◦ Capping / Severing

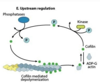


· (+) end

· Ca²⁺

5) Upstream regulation

→ actin kinase, Phosphatase



1) Cofilin Phosphate

ADP actin Depolymerize

2) kinase Cofilin Inactive

3) Phosphatase Cofilin Active

Intermediate filament (10 nm)

· Tensile strength | Cyto

· Tissue specific marker

Class	ชื่อโปรตีน IF	ตำแหน่งเนื้อเยื่อเป้าหมาย	พยาธิวิทยาและโรคทางคลินิกที่เกี่ยวข้อง
Class I & II	Acidic & Basic **Keratins**	เซลล์บุผิว (Epithelial cells, Keratinocytes)	**Epidermolysis Bullosa Simplex (EBS)** ผิวหนังพองตุ่มน้ำง่ายจากแผลถลอกเล็กน้อย
Class III	**Vimentin**	เซลล์กำเนิดมีเซนไคม์ (Fibroblast, Endothelium)	มาร์กเกอร์ตรวจทางพยาธิวิทยาสำหรับ Sarcoma
Class III	**Desmin**	เซลล์กล้ามเนื้อทุกชนิด (ยึด Z-disc)	Desmin-related Myopathy & Familial Dilated Cardiomyopathy
Class III	**GFAP**	แอสโทรไซต์และกลีอัลเซลล์ในสมอง	มาร์กเกอร์ตรวจ Astrocytoma / Glioblastoma; Alexander Disease
Class IV	**Neurofilaments (NF-L/M/H)**	เซลล์ประสาท (Axon & Soma)	**Amyotrophic Lateral Sclerosis (ALS)** การสะสมโปรตีนทำลายเซลล์ประสาทสั่งการ
Class V	**Nuclear Lamins (Lamin A/B/C)**	เยื่อหุ้มนิวเคลียสชั้นใน (Nuclear Lamina)	**Hutchinson-Gilford Progeria Syndrome** (กลายพันธุ์สร้าง Progerin แก่ชราก่อนวัย)

Carcinoma

Sarcoma

Glioma

Nestin → Neural stem cell

Cell

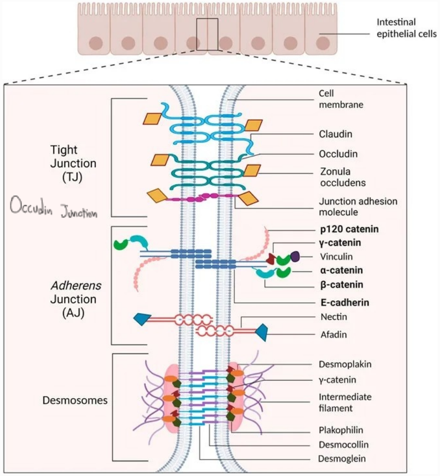
Immunohistochemistry

keratin → epithelial cell

Carcinoma

Cell to cell interaction

line of thought
→ what's occludin
→ Desmosome ? → Pic?


Intestinal epithelial cells
Cell membrane
Claudin
Occludin
Zonula occludens
Junction adhesion molecule
Tight Junction (TJ)
Occudin Junction
p120 catenin
γ-catenin
Vinculin
α-catenin
β-catenin
E-cadherin
Nectin
Afadin
Adherens Junction (AJ)
Desmoplakin
γ-catenin
Intermediate filament
Plakophilin
Desmocollin
Desmoglein
Desmosomes

1) Tight junction (Occuding Junction)

- ป้องกัน Paracellular Movement
- แบ่งฝั่ง Apical / Basolateral
- Occludin & Claudin
- แยกออก แล้ว เชื่อมใหม่ได้ ตอนเม็ดเลือดขาว แทรกต่ำแหน่งเนื้อเยื่อ

2) Gap / Communicating Junction

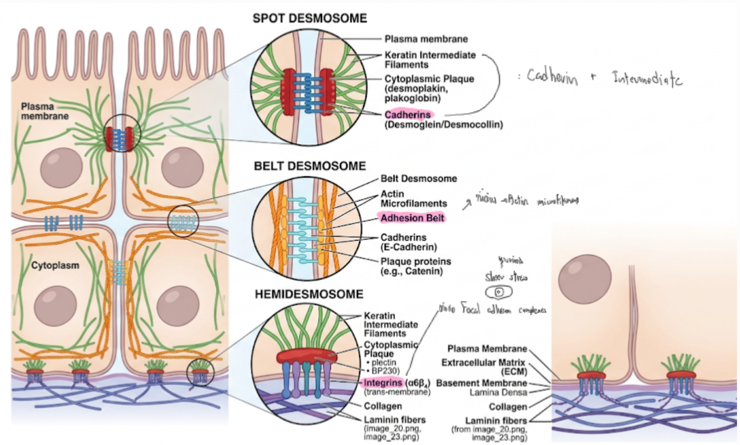
- ส่ง สัญญาณ เคมีหรือไฟฟ้า Cell 2 cell
- เกิดจาก

↓ รูใหญ่มากเลยให้ Ion, น้ำ, Amino ผ่านได้
↳ ปิดลงเมื่อ PH ลดลง ∴ เลือดเป็นกรด ← เพราะ: ป้องกัน เซลล์ที่เป็นกรดมาก ส่งต่อ H^+

- เช่น Gap Junction ของ Cardiac myocyte ทำให้ Ca^{2+} เคลื่อน Cell 2 cell

3) Desmosome (Anchoring Junction)

- ช่วยกระจายแรงกลไปทั่ว Cell ไม่ให้ฉีกขาดเวลาโดนดึง


SPOT DESMOSOME
Plasma membrane
Keratin Intermediate Filaments
Cytoplasmic Plaque (desmoplakin, plakoglobin)
Cadherins (Desmoglein/Desmocollin)
: Cadherin + Intermediate
BELT DESMOSOME
Belt Desmosome
Actin Microfilaments
Adhesion Belt
Cadherins (E-Cadherin)
Plaque proteins (e.g., Catenin)
HEMIDESMOSOME
Keratin Intermediate Filaments
Cytoplasmic Plaque
• plectin
• BP230
Integrins (α6β4) (trans-membrane)
Collagen
Laminin fibers
(image_20.png, image_23.png)
Focal adhesion complexes
Shear stress
Plasma Membrane
Extracellular Matrix (ECM)
Basement Membrane
Lamina Densa
Collagen
Laminin fibers
(from image_20.png, image_23.png)
Plasma membrane
Cytoplasm

Pemphigus vulgaris
(Pemphix → ตุ่มน้ำ; Vulgus → common ∴ โรคตุ่มน้ำที่พบได้ทั่วไป)
→ ภูมิต่อต้านตัวเองร่างกายสร้าง Antibody : Cadherin

Non Desmosome

Biosynthetic machinery

- *Rough endoplasmic reticulum (RER):* Membrane-bound ribosomes on the cytosolic face of RER translate mRNA into proteins that are extruded into the ER lumen or become integrated into the ER membrane. This process is directed by specific signal sequences on the N-termini of nascent proteins; synthesis of proteins with signal peptides is initiated on free ribosomes, but the complex then becomes attached to the ER membrane, and the protein is inserted into or passed across the ER membrane as it is translated. For proteins lacking a signal sequence, translation remains on free ribosomes in the cytosol, forming polyribosomes as multiple ribosomes attach to the mRNA; such transcribed proteins remain within the cytoplasm.

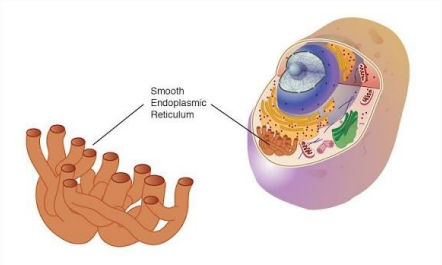
  Proteins inserted into the ER fold into their active conformation and can form polypeptide complexes (oligomerize); in addition, disulfide bonds are formed, and N-linked oligosaccharides (sugar moieties attached to asparagine residues) are added. Chaperone molecules assist in folding and retaining proteins in the ER until the modifications are complete and the proper conformation is achieved. If a protein fails to appropriately fold or oligomerize, it is retained and degraded within the ER. A good example of this is the most common mutation of the CFTR protein in cystic fibrosis. In mutant CFTR, a codon deletion leads to the absence of a single amino acid (Phe508) which results in its misfolding, ER retention and catabolism and therefore reduced surface expression. Moreover, excess accumulation of misfolded proteins—exceeding the capacity of the ER to edit and degrade them—leads to the *ER stress response* (also called the *unfolded protein response [UPR]*) (Fig. 1.10B). Detection of excess abnormally folded proteins leads to a reduction in protein synthesis overall with a concurrent increase in chaperone proteins; failure to correct the overload can trigger cell death through *apoptosis* (Chapter 2).

- *Golgi apparatus:* From the RER, proteins and lipids destined for other organelles or extracellular export are shuttled into the Golgi apparatus. This consists of stacked cisternae that progressively modify proteins in an orderly fashion from *cis* (near the ER) to *trans* (near the plasma membrane). Cisternal progression, i.e., movement of *cis*-face cisternae to the *trans* aspect of the Golgi, akin to steps on an escalator, allows sequential processing of newly synthesized proteins and can be facilitated by small membrane-bound vesicles. Similar vesicles shuttle Golgi-resident enzymes from *trans* to *cis* in order to maintain the different cisternal contents along this assembly line. As cisternae mature, the N-linked oligosaccharides originally added in the ER are pruned and extended in a stepwise fashion; O-linked oligosaccharides (sugar moieties linked to serine or threonine) are also appended. Some of this glycosylation is important in sorting molecules to lysosomes (via the mannose-6-phosphate receptor); other glycosylation adducts are important for cell-cell or cell-matrix interactions or for clearing senescent cells (e.g., platelets and erythrocytes). In the *trans Golgi network*, proteins and lipids are sorted and dispatched to other organelles, plasma membrane, or secretory vesicles. The Golgi complex is especially prominent in cells specialized for secretion, including goblet cells of the intestinal or bronchial epithelium, which secrete large amounts of polysaccharide-rich mucus. In plasma cells that secrete antibodies, the Golgi can be recognized as a perinuclear hoff on simple hematoxylin and eosin stains (Chapter 6).

SER

- *Smooth endoplasmic reticulum (SER)*: In most cells, the SER is relatively sparse and primarily exists as the transition zone extending from RER to generate transport vesicles that carry newly synthesized proteins to the Golgi apparatus. The SER may, however, be particularly conspicuous in cells that synthesize steroid hormones (e.g., within the gonads or adrenals) or that catabolize lipid-soluble molecules (e.g., hepatocytes). Indeed, repeated exposure to compounds that are metabolized by the SER (e.g., phenobarbital, which is catabolized by the cytochrome P-450 system) can lead to SER hyperplasia. The SER is also responsible for sequestering intracellular calcium, which, when released into the cytosol, can mediate a number of responses to extracellular signals (including apoptotic cell death). In muscle cells, specialized SER called sarcoplasmic reticulum is responsible for the cyclic release and sequestration of calcium ions that regulate muscle contraction and relaxation, respectively.

Phenobarbital → hepatomegaly



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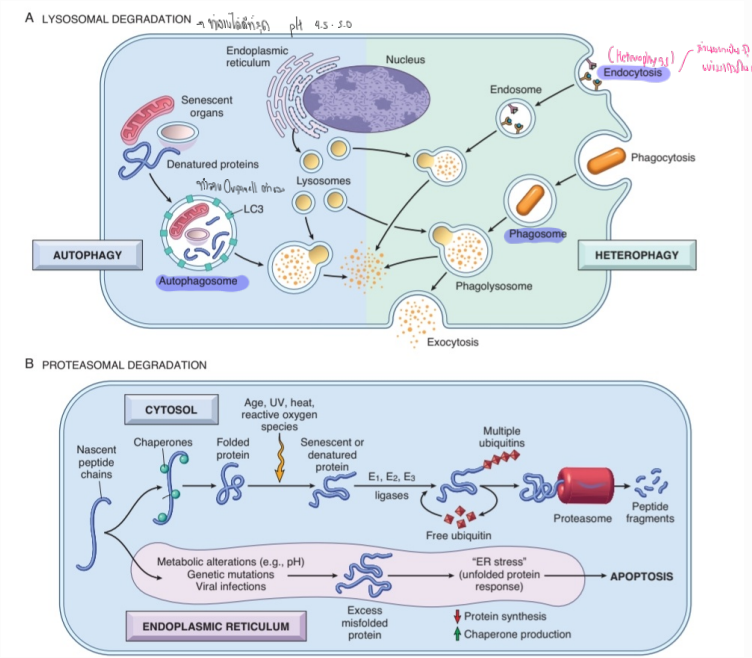
waste disposal



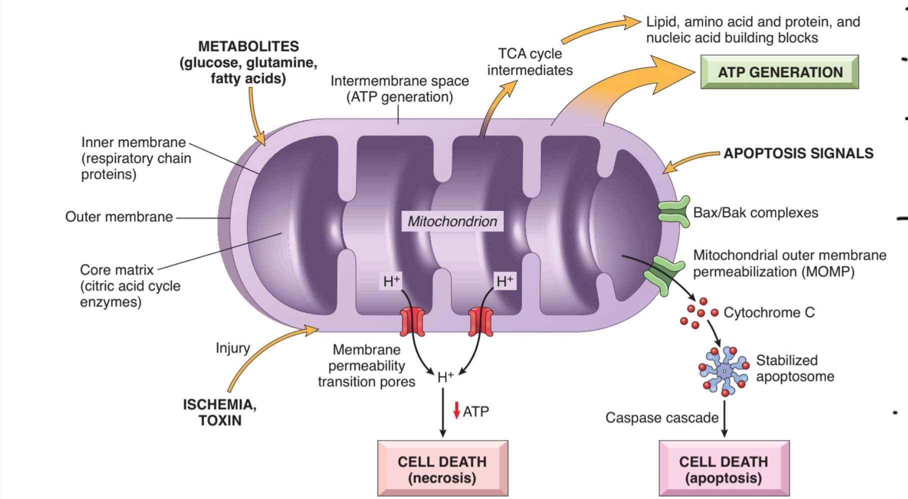
1) miss fold

2) Ubiquitin มาแปะ

3) ส่งเข้า Proteasome ย่อยด้วย เป็น กรดอะมิโน เรียงกลับ ไปทำใหม่

ถ้าเยอะเกินกว่าเกิด ER stress → + chaperone
→ ↓ Protein synthesis
↳ Apoptosis

Mitochondria



METABOLITES (glucose, glutamine, fatty acids)
Intermembrane space (ATP generation)
TCA cycle intermediates
Lipid, amino acid and protein, and nucleic acid building blocks
ATP GENERATION
Inner membrane (respiratory chain proteins)
Outer membrane
Mitochondrion
Core matrix (citric acid cycle enzymes)
APOPTOSIS SIGNALS
Bax/Bak complexes
Mitochondrial outer membrane permeabilization (MOMP)
Cytochrome C
Stabilized apoptosome
Caspase cascade
H+
H+
H+
↓ATP
Injury
Membrane permeability transition pores
ISCHEMIA, TOXIN
CELL DEATH (necrosis)
CELL DEATH (apoptosis)

- mDNA เป็นวงกลม (มาจากแม่ทั้งหมด)
- translation เริ่มด้วย N-formylmethionine
- Fission Fusion บ่อย
- อายุไข 10 วัน

UCP-1 / Thermogenin

พบใน Brown fat → การไหลของโปรตอนไม่สร้าง ATP
↓
ความร้อน

- เกิด ROS เสมอใน CR
  - └→ ถ้าเป็น Hypoxia จะยิ่งมาก
    - └→ Oxidative stress

- 36-38 ATP per glucose แต่ ได้แค่ CO_2, H_2O เป็นของเหลือใน Cell ที่แบ่ง Cell ไวจึงเกิด Warburg effect

↓

ใช้แค่ Glycolysis

Cell Death control

- Necrosis
  - └ Ischemia, สารพิษ → MPT pore จะเปิด → เซลล์บวมแตก
  - ↑ No ATP
- Apoptosis
  - └ รูรั่ว MOMP (M. outer membrane permeabilization) (ผ่าน Bax/Bak (pro apoptotic membrane)) → ปล่อย Cytochrome c → Apoptosome → Pro caspase 9 → Caspase 3, 6

Cellular activation

Cell signaling

แบ่งตามระยะทาง

- paracrine ใกล้
- Autocrine
- Synaptic
- Endocrine

ตัวรับสัญญาณ

- Intracellular
  - ↳ Vit D . NO . steroid
- Cell surface

Transcription factor (TFs)

มี:

- DNA binding domain
- Protein - Protein - interaction domain
  - เช่น Histon Acetyl tranferase

Signal tranduction pathway

- Receptor Tyrosine kinase

dimerization ของ Her 2

⊢ Herceptin (Trastuzumab)

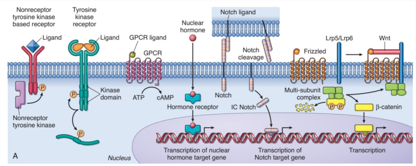
↓

EGF receptor

ERBB2

RAS → RAS GTP ↓ MAPK ↓ TF (myc) → มะเร็ง

} เกิดจาก Tyrosine kinase แบบ: RAs



- G - Protein Couple receptor

GDP → GTP → 2nd messenger

- *Nuclear receptors*. Lipid-soluble ligands can diffuse into cells where they interact with intracellular proteins to form a receptor-ligand complex that directly binds to nuclear DNA; the results can be either activation or repression of gene transcription.
- *Other classes of receptors*. Other receptors—originally recognized as important for embryonic development and cell fate determination—are now recognized to participate in the functioning of mature cells, particularly within the immune system. Rather than enzymatic activity, these pathways rely on protein-protein interactions to transduce signals.
  - Receptor proteins of the *Notch* family fall in this category; ligand binding to Notch receptors leads to proteolytic cleavage of the receptor and subsequent nuclear translocation of the cytoplasmic piece (intracellular Notch) to form a transcription complex.
  - *Wnt* protein ligands can also influence cell development through a canonical pathway involving transmembrane *Frizzled* family receptors, a distinct set of GPCRs that regulate intracellular levels of *β-catenin*. Normally, β-catenin is continuously targeted for ubiquitin-directed proteasomal degradation. However, Wnt binding to frizzled (and other coreceptors) recruits yet another intracellular protein *(Disheveled)* that leads to disruption of the degradation-targeting complex. This stabilizes β-catenin, allowing it to translocate to the nucleus and form a transcription complex.

Modular signaling

Signal tranduction pathway ไม่ได้เริ่มตามลำดับ หรือจาก ลงไป

1) Adaptor Protein
   - ↳ link enzyme
   - ↳ ① complex formation
   - ↳ เกิด Protein : Protein complex เช่น SH2 SH3 (tyrosine, proline)

2) Node
   - ↳ จุด Protein ร่วมกัน
   - ↳ Hub เชื่อมต่อ

Growth factor

- Tissue repair
- Proto oncogenes
  - gain of function
- Therapeutic target

EGFR1 → ผิวหนังบวม

HER 2 (ERBB2) → มะเร็งเต้านม

epithelial + fibroblast ของแผล

Table 1.1 Growth Factors Involved in Regeneration and Repair

Growth Factor	Sources	Functions
Epidermal growth factor (EGF)	Activated macrophages, salivary glands, keratinocytes, many other cells	Mitogenic for many cell types; stimulates epithelial cell migration; stimulates formation of granulation tissue
Transforming growth factor-α (TGF-α)	Activated macrophages, keratinocytes, many other cells	Stimulates proliferation of hepatocytes and many other epithelial cells
Hepatocyte growth factor (HGF) (scatter factor)	Fibroblasts, stromal cells in the liver, endothelial cells	Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility → สร้าง Cell ขึ้น
Vascular endothelial growth factor (VEGF)	Mesenchymal cells	Stimulates proliferation of endothelial cells; increases vascular permeability
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial cells, and other cells; stimulates ECM protein synthesis → ดึงดูด MΦ และ fibroblast
Fibroblast growth factors (FGFs) including acidic (FGF-1) and basic (FGF-2)	Macrophages, mast cells, endothelial cells, many other cell types	Chemotactic and mitogenic for fibroblasts; stimulates angiogenesis and ECM protein synthesis
Transforming growth factor-β (TGF-β)	Platelets, T lymphocytes, macrophages, endothelial cells, epithelial cells, smooth muscle cells, fibroblasts	Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation → (+) collagen (-) Svabe → Scar formation
Keratinocyte growth factor (KGF) (i.e., FGF-7)	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

ECM, Extracellular matrix.