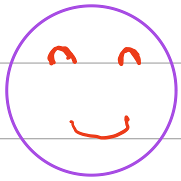
Apoptosis → زمة محترم



→ بموت بكيفني — بوضي أنظر → Physiological / → Pathological } → بدون أي Inflammation

ليش؟ لأنه ال Plasma membrane remains intact

ما بتكسر زي ال Necrosis

Physiological →

1. During Embryogenesis → Implantation / Involution / Organogenesis

Ex. separation of Fingers [ ] → [ ]

2. In adult multicellular organisms → [Tadpole → Frog]
ضفدع بـ ذيل → ضفدع طبيعي

بالأصابع ← لو ما صار انفصال بشكل كامل حيكون في أصابع ماسكين

ببعض ← Syndactyly ف بصير عندي أقل من (5) أصابع (Oligodactyly)

← لو صار انفصال بشكل زيادة ← أكثر من (5) أصابع (Polydactyly)

Apoptosis حبوب عشان يصير فعّل ال انزيم Caspase

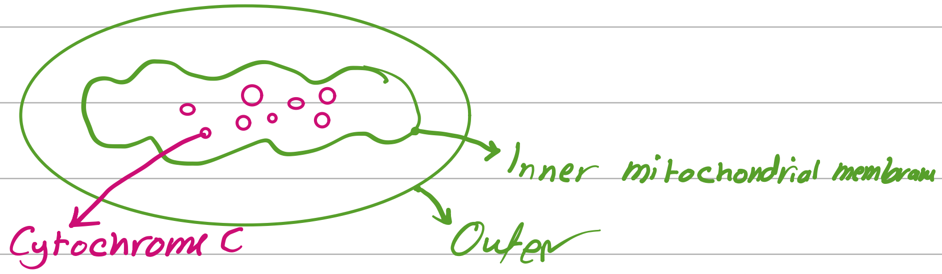
تمام؟

والفكرة بأنه عندك طريقتين لتفعيله وهي

Intrinsic (mitochondria)

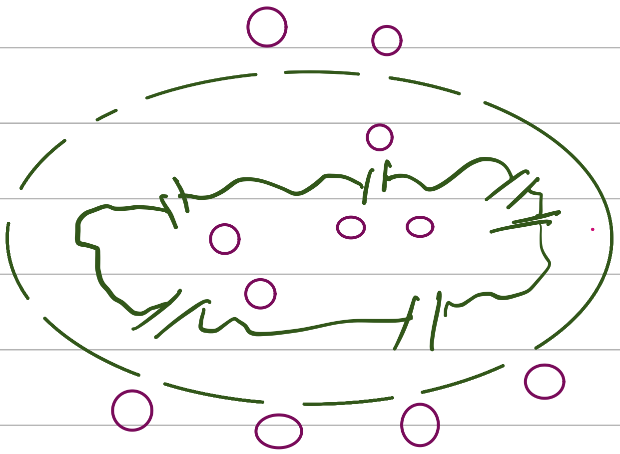
Extrinsic وثانية

Mitochondrial - Intrinsic



هذا بالوضع الطبيعي بدون Apoptosis

- In most physiologic and pathologic conditions
- It's all about Cytochrome C



→ ↑ Mitochondrial permeability

→ Leakage of cytochrome C

→ Triggers Caspase 9 ← تسعة اوكيه؟

→ Apoptosis starts

ليش بتزيد ال Permeability طيب؟

لأنه عندنا عيلة بروتين BCL_2 فيها >20 فرد و بتتحكم بنفاذية غشاء الميتوكندريا!!

إما

بتمنع النفاذية ونسميهم Antiapoptotic ← → بتزيد النفاذية و تحفز ال Apoptosis ونسميهم Proapoptotic

Proapoptotic:

* BaX * Bak

يحفّزهم بروتين BH3

Antiapoptotic:

* BCL-2 * BCL-XL

بطلعوا استجابة ل

1. Growth factors
2. Survival signals

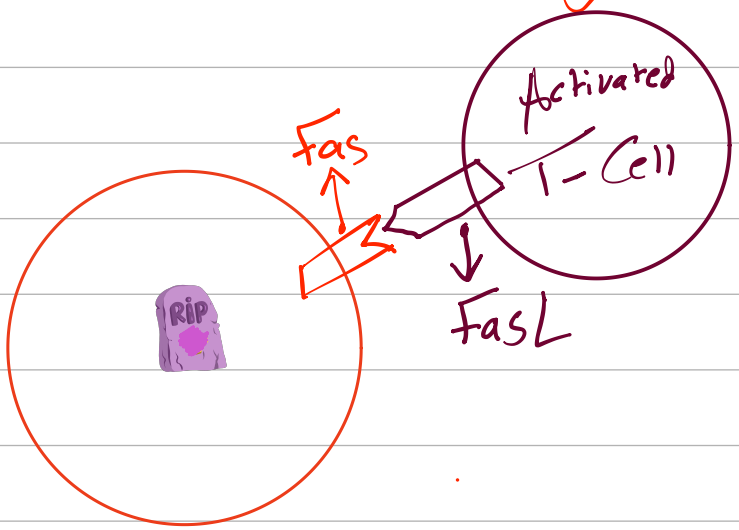
- They Dimerize
  → Inert into mito membrane
  → Form channels
  → Cytochrome C يخرج من الميتوكوندريا للسيتوبلازم

- Maintain the Integrity of mitochondrial membrane
  → Holding Proapototic in check.

- BH_3 → sensor Protein
  - Activated when
  1. Cells are deprived of growth factors & survival signals
  2. Cells are exposed to agents that damage the DNA
  3. ↑ Misfolded Proteins inside the cell

Extrinsic – Death Receptor pathway

Tumor necrosis factor (TNF) Receptor family



* Mechanism → 1. T-cell Recognizes the cells expressing Fas
2. Fas & FasL are crossed linked
3. The cross linking activates Caspase 8
لـ ثمانية مش تسعة، اوكيه

* Proapoptotic death Receptors:-
1. Type (1) TNF
2. Fas (CD95)

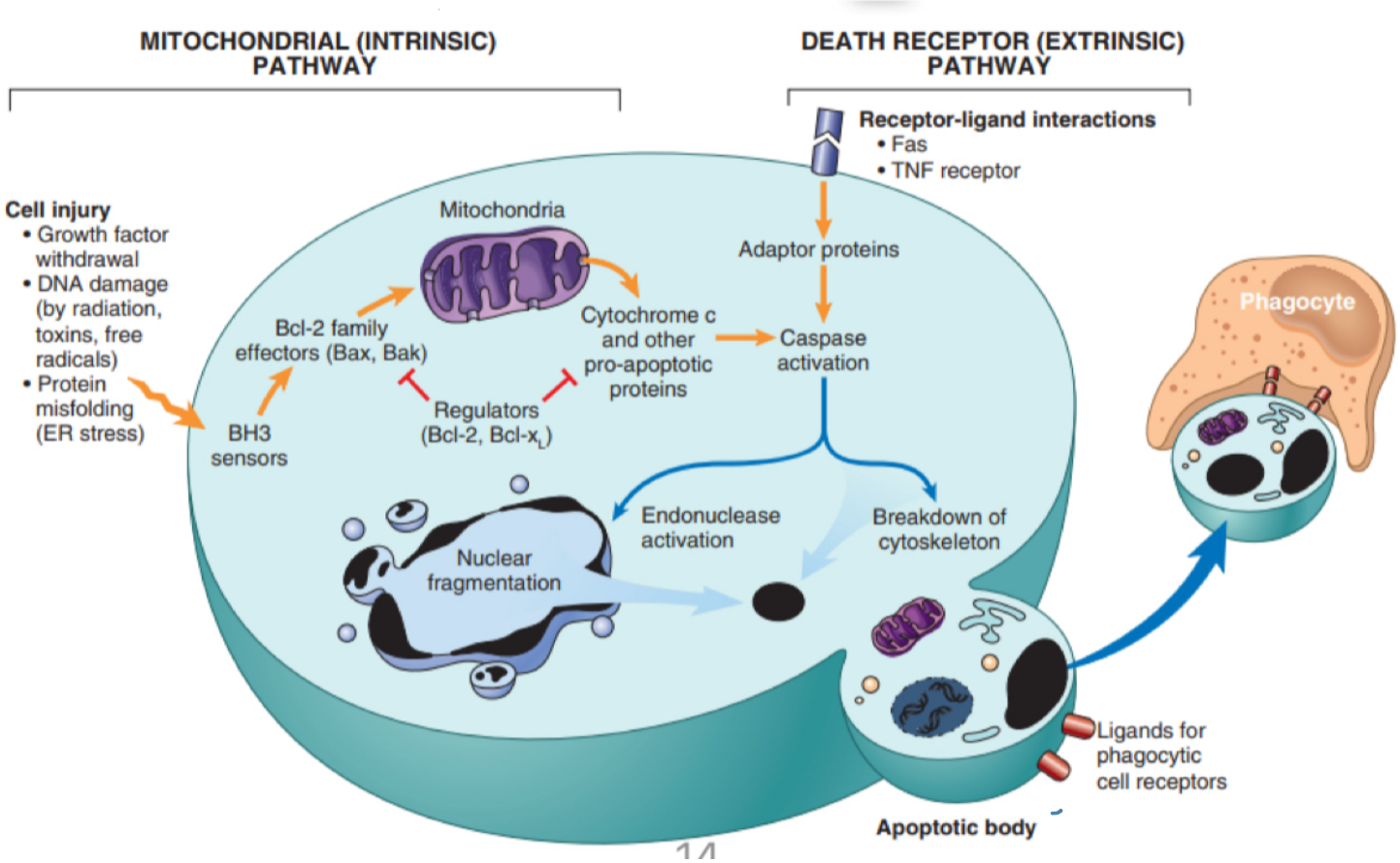
* Cytoplasmic region → Death domain

- Either caspase 8/9 → it cleaves and activates other caspases → Activation of enzymes that degrade DNA and nucleus

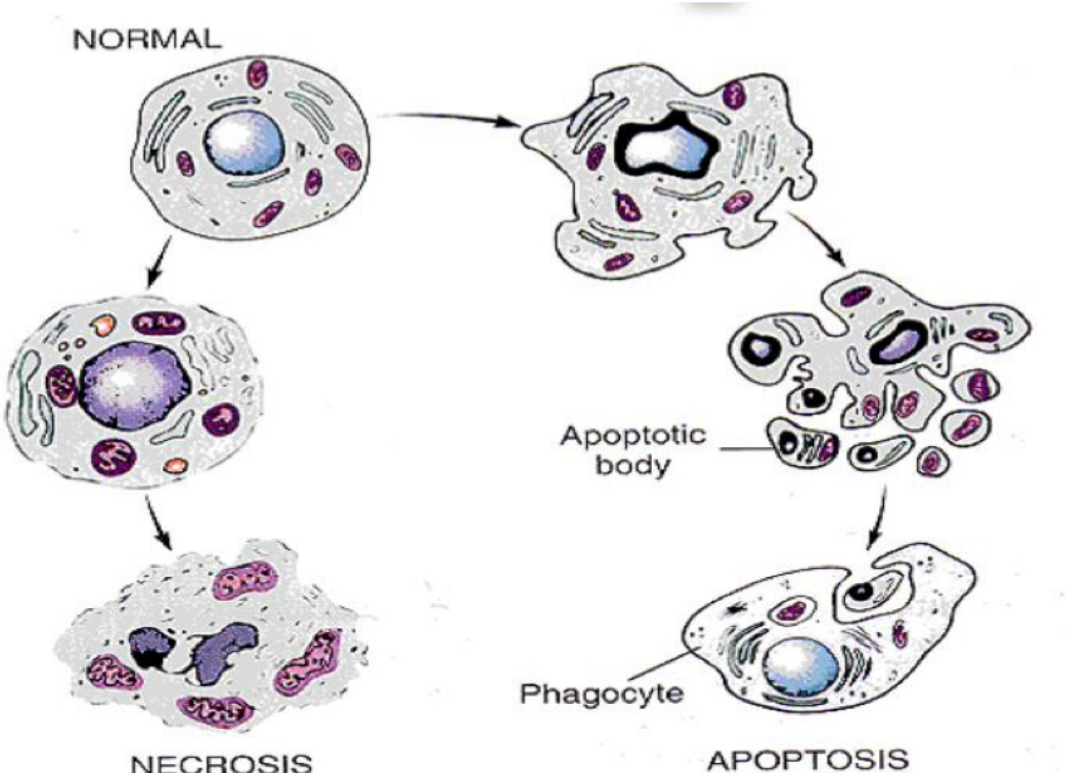
Clearnce by phagocytes?

Phosphotidyserine out

Soluble factors



Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-sized fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA and protein damage



Condition	Mechanism of Apoptosis
Physiologic	
During embryogenesis	Loss of growth factor signaling (presumed mechanism)
Turnover of proliferative tissues (e.g., intestinal epithelium, lymphocytes in bone marrow, and thymus)	Loss of growth factor signaling (presumed mechanism)
Involution of hormone-dependent tissues (e.g., endometrium)	Decreased hormone levels lead to reduced survival signals
Decline of leukocyte numbers at the end of immune and inflammatory responses	Loss of survival signals as stimulus for leukocyte activation is eliminated
Elimination of potentially harmful self-reactive lymphocytes	Strong recognition of self antigens induces apoptosis by both the mitochondrial and death receptor pathways

Pathologic	
DNA damage	Activation of proapoptotic proteins by BH3-only sensors
Accumulation of misfolded proteins	Activation of proapoptotic proteins by BH3-only sensors, possibly direct activation of caspases
Infections, especially certain viral infections	Activation of the mitochondrial pathway by viral proteins Killing of infected cells by cytotoxic T lymphocytes, which activate caspases

Necroptosis

- Features of **both** necrosis and apoptosis.
- initiated by engagement of TNF receptors → receptor interacting protein (RIP) kinases are activated→ initiating dissolution of the cell like necrosis

Pyroptosis

- activation of a cytosolic danger-sensing protein complex called the **inflammasome.**
- Greek, *pyro* = fire
- Used by infectious microbes
- Fever + inflammation + apoptosis

Autophagy

- **("self-eating")**
- **refers to lysosomal digestion of the cell's own components.**
- Nutrient deprivation
- Survival pathway