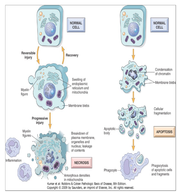
Apoptosis

the cell die in programmed way that does nit cause inflammatory response

What happen in apoptosis?
- Shrinkage of the cell
- Fragmentation
  - The whole cell turn into membrane bound structures (vesicles) because of that the cell does not go on inflammation all the enzymes and cytokinase are still in the plasma do not go to the surrounding environment to recruit inflammation
- Phagocyte engulf the apoptotic body and get rid of them

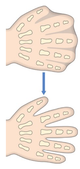


Feature	necrosis	Apoptosis
Cell size	Enlarged(swelling)	Reduced(shrinkage)
Nucleus	Pyknosis, Karyorrhexis, karyolysis	Fragmentation into nucleosome- size fragments
Plasma membrane	**Disrupted** *Hyper trophy	**Intact**, altered structure, especially orientation of lipids
Cellular content	Enzymatic digestion, may leak out of cell	Intact, may be released in apoptotic bodies.
Adjacent inflammation	**Frequent**	**No**
Physiologic or pathologic role	Invariably pathologic	Often physiologic

- The plasma membrane of the apoptotic cells remain intact
- Each fragment of the cell contain nuclear & mitochondrial structure to stay alive for short time until its being engulfed by phagocyte

Apoptosis in Physiologic Situations

- **Normal phenomenon** to **eliminate cells that are no longer needed** and to maintain a constant number of cells of various types in tissues:
- The programmed destruction of cells **during embryogenesis**
- **Involution** of **hormone-dependent tissues :** regression of the lactating breast after weaning
- Cell loss in proliferating cell populations: intestinal crypt epithelia, to maintain a constant number
  - Proliferating cells go under apoptosis to maintain normal cell number in tissues(شرح)



- Elimination of **cells that have served their useful purpose**: neutrophils
- Elimination of **potentially harmful self-reactive lymphocytes**.
- **Cell death induced by cytotoxic T lymphocytes**, to kill virus-infected and neoplastic cells.
  - Cells affected with virus under go apoptosis to prevent the replication of the virus

If reactive lymphocytes did not under go apoptosis it will cause auto immune disease

- Apoptosis eliminates cells that are genetically altered or injured beyond repair:
- **DNA damage**: **Radiation, cytotoxic anticancer drugs, extremes of temperature, and even hypoxia**
  - Apoptosis if the insult is mild, but larger doses of the same stimuli result in necrosis.
- Accumulation of **misfolded proteins**.

Mechanisms of Apoptosis

We have 2 pathways to induce apoptosis
- Intrinsic pathway
  - start from inside the mitochondria
- Extrinsic pathway
  - Signals coming to the cell from outside and bind to certain receptor on the outer surface

eliciting factor : العامل المحرز

Intrinsic pathway

- Eliciting factor for initiating this pathway is DNA damage
- ATM is protein when it is activated it bind to P53 (one of the tumour suppressor genes) this will activate group of protein called BAX *there is another group called BAK have the same function.
  - Make pores in the mitochondria release Ca+2 and some radicals(H+) but the most important is Cytochrome c
- Cytochrome c bind with APAF molecule then bind with procaspase 9 converting it to active form caspase 9
- Caspase 9 cleave the protien

P53: is protein function as tumour suppressor

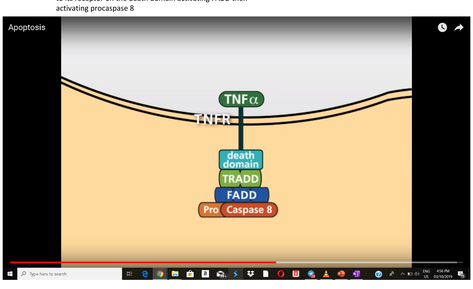
P.S: apoptosis is mediated through caspases they are different types and given numbers

Caspases have to be activated . Inactive form is procaspase .

Caspase cascade : one of the caspases activate the same type or other types of caspases

Extrinsic pathway

- Signals come from outside from lymphocyte normally like (Tumour necrosis factor TNFR) TNFa bind to to its receptor on the surface activate death domain protein / TRADD bind to its receptor on the death domain activating FADD then activating procaspase 8



Caspase 3
- cleave the DNase inhibitor activating Dnase enzyme
- make cleavage at certain site of the DNA
- Cleave cytoskeleton structure

We have resident macrophages in tissue ready to engulf cells undergo apoptosis

The Mitochondrial (Intrinsic) Pathway

- Responsible for apoptosis **in most situations**.
- Mitochondria contain several proteins that are capable of inducing apoptosis: **cytochrome c** and other proteins
- The permeability of mitochondria, is controlled by **Bcl-2** family
- Sensors are activated:
  - When cells are deprived of growth factors and other survival signals, or are exposed to agents that damage DNA, or accumulate unacceptable amounts of misfolded proteins.
- The Sensors:
  - Activate **two pro-apoptotic members of the family called Bax and Bak**, which dimerize, insert into the mitochondrial membrane, and form channels through which cytochrome c and other proteins escape into the cytosol.
  - Inhibit the **anti-apoptotic molecules Bcl-2 and Bcl-x**
- Cytochrome c activates caspase-9
- Other proteins that leak out of mitochondria block the activities of caspase antagonists

BCL2 : primarly anti apoptotic

Bax & Bak make pores in the mitochondria