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PATHOLOGY

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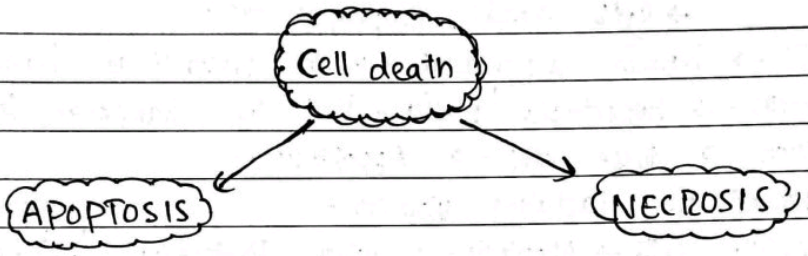
APOPTOSIS

* Literally → leaves falling from a tree.
* Programmed cell death ⟶ Apoptosis.



* Sucidal death of cell.
* Usually one cell is involved.
* May be due to external or internal factors.
* Cells → shrinks usually.
* Cells → membranes → disrupted → enzyme/lysosome → affect nearby healthy cells → Inflammation → → so necrotic Tissue have Inflammatory Zone Around it.

* Mass Murder of Cells.
* Group of cell/Tissue → involved.
* Usually due to external factors.
* cells → swells up.

* Apoptotic cells → into Apoptotic granules → express "Opsonins" on its Surface → phapocytozed by macrophages → → Sorrounding cells → not disrupted.

* Apoptosis → may be physiological or pathological.

* Necrosis → Alway → Pathological.

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WHY APOPTOSIS OCCURS?/ Significance:

Physiological

* Embryological → Different structure → undergoes apoptosis → to achieve adult functional shape.
  → e.g: hands, esophagus etc.
* Some cells → harmone dependant → in presence of harmones → → these cells → hypertrophy / plasia - But if harmonal support → → withdrawn → these cells → Appoptosis.
  → e.g: → Breasts of lactating women.
  → Endometrial cells → Apoptosis → when Progesterone ↓↓↓ → Before menstrual Bleeding
  → Prostatic Atrophy after Testis castration.
* Deletion of Some Immune cells.
  → e.g: Auto-Reactive T-cells deletion → in Thymus.
* Bone Marrow + GIT + Skin → cells → Continuously Proliferating → Appoptosis as well → so cell count → balanced.

Pathological

* When Genetic material of the cell → So badly damaged that it cannot be repaired → the apoptosis should occur.
* In Severe Thermal injury or hypoxia → Apoptosis.
* Hepatocytes → loaded wd virus → In hepatitis → Appoptosis.

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* Endoplasmic Ret- stress → loaded wd too much un-folded protiens → E.R stress → Sucidal death.

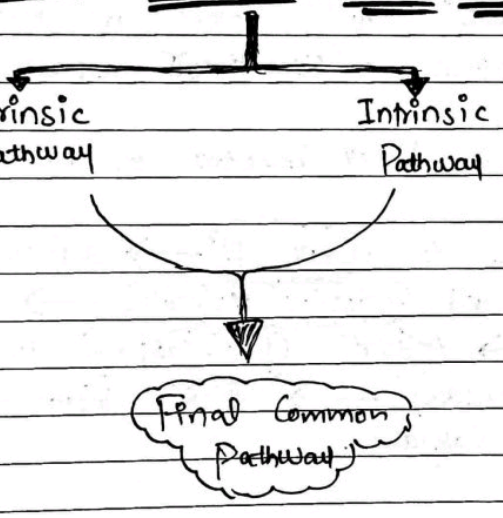
* Duct of glandular structure → blocked → Appoptosis.

* Mutation in genes → too much → P53 gene → Activated → → Force the cell to Commit Suicide.

P53

→ Guardian of Genome.
→ Stops cell cycle & activate repairing enzymes during mutation.
→ If no repair → then forces the cell → to Apoptosis.
→ In People who have difficiency of P53 → → chances of Cancer → ↑↑

Molecular Mechanism OF APoptosis :



Extrinsic Pathway :

→ Depends upon special receptors on cell membrane → → called → "Death Receptors".
e.g: FAS molecules or TNF- Receptor.

"Death Inducers" (FAS-Ligand) binds wd Death Receptors.

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→ Death Receptors have intracellular "Death Domain" into w/c "Adoptor Molecules" binds w/c also have "Death domain".

→ Now cell have proteoletic Enzymes (CASPASES) w/c have cystiene containg in their Active pockets and have cutting activity at Aspartate specific.

→ Initially they are inactive → Pro-Enzyme (Pro-CASPASES) → then Activated.

→ Some caspases are activated at inital phase of Apoptosis → "Initiator Caspases" while other are activated at advance phase of Apoptosis → "Executioner Caspases."

→ Almost All the cells have Death Receptors on their Surface.

→ First (Death Inducers) binds to (Death R) → Activate its Death Domain → Binds wd (Adoptor Molecules) → → Activate it Death Domain → Activate (Pro-Caspase) to Active (Caspases) (Initiator Caspase) → then initator Casp. → → activate Executioner Caspases.

→ Then Executioner Caspase causes proteolysis of:
* Cytoskeleton of cytoplasm-
* Scaffolding Protien for Nucleus-
* Activate DNAases enzymes w/c digest Inter Nucleosomal DNA-

→ As a result most of Pratiens, nuclear material etc is digested → & cell membrane undergoes some changes & & bud out → make Apoptotic Bodies.

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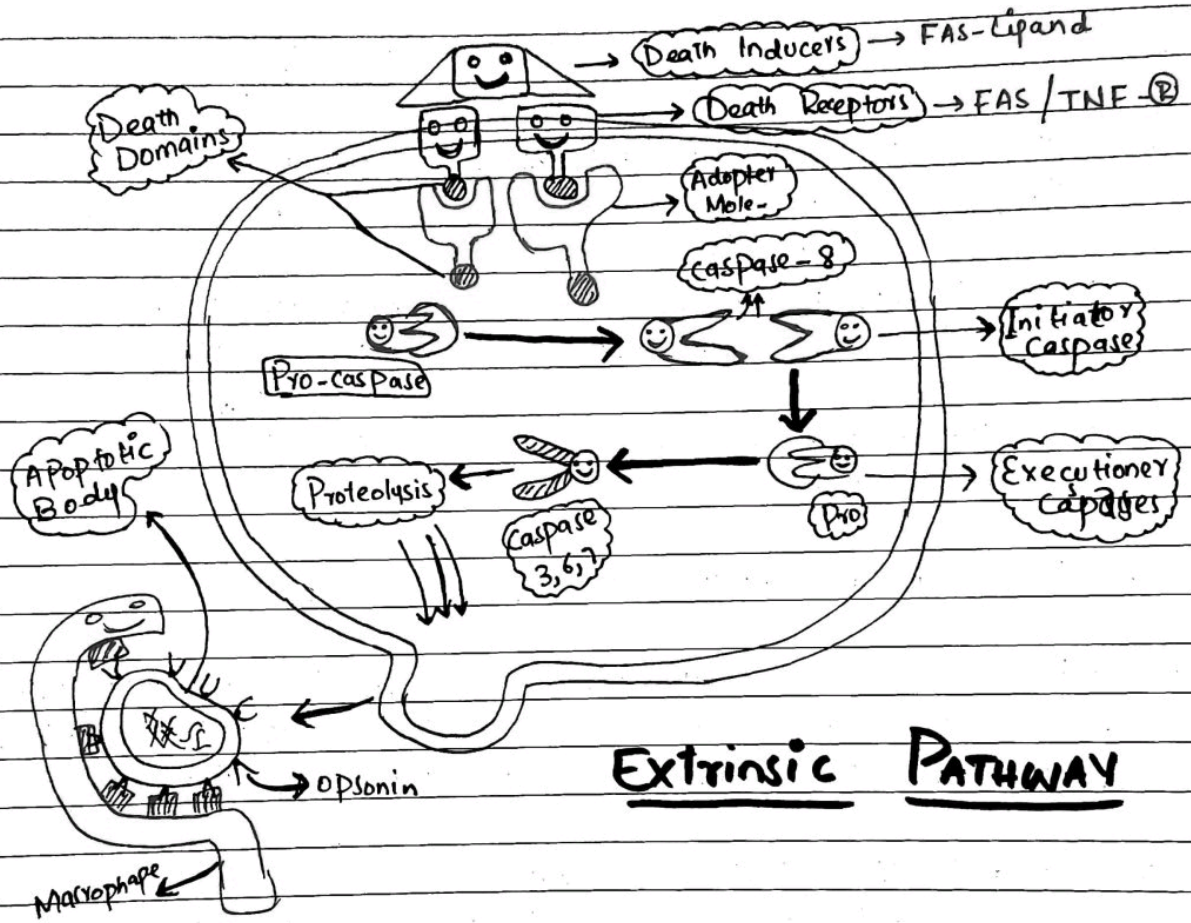
→ These Apoptotic bodies express special molecules → "Opsonins" w/c is a signal for Macrophages & they also secrete molecules w/c binds wd opsonins & phagocytosis occurs.



Extrinsic Pathway

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Intrinsic Pathway

* Also called → Mitochondrial Pathway.

Why Different cells have Different Life Span?

→ Actually Every cell have "Pro-Apoptotic / Pro-Death" genes & "Anti-Apoptotic / pro-life" genes. There is balance b/w these ② types of Genes → w/c determine life of cell.
→ If Pro-Apoptotic genes expresses more → Apoptosis occur early & vice versa if Anti-Apoptotic genes expresses more.

* Pro Apoptotic → Bad, Box, Bak
* Anti- " → Bcl2, BCl-x

DR-NID ☺

* The Real bad Poison are Present in Mitochondria.

→ Mitochondria have cytochrome-C & Apoptosis Inducing Factor (AIF).
→ There are channels in mitoch- membrane → (Mito- Permeability Transition Pores) →
→ thro. w/c cyt-C & AIF can Escape out.

→ Normally the products of Pro-life genes make Homo-Dimers wd each other or Hetero-dimer wd pro-death genes product and block / plug the Transition pores & also inhabits. Apoptosis Activating Factor w/c is present in cytoplasm. (AAF)

→ when cell is going to die → the Process reverses → Pro-death genes products → dimer → cannot plug the Pores and thus cyt-C and AIF come out of mito-.

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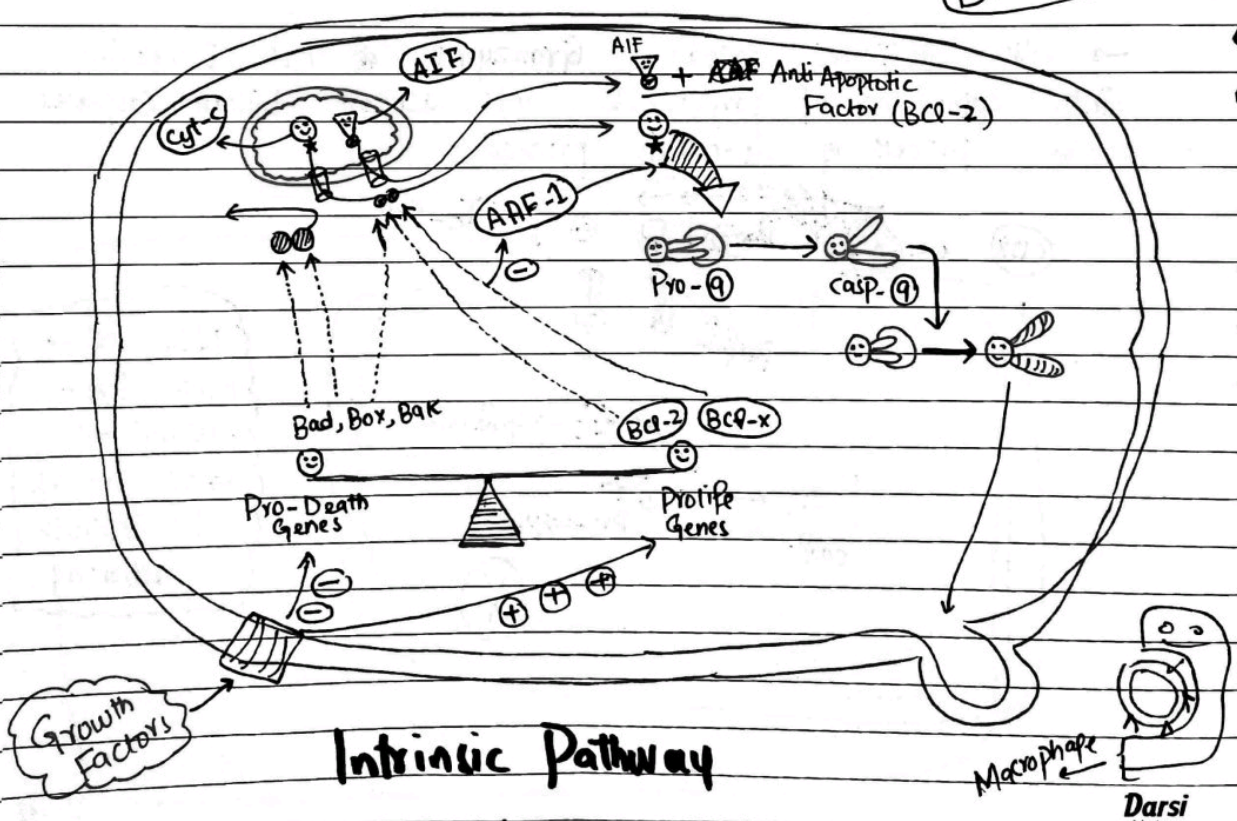
→ AIF → inhabits Anti-Apoptosis Factor / Bcl-2, X etc.
→ Cyt-C along wd AAF activates initator Caspases w/c will inturn activate Executioner caspases & remaining Pathway is same as Extrinsic pathway.

● Activation of Pro-life & Pro-death Genes is dependant upon Growth Factors, Harmones etc.
i.e If Growth Factors are present → they signal Pro-life Gene positively & Pro-death genes nepatively.
→ But if G.F aren't they Pro-death genes are activated & Apoptosis occurs.

DR.NID



Intrinsic Pathway

Darsi Notes

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How Cytotoxic T-cell Kill the Cell / Apoptosis :

→ When a cell is infected wd virus → viral protiens are expressed on surface of cell along wd class-1 MHC molecule.

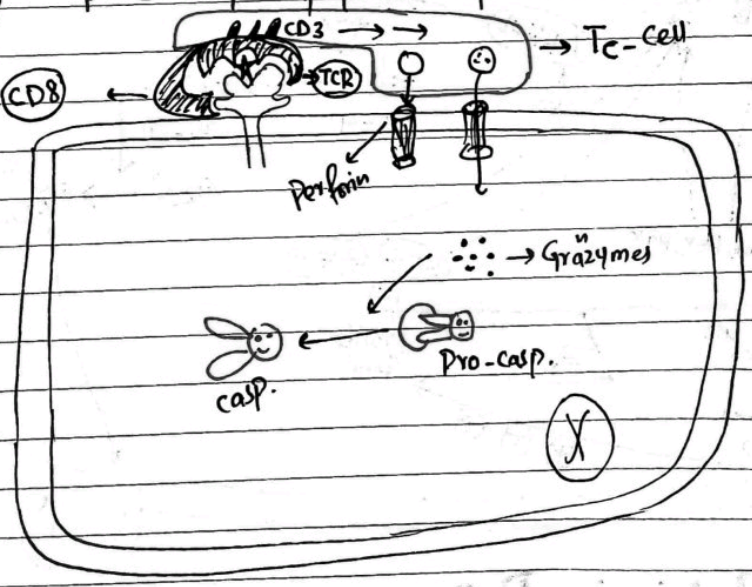
→ Cyt-T-cell → attach to viral protien thru TCR (T-cell Receptor) &p also thru CD-8 to MHC to confirm whether viral protien is present or not.

→ When binds then → it give signals to the CD_3 molecule.

→ Cyt-T-cell become activated → it come near to ~~near~~ cell →

→ release pre-formed peptides (Perforins) → w|c make holes | pores in cell surface membrane.

→ Also cyt-T cell release Granzyme thru perforins into cytoplasm of target cell w|c activate initiator caspases &p process of apoptosis proceeds.



NK-cell → have FAS-Lpand → → kill the cell By Extrinsic Pathway.

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How P53 Gene Induce Apoptosis :

* P53 → Guardian of Genome.

Normally when DNA Replication is going on → there are Proof reader Genes w/c check the mismatched pair in DNA. When error occurs → proof reader signals the P53 gene w/c activate cell cycle Arrest gene to Arrest the cell cycle & P53 also activate DNA repair gene to repair the error.

→ But If Irrepairable loss occur to DNA → Proof reader Stimulate / Irritate P53 too much that it activate another pathway → Stimulate Pro Apoptotic gene & inhabit Anti-Apoptotic genes → As as result → → intrisic pathway is activated → & Apoptosis occurs.