MOLECULAR MECHANISM OF CELL DEATH

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Introdution:

CELL DEATH:

- When cells are injured they die by different mechanism,depending on the nature &seveeriy of the insult.
- Sever disturbaces ,such as loss of oxygen & nutrient supply & the actions of toxins cause arapid & uncontrollable form of death,that has been called “accidental “cell death.

- Necrosis is not thought to be regulated by specific signals or biochemical mechanisms (happens accidentlly).
- In contrast ,when the injury is less sever or cells need to be eliminated during normal processes ,they activate aprecise set of molecular pathways that end in death.It said to be regulated cell death(apoptosis).

APOPTOSIS”falling off”

- Apopyosis is pathway of cell death in which cells activate enzymes that degrade the cells own nuclear DNA and nuclear and cytoplasmic proteins.
- Apoptotic cells break up into plasma membrane bound fragments called apoptotic bodies which contain portions of the cytoplasm and nucleus.

- The plasma membrane remains intact and the dead cell and its fragments are cleared with little leakage of cellular contents, so apoptotic cell death does not elicit an inflammatory reaction.

Mechanism of Apoptosis:

Apoptosis is mediated by caspases that activate proteases & endonucleases.

1. Proteases break down the cytoskeleton.
2. Endonucleases break down DNA.

❖Caspases are activated by multiple pathways:

1.Intrinsic mitochandrial pathway

❖It is initiated by avariety of microenviromental pertubations including:

1. Growth factor with drawal.
2. DNA damage.
3. Endoplasmic reticulum stress.
4. Reaction oxygen species.

5. Replication stress.
6. Microtubular alteration or mitotic defect.

- The critical step for intrinsic apoptosis is irreversible and wide spread mitochondrial outer membrane permeabilization(MOMP) which is controlled by proapoptotic and antiapoptotic members of the BCL2 family.

- In response to apoptotic stimuli,MOMP is mediated by:

➢ BCL2 associated X.

➢ Apoptosis regulator(BAX).

➢ BCL2 antagonist/Killer 1(BAK 1;best known as BAK).

- In physiological condition BAX continously cycles between the outer mitochondrial membrane(OMM) and cytosol.

- In contrast BAKresides at the OMM where it inserts within the lipid bilayer.
- These proapoptotic members of the BCL2 protein family are activated transcriptionally or post translationally as specific organelles or cellular compartments experience pertubation of homeostasis defacto operating as cellular transducers of stress signaling.

- Some protain called NOXA,BID,PUMA share the ability to physically interaction with the mitochondrial pool of BAX and \or BAK to promote aseries of conformational changes lead to activation of proapoptotic protein.
- On the other hand MOMP is antagonised by antiapoptic members of bcl2 itself,bcl2 like 1 and others.

- These antiapoptic members inserted into outer mitochondrial membrane or the ER membrane and exert antiapoptotic function by binding proapoptotic members of the BCL2 family(BAX and BAK) and preventing their oligomerization and pore forming activity.

REGULATION OF APOPTOSIS

Bcl-2 family of genes

Chromosome 18

PRO APOPTOTIC

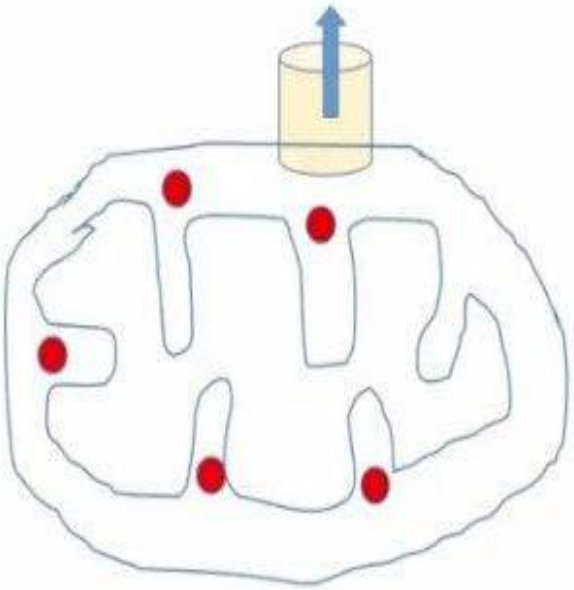
bax, bak, bcl-xS

SENSORS

Bad, bim, bid, puma

ANTI APOPTOTIC

bcl-2, bcl-xL, mcl-1

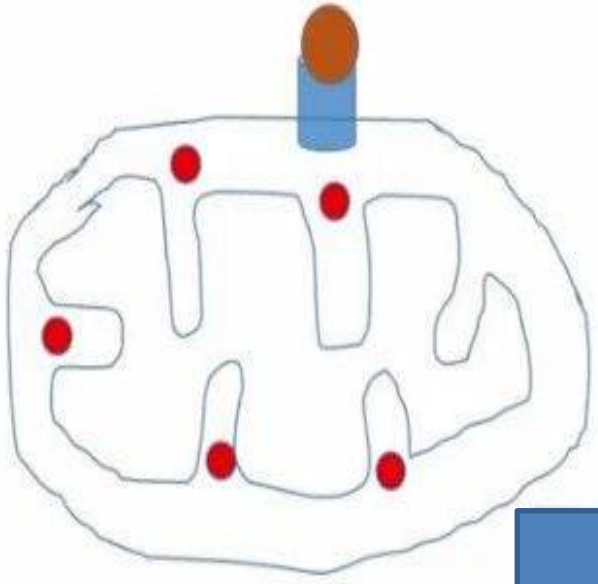


Inactivates

Antiapoptotic genes

Activate

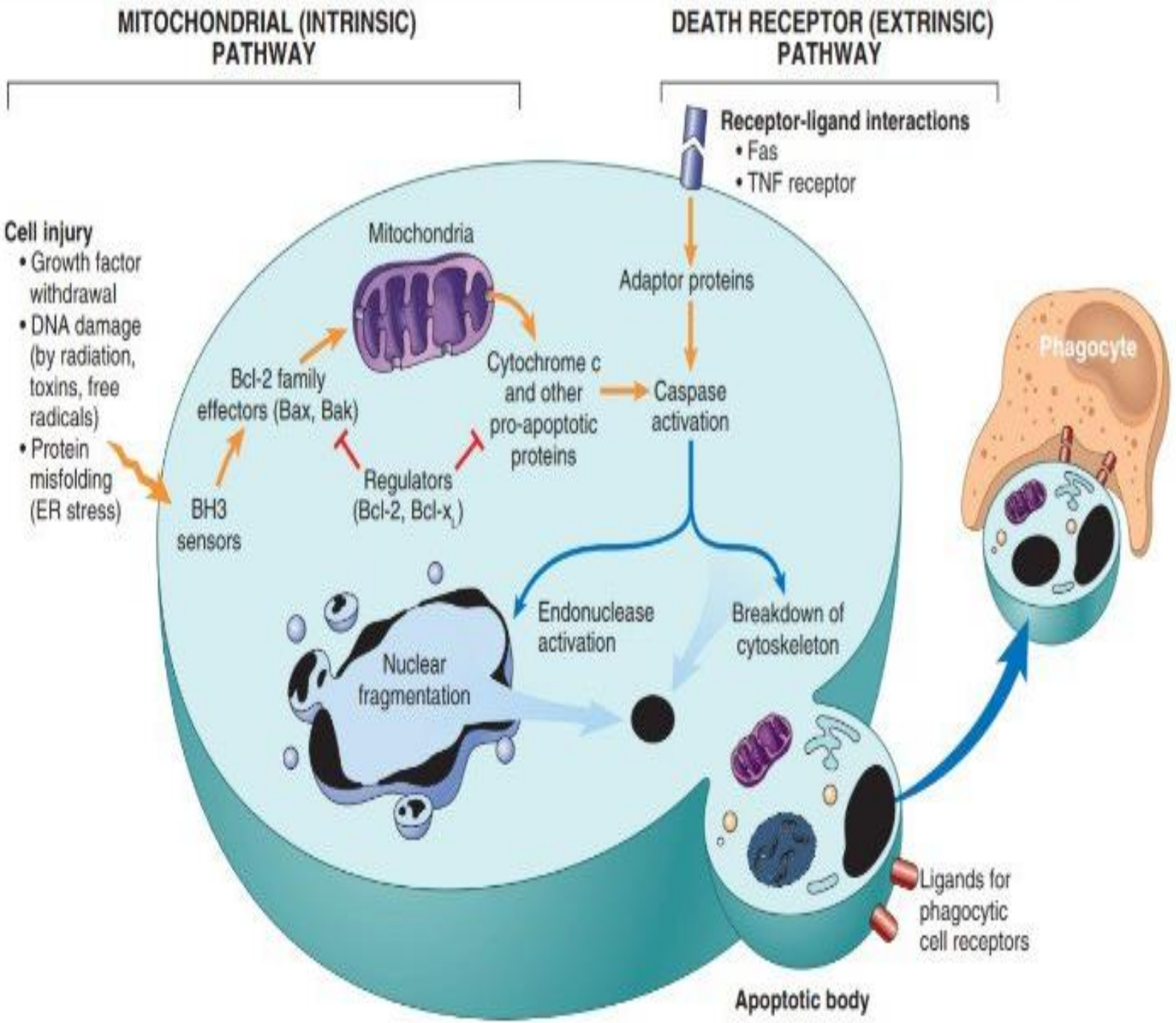
proapoptotic genes



Cessation of Growth factors

Growth factors

- MOMP is directly promotes the cytosolic release of apoptogenic factors that normally reside in the mitochondrial intermemrane space(cytochrome c and Second Mitochondrial Activator of Caspases SMAC).
- The cytochrome c bind to apoptoticpeptidase activating factor 1(ADAF1) and procaspase 9 to form complex known asapoptosome which responsibe which responsible for CASPASE 9 activation.


MITOCHONDRIAL (INTRINSIC) PATHWAY
DEATH RECEPTOR (EXTRINSIC) PATHWAY
Receptor-ligand interactions
• Fas
• TNF receptor
Cell injury
• Growth factor withdrawal
• DNA damage (by radiation, toxins, free radicals)
• Protein misfolding (ER stress)
Mitochondria
Adaptor proteins
Bcl-2 family effectors (Bax, Bak)
Cytochrome c and other pro-apoptotic proteins
Caspase activation
BH3 sensors
Regulators (Bcl-2, Bcl-x)
Endonuclease activation
Breakdown of cytoskeleton
Nuclear fragmentation
Phagocyte
Ligands for phagocytic cell receptors
Apoptotic body

- Activation of CASASE 9 lead to activation of CASPASE 3,6 and 7.

The death receptor(extrinsic)pathway of apoptosis:

- Many cells express surface molecules called death receptors that trigger apoptosis.
- Death receptors:

1.Type 1 TNF receptor.

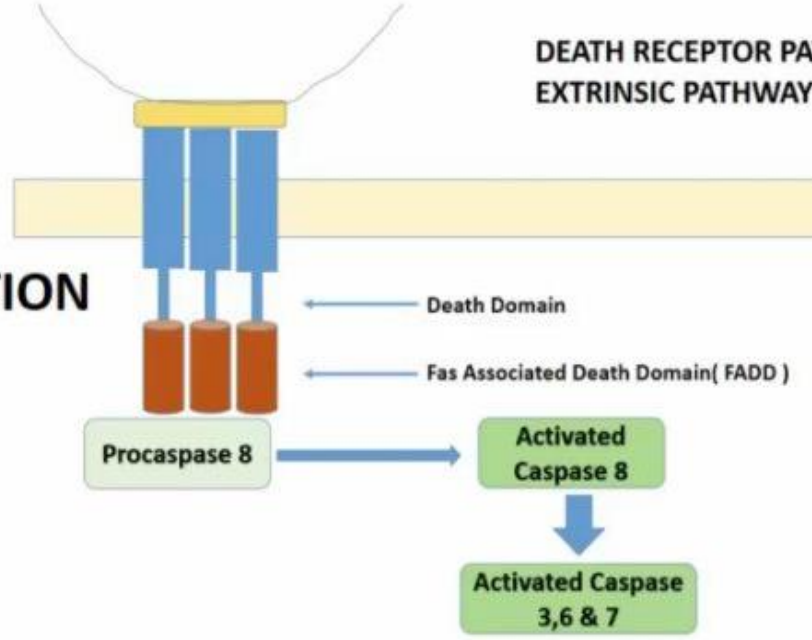
2.FAS (CD95) receptor.

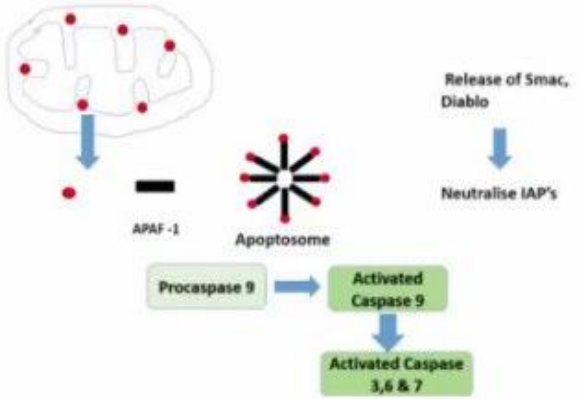
- Most of these are members of the TNF receptor family which contain in yheir cytoplasmic regions adeath domain it so named because it mediates interaction with other proteins involved in cell death.
- FAS ligand (FAS L) is amembrane protein expressed mainly on activated T lymphocytes.

DEATH RECEPTOR PATHWAY /
EXTRINSIC PATHWAY

INTRINSIC PATHWAY
MITOCHONDRIAL PATHWAY

INITIATION





EXECUTION

Nuclear Breakdown
By Endonuclease
activation

Breakdown of
cytoskeleton

- When these T cells recognize FAS expressing targets, FAS molecules are crosslinked by FAS L

and some conformational changes occure lead to binding of death receptor with Fas Associated Death Domain (FADD) via death domain.

- The basic function of FADD is activation of procaspase 8 this lead to activation of caspase 3,6 and 7.

- The activated caspases cause nuclear break down by endonuclease activation and breakdown of cytoskeleton and formation of apoptotic body which phagocytosed by macropnage.

Thank you

Reference

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- PATHOLOGY OUTLINES.
- ROBBINS PATHOLOGY.