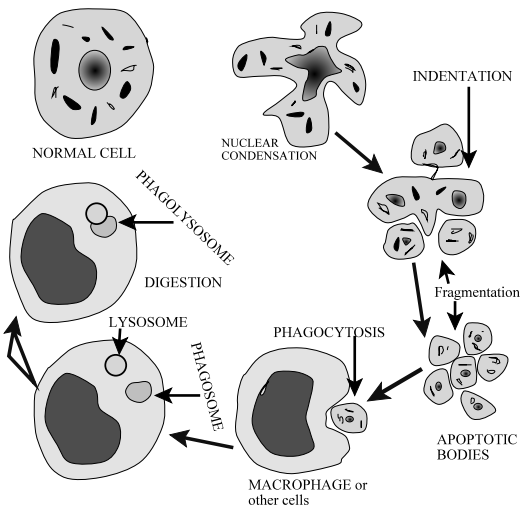
APOPTOSIS

- Embryogenesis
- Cells undergoing normal turnover in postnatal life,
- Involution of the uterus
- Atrophy,
- Regression of hyperplasia.
- Neoplasia
- Certain drugs, toxins, mild hyperthermia and irradiation
- Cell infected with viruses
- Cells with DNA damage
- Cells of immune system

CELLS THAT ARE INDUCED TO COMMIT SUICIDE

- Shrink
- Mitochondria break down — release of cytochrome-C
- Develop blisters on the surface
- DNA and nucleoprotein degraded
- Break into small, membrane-wrapped, fragments
- The **phosphatidylserine**, which is normally hidden within the plasma membrane is exposed on the surface.
- Phagocytic cells like macrophages and dendritic cells engulf the cell fragments.
- The phagocytic cells secrete cytokines that inhibit inflammation.



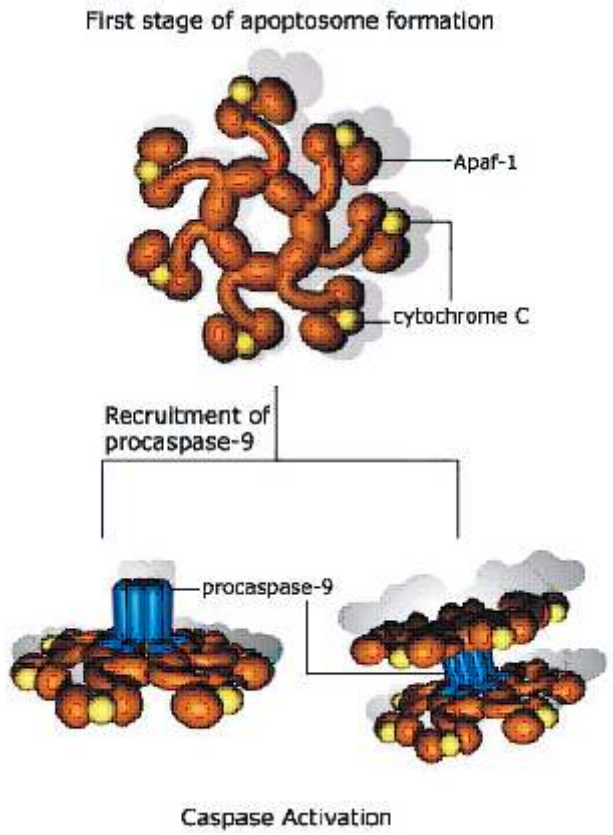
APOPTOSIS PROCESS

TWO MAJOR PATHWAYS OF APOPTOSIS

1. APOPTOSIS TRIGGERED BY INTERNAL SIGNALS

- Outer membranes of mitochondria express – Bcl-2
- Bcl-2 is bound to a molecule of the protein Apaf-1.
- Internal damage in the cell causes Bcl-2
  - to release Apaf-1
  - to no longer keep cytochrome-C from leaking out of the mitochondria
- The released cytochrome-C and Apaf-1 bind to molecules of caspase 9.
- The resulting complex of
  - cytochrome-C
  - Apaf-1
  - caspase 9
  - and ATP

  is called the apoptosome.



- Caspase 9 cleaves and, in so doing, activates other caspases.
- The sequential activation of one caspase by another creates an expanding cascade of proteolytic activity which leads to
  - digestion of structural proteins in the cytoplasm
  - degradation of chromosomal DNA

2. APOPTOSIS TRIGGERED BY EXTERNAL SIGNALS

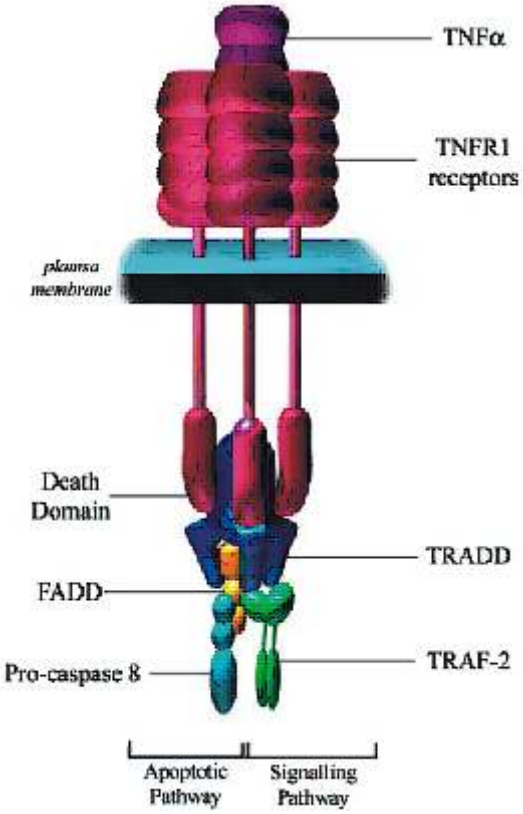
DEATH RECEPTORS

- Receptors that transmit apoptosis signals initiated by specific ligands.
- Activate a caspase cascade within seconds of ligand binding.
- Induction of apoptosis via this mechanism is therefore very rapid.
- Death receptors belong to the tumour necrosis factor (TNF) gene superfamily

- The best characterised of the death receptors are
  - CD95 (or Fas),
  - TNFR1 (TNF receptor-1)
  - TRAIL (TNF-related apoptosis inducing ligand) receptors DR4 and DR5.

SIGNALLING BY TUMOUR NECROSIS FACTOR RECEPTOR-1 (TNFR1)

- TNF -- secreted by T-cells and activated Macrophages
- Bind with TNFR1,
- Binding of TNF alpha to TNFR1 results in apoptosis.
- This allows binding of an intracellular adapter molecule called TRADD (TNFR associated death domain) via interactions between death domains.
- TRADD has the ability to recruit a number of different proteins to the activated receptor.
  - Recruitment of TRAF2 (TNF associated factor 2).
  - And interaction with FADD, which leads to the induction of apoptosis via the recruitment and cleavage of **pro-caspase 8**.
- TNFR1 — mediate apoptosis through RAIDD (RIP-associated ICH-1 / CED-3 homologous protein with a death domain).
  - RAIDD can recruit caspase 2
  - Recruitment of caspase 2 leads to induction of apoptosis.

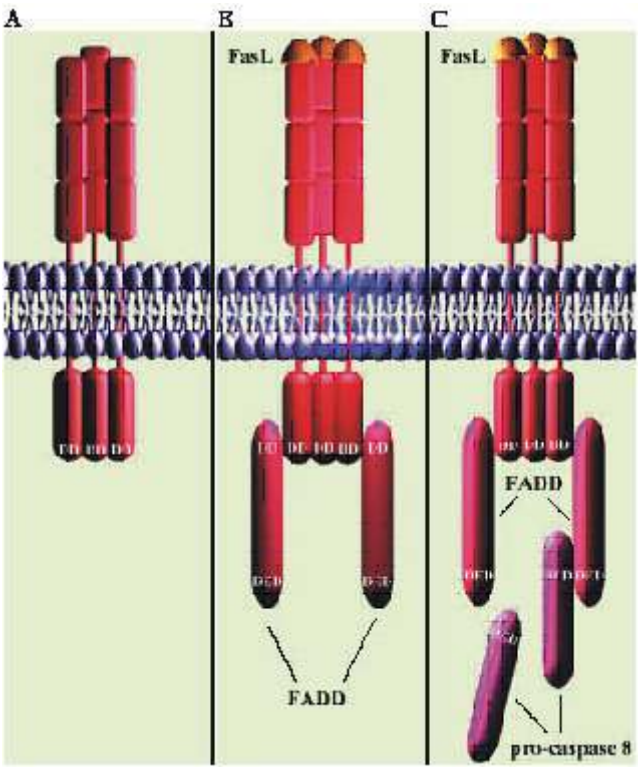


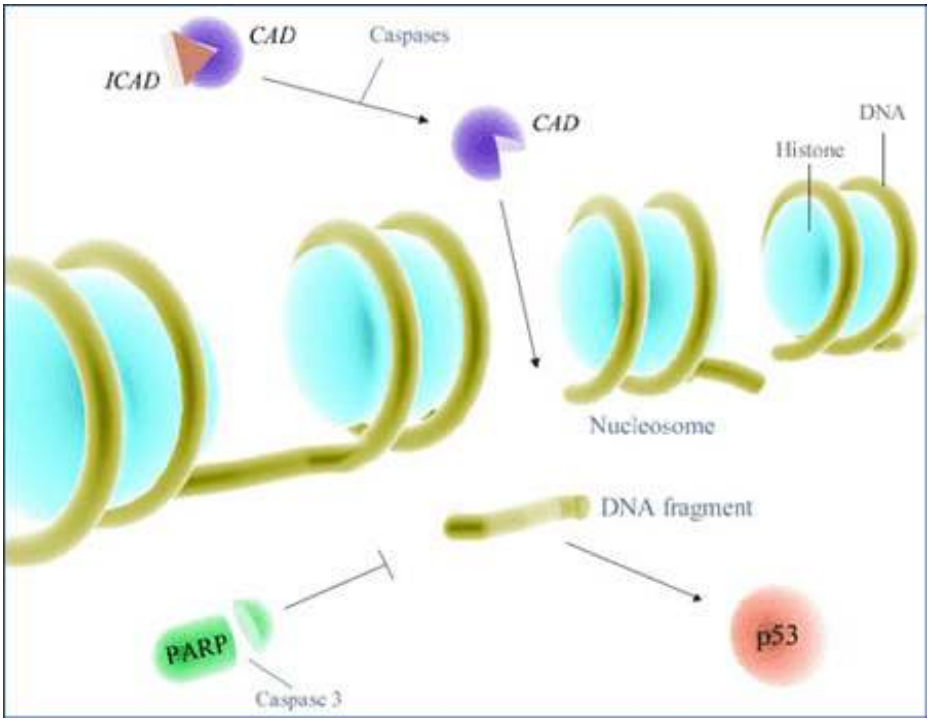
SIGNALING BY CD95 / FAS

There are three main roles of CD95:

1. Cytotoxic T-cell mediated killing of cells
2. Deletion of activated T-cells at the end of an immune response
3. Destruction of inflammatory and immune cells in immune-privileged sites

- Ligand for CD95 (CD95L or FasL) allows an adapter protein called FADD (Fas-associated death domain) to associated with the receptor through an interaction between homologous death domains on the receptor and on FADD. FADD also contains a death effector domain (DED).
- The death effector domain allows binding of pro-caspase 8 to the CD95-FADD complex.
- Pro-caspase 8 immediately cleaved to produce caspase 8.
- This then triggers activation of execution caspases such as **caspase 9**.





NECROSIS

- Cell Death, Lethal Injury, **Death of cells in living organisms**
- Morphological changes – 6-8 hours after the cell death,
- Autolysis, release of lysosomal enzymes - heterolysis

CHANGES

- Cytoplasm
  - Eosinophilic arginine and lysine
  - **Hyalinized** cytoplasm (glycogen loss) or moth-eaten (organelle) Granular (eosinophilia of organelles)
- Nucleus
  - Pyknosis
    - more dark nucleic acid set free
    - lack nucleolus
  - Karyorrhexis
  - Karyolysis DNAse

- Loss of cell outline
- Loss of differential staining
- Absence of cells

GROSS

- Lighter colour coagulation of proteins, reduction of blood supply
- May be swollen area or Depressed
- May be Softer to Touch
- Loss of Strength
- Red zone of congestion 2 - 3 days old