GENERAL PATHOLOGY

L-13 APOPOTOSIS

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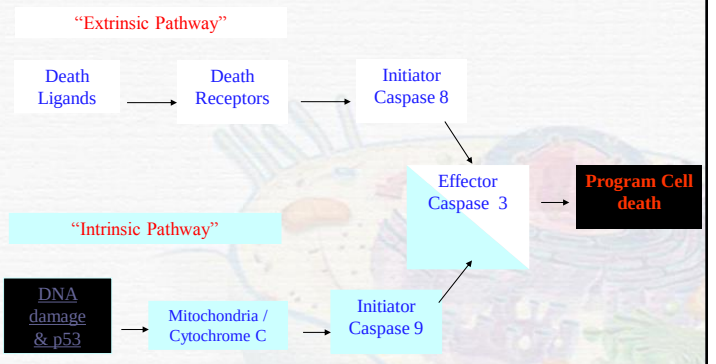
Apoptosis: Pathways



Cysteine-dependent aspartate-specific proteases (caspases)

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TWO MAJOR PATHWAYS OF APOPTOSIS

1. **APOPTOSIS TRIGERED 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** (B-cell lymphoma-2)
  - to release Apaf-1
  - cytochrome-C is set free and leaks 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

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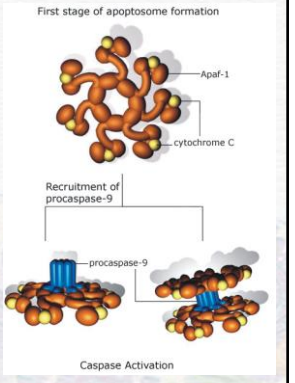
1. **Contd…**

- Caspase 9 is cleaved 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



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- All of the Bcl-2 family members are present on the outer mitochondrial membranes as dimers where they control membrane permeability in ion channel fashion or through the creation of pores.
- This Bcl-2 family of proteins is subdivided into 3 groups based on structural similarities and functional criteria.
  - Group I possess anti-apoptotic activity (Bcl-2 and Bcl-xL)
  - Groups II and III are Pro-apototic (Bax and Bak or Bad).

➢ A third type of pro-apoptotic activity is through the cytoplasmic protein, Bid. (t-Bid --- activated form)

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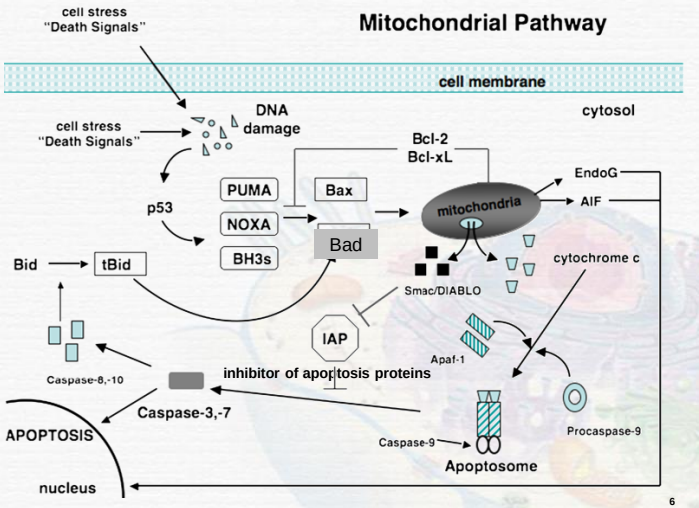

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2. APOPTOSIS TRIGGERED BY EXTERNAL SIGNALS

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

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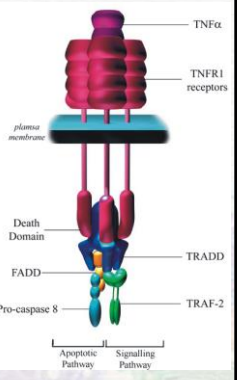
SIGNALLING BY TUMOUR NECROSIS FACTOR RECEPTOR-1 (TNFR1)

- 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 (TNFR 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 death domain).
  - RAIDD can recruit caspase 2
  - Recruitment of caspase 2 leads to induction of apoptosis.



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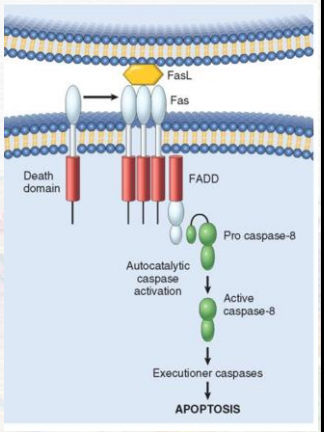
SIGNALING BY CD95 / FAS

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 be 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 3, 6, 7.**



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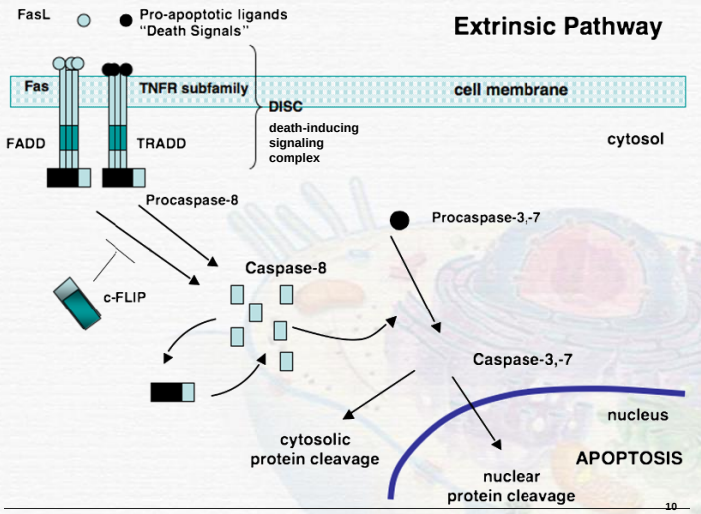

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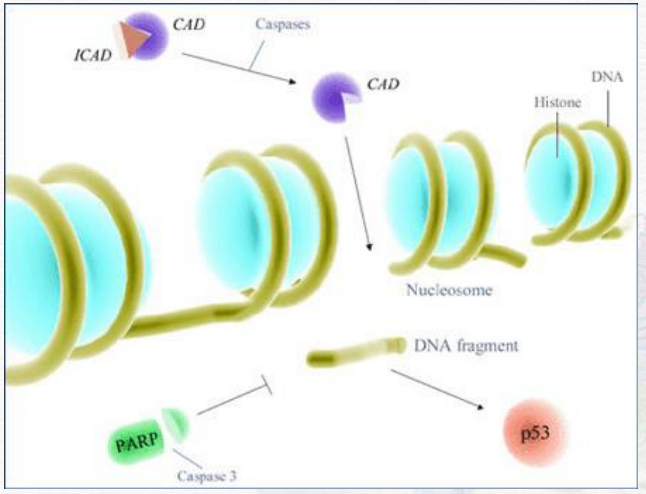

Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged	Reduced
Nucleus	Pyknosis/karyorrhexis/karyolysis	Fragmentation
Plasma membrane	Disrupted	Intact
Cellular contents	Enzymatic digestion	Intact
Inflammation	Frequent	None
Physiologic/pathologic	Pathologic	Physiologic/Path

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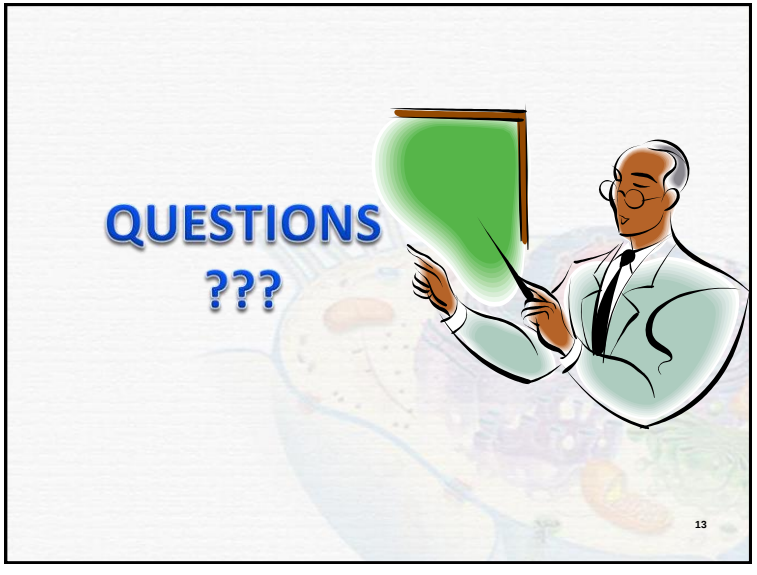
QUESTIONS
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