Apoptosis

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Definition

Apoptosis (sometimes called programmed cell death) is a cell suicide mechanism that enables multicellular organisms to regulate cell number in tissues and to eliminate unneeded or aging cells as an organism develops.

Types of cell death

Necrosis:

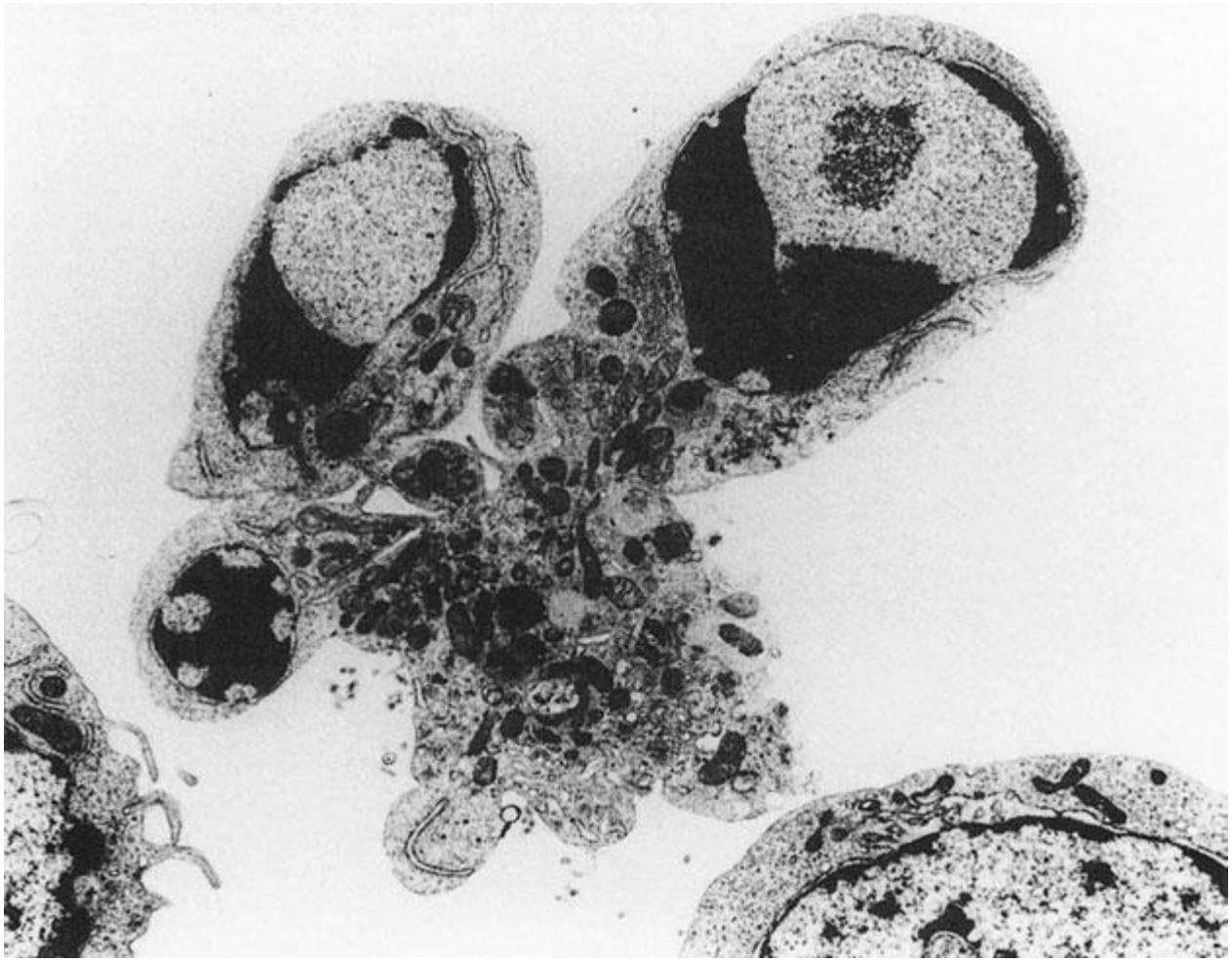
- Clumping of chromatin into ill-defined masses
- Swelling of organelles, membrane disintegration and infiltration of inflammatory cell.

Exercise: figures for necrosis

Apoptosis : ‘‘physiologic cell death.’’

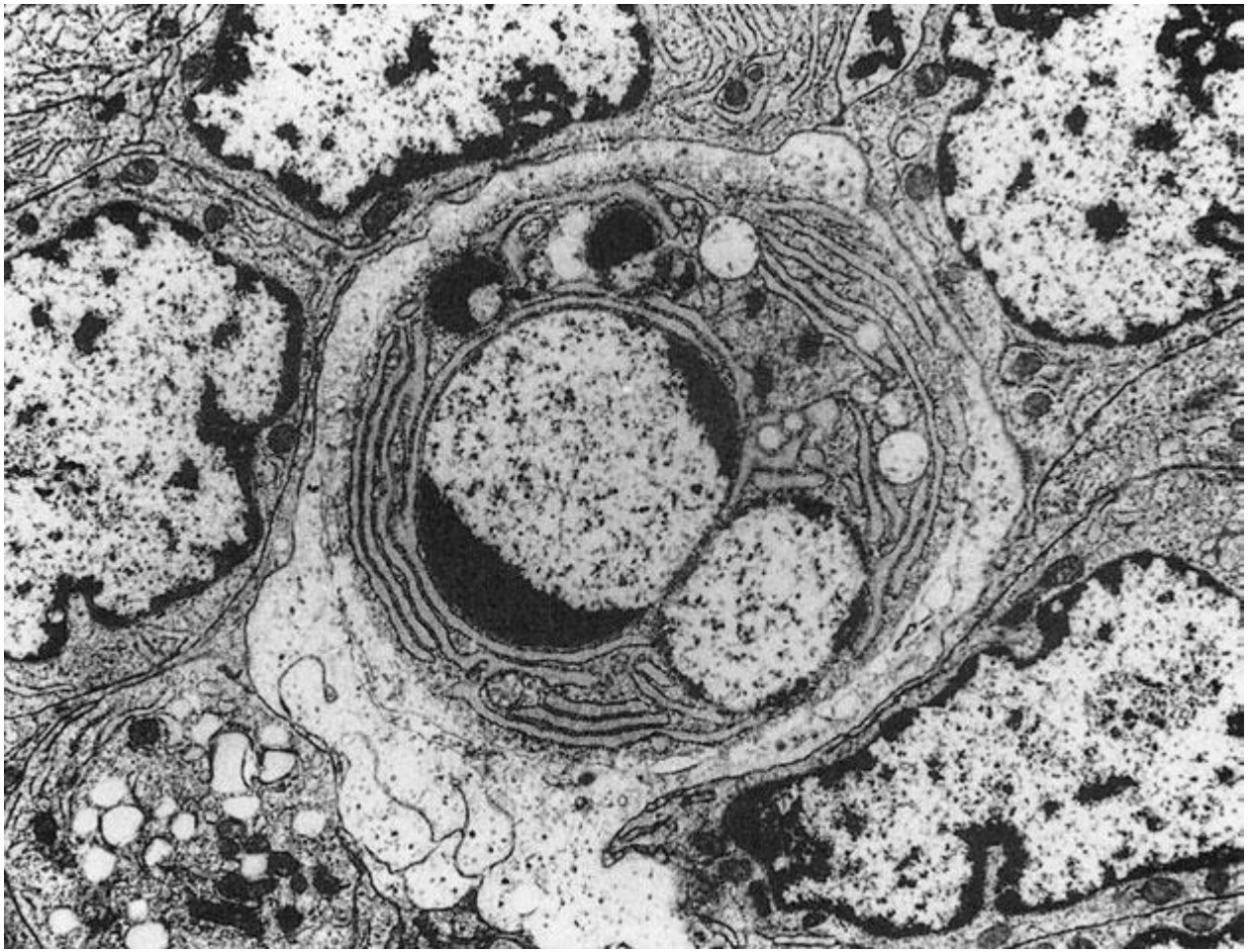
- Chromatin compacted into sharply delineated masses
- Condensation of the cytoplasm, and outcropping of cytoplasmic ‘‘blebs’’ or proturberances
- No inflammatory reaction

Characteristics of Apoptosis



Characterestics of Apoptosis

Apoptotic bodies •



Characterestics of Apoptosis

Apoptotic DNA ‘‘ladders

Intranucleosomal degradation of chromosomal DNA, by the endonuclease responsible for this effect is called caspase-activated DNase, or CAD.

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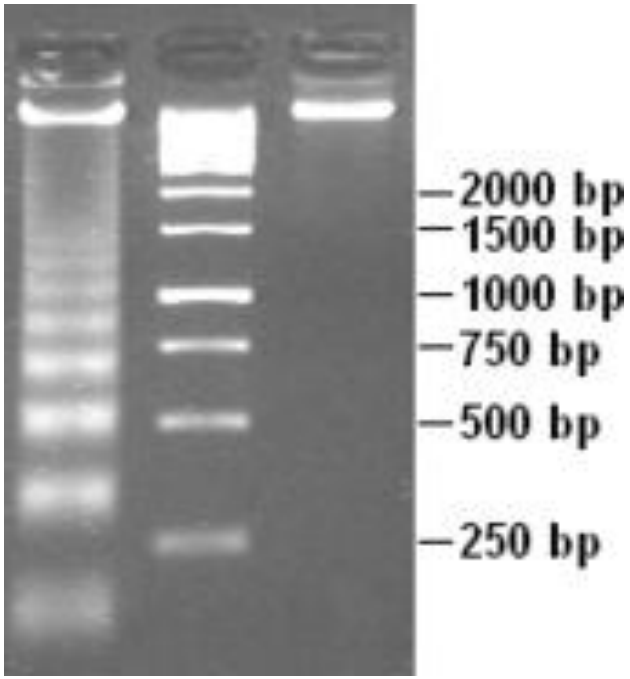
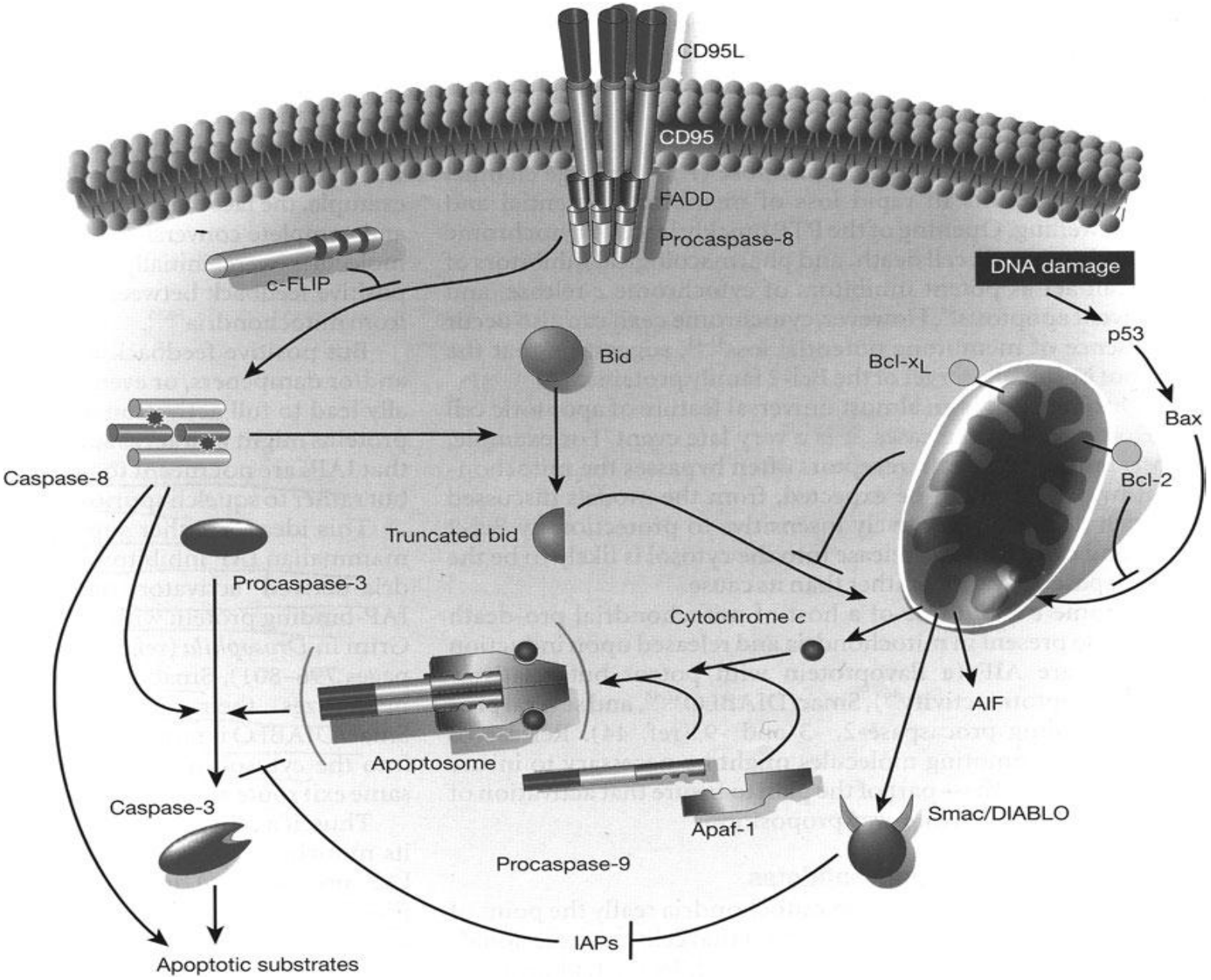


Cellular regulation of Apoptosis

Initiation of apoptosis

- Tissue differentiation during development
- Rremoval of growth factors or hormones
- Exposure to TGF-b, TNF to their negative regulation
- Exposure to DNA damaging anticancer drugs or environmental toxins.
- Increases in intracellular free Ca2

Apoptosis Pathways



Death Receptors

- Death receptors are cell surface receptors that transmit apoptotic signal initiated by death ligands.

- These receptors can activate the death caspases within seconds of ligand binding and induce apoptosis within hours.

- Death receptors belong to the tumor necrosis gene superfamily factor (TNF) receptor

- Typical cystine rich extracellular domains and an additional cytoplasmic sequence termed the death domain.

Examples:

- CD95 (also called Fas or Apo1)
- TNF receptor TNFR1 (also called p55 or CD120a).

Caspases

Caspases are a family of cysteine proteases

- Over 12 caspases have been Identified

initiator (apical) caspases and **effector (executioner) caspases**.

Initiator caspases (e.g., CASP2, CASP8, CASP9, and CASP10) cleave inactive pro-forms of effector caspases, thereby activating them.

Effector caspases (e.g., CASP3, CASP6, CASP7) in turn cleave other protein substrates within the cell, to trigger the apoptotic process.

Caspase cascade

- Synthesized as inactive *pro-caspases*

- Consist of a prodomain, a small subunit and a large subunit.

- The prodomain of the initiator caspases contain domains such as a CARD domain (**Caspase recruitment domains)** (e.g., caspases-2 and -9) or a **death effector domain** (DED) (caspases-8 and -10) that enables the caspases to interact with other molecules.

Role of Mitochondria in Apoptosis

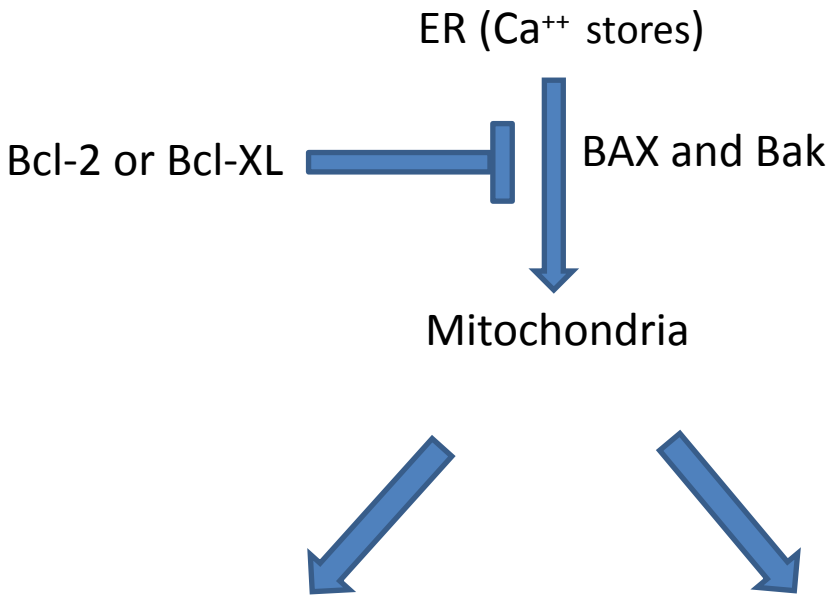
Cytochrome C -

Smac/DIABLO -

- Apoptosis-inducing factor (AIF) and the endonuclease CAD

Role of Mitochondria in Apoptosis

- **Mitochondrial permeabilization**



voltage-dependent anion channels (VDACs) in the outer membrane

and the adenine-nucleotide translocase (ANT) in the inner membrane.

Anoikis

Definition: Anoikis is a form of apoptosis that occurs in normal cells that lose their adhesion to the substrate or extracellular matrix (ECM)

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Importance of the apoptotic pathway in cancer progression

Mutations that alter the ability of the cell to undergo apoptosis and allow transformed cells to keep proliferating rather than die.

Examples:

1- The translocation of the bcl-2 gene in lymphomas that prevents apoptosis and promotes resistance to cytotoxic drugs.

2- Various oncogene products can suppress apoptosis. These include adenovirus protein E1b, ras, and n-abl.

Role of Apoptosis in the treatment of cancer

It would be therapeutically advantageous to tip the balance in favor of apoptosis over mitosis in tumors, if that could be done. It is clear that a number of anticancer drugs induce apoptosis in cancer cells. The problem is that they usually do this in normal proliferating cells as well. Therefore, the goal should be to manipulate selectively the genes involved in inducing apoptosis in tumor cells. Understanding how those genes work may go a long way to achieving this goal.

Questions