

APOPTOSIS

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APOPTOSIS

- Competency PY 1.4
- Describe apoptosis

APOPTOSIS

- Programmed cell death
- Greek word- meaning
- “ falling off” or “ dropping off ‘
- Form of coordinated and internally planned cell death
- Has got genetic control

APOPTOSIS

- Examples
- Importance

SCIENTISTS

THE 2002 NOBEL PRIZE WINNER



Sydney Brenner



H. Robert Horvitz



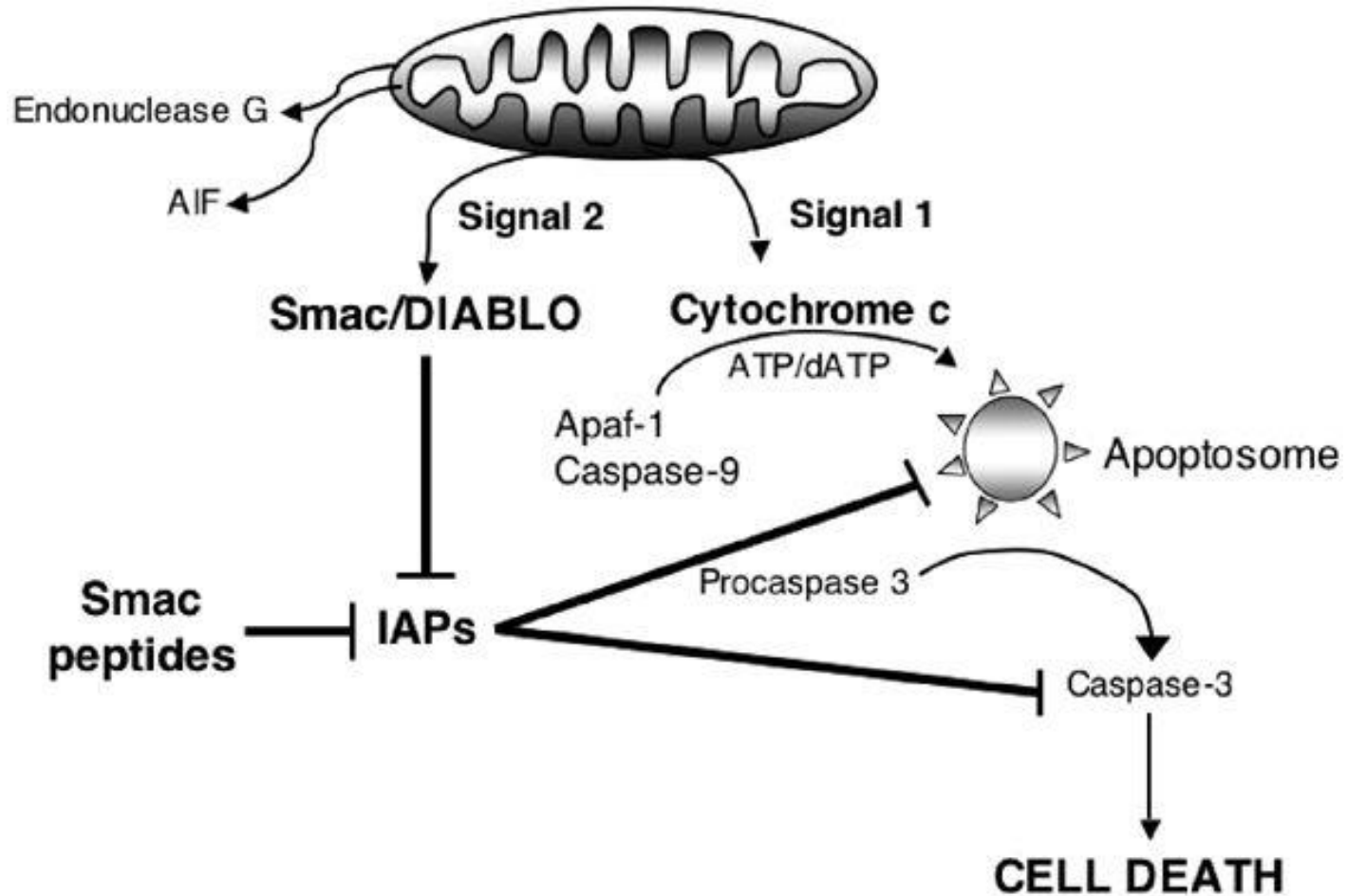
John Sulston

PCD has been the subject of increasing attention and research efforts. This trend has been highlighted with the award of the 2002 Nobel Prize in Physiology or Medicine to Sydney Brenner (United Kingdom), H. Robert Horvitz (US) and John E. Sulston (UK)

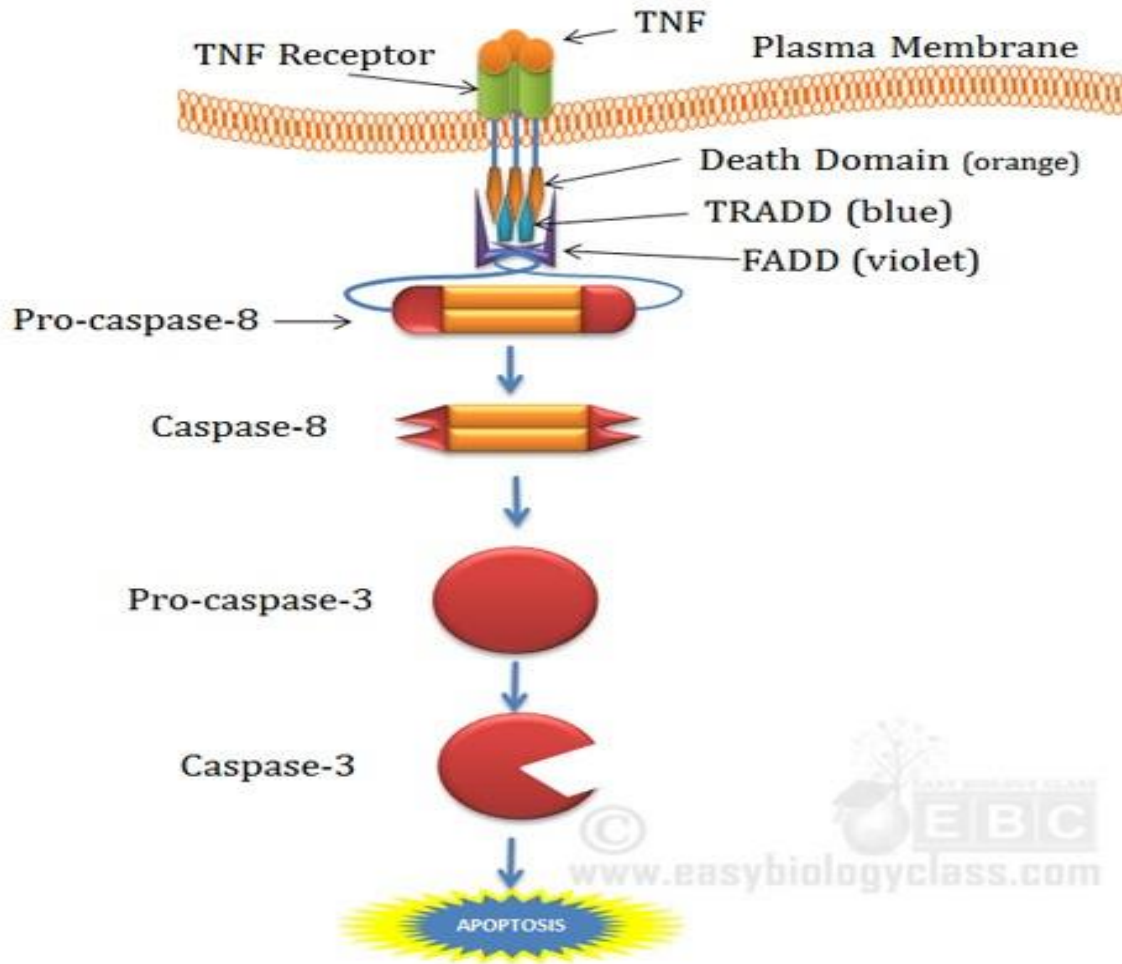
MECHANISM

- Apoptosis is triggered by activation of cysteine proteases in the cells called caspases
- Internal stimuli
- External stimuli

INTERNAL STIMULI



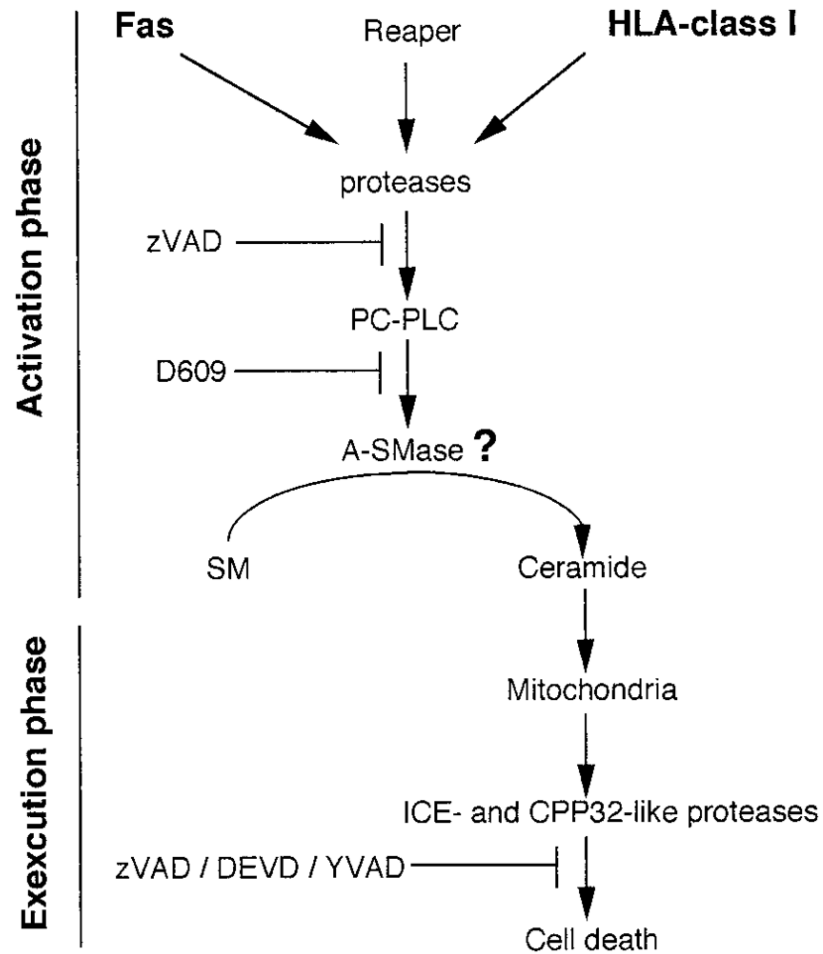
EXTERNAL STIMULI



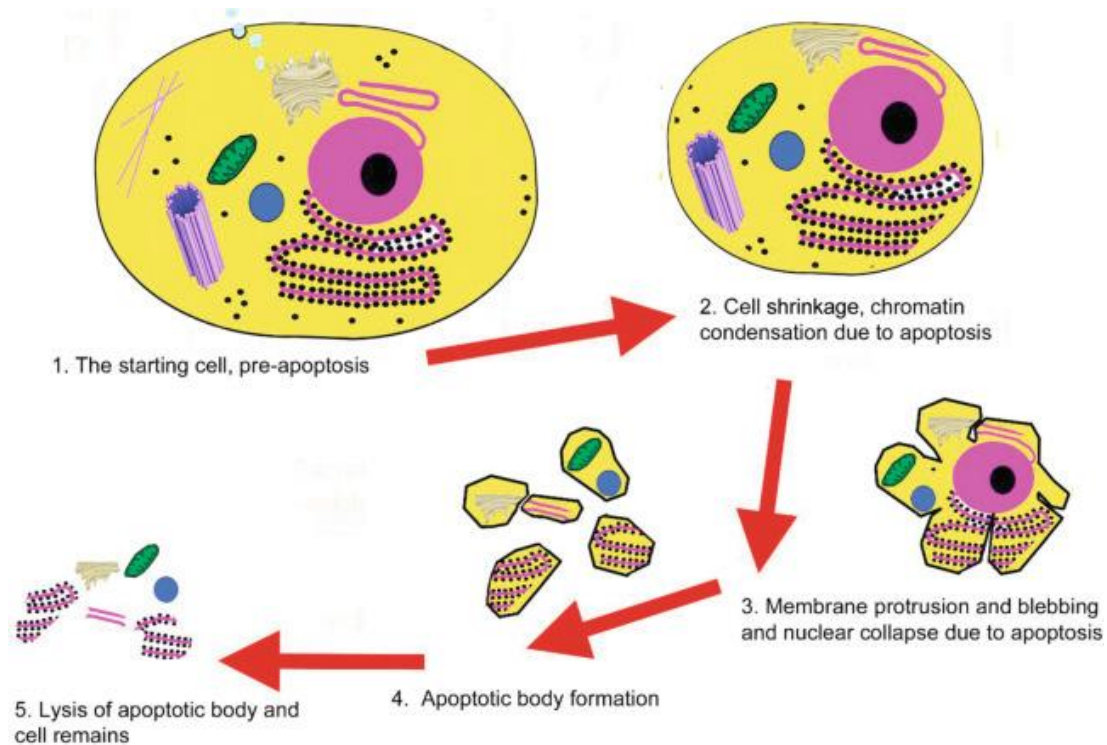
Extrinsic Pathway of Apoptosis

- Activation of Caspase promotes DNA fragmentation & chromatin condensation

STEPS IN APOPTOSIS

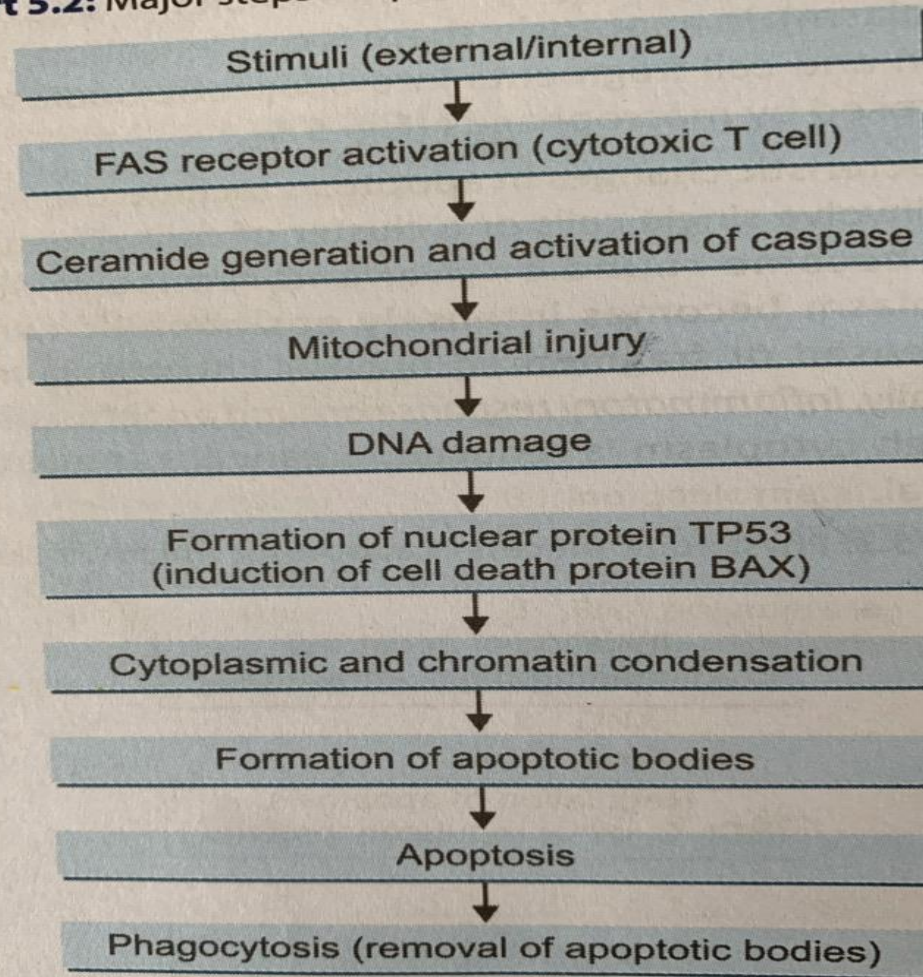


STEPS IN APOPTOSIS



STEPS IN APOPTOSIS

Flowchart 5.2: Major steps of apoptosis.



integral membrane

Flowchart 1.3: Mechanism of apoptosis

Outer membranes of healthy cell mitochondria have receptor for the protein **Bcl-2** on their surface. Bcl-2 **inhibits** apoptosis

The intrinsic damage to the cell causes **Bax** (a related protein) to migrate to the surface of the mitochondrion inhibiting the protective effect of Bcl-2. It inserts itself into the outer mitochondrial membrane forming punch hole through which cytochrome c leak out

Cytochrome c binds to the protein **APAF-1** ("apoptotic protease activating factor-1) to form **apoptosomes**. The apoptosomes further bind and activate **caspase 9**

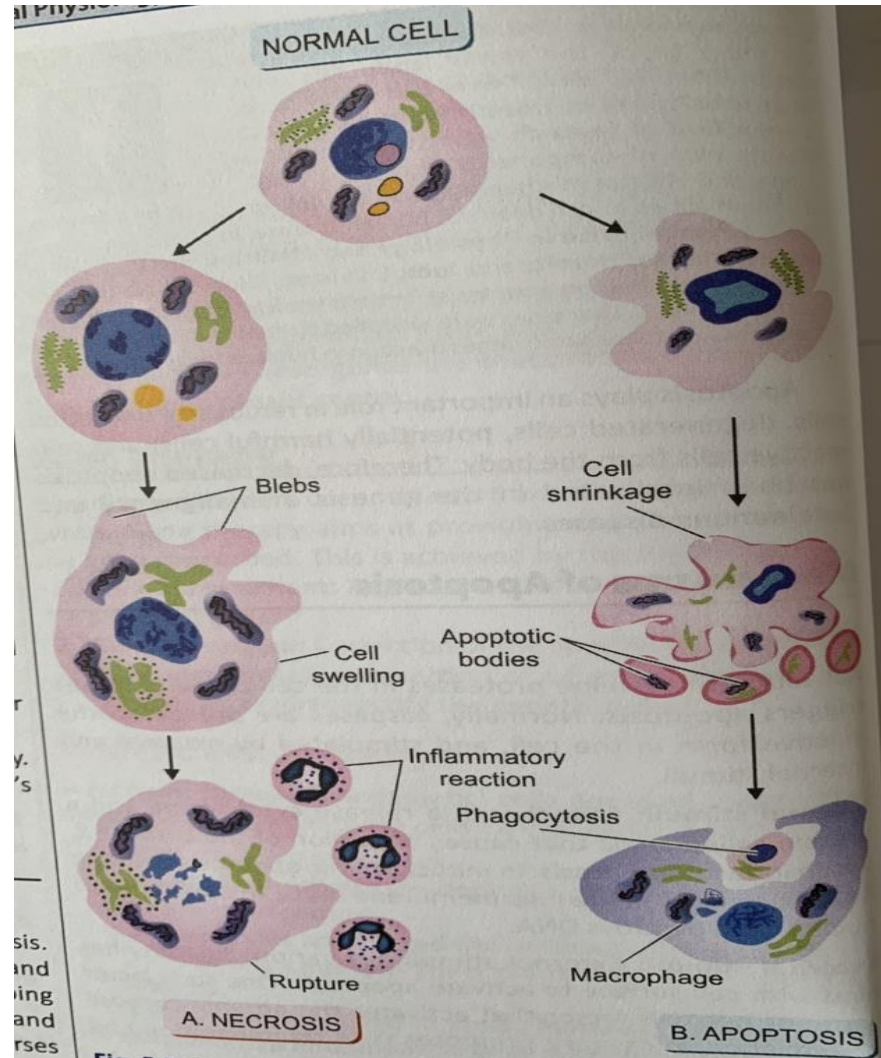
Caspase-9 activates other caspases (caspases 4 and 7)

The cascade of proteolytic activity of caspase leads to digestion of structural proteins in the cytoplasm, degradation of chromosomal DNA, and phagocytosis of the cell

APOPTOSIS- PHYSIOLOGIC PROCESS

APOPTOSIS- PATHOLOGIC PROCESS

CHANGES IN APOPTOSIS



NECROSIS Vs. APOPTOSIS

- NECROSIS
 - Homogenously eosinophilic cytoplasm
 - Nuclear Changes
 - Pyknosis
 - Karyolysis
 - Karyorrhexis
- APOPTOSIS
 - Condensation of nuclear chromatin
 - Fragmentation of cells in to apoptotic bodies
 - Phagocytosis by macrophages

BIOCHEMICAL CHANGES

- Proteolysis of cytoskeletal protein
- Cross- linking of protein molecules
- Fragmentation of nuclear protein by activation of nuclease
- Recognition by macrophage for phagocytosis-
Role of Thrombospondin and phosphatidyl serine

DETECTION OF APOPTOSIS

- DNA fragmentation assay by electrophoresis
- TUNEL staining
- Demonstration of chromatin condensation by H&E
- Estimation of cytosolic chromosome C, activated caspase, annexin V

REGULATION OF APOPTOSIS

- Balance between pro apoptotic and anti-apoptotic proteins
- Proapoptotic protein- BAX, BAC
- Antiapoptotic protein- BCL-2, BCL XL, MCL-1
- Other factors
 - TP53, Caspase, Viruses – adeno, paillooma, hepatitis B

APPLIED PHYSIOLOGY

- Disorders with reduced apoptosis
 - Cancer
 - Autoimmune diseases
- Disorders with increased apoptosis
 - Neurodegenerative diseases-
 - Ischemic injury

APPLIED PHYSIOLOGY

- Genetic defects in apoptosis – Mutation in the gene for Fas
- Produces Autoimmune Lymphoproliferative syndrome (ALPS)
- Characterised by accumulation of lymphocytes in the spleen and lymph node
- Splenomegaly, Lymphadenopathy
- Appearance of clones of lymphocytes-
haemolytic anaemia, thrombocytopenia