CELL BIOLOGY

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Lecture 14 **3/1/2022**

Cell death

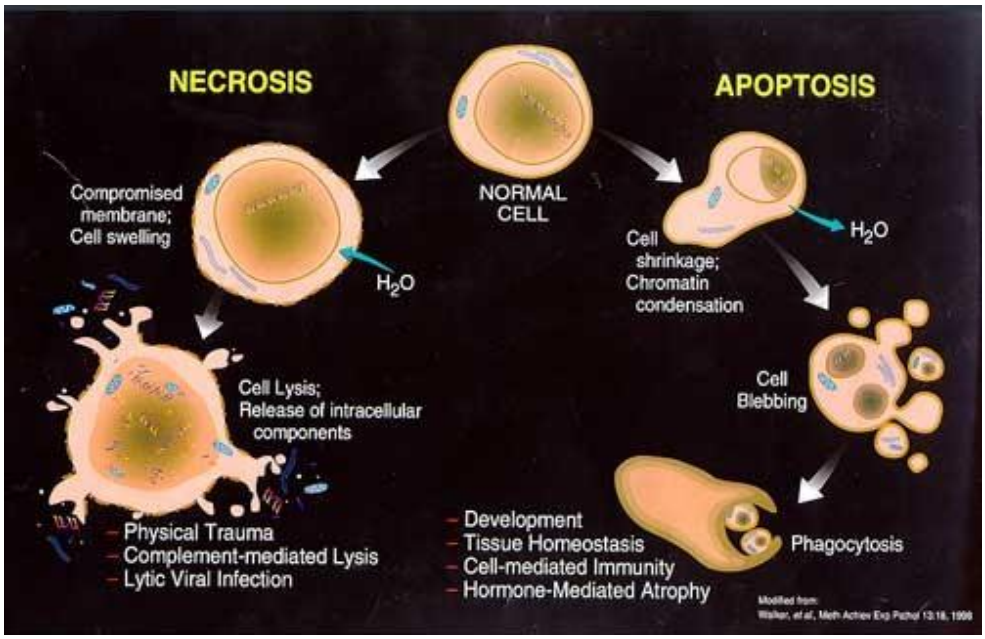
The body is very good at maintaining a constant number of cells. For every cell, there is a time to live and a time to die.

- So there have two mechanisms for cells death in the body:-
  - **Cell death by suicide (**Apoptosis - suicide - programmed cell death)
    -Internal signals
    -External signals
  - **Cell death by injury (**Necrosis - killing - decay and destruction)
    -Mechanical damage
    -Exposure to toxic chemicals

Apoptosis definition (programmed cell death): a physiological process by which unwanted or useless cells are eliminated during the development and other normal biological processes. Often found during tissue homeostasis, embryogenesis, immunological reactions and development of nervous systems. During apoptotic cell death, the cells undergo some characteristic events such as chromatin condensation, nuclear and cytoplasmic aggregation and partitions of cytoplasm and nucleus into membrane bound vesicles called apoptotic bodies containing ribosomes and mitochondria. Apoptotic bodies are recognized and phagocytized by either by macrophages or adjacent cells and thus no inflammatory response are elicited during apoptotic cell death.

Necrosis definition: (accidental cell death) a pathological process occurs when the cells are exposed to serious physical or chemical insults. Occur during pathological infections such as bacterial and fungal infections, hypothermia and hypoxia conditions. The cell and cellular organelles swell and ruptures to release the entire cell content including lysosomal enzymes into the extracellular fluid. Due to this, necrotic cell deaths are always associated with severe inflammatory response in the surrounding tissues.

Apoptosis	Necrosis
• Controlled death of individual cells • Induced by physiological stimuli • No inflammation • Shrinking of cytoplasm and condensation of nucleus • Blebbing of plasma membrane with no loss of integrity • Energy (ATP)-dependent; active process; functional mitochondria • Cell death pathway activation	• Affects groups of cells • Evoked by non-physiological events (viruses, ischaemia, toxins, etc) • Inflammation • Swelling of the cytoplasm and mitochondria • Loss of plasma membrane integrity • No energy requirement; passive process • Calcium overload a key feature



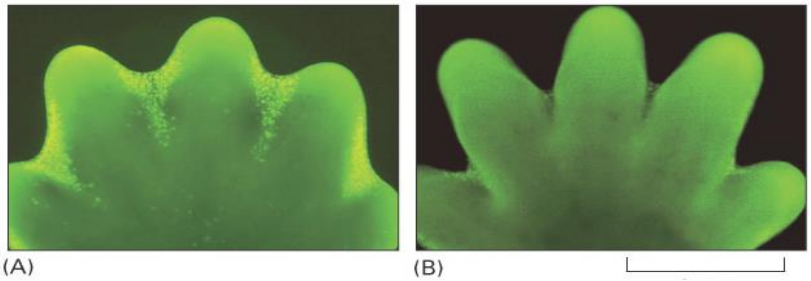
Programmed cell death or apoptosis.
Why should a cell commit suicide?

- **Apoptosis is needed for proper development for examples:**
  - The resorption of the tadpole tail
  - The formation of the fingers and toes of the fetus
  - The sloughing off of the inner lining of the uterus
  - The formation of the proper connections between neurons in the brain

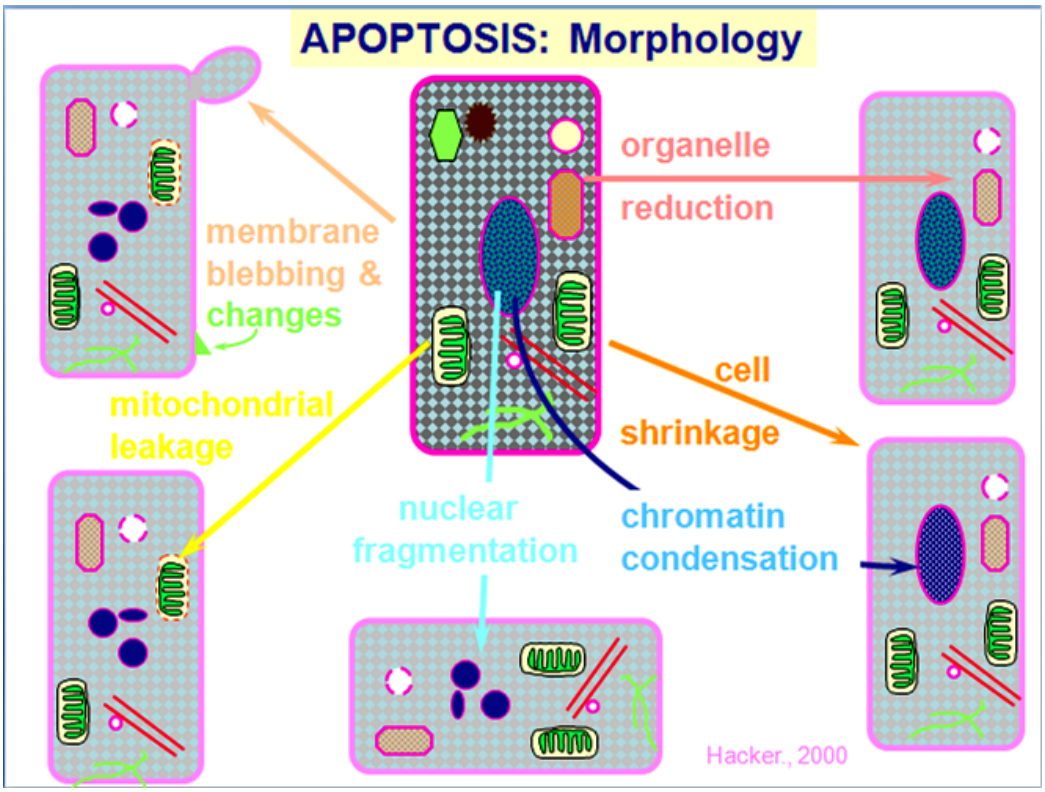
- **Apoptosis is needed to destroy cells for examples:**
  - Cells infected with viruses
  - Cells of the immune system
  - Cells with DNA damage
  - Cancer cells

Cell Death -occurs more often than one imagines!

a) Most embryo development involves programmed cell death.
b) Between 50 and 70 billion cells die each day due to apoptosis in the average human adult. For an average child between the ages of 8 and 14, approximately 20 to 30 billion cells die a day



Apoptosis results in a quick and clean cell death, without damaging its neighbours, or eliciting an immune response. Every cell is equipped with the 'cell death pathway'. Apoptosis is an intracellular proteolytic pathway. The DNA is broken into small 200 bp units.



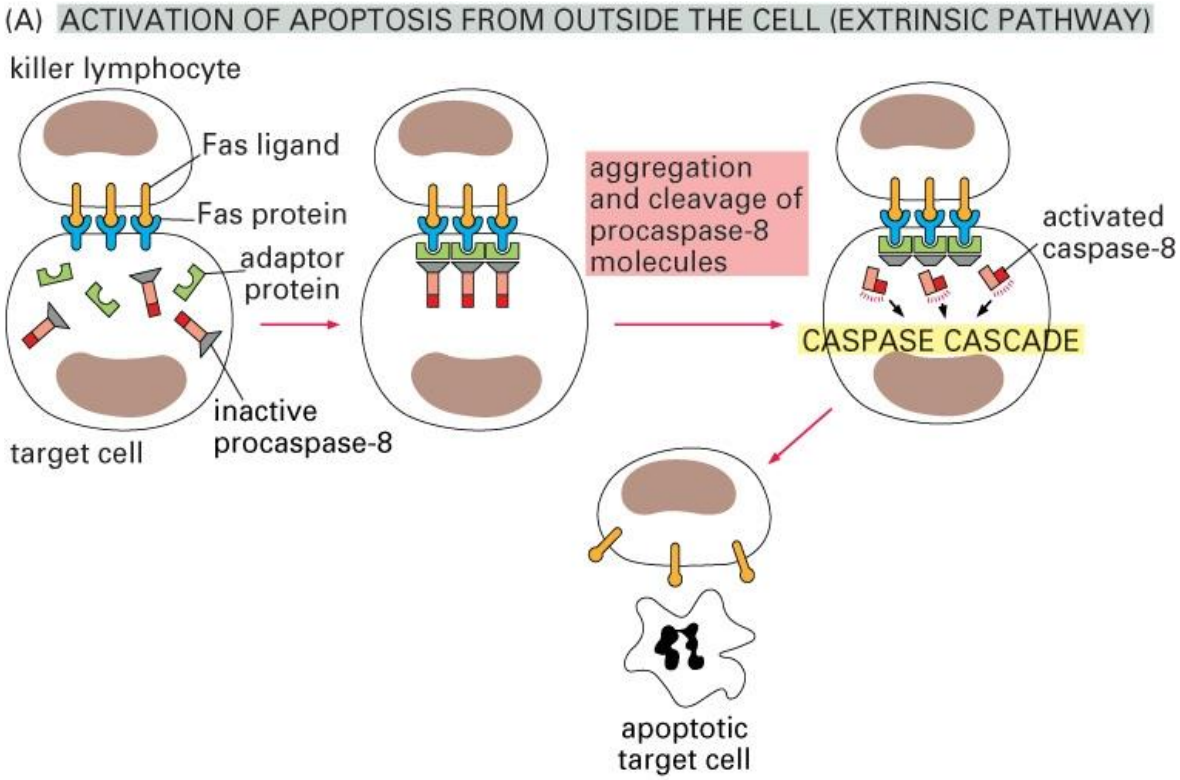
The Mechanisms of Apoptosis
There are 3 different mechanisms by which a cell commits suicide by apoptosis.

1. One generated by signals arising within the cell;
2. another triggered by **death activators** binding to receptors at the cell surface:
    - TNF-α
    - Lymphotoxin
    - Fas ligand (**FasL**)
3. A third that may be triggered by dangerous reactive oxygen species.

Apoptosis: Pathways
Apoptosis can be initiated through one of two pathways. In the **intrinsic pathway** the cell kills itself because it senses cell stress, while in the **extrinsic pathway** the cell kills itself because of signals from other cells.

Extrinsic apoptosis

The extrinsic pathway mediated by the death receptor. The death receptors include Fas receptors, tumor necrosis factor (TNF) receptors, and TNF-related apoptosis-inducing ligand (TRAIL) receptors. As a surface receptor, for example, TNF receptor-1 (TNF-R1), it will interact with TNF to induce the recruitment of adaptor proteins such as Fas-associated protein with death domain (FADD) and Tumor necrosis factor receptor type 1-associated DEATH domain protein (TRADD), which recruits a series of downstream factors, including Caspase-8, which is a critical mediator of the extrinsic pathway, resulting eventually in cell apoptosis.



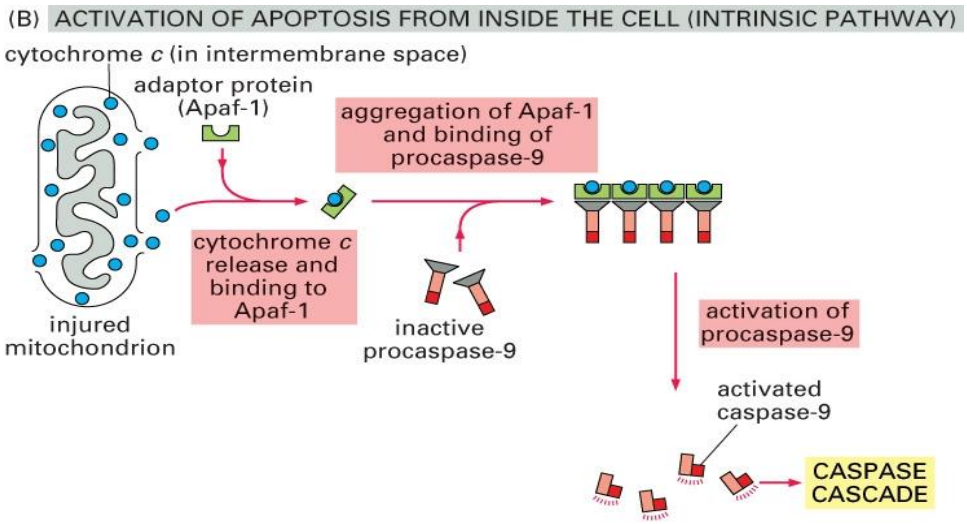
Intrinsic apoptosis

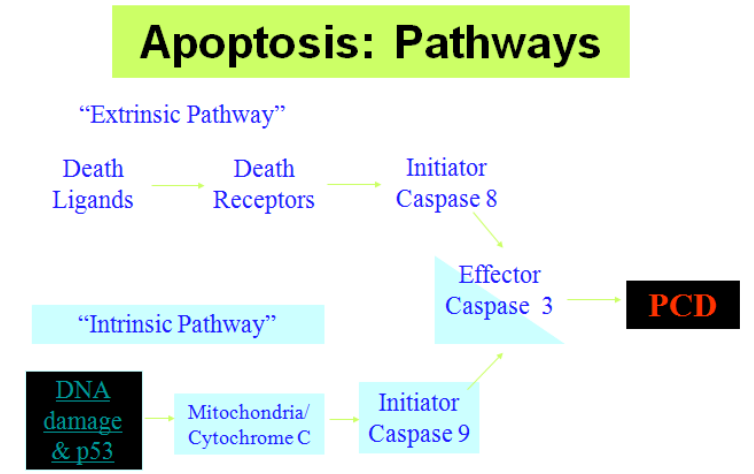
The intrinsic pathway is also known as the mitochondrial pathway. Mitochondria play an important role in the regulation of cell death. Apoptotic proteins that target mitochondria affect them in different ways. They may cause mitochondrial swelling through the formation of membrane pores, or they may increase the permeability of the mitochondrial membrane and cause apoptotic effectors to leak out.

During apoptosis, cytochrome *c* is released from mitochondria through the actions of the proteins Bax and Bak. Once cytochrome *c* is released it binds with Apoptotic protease activating factor – 1 (*Apaf-1*) and ATP, which then bind to *pro-caspase-9* to create a protein complex known as an apoptosome. The apoptosome cleaves the pro-caspase to its active form of caspase-9, which in turn cleaves and activates pro-caspase into the effector *caspase-3*.

Mitochondria also release proteins known as SMACs (second mitochondria-derived activator of caspases) into the cell's cytosol following the increase in permeability of the mitochondria membranes. SMAC binds to *proteins that inhibit apoptosis* (IAPs) thereby deactivating them, and preventing the IAPs from arresting the process and therefore allowing apoptosis to proceed. IAP also normally suppresses the activity of a group of cysteine proteases called caspases which carry out the

degradation of the cell. Therefore, the actual degradation enzymes can be seen to be indirectly regulated by mitochondrial permeability.





P53 & Apoptosis

p53 is a tumor suppressor protein encoded in humans by the TP53 gene. It is a crucial component in multicellular organisms, as it regulates the cell cycle and helps prevent cancer. ... **p53** has many mechanisms of anticancer function, and plays a major role in inhibition of angiogenesis.

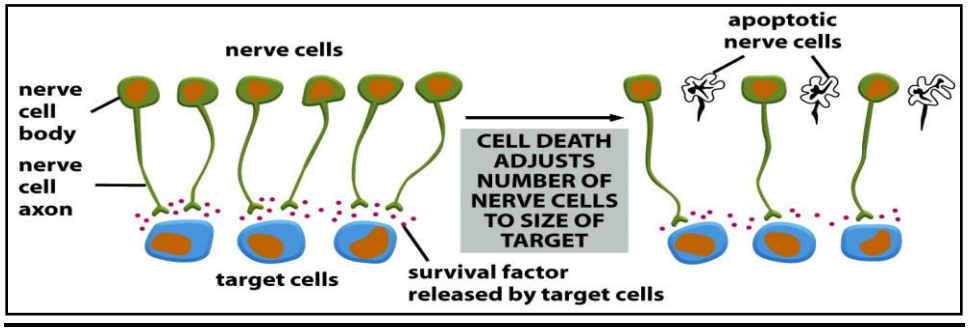
p53 first arrests cell growth between G1 → S This allows for DNA repair during delay If the damage is too extensive then p53 induces gene activation leading to apoptosis (programmed cell death)

One of the several biological functions attributed to p53 is the ability to induce apoptotic cell suicide. It has become clear that this apoptotic activity of p53 is central to its role as a tumor suppressor.

Exposure to cellular stress can trigger the **p53** tumor suppressor, a sequence-specific transcription factor, to **induce** cell growth arrest or **apoptosis**.

Role of Apoptosis:

- **Important in Development of the nervous system during embryogenesis**



- **Apoptosis in Adult**: Immune privilege, DNA Damage and wound repair.

- Excess apoptosis
  - Neurodegenerative diseases
- Deficient apoptosis
  - Cancer
  - Autoimmunity

Diseases Associated with the Inhibition of Apoptosis	Diseases Associated with Increased Apoptosis
1. Cancer	1. AIDS
Follicular lymphomas	2. Neurodegenerative disorders
Carcinomas with *p53* mutations	Alzheimer's disease
Hormone-dependent tumors	Parkinson's disease
Breast cancer	Amyotrophic lateral sclerosis
Prostate cancer	Retinitis pigmentosa
Ovarian cancer	Cerebellar degeneration
2. Autoimmune disorders	3. Myelodysplastic syndromes
Systemic lupus erythematosus	Aplastic anemia
Immune-mediated glomerulonephritis	4. Ischemic injury
3. Viral infections	Myocardial infarction
Herpesviruses	Stroke
Poxviruses	Reperfusion injury
Adenoviruses	5. Toxin-induced liver disease
	Alcohol

Fig. 4. Diseases associated with the induction or inhibition of apoptotic cell death.