Pathology

Sheet Slide

number

4

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APOPTOSIS: PROGRAMMED CELL DEATH

Many examples: embryogenesis; some tissue/ organs produced, and then undergo apoptosis to be replaced by mature tissues.

This is physiological apoptosis, if this death of cells doesn't happen, there will be a problem. It can cause 2 types of diseases: 1)cancer 2) autoimmune disease- recognize the cells as foreign bodies and attack them.

Differences between apoptosis and necrosis:

1. Necrosis is always pathologic (abnormal), but apoptosis can be either pathologic or physiological.
2. Apoptosis can affect a single cell (one cell affected by apoptosis and dies), or a group of cells, but necrosis always affects a group of cells.

3. Pyknosis can occur in the 2 processes, while Karyorrhexis and Karyolysis can only occur in necrosis.
4. **Necrosis is always associated with inflammation**, but apoptosis is NOT associated with inflammation.

Pathologic apoptosis causes mild injury, and it can send a signal to the cell to make it undergo death by apoptosis.

What are the mechanisms of apoptosis? (mechanisms):-

There are 2 families of protein (essential for apoptosis):

- Group of cytosolic proteins called **Caspases** (in cytosol)

Casp: protein rich in Cysteine and aspartic acid, ase: enzyme.
Caspases are usually (as all enzymes) inactive, they should receive signals (intracellular or extracellular) to be activated when apoptosis occurs. And they are two types (subfamilies):

- Initiators (القرار) : to start (begin) the process of apoptosis and they aren't found in all cell types (found only in certain cells).
- Effectors (تنفيذ) : execution of apoptosis, and they are found in all cells.

Apoptosis happens as a cascade, cells that have initiators start the process of apoptosis spontaneously (initiators- themselves- activate and give a signal to effectors), but in cells with no initiators ,cells should receive external signals (they don't undergo the cascade spontaneously).

Types of signals to start apoptosis:

- Intrinsic signal: there are initiators in the cell.
- extrinsic signal: in cells with no initiators.

- Mitochondrial proteins called BCL-2 family (in mitochondria)

Function: to regulate the process of apoptosis

بين بعضنا البروتينات هاي عبارة عن "عناصر أمن" بتمسح للإشارات أنها تعديها أو لا .

They are two types (subfamilies):

- Inhibitors **(suppress apoptosis _BCL-2 / BCL-XL):**they work if cell can repair itself and keep alive.
- Enhancers **(Bax / Bad):**activate cascade of apoptosis.(يشجع الخلية على الانتحار)

Mechanisms of apoptosis: BCL-2 family:

Cytochrome-C in mitochondria , if cytochrome-c leak out to the cytosol, it will encourage cell death.

- Activation of bax/bad will open mitochondrial membrane channel pores and cytochrome-C (cofactor/ signal) will go to cytosol and activate caspases.(and there is another factor called: apoptotic activating (inducing) factor).

عشان ما حد يتخربط و يحكي أنه "السايتوكروم سي" موجود بكل الخلايا و هو السيجنال "السيجنال داخليه او خارجية هي الي بتحفز اخراج السايتوكروم سي"

- Activation of BCL-2 / BCL-XL will keep the mitochondrial membrane channel pores closed and cytochrome-C will remain inside the mitochondria.

Mechanisms of apoptosis:

- Signaling: intrinsic or extrinsic triggers(radiation, toxins, mild injury, free radical) to induce apoptosis
- Control and integration: by the BCL-2 family that can either inhibit (BCL-2 / BCL-XL) or promote(bad/bax) cell death.
- Execution: by the activation of caspases.
- Removal of dead cells: (phagocytosis), if dead cells are of stable or permanent tissues (regeneration will occur), if dead cell are of tissues that can't divide, they will be replaced by fibrous tissue.

Changes under the microscope:

Necrosis: Pyknosis-Karyorrhexis-Karyolysis-the nucleus disappears completely (by DNAase) and cell membrane is disructured.

Endonuclease: divide chromatin to fragments (DNA).

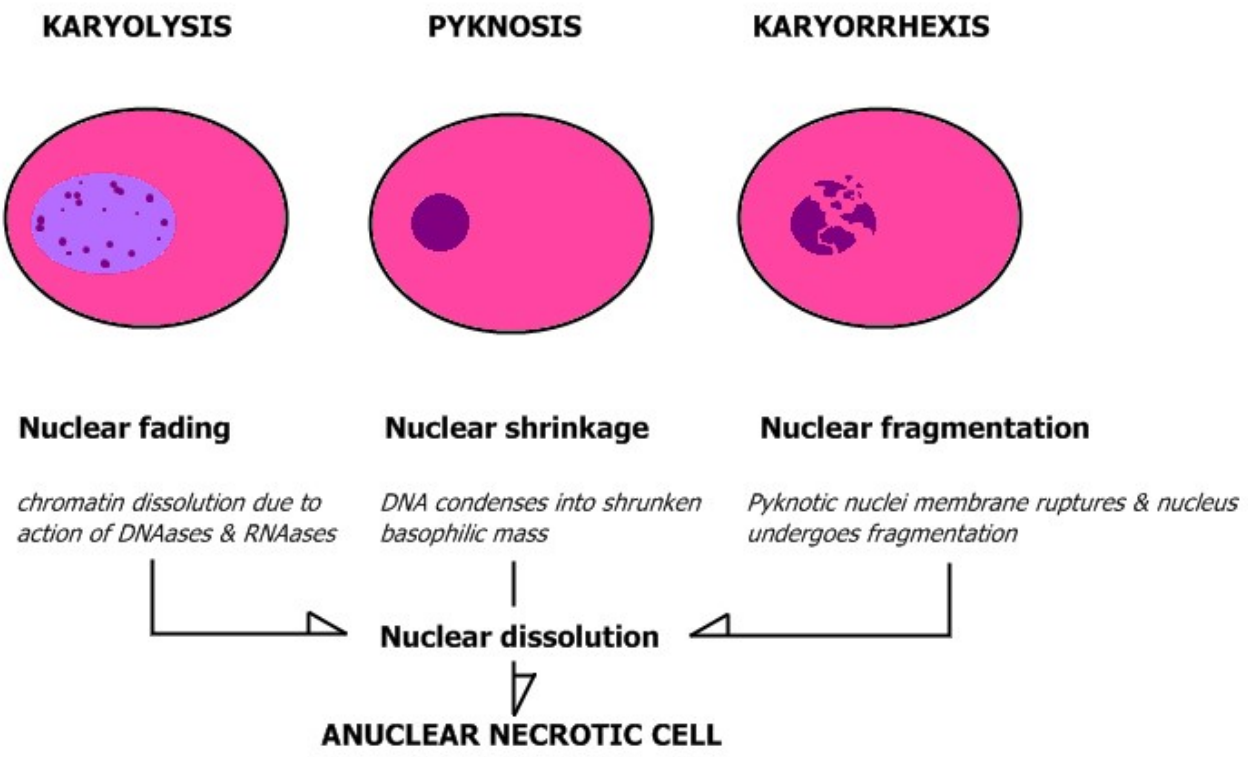
Apoptosis: Pyknosis: chromatin clumping.

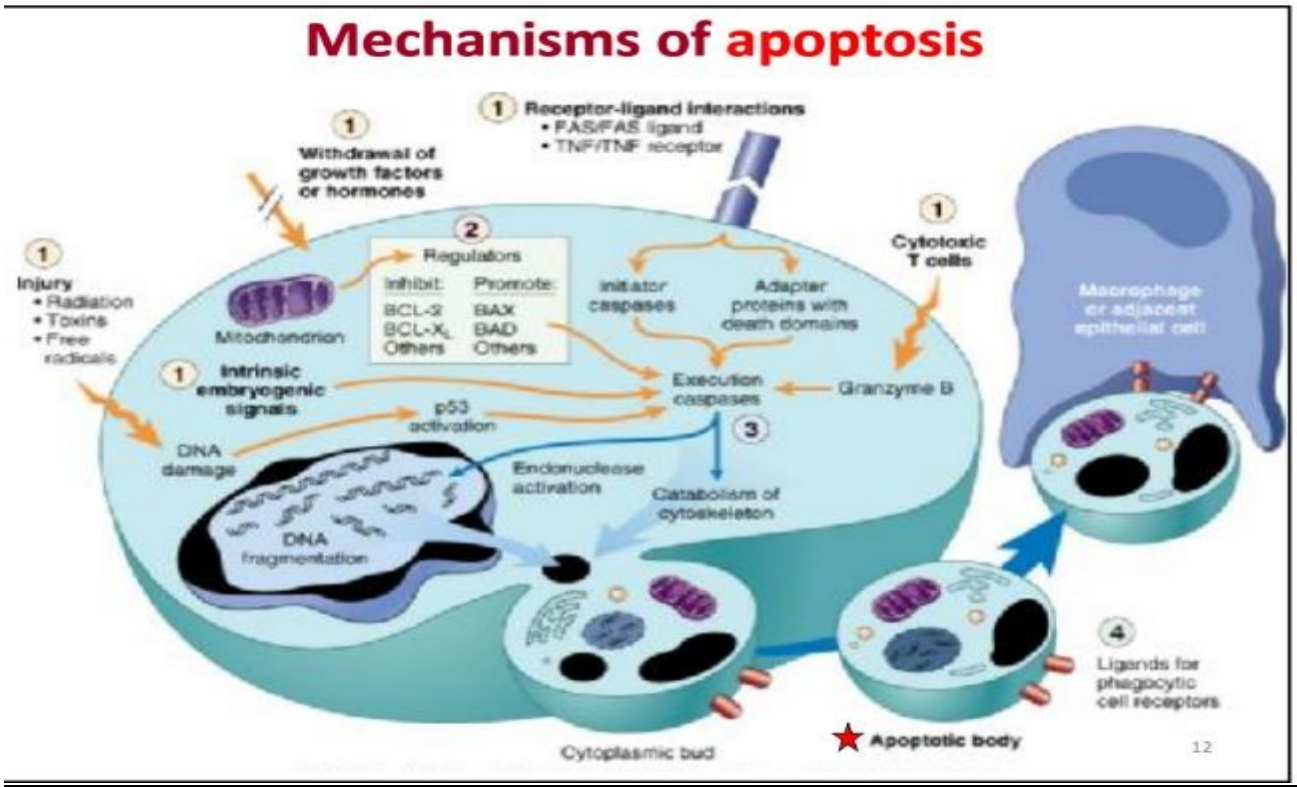
* but after that there will be no karyorrhexis or karyolysis, fragmentation occurs for all cell components **(and cell membrane remains intact to make cellular budding)**

apoptotic body(bud): each group of organelles take part from cell membrane??? ,(so there isn't splitting of cell membrane (no dissolution).

And phagocytosis occurs (step 4: removal of dead cells).

Chromatin clumping : The whole chromatin is gathered in one area so the nucleus shrinks, gets darker and basophilia will increase. Condensation is similar to chromatin clumping but happens mostly near the nuclear membrane.





كل ما عليه رقم 1 في الصورة عبارة عن شكل من أشكال من السيجنال

Intracellular accumulation:

Accumulation of abnormal amounts of substances (materials) inside the cell either in the cytoplasm (typically lysosomes) or in the nucleus.
The accumulated substance might be synthesized by the affected cells or come from outside.
Ex: Plasma cells produce anti bodies (proteins that can cause autoimmune diseases), if plasma cells produce larger amount of anti-bodies than normal, these antibodies won't leave the cytoplasm or the nucleus of plasma cells. (accumulation of material that was previously normal but can't be secreted).

Ex: lipofuscin pigment: (indigestible) some of these pigments will remain in lysosome for many years or forever (residual bodies).
Ex: black carbon particles (not completely digestible by phagocytosis) in lung/lymph nodes lead to anthracosis disease, and the color of the lung or the lymph node will change to black.

Other examples of intracellular accumulations:
Fatty chain : cholesterol.
Hemosiderin (iron).
Triglyceride.
Infectious organisms :viruses or bacteria(mycobacteria TB) that can live in cells for years
General pathways for intracellular accumulation:

- Abnormal metabolism of substances, e.g. fatty liver (absence of enzymes).
- Defective folding and transport of proteins, e.g. alpha-1 antitrypsin deficiency (inhibitor for enzymes, so if alpha-1 antitrypsin has a defect, enzymes won't work and their substrates will accumulate).
- Genetic or acquired lack of enzymes, e.g. some people have sensitivity to milk because absence of lactase.
- Accumulation of exogenous indigestible materials, e.g. carbon.
  2 types of indigestible material:
  Endogenous: pigment normally found in the body(in human: lipofuscin, melanin , hemosiderin).
  exogenous: carbon particles.