[A QUICK SUMMARY]

[pathology, 2nd+4th lecs]

OCTOBER 31, 2020

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[Doctor 2019]

Definitions:

Necrosis = when the cell dies because of the irreversible injury or a pathogenic reasons.

Apoptosis = Programmed cell death / a genetically determined process of cell self-destruction(physiological or pathological condition)/ a pathway of cell death in which cells activate enzymes that degrade the cells' own **nuclear DNA** and **nuclear and cytoplasmic proteins**.

Types of cell injuries

reversible

Cell can get back to normal
No damaged compartments
Little function , but still alive.

Morphologic changes:

-dilation of **ER**
-**mitochondrial** swelling and densities
-Cytoplasmic **myelin figures** appearance.
-**plasma membrane** blebbing and blunting
-nuclear clumping of **chromatin**.

ultra-structural changes>>>**EM**

*-Cell **swelling** (hydropic change), k^+-Na^+ pumps aren't working>>>swelling of the whole organ

*-**Fatty** change (damage of membranes phospholipids so they accumulate in the cytoplasm, forming fatty droplets.)

***Cell damage = enzyme leakage to the blood stream.**

***Activation of enzymes called caspases**

irreversible

Very severe injury
Irreversible injury=cell death or necrosis

Morphologic changes:

*-**Mitochondrial** densities & dysfunction.

*-Loss of **plasma membrane** and **intracellular membranes** >>> cellular enzymes leak out.

*-Loss of **DNA** and **chromatin** structural integrity.

-dilatation of **ER**, **mitochondria**.
-More **myelin figures**
-Increased cytoplasmic **eosinophilia**
-**Nuclear** changes:
*Pyknosis: shrinkage and increased basophilia
*Karyorrhexis: fragmentation
*Karyolysis: basophilia fades

Types of cell death

necrosis

-**rapid, uncontrollable**
-leads to **severe** disturbances
Causes: ischemia, toxins, infections, traumas.
-leads to Local inflammation

necroapoptosis

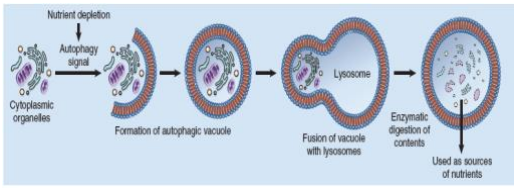
Eg: when ischemia happens, some cells die by necrosis & others by apoptosis

apoptosis

-**Controlled, regulated** by **genes** & **regulatory pathways**
-Can be **modified**
-It is the basic mechanism of some chemotherapeutic agents that **treat cancer**.
-**Causes**: sun induced injury & growth factors.
-the dead cells are removed by macrophages
-peaceful cell death (no inflammation reaction)
-Form **apoptotic bodies** (releasing of cellular content without disrupting of the plasma memb.) no leak of enzymes

Autophagy

-**Self-eating** (Lysosomal digestion of the cells own components)
Survival mechanism in times of nutrient deprivation and starvation, by recycling cells contents to provide nutrients and energy.
involves formation of autophagic vacuoles which are derived from the ER, vacuole fuses with lysosome to form autophagolysosome.
-May lead to **atrophy**.
-Failure of adaptation causes **apoptosis**.



mechanism

Mitochondrial phathway

-**Intrinsic** (because the process starts in the mitochondria)
-Regulated by Bcl-2 protein family which **control mitochondrial membrane permeability** & it is composed of:
Bcl2 & BclX (antiapoptotic -prevent apoptosis-)
Bax & Bak (proapoptotic -activate apoptosis.)
BH3 (sensors in the cytoplasm.)

Death receptor pathway

-**Extrinsic** (because the process starts outside at the surface of the cell)
E.g: elimination of self-reactive lymphocytes & killing target cells
-Death receptors includes a family of TNF receptor which have a cytoplasmic domain causes cell death.
-The prototypes of these receptors:
1) **TNF1** (Type1 tumor necrosis factor) receptors.
2) **Fas** receptors.

It can be

physiologic

1-during **embryogenesis** of the uterus.
2-**hormonal** deprivation *endometrium (apoptosis due to lack of estrogen) & *lactating breast cells.
3-**steady state** population (gut, skin)
-**End** of function (eg: neutrophils apoptosis in the site of inflammation.)
-**Self-reacting** lymphocytes

pathologic

1-**DNA** damage (Rx, chemoTx, temperature, UV, hypoxia)>>> activate **p53** to repair the damage if it doesn't repair the damage the cell will die by apoptosis.

2-Accumulation of misfolded **proteins**

3-Some **infections** (adenovirus, HIV, hepatitis viruses)

This page is about the important details of **apoptotic mechanisms** (that we can't ignore)

Mitochondrial phathway **In <u>normal</u> situations:**

The cell is receiving survival signals, growth factors and no hypoxia, ischemia and DNA damage, these signals will improve the production of the anti-apoptotic proteins (Bcl-2 & Bcl-X).

-The mitochondria stores a substance called "cytochrome C".

-Bcl-2 & Bcl-X guard (يحرس) the membrane to keep the cytochrome C inside the mitochondria in normal conditions and prevent its leakage to the cytoplasm, leads to cell <u>survival</u> and prevention of apoptosis.

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Mitochondrial phathway **In <u>abnormal</u> situations:**

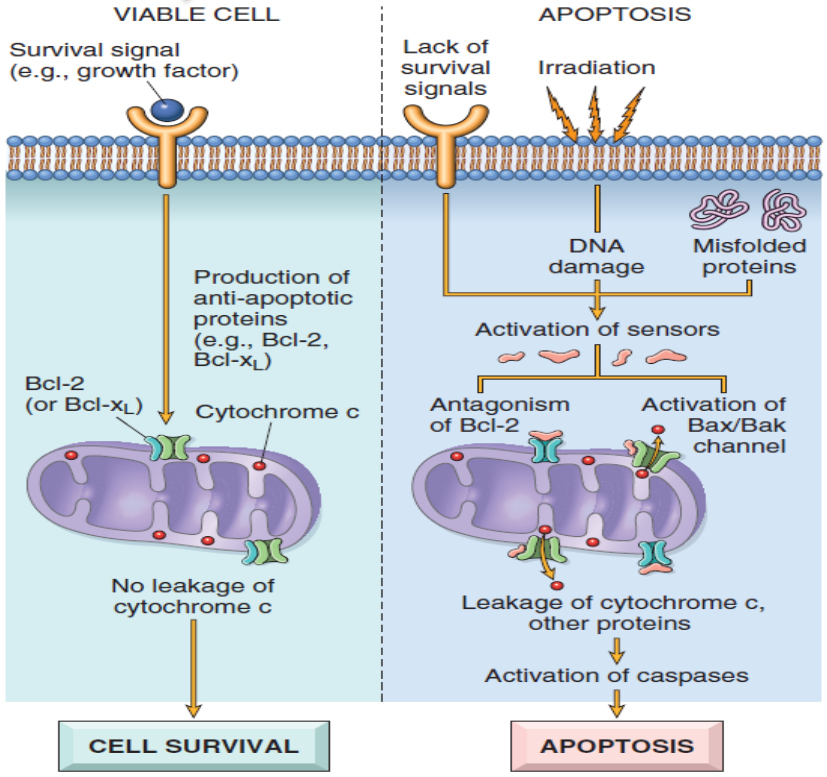
When the cells expose to radiation which can lead to

-DNA damage,

-lack of survival signals and growth factors stimulations

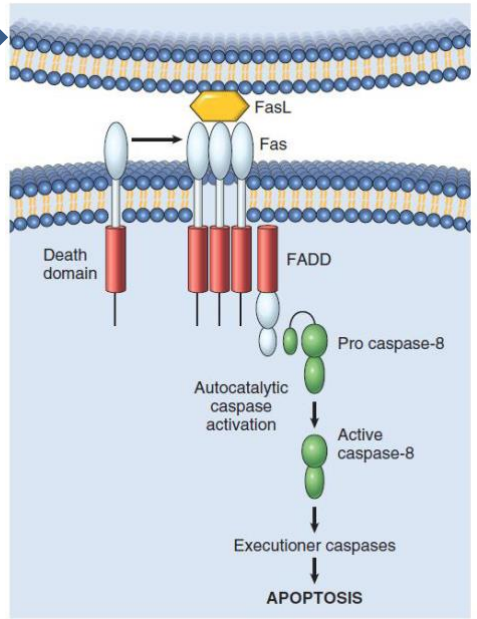
-accumulation of misfolded proteins

BH3 sensors are activated, Bax and Bak are activated too and they will antagonize the action of Bcl-2 and Bcl-X, then bax and bak will dimerize in the wall of mitochondria forming a channel, allowing the leakage of cytochrome C and other pro-apoptotic proteins to the cytoplasm, then cytochrome C activates **caspase-9** which will start a sequence of events that will lead to cell death.



Death receptor pathway

When **T** lymphocytes is activated, **Fas ligand** binds <u><Lock and key binding></u> with the cells that express **Fas receptors** {the cells that are going to die by apoptosis}, the death domain in the cytoplasm is activated, then it will activate **caspase-8** which activate subsequent caspases that lead to destruction of cellular proteins and enzymes and forming of apoptotic bodies.



Morphologic patterns of tissue necrosis

Coagulative necrosis

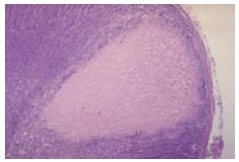
Causes: **ischemia** all solid organs except in the brain

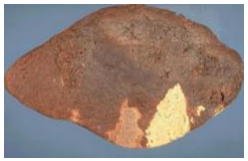
Shape: wood shape, pale area

Others: -Protein & enzymes denaturation.

-The inflammatory cells clean the eosinophilic dead cells.

-**preserved** for many hours or days





gangrenous necrosis

Causes: ischemia, coagulation necrosis at diff. planes of the organ.

Others:

It is a clinical term.

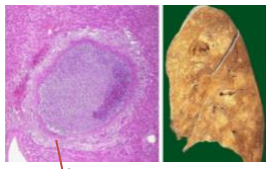
Can be dry or wet.

Liquefactive necrosis

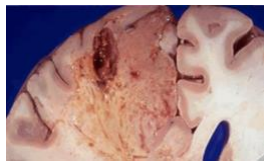
Causes: bacteria or fungal infections, ischemia or CNS infraction

shape: viscous fluid, creamy-yellowish pus

places: brain, lungs



accumulation of inflammatory



Caseous necrosis

Shape: Cheese-like acellular center surrounded by macrophages & inflammatory cells (granulomatous inflammatory borders)=**granuloma**

Others: -**isn't** preserved

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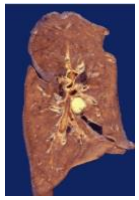
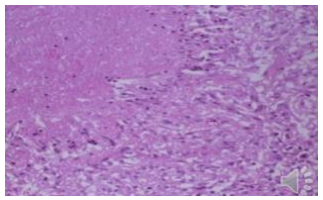
caseous nec.

هو ال

TB (tuberculosis)





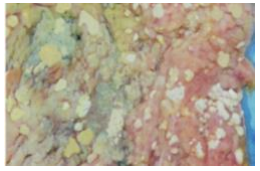
Fat necrosis

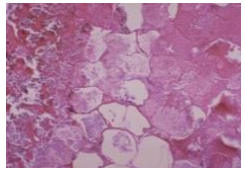
Causes: Lipase enzyme released to the peritoneum and destruct fats, & ca^{2+} binding.

Shape: whitish foci, chalky-like (saponification)

under the microscope: fatty acid shadows without nuclei.

Others: associated with **acute pancreatitis**





fibrinoid necrosis

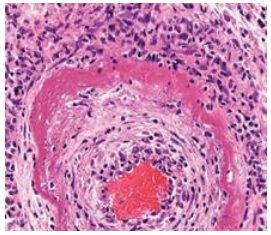
Causes: Fibrin deposition due to antigen-antibody rection in the walls of blood vessels

Shape: pink accumulations (due to the pinkish material in the fibrin.

Others:

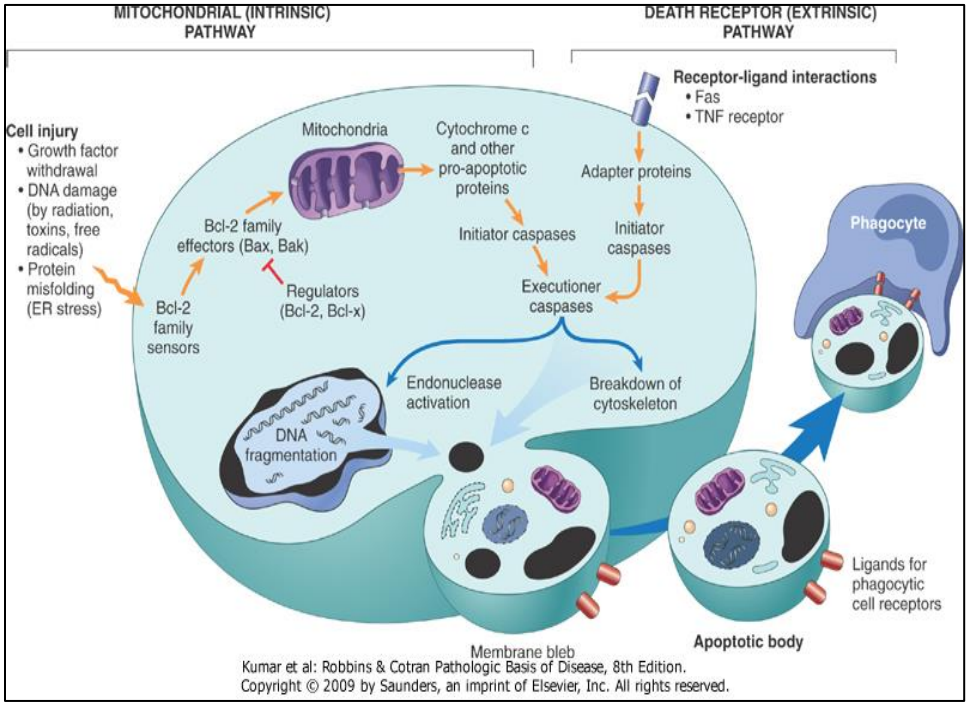
-This disease is associated with vasculitis.

-can **only** be seen under the microscope



Important pics & tables

Feature	necrosis	Apoptosis
Cell size	Enlarged(swelling)	Reduced(shrinkage)
Nucleus	Pyknosis, Karyorrhexis, karyolysis	Fragmentation into nucleosome- size fragments
Plasma membrane	**Disrupted**	**Intact**, altered structure, especially orientation of lipids
Cellular content	Enzymatic digestion, may leak out of cell	Intact, may be released in apoptotic bodies.
Adjacent inflammation	**Frequent**	**No**
Physiologic or pathologic role	Invariably pathologic	often physiologic and may be pathologic



Condition	Mechanism of Apoptosis
Physiologic	
During embryogenesis	Loss of growth factor signaling (presumed mechanism)
Turnover of proliferative tissues (e.g., intestinal epithelium, lymphocytes in bone marrow, and thymus)	Loss of growth factor signaling (presumed mechanism)
Involution of hormone-dependent tissues (e.g., endometrium)	Decreased hormone levels lead to reduced survival signals
Decline of leukocyte numbers at the end of immune and inflammatory responses	Loss of survival signals as stimulus for leukocyte activation is eliminated
Elimination of potentially harmful self-reactive lymphocytes	Strong recognition of self antigens induces apoptosis by both the mitochondrial and death receptor pathways
Pathologic	
DNA damage	Activation of proapoptotic proteins by BH3-only sensors
Accumulation of misfolded proteins	Activation of proapoptotic proteins by BH3-only sensors, possibly direct activation of caspases
Infections, especially certain viral infections	Activation of the mitochondrial pathway by viral proteins Killing of infected cells by cytotoxic T lymphocytes, which activate caspases