APOPTOSIS

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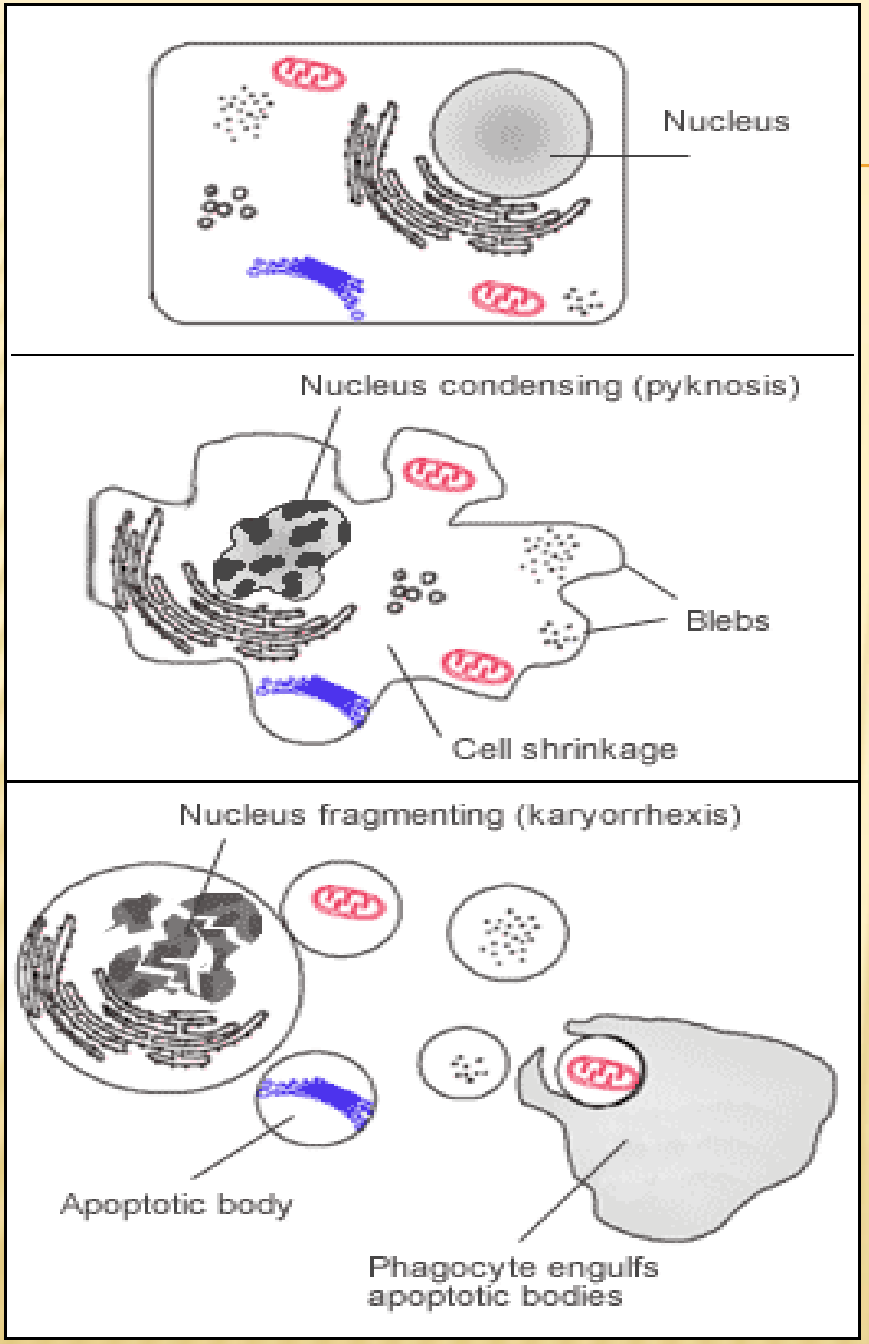
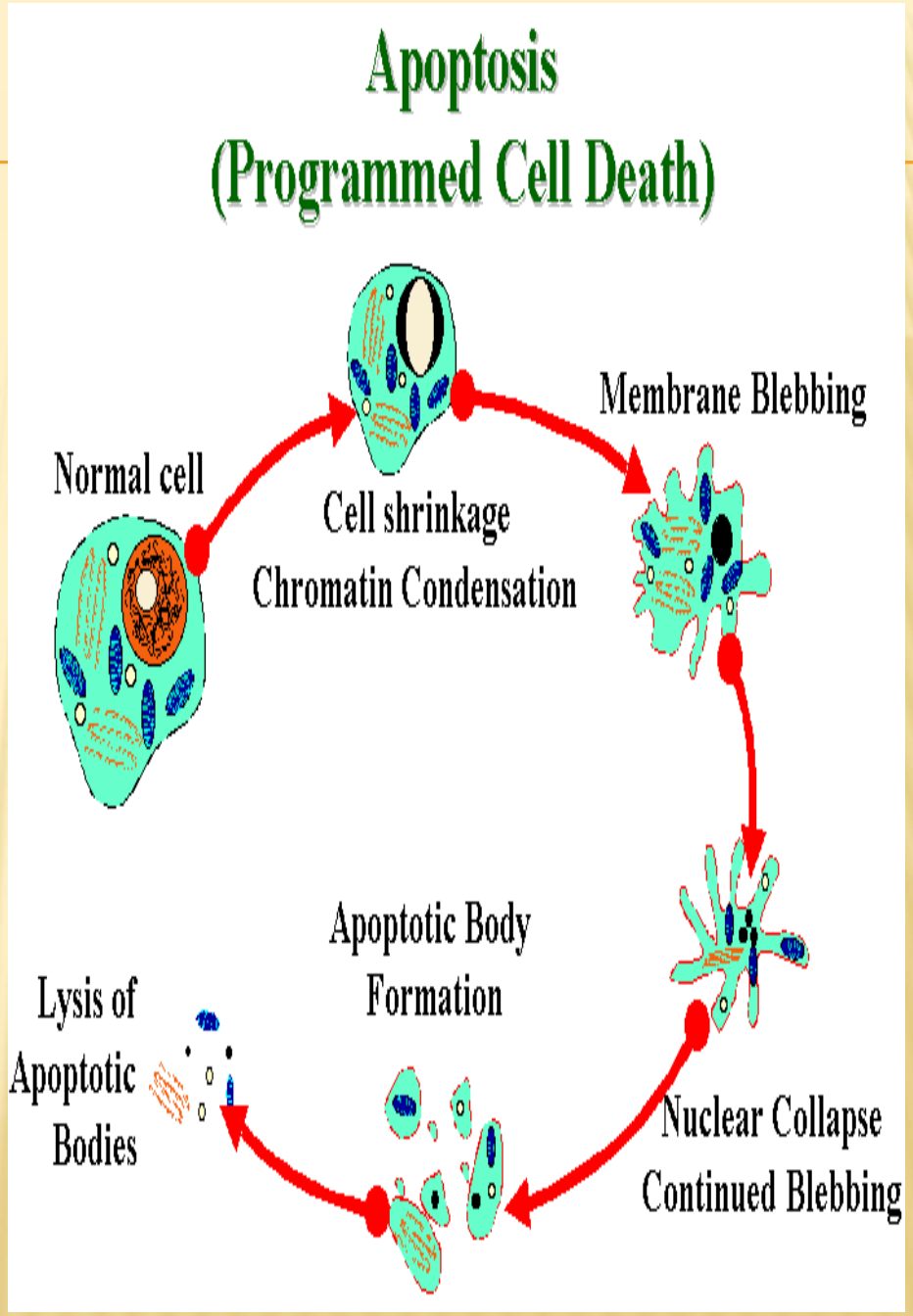
- What the Apoptosis means?
- Is the Apoptosis a normal process?
- Modes of cell death?
- Terminal differentiation & replicative senescence, Necrosis


Nucleus
Nucleus condensing (pyknosis)
Blebs
Cell shrinkage
Nucleus fragmenting (karyorrhexis)
Apoptotic body
Phagocyte engulfs
apoptotic bodies


Apoptosis
(Programmed Cell Death)
Normal cell
Cell shrinkage
Chromatin Condensation
Membrane Blebbing
Apoptotic Body
Formation
Nuclear Collapse
Continued Blebbing
Lysis of
Apoptotic
Bodies

– Apoptosis Characterizations:

1.process with controlled fashion

2. Cell with apoptosis develop multiple blebs on their surface.

3. lose of cell-cell connection.

4. Lose their connection to the extracellulatr matrix.

5. Round of and fragmented into small membrane enclosed particles phagocytosed and lost from tissue.

6. DNA will fragmented into large- more than 50 Kb- fragments- nucleosomal units- nucleosomal ladder

7.Apoptosis dose not evoke an inflammatory reaction.

Necrosis Characterizations

1. Uncontrolled process .1
2. Occurred in the damaged cells .2
3. Necrotic cells, swelling , burst , releasing their content. .3
4. Induce inflammation .4
5. Occurred with out energy .5

. .6

Terminal Differentiation

– Process like apoptosis attack the differentiated cells and stopping cells in cell cycle for check then allow it to go for next step.

–Its low or disappear in cancer.

- Multinuclear cells or cells with polyploid are target for this process.

Terminal Differentiation & Cancer

– Low rate in cancer

– or complete lack

Replicative senescence

– Presents a limit to the life span of normal human somatic cells and stimulate by telomere degrading and p53 , RB genes.

– In fibroblast 50-80 cell doublings

– In epithelial cells its much earlier.

– RS can be prevented by DNA viruses infection, SV40

-The process talk out the cells from cycle for differentiation with irreversible step.

RS characterization

–Irreversible exit from the cell cycle

–Cells undergoing RS often take on a characteristic morphology like:

– Flattened appearance

– Large nuclei

–With many small granules

–Express some characteristic proteins such as, SAB-GAL, B-galactosidase

–With high level of CDK such as p21 CIPI ,p16INK4A

Induction of RS

By two different instances:

1. Classic mode which occurred after propagation of normal human cells over many passages.
2. Rapid mode long before cells have exhausted their normal life span by inappropriate proliferation signals of mutated ras protein.

RS in germ lines ,stem cells, early precursor cells and cancer cells

– with lower degree than differentiated somatic cells.

– more than 100 division

–immortalization of cancer tissue culture versa human body cancer

– cancer can avoid RS by acquiring a kind of stem cell character, testes cancer, ovary cancer , basal cell carcinoma of the skin, colon carcinoma.

Mechanisms of Apoptosis

Stages of Apoptosis

1. Initiation , performed by Intrinsic & extrinsic pathway toward execution pathway. .1
2. Execution .2
3. Removal

Intrinsic Pathway

– Mitochondrial Pathway

–Response to internal signal such as DNA defects Or cellular disfunction.

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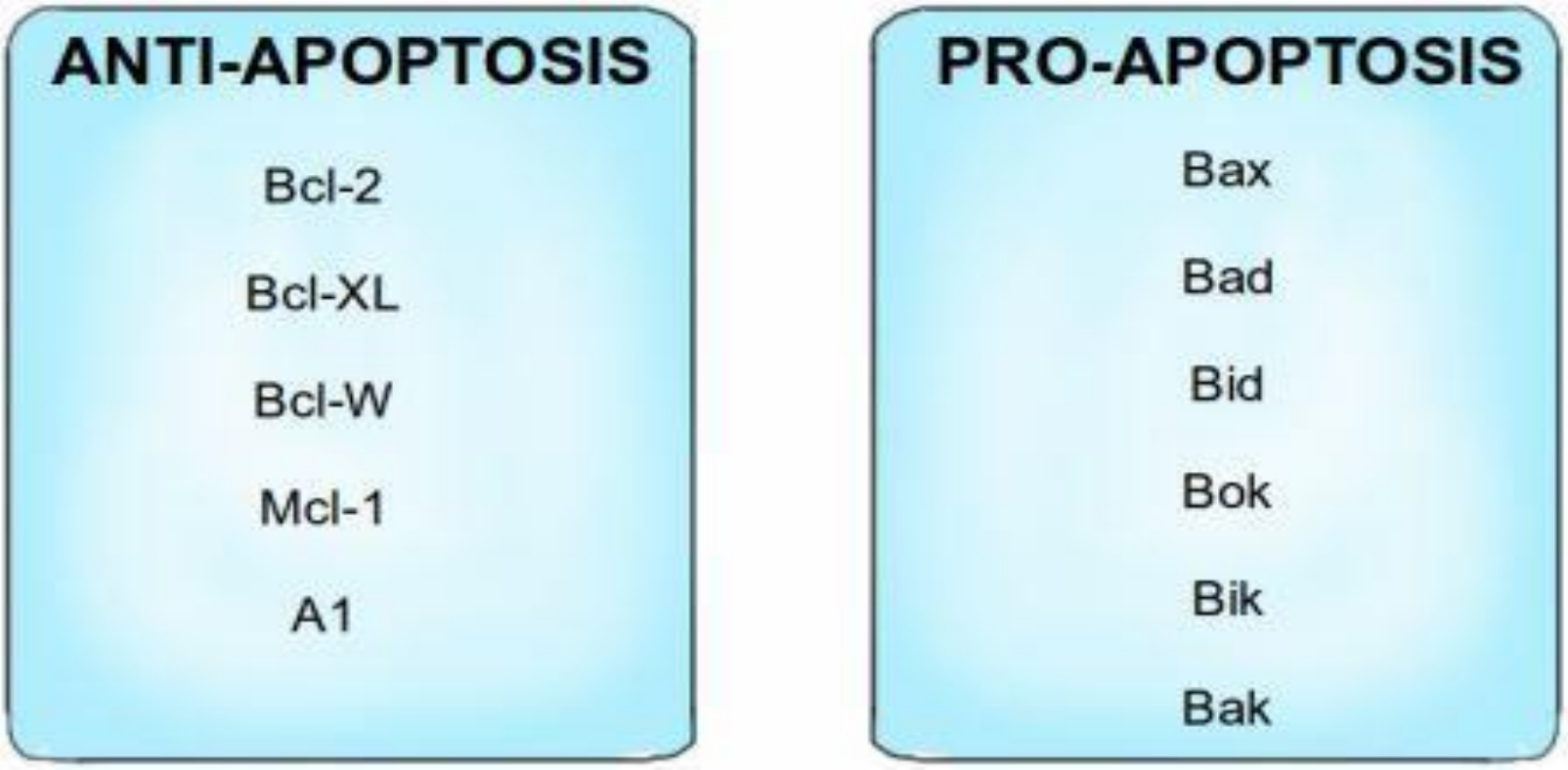
The pathway include three types of proteins of Bcl2 family- C-oncogenes:

1.Pro-apoptotic proteins such as NOXA, PUMA

2. Anti-apoptotic proteins (Inhibitor of apoptosis, IAPs) such as Bcl2, Bcl-XL, smac,DIABLO

3. Inhibitors proteins to anti-apoptotic proteins such as BAX , BAK.


ANTI-APOPTOSIS
Bcl-2
Bcl-XL
Bcl-W
Mcl-1
A1
PRO-APOPTOSIS
Bax
Bad
Bid
Bok
Bik
Bak

Induction of Apoptosis:

1. Inhibition of anti-apoptotic proteins.
2. Expression of Pro-apoptotic proteins such as NOXA, PUMA and p53 which stimulate BID protein to split into p13 and p15 small proteins.

3. This lead to inhibit the BAK and BAX protein- proteins keep normal permeability in mitochondria .1

4. This will increase the permeability of mitochondria with the help of Caspase 8 &10 enzymes. Pores formation- .2

5.Apoptotic inducing factors-AIF- will secreted by mitochondria such as cytochrome C and SMAC\Diablo protein. .3

6. In the cytoplasm, 8 molecules of cytochrome C will bind to 8 molecules of APAF1 to produce spokes of a wheel- Death Wheel- Apoptosome .4

Stopping apoptosis

–Via caspases inhibition using small proteins called Inhibtor of apoptosis proteins-IAPs such as BIR , XIAP , Survivin against caspases 9 &3.

– Viruses secrete IAPs analogs to inhibit the intrinsic pathway of apoptosis.

Extrinsic Pathway:

.– Induced by external signal- ligand

–Attacked infected cells with death receptors- TNFR-CD95-FAS

—Cytotoxic T cells & Natural Killer cells – CD95L-FAS L

– MHC –Class 1 histocompatibility of infected cell bind to CD8+ of T-cell.

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