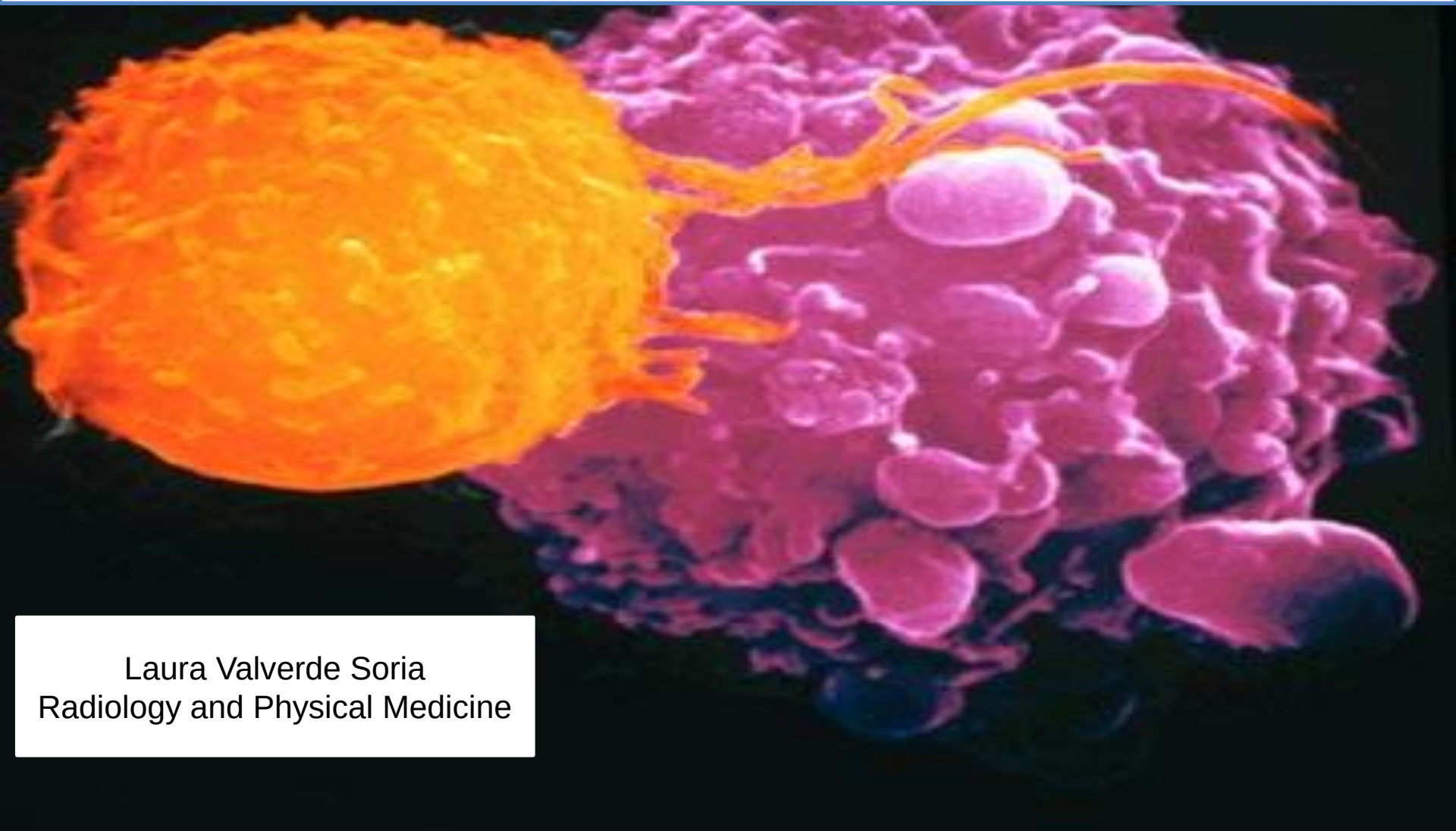
APOPTOSIS AND RADIATION



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APOPTOSIS

APOPTOSIS → PROGRAMMED CELL DEATH

- ✓ Apoptosis is a natural phenomenon: each cell contains in its genome the information that establishes the number of divisions that that cell is going to suffer, as well as its average life expectancy.
- ✓ This natural apoptosis allows homeostasis: in a certain tissue, the number of cells that are created equals the number of cells that disappear due to apoptosis.
- ✓ This balance might be altered by external agents such as radiation.
- ✓ Apoptosis is a very well regulated mechanism and it's triggered by intra or extra cellular signals (intrinsic or extrinsic route).

Apoptosis is different both at morphological and molecular level from other kinds of cell death

The DNA molecule is fragmented at certain points, the nucleosomes

DNA fragments that correspond to multiples of 200 base pairs are obtained. Electrophoresis shows a “ladder pattern”.

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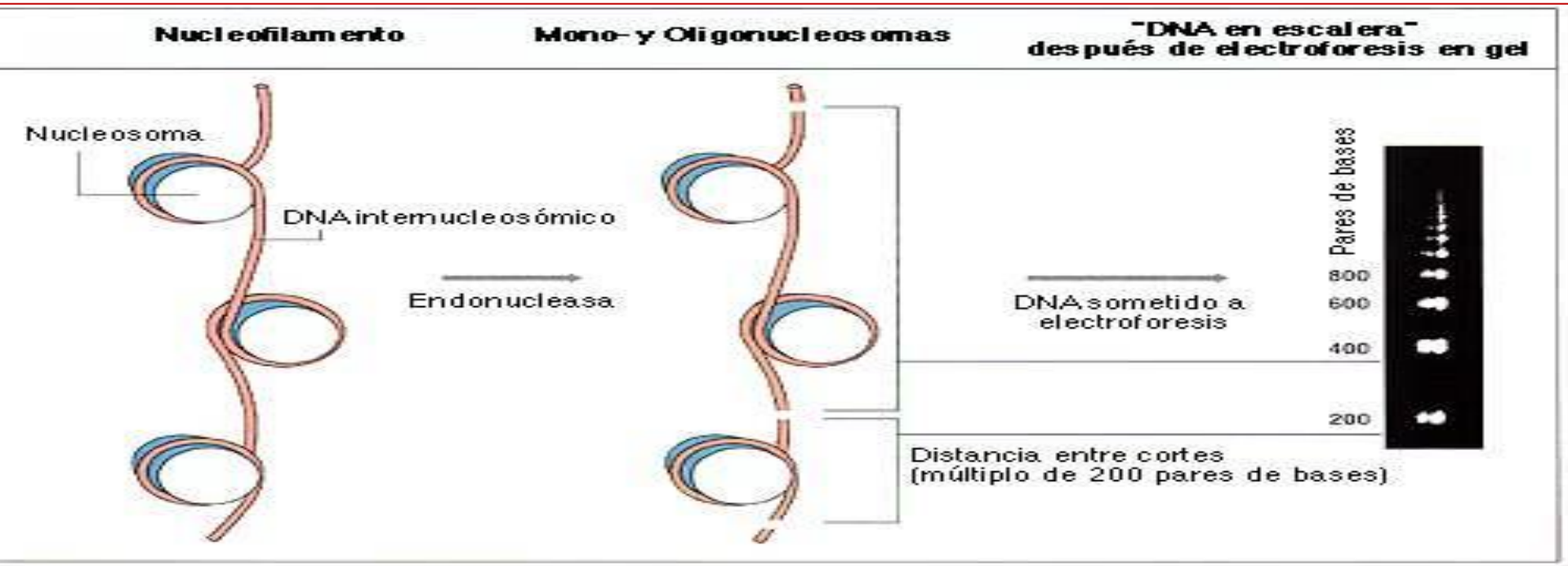
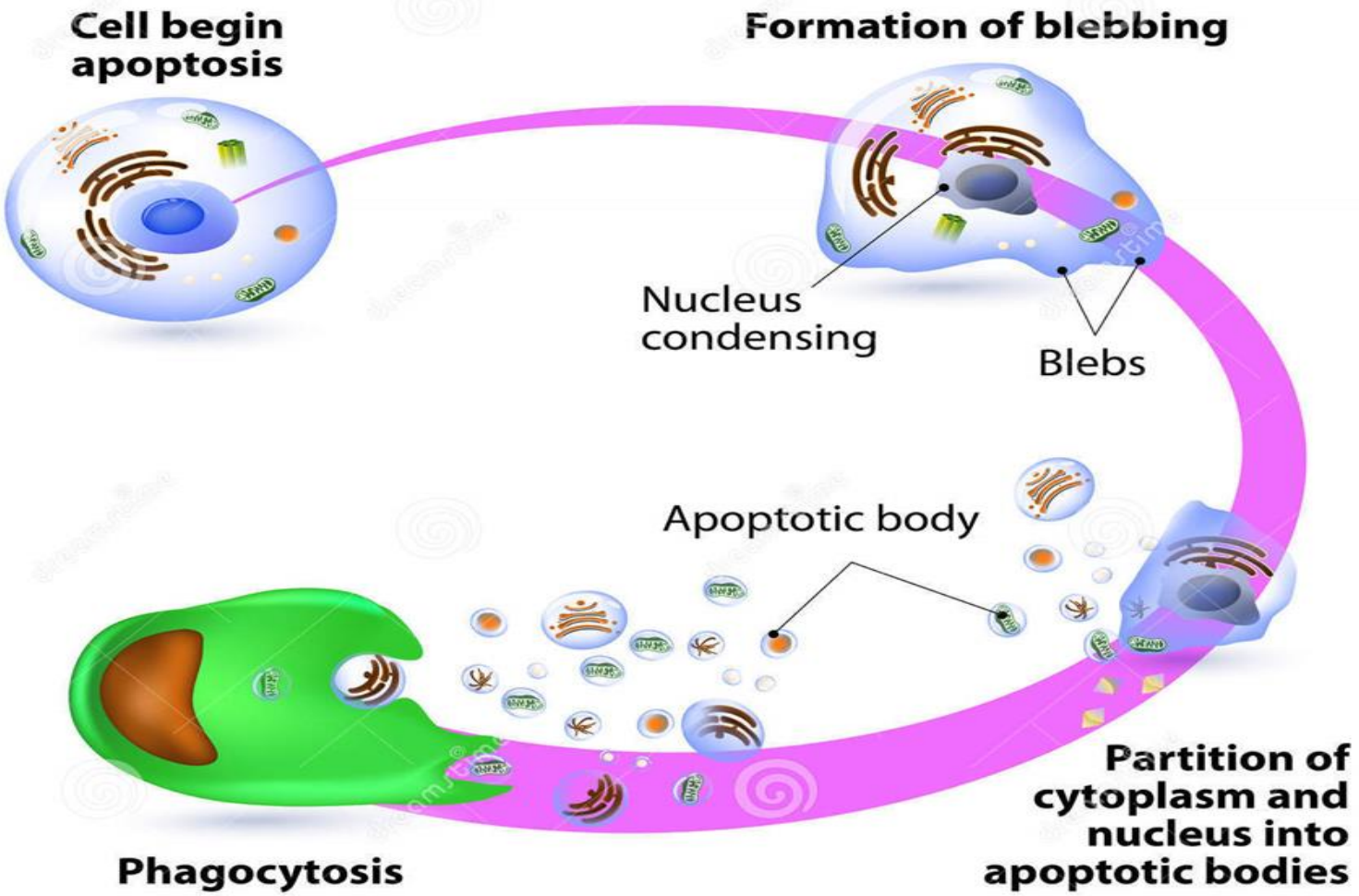


MORPHOLOGICAL CHANGES

1. Evaginations appear in the cell membrane.
2. Chromatin condensation and DNA fragmentation.
3. Citoskeleton destruction
4. Pyknoctic nucleus
5. The cell is fragmented into apoptotic bodies that are phagocytized.

THERE ARE NO INFLAMMATORY CHANGES

APOPTOSIS


Cell begin apoptosis
Formation of blebbing
Nucleus condensing
Blebs
Apoptotic body
Partition of cytoplasm and nucleus into apoptotic bodies
Phagocytosis

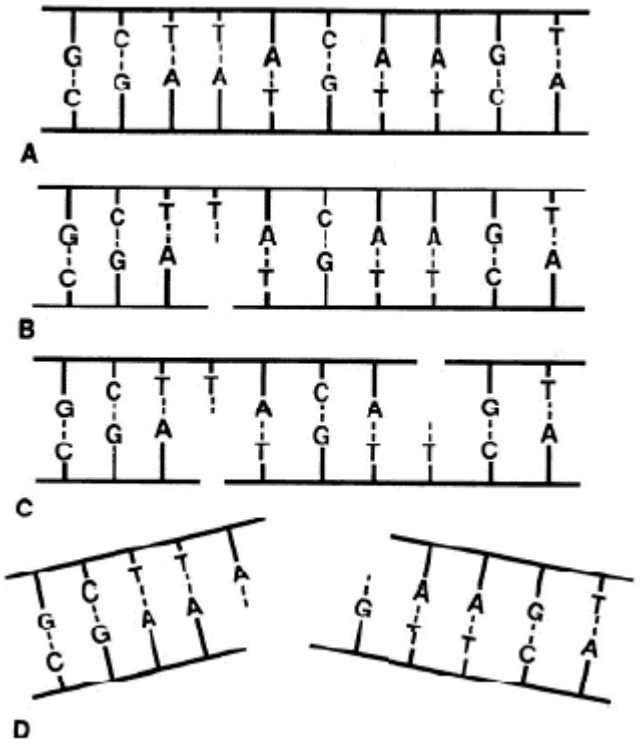
IONIZING RADIATION

The initial effects of ionizing radiation are the ionization and excitation of the atoms or molecules found in its trajectory

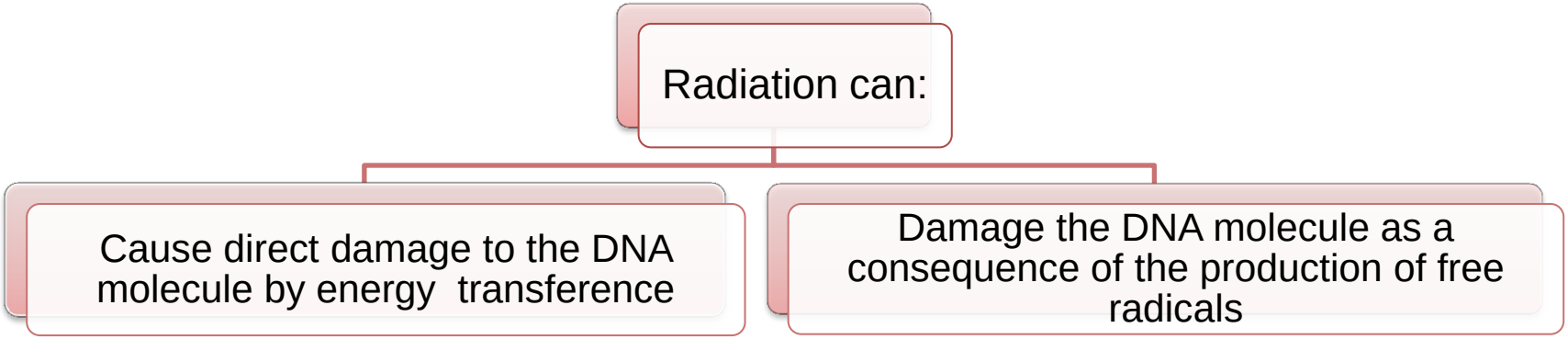
The deposit of this energy is responsible for the biological effects, which stem mainly from the damage to the chemical structure of the cells, especially to the DNA molecule (2)

Type of DNA lesions caused by radiation

- ✓ Damage to the nitrogenous bases
- ✓ Single strand breakage:
  - In one strand (B)
  - In both strands but far from each other (C)
- ✓ Double strand breakage(D)
- ✓ Multiple located damage



(3)

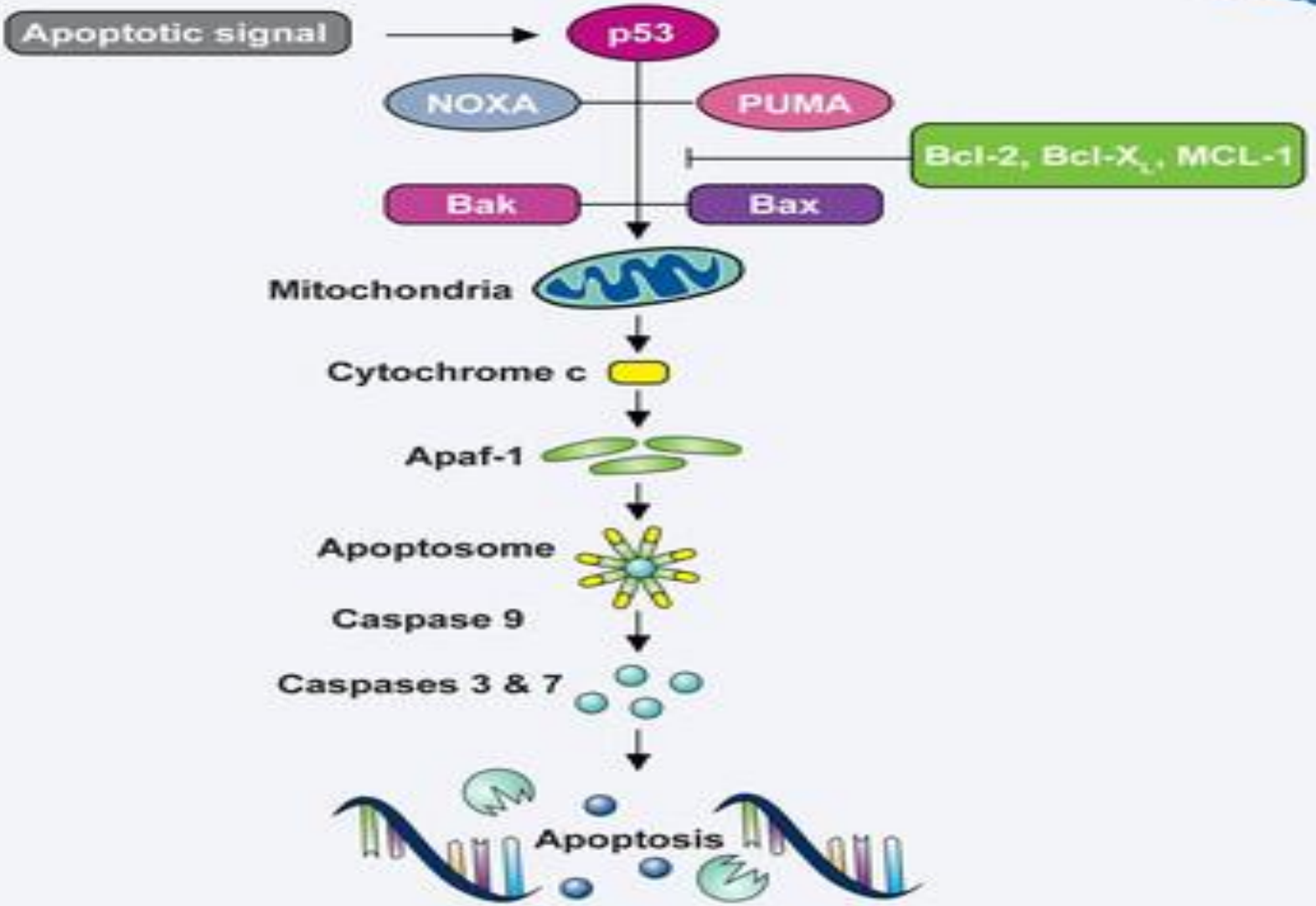


THIS DAMAGE TRIGGERS THE CELLULAR <u>DNA DAMAGE RESPONSE (DDR):</u>

1º. A sensor molecule warns about the damage

2º. Transductor and effector molecules that are activated make the cell stop at the different check points of the cell cycle.

Radioinduced apoptosis usually involves the INTRINSIC route, dependent on the mithocondria



CLINICAL USE

Knowing the DDR pathways we can act on them in order to increase the tumoral cells response to radiotherapy, inhibiting their damage repair mechanisms.

DDR defects are a common feature of a lot of tumors which affect the response to radiation

EXAMPLE:

- ✓ Generally, the activation of the G1/S check points does not happen in tumoral cells (due to the alteration of p53 or changes on the ATM or ATR proteins that are involved on the S phase check point)
- ✓ This cells only have the G2 control mechanism

  We can develop strategies that inhibit this mechanism (such as **AZD7762** which is provided together with radiotherapy (4)) → mutated cells do not stop their progress along the cell cycle, they keep on dividing, accumulating more mutations → CELL DEATH.

BIBLIOGRAFHY

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(3) *http://sisbib.unmsm.edu.pe/bibvirtualdata/tesis/basic/bernui_vm/Cap4.PDF*

(4) *Zabludoff SD, Deng C, Grondine MR, Sheehy AM, Ashwell S, Caleb BL et al. AZD7762, a novel checkpoint kinase inhibitor, drives checkpoint abrogation and potentiates DNA-targeted therapies.* Mol Cancer Ther [Internet] 2008 Sep [cited 2015 May 15]: 7(9):2955-66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18790776