
GOOD
MORNING!

ABNORMAL CELL GROWTH

Dr. Ahmad Salahuddin

Cells are often lost.

Cells are often replaced at the same rate they are lost in a highly regulated state of balance.

If normal cellular regulatory mechanisms malfunction, unregulated and unchecked cell division may result, a condition known as cancer.

GENES AND CANCER

Cancer is a stepwise process. Often, several genetic alterations must occur at specific sites before malignant transformation is seen.

Normal cells respond to a complex set of biochemical signals, which allow them to develop, grow, differentiate, or die.

Cancer results when any cell is freed from these types of restrictions and the resultant abnormal progeny of cells are allowed to proliferate.

Mutations in the key genes have to accumulate over time to create a progeny of cells that have lost most control over growth.

Each individual mutation contributes in some way to eventually producing the malignant state.

The accumulation of these mutations spans several years and explains why cancers take a long time to develop in humans.

Both exogenous (environmental insults) and endogenous processes (carcinogenic products generated by cellular reactions) may damage DNA.

DNA damage that goes unrepaired may lead to mutations during mitosis.

Cells become cancerous when mutations occur in protooncogenes and tumor suppressor genes.

Protein products of protooncogenes are involved in growth stimulation;

the protein products of tumor suppressor genes repress cell growth and division.

Therefore, loss of gene function can lead to cell transformation by removing the restraints that normally regulate cell growth.

Protooncogenes and oncogenes

Protooncogenes stimulate the cell cycle and control cell growth, proliferation, and differentiation.

Mutations that alter protooncogenes may convert them from regulatory genes into cancer-causing oncogenes.

When such mutations accumulate, the progressive deregulation of growth eventually produces a cell whose progeny forms a tumor.

Tumor suppressor genes

Tumor suppressor genes are important for maintaining normal cell growth control by halt unregulated progression through the cell cycle.

Situations that diminish tumor suppressor gene function may lead to neoplastic changes.

The most frequently inactivated tumor suppressor gene is the p53 gene, which encodes p53, which is most often implicated in cancer development. More than half of human cancers show p53 mutations.

p53 is important in preventing cancer because of its unique functional capabilities as it

- regulates gene expression and controls several key genes involved in growth regulation.
- facilitates DNA repair. When DNA damage is encountered, p53 senses the damage and causes G1 arrest of the cells, until the damage is repaired.
- activates apoptosis of damaged cells. When damage to DNA within cells is beyond repair, p53 functions to trigger apoptosis in these cells.

Tumor progression

Cancer cells gain metastatic abilities as they evolve.

Among these are genes whose products allow the breakdown of tissue structure and invade the basement membrane, allowing cells to migrate to other sites.

As tumors accumulate in cellular mass, it is critical that they induce the growth of blood vessels, or angiogenesis, to supply the growing tumor with adequate nutrition and oxygen for its continued growth and survival.

Angiogenesis and tumor progression

As cancers progress, they accumulate in mass. To obtain the necessary nutrition and oxygen for their continued growth and survival, it is critical for tumors to have adequate blood supply.

Cancer cells create new blood supply to sustain their growth by several mechanisms.

Angiogenesis, or neovascularization, can be both activated and inhibited.

Under normal physiologic conditions, angiogenic inhibitors predominate, blocking the growth of new blood vessels.

When there is a need for new vasculature, activators increase in number and inhibitors decrease.

Tumors release two proangiogenic factors, which are important for sustaining tumor growth: vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).

One mechanism for tumor neovascularization involves mutation of p53 gene.

Typically, p53 regulates the expression of thrombospondin (an angiogenesis inhibitor).

Mutations in p53 facilitate neovascularization due to the lack of production of thrombospondin.

Apoptosis and Cancer

There are many ways a malignant cell can acquire reduction in apoptosis or apoptosis resistance.

Generally, the mechanisms by which evasion of apoptosis occurs can be broadly dividend into:

1. disrupted balance of pro-apoptotic and anti-apoptotic proteins,
2. reduced caspase function and
3. impaired death receptor signaling

Disrupted balance of pro-apoptotic and anti-apoptotic proteins:

Anti-apoptotic Bcl-2,

Mutant p53, and

Inhibitor of apoptosis proteins (IAPs).

The Bcl-2 family of proteins is comprised of pro-apoptotic and anti-apoptotic proteins that play a pivotal role in the regulation of apoptosis.

When there is disruption in the balance of anti-apoptotic and pro-apoptotic members of the Bcl-2 family, the result is dysregulated apoptosis in the affected cells.

This can be due to an overexpression of one or more anti-apoptotic proteins or an underexpression of one or more pro-apoptotic proteins or a combination of both.

Resistance to cancer chemotherapy in some tumors may also be caused by the overexpression of Bcl-2 and defective apoptosis.

IAPs are a group of structurally and functionally similar proteins that regulate apoptosis, cytokinesis and signal transduction.

IAPs are endogenous inhibitors of caspases.

Reduced caspase function:

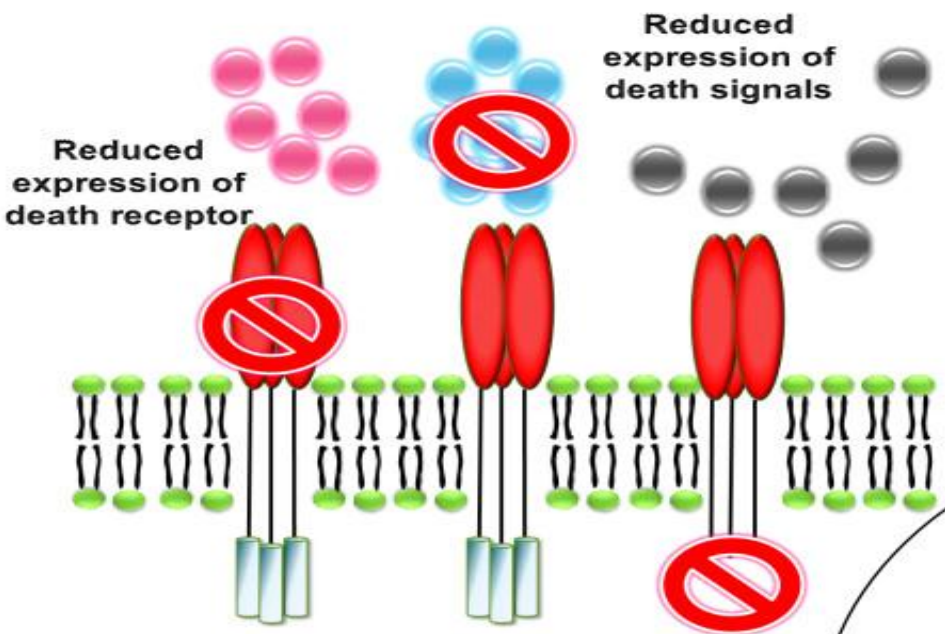
Caspases remain one of the important players in the initiation and execution of apoptosis.

It is therefore reasonable to believe that low levels of caspases or impairment in caspase function may lead to a decreased in apoptosis and carcinogenesis.

Impaired death receptor signaling:

Several abnormalities in the death signaling pathways that can lead to evasion of the extrinsic pathway of apoptosis have been identified.

Such abnormalities include reduced expression of death receptor, reduced expression of death signals, or expression of receptor trimmers without death domain.



Impaired receptor signaling pathway

Overexpression of antiapoptotic proteins

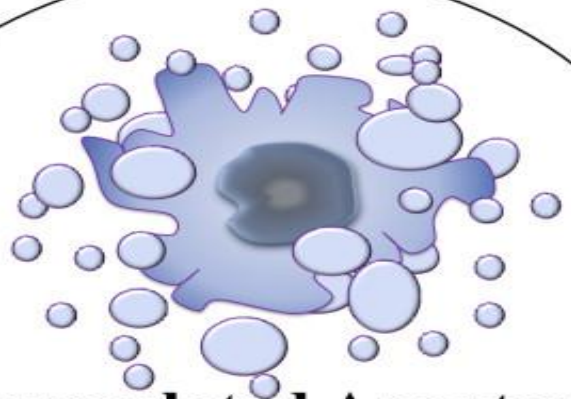
Group I
Bcl-2, Bcl-xL, Mcl-1, Bcl-w, A1/BF-1, BclB/Bcl2L10

Underexpression of proapoptotic proteins

Group II
Bid, Bim, Puma, Noxa,Bad, Bmf, Hrk, Bik

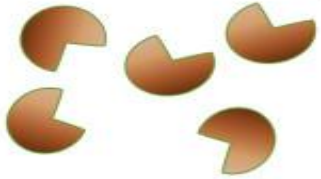
Group III
Bax, Bak, Bok/Mtd

Disrupted balance of Bcl-2 family of proteins

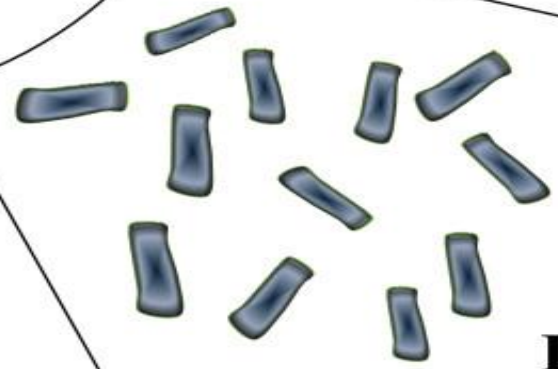


Dysregulated Apoptosis & Cancer

Defects/ mutations in p53



Reduced expression of caspases



Increased expression of IAPs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wonderful
monday