SAWA UNIVERSITY

BASIC PATHOLOGY/FIRST COURSE

CARCINOGENESIS

Sawa University — جامعـــــة ســـــــاوة الاهلية

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. Third Stage — المرحلـــــــــــة الثالثة

محاضرة رقم :4

الجانب النظري

Lecture No. FOUR

Theoretical

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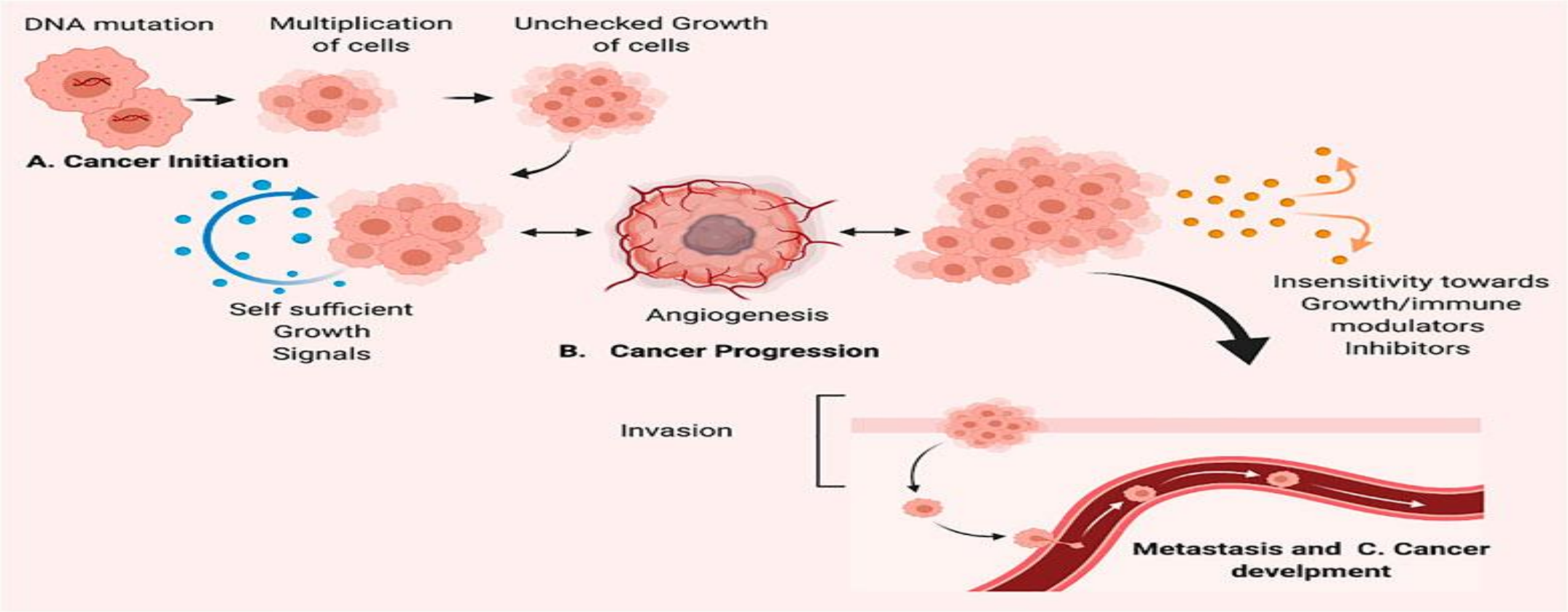
MOLECULAR BASIS OF CANCER (CARCINOGENESIS):



FUNDAMENTAL PRINCIPLES OF CARCINOGENESIS:

Nonlethal genetic damage lies at the heart of carcinogenesis.

*This genetic damage (or mutation) may be acquired by the action of environmental agents

like (chemicals, radiation, viruses), or may be inherited in the germ line.

*Tumors are monoclonal: A tumor is formed by the clonal expansion of a single precursor

cell that has acquired genetic damage (founding cell)

*FOUR CLASSES OF GENES ARE THE PRINCIPAL TARGETS OF GENETIC DAMAGE:

*Four classes of genes are the principal targets of genetic damage:

I. Growth promoting protooncogenes (dominant genes, can transform cells into malignant

cells with single allele is damaged).

II. Growth inhibiting cancer suppressor genes (recessive genes, can transform cells into

malignant cells only if both alleles of gene are damaged).

III. Genes that regulate the apoptosis.

IV.DNA repair gene, disability of DNA repair genes can predispose to widespread

mutation & neoplastic transformation.

CARCINOGENESIS

is a multistep process resulting from the accumulation of multiple

mutations. These mutations accumulate independently in different clonal cells, generating

subclones with varying abilities to grow, invade, metastasize, and resist (or respond to)

therapy. Over a period of time tumors not only increase in size but become more

aggressive and acquire greater malignant potential (tumor progression).

MECHANISMS OF ACTION OF ONCOPROTEINS:

A. Growth factors:

All normal cells require stimulation by growth factors to undergo proliferation. Most soluble growth factors are made by one cell type and act on a neighboring cell to stimulate proliferation (paracrine action). In contrast Many cancer cells acquire growth self sufficiency by synthesizing the same growth factors to which they are responsive (autocrine action). For example:

*Many glioblastomas secrete platelet-derived growth factor (PDGF) and express the PDGF receptor.

*Many sarcomas make both transforming growth factor-α (TGF-α) and its receptor.

B. Growth factor receptors: Mutant genes lead to one of two consequences:

1. Formation of mutant receptor proteins that deliver continuous mitogenic signals to cells,

even in the absence of the relevant growth factor in the environment.

2. Overexpression of growth factor receptors, which can render cancer cells hyper responsive to normal levels of the growth factor that would not normally trigger proliferation. For example:

*EGFR (ERBB1); is overexpressed in 80% of squamous cell carcinomas of the lung, 50%

or more of glioblastomas, and 80% to 100% of epithelial tumors of the head and neck.

*HER2/NEU (ERBB2); is amplified in approximately 20% of breast cancers.

C. Signal transduction proteins:

*Cancer cells acquire autonomous growth is by mutation in these genes that control the

signaling pathway (transfer of signal from inner side of cell membrane to nucleus).

*Two important genes that control this pathway (Ras…. increase cells proliferation &

ABL……inhibit cell proliferation).

D. Nuclear Transcription Factors:

Mutations affect the genes that regulate transcription of DNA may result in autonomous

growth of cancers.

e.g. Myc gene; -Dysregulation of MYC expression is seen in Burkitt's lymphoma
-MYC is amplified in some cases of breast, colon, lung, and many other carcinomas.

-Normal cell cycle is consisting of five phases (G0, G1, S, G2, M). -All these phases are under control of proteins (Cyclins & Cyclins dependent Kinase). -Mutations that dysregulate the activity of cyclins and CDKs would favor cell proliferation. -Cyclin D overexpress

TUMOR SUPPRESSOR GENES

cause inhibition of cell growth by two pathways: -

1. Stimulate antigrowth signal, causing cells to enter G0 phase.

2. Prevent the cell to pass from phase G1 to S phase.

*Disruptions of tumor suppressor genes make the cells resistant to inhibition of growth &

increase their proliferation.

EXAMPLES OF TUMOR SUPPRESSOR GENES:

1. RB gene:

This is the first discovered suppressor gene, loss of normal RB gene was discovered

initially in Retinoblastoma, but recently proved it lost in many tumors (breast cancer,

bladder & lung cancer, osteosarcoma). Both alleles of RB gene must be mutant in order to regard this gene is mutant

2. Adenomatous Polyposis coli (APC) gene:

Loss of this gene can be seen in 70- 85% of sporadic carcinoma of colon.

Individuals born with Loss or mutant of one of alleles of APC gene, they develop hundreds

to thousands of adenomatous polyps in the colon which on second decade of life one or

more of these polyps will undergo malignant transformation.

-It is one of most commonly mutated gene in human cancers. -Normal p53 prevents neoplastic transformation by: -

I.

activation of temporary cell cycle arrest (quiescence),

II.

induction of permanent cell cycle arrest (senescence)

III.

triggering of programmed cell death (apoptosis). -In view of these activities, p53 has been rightfully called a "guardian of the genome." -More than 70% of malignant human tumor show defect in functions of TP53. -Most of mutations in TP53 are acquired & less commonly they are inherited mutations

like Li- fraumeni syndrome (patient have many cancers like sarcomas, breast cancer,

leukemia, brain tumors, adrenal tumors). -With homozygous loss of p53, DNA damage goes unrepaired, mutations become fixed in

dividing cells, and the cell turns onto a one-way street leading to

malignant transformation.

INVASION AND METASTASIS

The Metastatic pathway of cancer can be divided into two phases:

1. Invasion of Extracellular matrix: Include the following steps

I. Detachment of tumor cells from each other (by losing of E- cadherin & B- catenin

molecules).

II. Degradation of Extracellular Matrix (by Metalloproteinase).

III. Attachment of tumor cells to new Extracellular Matrix components.

IV. Migration of tumor cells to the vessels (mediated by Cytokines).

2. Vascular dissemination & Homing of tumor cells: -In circulation, Tumor cells are liable to destruction by host immune cells. To avoid such

destruction, tumor cells are arranged themselves into small emboli (by adhesion to

circulating leukocytes & platelets). -Then tumor cells leave circulation by adhesion to the endothelial cells & destruction of

basement membrane of vessels, to enter the extracellular matrix of metastatic site. -Distribution of metastasis can be predicted by the location of primary tumor & its

vascular & lymphatic drainage e.g. cancer of breast is expected to involve the lung &

bones of thorax. -Some cancers have unexpected metastatic pathway e.g. caner of lung metastasizes to the

adrenal glands.

SUMMARY

- **Carcinogenesis**: It means how normal cells turn into cancer cells. This happens because of changes (mutations) in the DNA.
- **Basic Principles**: Cancer starts when cells get damaged but don’t die. They keep growing and dividing in the wrong way.
- **Oncogenes**: These are genes that push cells to grow. If they become too active, they can cause cancer.
- **Tumor Suppressor Genes**: These are “brake” genes. They stop cells from growing too much. If they stop working, cancer can happen.
- **Tumor Progression and Spread**:
  - Cancer starts small, then grows and becomes more dangerous.
  - It can invade nearby tissues.
  - It can spread to other parts of the body (called metastasis), which makes it harder to treat.

QUIZ

Any questions?