Chemical Carcinogenesis and Mutagenesis

INTRODUCTION

Cancer is a classification of diseases in which there is an uncontrolled proliferation of cells that express varying degrees of fidelity to their precursor cell of origin.

This cell proliferation occurs in almost all tissues throughout a lifespan and is influenced by a variety of circumstances.

During the normal physiologic state, the delicate balance

between cell proliferation and apoptosis (programmed cell death) is perpetuated to ensure the integrity and proper function of organs and tissues.

Mutations in DNA that lead to cancer development interfere with this orderly process by disrupting its regulation.

Consequently, the initiation of a cancer is due to an abnormal and uncontrolled progression of cell proliferation characterized by unregulated cell division and metastasis (spreading) of foci of cells to distant tissues.

Most chemical carcinogens require metabolic activation before demonstrating carcinogenic potential.

Mutagenesis refers to the ability of a virus or chemical agent to induce changes in the genetic sequence of mammalian or bacterial cells, thus altering the phenotypic expression of cell characteristics.

Genotoxicity refers to the ability of an agent to induce heritable changes in genes that exercise homeostatic control in somatic cells while increasing the risk of influencing benign or malignant transformation.

By definition, cancer must have at least six criteria:-

1-Self-sufficiency in growth signals .

2-Insensitivity to antigrowth signals .

3-Evasion of apoptosis .

4-Tissue invasion and metastasis .

5-Sustained angiogenesis.

6-Limitless replicative potential.

MECHANISMS OF CHEMICAL CARCINOGENESIS

Metabolism

Carcinogenic agents initiate cancer progression by using one of two pathways:-

1-Parent chemicals can cause cancers directly, such as with heavy metals.

2-Some chemicals, such as organic chemicals, require metabolic activation to reactive intermediates to affect the carcinogenic process.

carcinogens that require metabolic activation to exert their carcinogenic effects are termed procarcinogens, whereas their highly reactive metabolites are designated ultimate carcinogens.

Cytochrome P450 Phase 1 and Phase 2 enzymes are involved in the metabolism of carcinogens and usually result in the formation of reactive metabolites.

Phase 2 enzyme-catalyzed reactions often lead to detoxification and elimination, which effectively protects against chemical carcinogenesis.

Free Radicals and Reactive Oxygen Species

As with the chemical activation of procarcinogens to proximate and ultimate carcinogens the bioactivation of chemicals also results in the formation of free radicals and reactive oxygen species (ROS)—that is, chemical species that **cause oxidative damage to biomolecules, including nucleic acids (DNA), proteins, and lipids.**

These reactive species are generated by ionizing radiation, ultraviolet light, and a variety of exogenous and endogenous cellular sources.

ROS interaction with DNA induces the formation of adducts, which may lead to the activation of proto-oncogenes and/or the inactivation of tumor suppressor genes. Free radicals and ROS are also able to target cell signaling molecules, including transcription factors and protein kinase cascades, resulting in altered cell signal transduction and gene expression. The ability of free radicals and ROS to elicit DNA mutations and cause dysregulated cell signaling contributes to the multistage carcinogenesis.

Mutagenesis.

As mentioned previously, mutagenesis occurs when the mammalian or bacterial cell genetic sequence is altered such that transcription and translation are transformed.

This induces a modification of the phenotypic expression of cell characteristics which more often results in permanent pathologic changes rather than beneficial adjustments.

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Exogenous Sources	**Endogenous Sources**
UV light and Ionizing radiation, Organic chemicals Heavy metals, Airborne nanoparticlesa	**Mitochondria** **NAD(P)H oxidase** **Xanthine oxidase** **Transition metals**
Reactive Oxygen Species (ROS)	
Genomic DNA **Nucleotide base modifications** **Strand breakage** **Inhibition of DNA repair**	**Cell signal Transduction:** **Oxidation of** **transcriptional activators** **protein kinase cascades**

enzymes	
DNA mutations	**Dysregulation of Cell Growth** **Differentiation and Death**
MULTISTAGE CARCINOGENESIS	