General Toxicology

Non-Organ Directed Toxicity (Part I)
Carcinogenesis

Lec. 4
4th Year
2020-2021

Lecturer Rua Abbas Al-Hamdy
College of Pharmacy/Al Mustansiriyah University
Department of Pharmacology & Toxicology

Objectives of this lecture are to:

- Define carcinogenesis & its stages,
- Determine the modes of action of carcinogens,
- Explain the modes of action & classes of genotoxic carcinogens,
- Determine the modes of action of non-genotoxic carcinogens,
- Determine chemical carcinogenesis in humans,
- Identify some occupational human carcinogens, &
- Identify some human carcinogenic chemicals associated with medical therapy.

Carcinogenesis:

- Cancer is a disease of cellular mutation, proliferation, & aberrant cell growth.

- It ranks as one of the leading causes of death in the world.

- Estimates suggest that 70% to 90% of all human cancers have a linkage to environmental, dietary, & behavioral factors.

Multistage carcinogenesis:

Stages of carcinogenesis process involve:

- initiation,
- promotion, &
- progression.

Initiation:

- The first stage of the cancer process involves initiation, a process that is defined as a stable, heritable change.

- This stage is a rapid, irreversible process that results in a carcinogen-induced mutational event.

- Chemical & physical agents that interact with cellular components at this stage are referred to as initiators or initiating agents.

Promotion:

- The second stage of the carcinogenesis process involves the selective clonal expansion of initiated cells to produce a preneoplastic lesion.

- Both exogenous & endogenous agents that operate at this stage are referred to as tumor promoters.

- Promotion is reversible upon removal of the promoting agent.

- Tumor promoters generally show organ-specific effects, e.g., a tumor promoter of the liver, such as phenobarbital, will not function as a tumor promoter in the skin or other tissues.

Progression:

- Progression involves the conversion of benign preneoplastic lesions into neoplastic cancer.

- The progression stage is irreversible in that neoplasm formation, whether benign or malignant, occurs.

- With the formation of neoplasia, an autonomous growth &/or lack of growth control is achieved.

Mechanism of action of chemical carcinogens:

Carcinogens have frequently been divided into two major categories (Fig. 1) based on their general mode of action:

- Genotoxic &
- Nongenotoxic carcinogens.

Modes of action of carcinogens

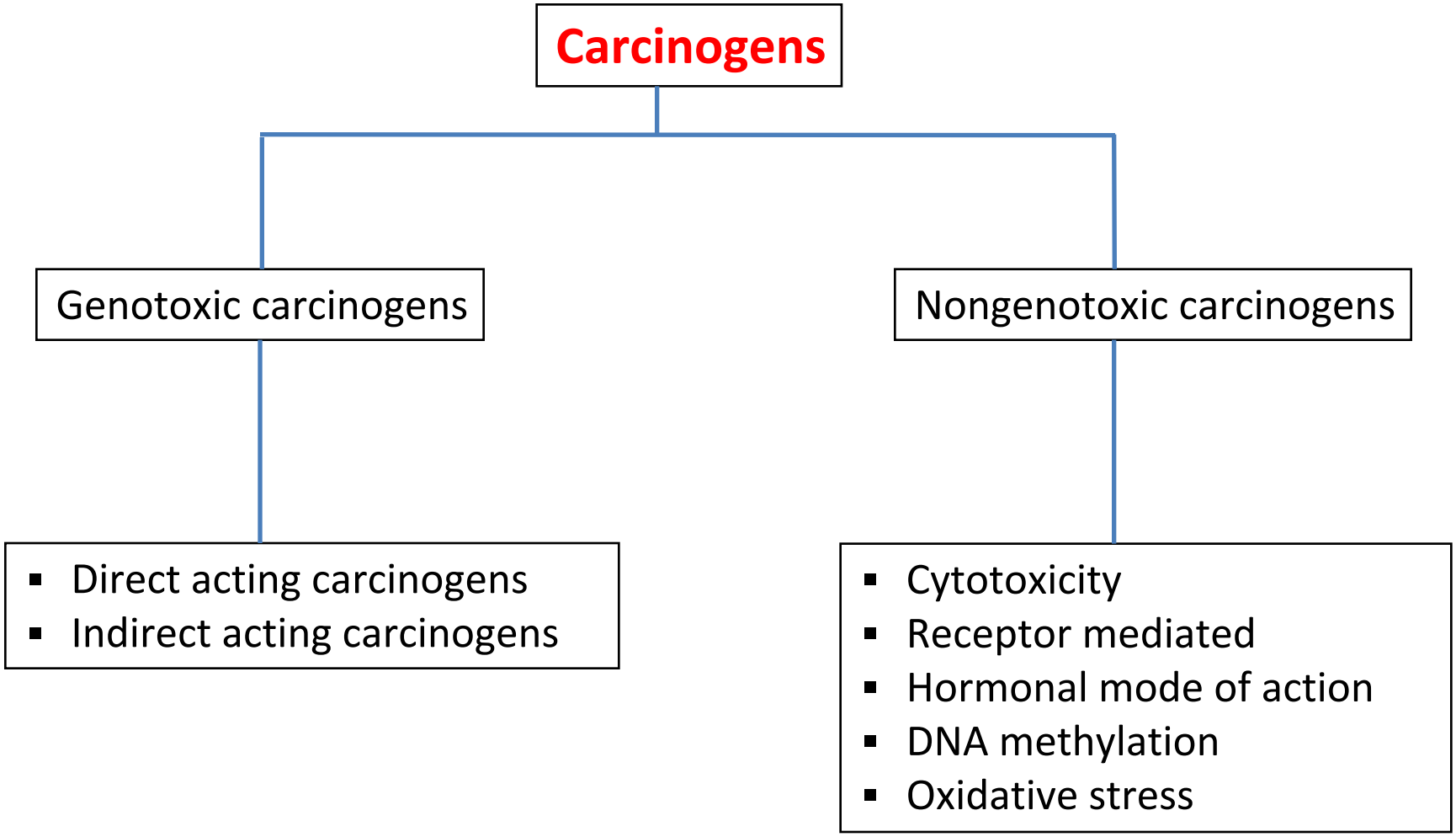

Figure 1. Modes of action of carcinogens

Genotoxic carcinogens:

- They interact with DNA to damage or change its structure.

- They are frequently mutagenic in a dose responsive manner.

Nongenotoxic carcinogens:

- They are the agents that do not directly interact with nuclear DNA.

- Nongenotoxic chemicals create a situation in a cell or tissue that makes it more susceptible to DNA damage from other sources.

Genotoxic/DNA-reactive carcinogens:

DNA reactive carcinogens can be further subdivided according to whether:

- they are active in their parent form (i.e., direct-acting carcinogens— agents that can directly bind to DNA without being metabolized) &

- those that require metabolic activation (i.e., indirect-acting carcinogens—compounds that require metabolism in order to react with DNA).

Direct-acting (activation-independent) carcinogens:

- Direct-acting carcinogens are highly reactive electrophilic molecules that can interact with & bind to nucleophiles, such as cellular macromolecules, including DNA without needing to be biotransformed into a reactive toxicant.

- Generally, these highly reactive chemicals frequently result in tumor formation at the site of chemical exposure.

- Direct-acting carcinogens include:

- sulfur mustard (mustard gas), & nitrogen mustards (e.g., chlorambucil , & cyclophosphamide).
- epoxides, &
- imines.

Indirect -acting genotoxic carcinogens:

- The majority of DNA reactive carcinogens are found as parent compounds, or procarcinogens, chemicals that require subsequent metabolism to be carcinogenic.

- Terms have been coined to define the parent compound (procarcinogen) & its metabolite form, either intermediate (proximate carcinogen) or final (ultimate carcinogen), that reacts with DNA.

- Indirect-acting genotoxic carcinogens usually produce their neoplastic effects at the target tissue where the metabolic activation of the chemical occurs & not at the site of exposure (as with direct-acting genotoxic carcinogens).

- Indirect-acting genotoxic carcinogens include:

- polycyclic polyaromatic hydrocarbons
- nitrosamines
- aromatic amines, &
- aflatoxin B1.

Classes of genotoxic carcinogens:

- Polyaromatic hydrocarbons
- Alkylating agents
- Aromatic amines & amides

Polyaromatic hydrocarbons:

Polyaromatic hydrocarbons such as benzo(a)pyrene are found at high levels in charcoal broiled foods, cigarette smoke, & in diesel exhaust.

Alkylating agents:

- Whereas some alkylating chemicals are direct-acting genotoxic agents, many require metabolic activation to produce electrophilic metabolites that can react with DNA.

- The N7 position of guanine & the N3 position of adenine are the most reactive sites in DNA for alkylating chemicals.

Aromatic amines & amides:

- Classically, exposure to these chemicals was through the dye industry, although exposure still occurs through cigarette smoke & other environmental sources.

- The aromatic amines undergo phase-I (hydrolysis, reduction, & oxidation) & phase-II (conjugation) metabolism.

- Phase-I reactions occur mainly by cytochrome P450–mediated reactions, yielding hydroxylated metabolites.

- These metabolites are often associated with adduct formation in proteins & DNA, & produce carcinogenicity.

Nongenotoxic (epigenetic) carcinogens:

Modes of action of nongenotoxic (epigenetic) carcinogens are:

- Cytotoxicity
- Receptor mediated
- Hormonal mode of action
- DNA methylation & carcinogenesis
- Oxidative Stress & chemical carcinogenesis

Cytotoxicity:

- Chemicals that function through this mechanism produce sustained cell death that is accompanied by persistent regenerative growth (compensatory hyperplasia).

- This results in the potential for the acquisition of “spontaneous” DNA mutations & allowing mutated cells to accumulate & proliferate.

- Chloroform has been shown to induce mouse liver tumors only at doses of compound that produce liver necrosis, thus demonstrating an association between necrosis with compensatory hyperplasia & the resulting tumorigenicity.

- The induction of cytotoxicity may be observed with many carcinogens both genotoxic & nongenotoxic when high toxic exposures occur.

Receptor mediated mechanism:

- Constitutive androstane receptor (CAR) (phenobarbital-like carcinogens)
- Peroxisome proliferator–activated receptor-α (PPARα)

CAR Receptor-Mediated (Phenobarbital-like carcinogens):

- Phenobarbital is a commonly studied non-DNA reactive compound that is known to cause tumors by a nongenotoxic mechanism involving liver hyperplasia.

- One feature seen following phenobarbital exposure is the induction of P450 enzymes, particularly Cyp2b.

- The induction of Cyp2b by phenobarbital is mediated by activation of the constitutive androstane receptor (CAR), a member of the nuclear receptor family.

Peroxisome proliferator–activated receptor-α (PPARα):

- Various chemicals are capable of increasing the number & volume of peroxisomes in the cytoplasm of cells.

- These so-called peroxisome proliferators include chemicals such as herbicides, chlorinated solvents (e.g., trichloroethylene), & lipid-lowering fibrate drugs (e.g., ciprofibrate & clofibrate).

- The currently accepted mode of action for this class of chemicals involves agonist binding to the nuclear hormone receptor, PPARα.

- PPARα is highly expressed in cells that have active fatty acid oxidation capacity (e.g., hepatocytes, cardiomyocytes, & enterocytes).

- It is well documented that PPARα plays a central role in lipid metabolism.

Hormonal mode of action:

- Hormonally active chemicals include biogenic amines, steroids, & peptide hormones that cause tissue-specific changes through interaction with a receptor.

- Trophic hormones are known to induce cell proliferation at their target organs.

- Estrogenic agents can induce tumors in estrogen-dependent tissue.

- A number of chemicals that reduce thyroid hormone concentrations (T4 &/or T3) & increase thyroid-stimulating hormone (TSH) have been shown to induce neoplasia in the rodent thyroid.

DNA methylation & carcinogenesis:

- Under normal conditions, DNA is methylated symmetrically on both strands.

- The degree of methylation within a gene inversely correlates with the expression of that gene.

- Several chemical carcinogens are known to modify DNA methylation, methyltransferase activity.

- During carcinogenesis, both hypomethylation & hypermethylation of the genome have been observed.

- Tumor-suppressor genes have been reported to be hypermethylated in tumors.

- Hypomethylation has been associated with increased mutation rates.

- Choline & methionine, which can be derived from dietary sources, provide a source of methyl groups used in methylation reactions.

- Rats exposed to choline &/or methionine-deficient diets resulted in hepatocellular proliferation & neoplasia thought to arise from hypomethylation.

- Reactive oxygen species have also been shown to modify DNA methylation by interfering with the ability of methyltransferases to interact with DNA; resulting in hypomethylation.

Oxidative stress & chemical carcinogenesis:

- Oxygen radicals can be produced by both endogenous & exogenous sources & are typically counterbalanced by antioxidants.

- Antioxidant defenses are both enzymatic (e.g., superoxide dismutase, glutathione peroxidase, & catalase) & nonenzymatic (e.g., vitamin E, vitamin C, β-carotene, & glutathione).

- Endogenous sources of reactive oxygen species include oxidative phosphorylation, P450 metabolism, peroxisomes, & inflammatory cell activation.

- Through these or other currently unknown mechanisms, a number of chemicals that induce cancer (e.g., chlorinated compounds, radiation, metal ions, barbiturates, & some PPARα agonists) induce reactive oxygen species formation.

- Reactive oxygen species could result in oxidative DNA damage, & could also affect cell growth regulation.

Oxidative DNA damage & carcinogenesis:

- In DNA, reactive oxygen species can produce single- or double-stranded DNA breaks, purine, pyrimidine, & DNA crosslinks.

- Compared to nuclear DNA, the mitochondrial DNA is relatively susceptible to oxidative base damage due to:

(1) close proximity to the electron transport system, a major source of reactive oxygen species;
(2) mitochondrial DNA is not protected by histones; &
(3) DNA repair capacity is limited in the mitochondria.

Oxidative stress & cell growth regulation:

- Many xenobiotics, by increasing cellular levels of oxidants, alter gene expression through activation of signaling pathways including:
  - cyclic adenosine monophosphate (cAMP)-mediated cascades,
  - calcium-calmodulin pathways, &
  - signaling through mitogen-activated protein (MAP) kinases.

- Activation of these signaling cascades ultimately leads to altered gene expression for a number of genes including those affecting proliferation, differentiation, & apoptosis.

Chemical carcinogenesis in humans:

- Infectious agents, lifestyle, medical treatments, & environmental & occupational exposure account for the majority of cancers seen in humans.

- The component that contributes the most to human cancer induction & progression is lifestyle: tobacco use, alcohol use, & poor diet.

- Tobacco usage is estimated to be responsible for 25% to 40% of all human cancers.

- In particular, a strong correlation between tobacco usage & mouth, larynx, lung, esophageal, & bladder cancer exists.

- Alcohol consumption contributes anywhere from 2% to 4% of cancers of the esophagus, liver, & larynx.

- High-fat & high-calorie diets have been linked to breast, colon, & gallbladder cancer in humans.

- Diets poor in antioxidants &/or vitamins such as vitamin A & vitamin E probably also contribute to the onset of cancer.

- The method of cooking may also influence the production of carcinogens produced in the cooking process.

- Carcinogenic heterocyclic amines & polycyclic aromatic hydrocarbons are formed during broiling & grilling of meat.

- Acrylamide, a suspected human carcinogen, has been found in fried foods at low concentrations.

Occupational human carcinogens:

A number of occupations associated with the development of specific cancers are listed in (Table 1).

Agent	Industrial process	Neoplasms
Asbestos	Construction & asbestos mining	Peritoneum, bronchus
Benzene	Chemical manufacturing	Bone marrow
Wood dust	Cabinet making	Nasal sinus
Formaldehyde	Plastic & chemical	Nasal sinus, & bronchus

Table 1. Occupational human carcinogens

Human carcinogenic chemicals associated with medical therapy:

A number of medical therapeutics have also been linked to the induction of human cancer (Table 2).

Drug	Associated neoplasms
Cyclophosphamide	Bladder, & leukemia
Azathioprine	Lymphoma, reticulum cell sarcoma,& skin
Chloramphenicol	Leukemia
Estrogens	Liver cell adenoma, endometrium, & skin

Table 2. Human carcinogenic chemicals associated with medical therapy


Thank
you