General Toxicology

Chemical Carcinogenesis
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OVERVIEW

- Cancer is a disease characterized by genomic mutation, modified gene expression, cell proliferation, and aberrant cell growth. It ranks as one of the leading causes of death in the world.
- Multiple causes of cancer have been established including infectious agents, radiation, and chemicals. Estimates suggest that 70% to 90% of all human cancers have a linkage to environmental, dietary, and behavioral factors.

- An understanding of the cellular and molecular aspects of the cancer process requires an understanding of the scientific terms involved in defining and describing the pathology of neoplasia.

Neoplasia	New growth or autonomous growth of tissue
Neoplasm Benign	The lesion resulting from the neoplasia Lesions characterized by expansive growth, frequently exhibiting slow rates of proliferation that do not invade surrounding tissues
Malignant	Lesions demonstrating invasive growth, capable of metastases to other tissues and organs
Metastases	Secondary growths derived from a primary malignant neoplasm
Tumor	Lesion characterized by swelling or increase in size, may or may not be neoplastic
Cancer	Malignant neoplasm
Carcinogen	A physical or chemical agent that causes or induces neoplasia
Genotoxic	Carcinogens that interact with DNA resulting in mutation
Non-genotoxic	Carcinogens that modify gene expression but do not damage DNA

- For the purpose of regulatory classification, carcinogens have frequently been divided simplistically into two major categories based on their general mode of action: genotoxic and non-genotoxic.

- Genotoxic carcinogens are those agents that interact with DNA to damage or change its structure.

- They are frequently mutagenic in a dose-responsive manner, and for regulatory purposes they are classified as exhibiting low-dose linear patterns, which approximates a straight line at very low doses without a threshold and a lack of reversibility of effect upon removal of the agent.

- Non-genotoxic carcinogens are the agents that do not directly interact with nuclear DNA.

- Non-genotoxic carcinogens may change gene expression, modify normal cell function, bind to or modify cellular receptors, and increase the number of cells in the target tissue.

- These agents work through epigenetic mechanisms that modify DNA and proteins associated with DNA which alter the gene expression or the cellular phenotype without modifying or directly damaging its structure.

- Non-genotoxic chemical carcinogens create a situation in a cell or tissue that makes it more susceptible to DNA damage from other sources, which in turn may increase the rate of mutagenesis and thus carcinogenesis.

- Non-genotoxic agents for regulatory purposes exhibit a nonlinear, threshold, and dose–response pattern in their carcinogenicity.

Features of genotoxic and Non-genotoxic Carcinogens

Genotoxic carcinogens

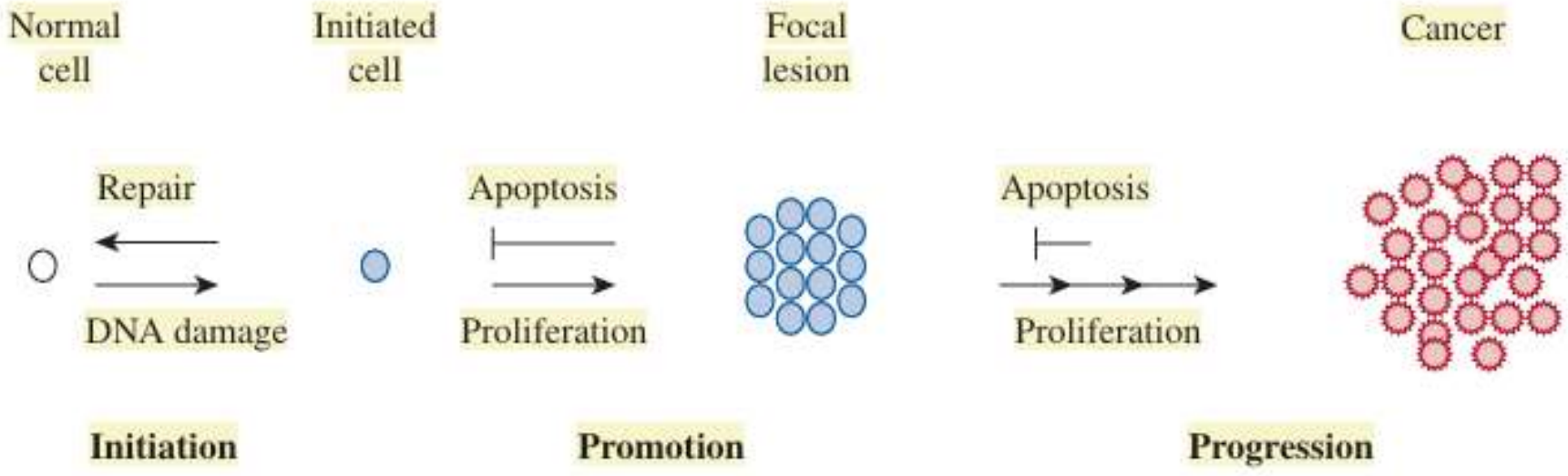
Mutagenic
Can be complete carcinogens
Tumorigenicity is dose responsive
No theoretical threshold

Non-genotoxic carcinogens

Nonmutagenic
Threshold, reversible
Tumorigenicity is dose responsive
May function at tumor promotion stage
No direct DNA damage
Species, strain, tissue specificity

Multistage Carcinogenesis

- Three defined stages, **initiation, promotion, and progression** have been identified in rodent studies.



Characteristics of the Stages of Carcinogenesis Process

Initiation

- DNA modification
- Mutation
- Genotoxic
- One cell division necessary to lock-in mutation
- Modification is not enough to produce cancer
- Nonreversible
- Single treatment can induce mutation

Promotion

- No direct DNA modification
- Non-genotoxic
- No direct mutation
- Multiple cell divisions necessary
- Clonal expansion of the initiated cell population
- Increase in cell proliferation or decrease in cell death (apoptosis)
- Reversible
- Multiple treatments (prolonged treatment) necessary
- Threshold

Progression

DNA modification

Genotoxic event

Mutation, chromosome disarrangement

Changes from preneoplasia to neoplasia benign/malignant

Irreversible

Number of treatments needed with compound unknown (may require only single treatment)

Initiation

- The first stage of the cancer process involves initiation, a process that is defined as a stable, heritable change. This stage is a relatively rapid, irreversible process that results in a carcinogen-induced mutational event.

- Chemical and physical agents that function at this stage are referred to as initiators or initiating agents. lead to genetic changes including mutations and deletions.

- Chemical carcinogens that covalently bind to DNA and form adducts that result in mutations are initiating agents.

- Initiating carcinogens are compounds such as polycyclic hydrocarbons and nitrosamines, biological agents, certain viruses, and physical agents such as x-rays and ultraviolet (UV) light.

- Most chemical carcinogens at the initiation stage are indirect-acting genotoxic compounds that require metabolic activation in the target cell to produce the DNA-damaging event.

Promotion

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

- Exogenous and endogenous agents that function at this stage are frequently referred to as **tumor promoters**.

- Compounds that function at the promotion stage are not mutagenic and generally are not able to induce tumors by them selves.

- They act though mechanisms that involve changes in gene expression that result in sustained cell number in the target tissue either through increases in cell proliferation and mitogenesis and/or the inhibition of apoptosis.

- Non-genotoxic carcinogens frequently function at the tumor promotion stage.

Progression

- A third stage, involves the conversion of the preneoplastic lesions to a neoplasm. Additional genotoxic events occur resulting in additional DNA damage including chromosomal damage such as aberrations and translocations.

- During the progression stage, the clonal nature of the neo plastic lesion is typically lost with a polyclonal appearance of cells within the lesion.

- By definition, the progression stage is an irreversible stage in that neoplasm formation, whether benign or malignant, occurs.

Mechanisms of Action of Chemical Carcinogens

Chemicals that induce cancer have been classified into one of two categories genotoxic (DNA-reactive) agents and non-genotoxic (epigenetic) agents.

- Genotoxic/DNA-Reactive Compounds: interact with nuclear DNA of a target cell producing unrepaired DNA damage that is inherited in subsequent daughter cells.

- DNA-reactive carcinogens can be further subdivided according to whether they are active in their parent form (i.e., direct-acting: chemicals that can directly bind to DNA without being metabolized) and those that require metabolic activation (i.e., indirect-acting carcinogens: compounds that require metabolism in order to react with DNA).

Examples of genotoxic Carcinogens

A. Direct-acting carcinogens

- Nitrogen or sulfur mustards
- Propane sulfone
- Methyl methane sulfonate

B. Chemicals requiring activation (indirect-acting carcinogens)

- Polycyclic aromatic hydrocarbons and heterocyclic aromatics
- Aromatic amines
- N-Nitrosoamines
- Azo dyes
- Aflatoxin
- Mycotoxin
- Carbamates

Direct-Acting (Activation-Independent) Carcinogens

- A class of carcinogens that do not require metabolic activation or modification to induce cancer are termed direct-acting or activation independent carcinogens. These chemicals are also defined as ultimate carcinogens.

- Examination of the chemical structure of these chemicals reveals that they are highly reactive electrophilic molecules that can interact with and bind to nucleophiles such as cellular macromolecules including DNA.

- Direct-acting carcinogens include epoxides, imines, alkyl and sulfate esters, and mustard gases.

Indirect-Acting genotoxic Carcinogens

- An important discovery in the understanding of chemical carcinogenesis came from the investigations of the Millers who established that many carcinogens are not intrinsically carcinogenic, but require metabolic activation to be carcinogenic.

- It has since been shown that the majority of DNA-reactive carcinogens are found as parent compounds, or procarcinogens. Procarcinogens are stable chemicals that require subsequent metabolism to be carcinogenic.

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

- The ultimate form of the carcinogen is most likely the chemical species that results in mutation and neoplastic transformation.

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

- Indirect-acting genotoxic carcinogens include the polycyclic PAHs, nitrosamines, aromatic amines, and aflatoxin B1.

Mutagenesis

Mutagenesis

- The reaction of a carcinogen with genomic DNA either directly or indirectly may result in DNA adduct formation or DNA damage, and frequently produces a mutation. Several mechanisms of mutagenesis are known to occur.

- Modification of DNA by electrophilic carcinogens can lead to a number of products. These events are dependent upon when in the cell cycle the adducts are formed, where the adducts are formed, and the type of repair process used in response to the damage.

- Transitions are a substitution of one pyrimidine by the other or one purine by the other (changes within a chemical class), whereas a transversion occurs when a purine is replaced by a pyrimidine or a pyrimidine is replaced by a purine (changes across a chemical class).

- Carcinogens can induce transitions and transversions several ways. In one scenario, when adducts (or apurinic or apyrimidinic sites) are encountered by the DNA replication processes, they may be misread. The polymerase may preferentially insert an adenine (A) in response to a noninformative site.

- A second scenario, a shift in the reading frame (resulting in a frame shift mutation) may also result from carcinogen–DNA adducts formation.

- In a third scenario, DNA strand breaks can also result from carcinogen–DNA adducts.

Damage by Alkylating Electrophiles

- As noted above, most chemical carcinogens require metabolic activation to exert a carcinogenic effect. The ultimate carcinogenic forms of these chemicals are frequently strong electrophiles that can readily form covalent adducts with nucleophilic targets.

- Because of their unpaired electrons, S:, O:, and N: atoms are nucleophilic targets of many electrophiles. The extent of adducts formed is limited by the structure of DNA where bulky electrophilic chemicals can bind, and size of the ultimate carcinogenic form.

- An important and abundant source of nucleophiles is contained not only in the DNA bases, but also in the phosphodiester backbone.

- Although carcinogen–DNA adducts may be formed at all sites in DNA, the most common sites of alkylation include the N7 of guanine, the N3 of adenine, the N1 of adenine, the N3 of guanine, and the O6 of guanine.

- Another common modification to DNA is the hydroxylation of DNA bases. Oxidative DNA adducts have been identified in all four DNA bases; however, 8-hydroxyguanine is among the most prevalent oxidative DNA adduct and an established biomarker of oxidative stress.
- The source of oxidative DNA damage is typically formed from free radical reactions that occur endogenously in the cell or from exogenous sources.
- Although a relatively large amount of oxidative DNA adducts have been proposed to be formed per day, repair mechanisms exist that maintain the cellular level low and keep endogenous mutations to a relatively low level.

DNA Repair Mechanisms

DNA Repair Pathways

1. Direct reversal of DNA damage
2. Excision repair systems
   - Base excision repair (BER)
   - Nucleotide excision repair (NER)
   - Mismatch repair (MMR)

3. Double-strand break repair
   - Homologous recombination (HR)
   - Nonhomologous end-jointing (NHEJ)

Mismatch Repair of Single-Base Mispairs:

- Depurination is a fairly common occurrence and spontaneous event in mammals, and results in the formation of apurinic sites. If these lesions are left unrepaired, mutations are generated during DNA replication as DNA synthetic machinery is unable to determine the appropri ate base with which to pair.

- All mammalian cells possess apurinic endonucleases that function to cut DNA near apurinic sites. The cut is then extended by exonucleases, and the resulting gap repaired by DNA polymerase and ligase.

Excision Repair:

DNA regions containing chemically modified bases, or DNA chemical adducts, are typically repaired by excision repair processes.

Homologous Recombination and Nonhomologous End Joining Repair of DNA:

- A cell that has double-strand breaks can be repaired by joining the free DNA ends. The joining of broken ends from different chromosomes, however, will lead to the translocation of DNA pieces from one chromosome to another, translocations that have the potential to enable abnormal cell growth by placing a protooncogene next to, and, therefore, under the control of another gene promoter.
- Double-strand breaks are correctly repaired only when the free ends of DNA rejoin exactly.
- Homologous recombination is one of two mechanisms responsible for the repair of double-strand breaks.

- In this process, the double-strand break on one chromo some is repaired using the information on the homologous, intact chromosome.

- The predominant mechanism for double-stranded DNA repair in multicellular organisms is nonhomologous repair and involves the rejoining the ends of the two DNA molecules.

- Although this process yields a continuous double-stranded mol ecule, several base pairs are lost at the joining point. This type of deletion may produce a possibly mutagenic coding change.

Classes of genotoxic Carcinogens

Polyaromatic Hydrocarbons:

- PAHs are found at high levels in charcoal-broiled foods, cigarette smoke, and in diesel exhaust.
- Benzo(a)pyrene is a representative polycyclic hydrocarbon that has been extensively studied.
- The ultimate carcinogen is a diol epoxide of benzo(a)pyrene, formed following three separate enzymatic reactions.

Alkylating Agents

- Alkylating agents represent an important class of chemical carcinogens. Although some alkylating chemi cals are direct-acting genotoxic chemicals, many require meta bolic activation to produce electrophilic metabolites that can react with DNA. Alkylating agents can be classified into several groups including the direct-acting alkylalkanesulfonates and nitrosamides and the indirect-acting nitrosamides.

- The N7 position of guanine and the N3 position of adenine are the most reactive sites for alkylating chemicals to bind to DNA.

Aromatic Amines and Amides:

- Aromatic amines and amides encompass a class of chemicals with varied structures. Because of their use in the dye indus try and other industrial processes, their carcinogen risk to humans was realized in the late 19th century.

- Exposure to these chemicals still occurs through cigarette smoke and environmental sources, even though proper industrial hygiene processes have considerably reduced the human exposure to aromatic amines and amides in the workplace.

- The aromatic amines undergo both phase I and phase II metabolism.

- Phase I reactions occur mainly by cytochrome P450 mediated reactions, yielding hydroxylated metabolites that are often associated with adduct formation in proteins and DNA, and produce liver and bladder carcinogenicity.

- Aromatic amines are capable of forming adducts with several DNA bases.

- Both heterocyclic amines (HCAs) and PAHs are formed when muscle meat, including beef, pork, fish, and poultry, is cooked using high- temperature methods, such as pan frying or grilling directly over an open flame. HCAs are also formed from fried foods, specifically fried meats.

Classes and Mode of Action of Non-genotoxic (Epigenetic) Carcinogens

- A number of chemicals that produce tumors in experimental animals following chronic treatment appear to act via mechanisms not involving direct binding, damage, or interaction of the chemical or its metabolites with DNA.

- Examples include chemicals that function via sustained cytotoxicity, receptor mediated (e.g., CAR, peroxisome proliferator– activated receptor alpha [PPARα], hormonal perturbation, as well as the induction of oxidative stress and modulation of methylation status.

Cytotoxicity:

- Cytotoxicity and consequent regenerative hyperplasia is well-documented mode of action for a variety of non DNA-reactive chemical carcinogens.

- Chloroform-induced liver and kidney tumors and melamine induced bladder tumors are classic examples of chemical carcinogens that are classified as functioning via a cytolethal mode of action.

- Chemicals that function through this mechanism produce sustained cell death, often related to metabolism of the chemical, that is accompanied by persistent regenerative growth, resulting in the potential for the acquisition of “spontaneous” DNA mutations and allowing mutated cells to accumulate and proliferate.

- This process then gives rise to preneoplastic focal lesions that upon further expansion can lead to tumor formation.

- 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 and the resulting tumorigenicity, and also supports that a threshold for the induction of tumors is likely at doses that do not produce toxicity.

- It is important to note that the induction of cytotoxicity may be observed with many carcinogens both genotoxic and non-genotoxic when high toxic exposures occur.

- Thus, the induction of cytotoxicity with compensatory hyperplasia may contribute to the observed tumorigenicity of many carcinogenic chemicals at high-dose levels.

Receptor-Mediated:

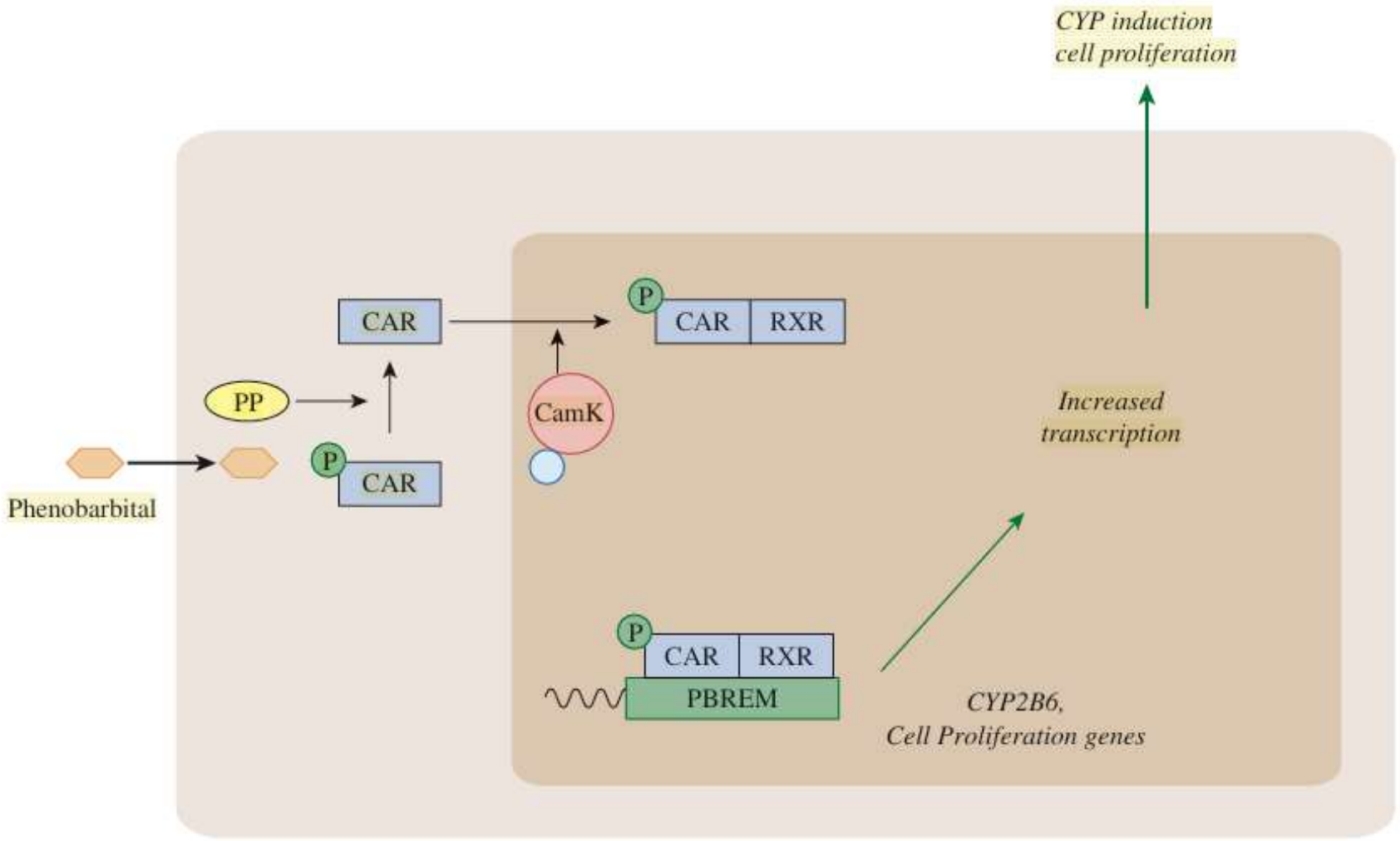
CAR Receptor-Mediated (Phenobarbital-Like Carcinogens):

- Phenobarbital is a commonly studied non–DNA-reactive com pound that is known to cause tumors by a non-genotoxic mechanism involving liver hyperplasia.

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

- Chemicals that functioned as P450 inducers in a manner similar to phenobarbital were classified as phenobarbital-like or P450 inducing carcinogens.

- Recent evidence has shown that the induction of Cyp2b is mediated by activation of the constitutive androstane receptor (CAR), a member of the nuclear receptor family.



Proposed mechanism for the involvement of the constitutive androstane receptor (CAR) in phenobarbital-induced gene expression changes. EGFR, epithelial growth factor receptor; PP2A, protein phosphatase 2A; RXR, retinoic acid receptor; PBREM, phenobarbital response element. Phenobarbital activates CAR indirectly by inhibiting EGFR. Following dephosphorylation of CAR by protein phosphatase 2A, CAR translocates to nucleus and forms a dimer with RXR and binds to PBREMs, resulting in increased gene expression.

Peroxisome Proliferator–Activated Receptor α

- A wide array of chemicals are capable of increasing the number and volume of peroxisomes in the cytoplasm of cells.

- These chemicals, termed peroxisome proliferators, include lipid-lowering fibrate drugs (e.g., ciprofibrate, clofibrate), herbicides (e.g., 2,4-dichlorophenoxy acetic acid), chlorinated solvents (e.g., trichloroethylene and per chloroethylene).

- In addition, many of the chemicals within this group produce liver enlargement and hepatocellular carcinoma in rats and mice through non DNA-reactive mechanisms.

- The currently accepted mode of action for this class of chemicals involves the agonist binding and/or activating the nuclear receptor, the 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 and acts as a transcription factor to modulate gene expression following ligand activation.

- This latter effect arises through the heterodimerization of PPARα and RXRα, which results in binding to response elements (PPREs) and subsequent modulation of target gene transcription.

- Following this event is the induction of cell proliferation and suppression of apoptosis.

Hormonal Mode of Action:

- Hormonally active chemicals include steroids and peptide hormones that produce tissue- specific changes through interaction with a receptor. A number of non–DNA-reactive chemicals induce neoplasia through receptor-mediated mechanisms, and/or perturbation of hormonal balance. Trophic hormones are known to induce cell proliferation at their target organs.

- This action may lead to the development of tumors when the mechanisms of hormonal control are disrupted and some or other hormone shows persistently increased levels.

- Several well-studied examples include the induction of ovarian neoplasms via decreased estradiol and increased luteinizing hormone (LH) levels, and the induction of thyroid tumors in rats by phenobarbital-type P450 inducers (which modulate T3 and T4).

Estrogenic Agents

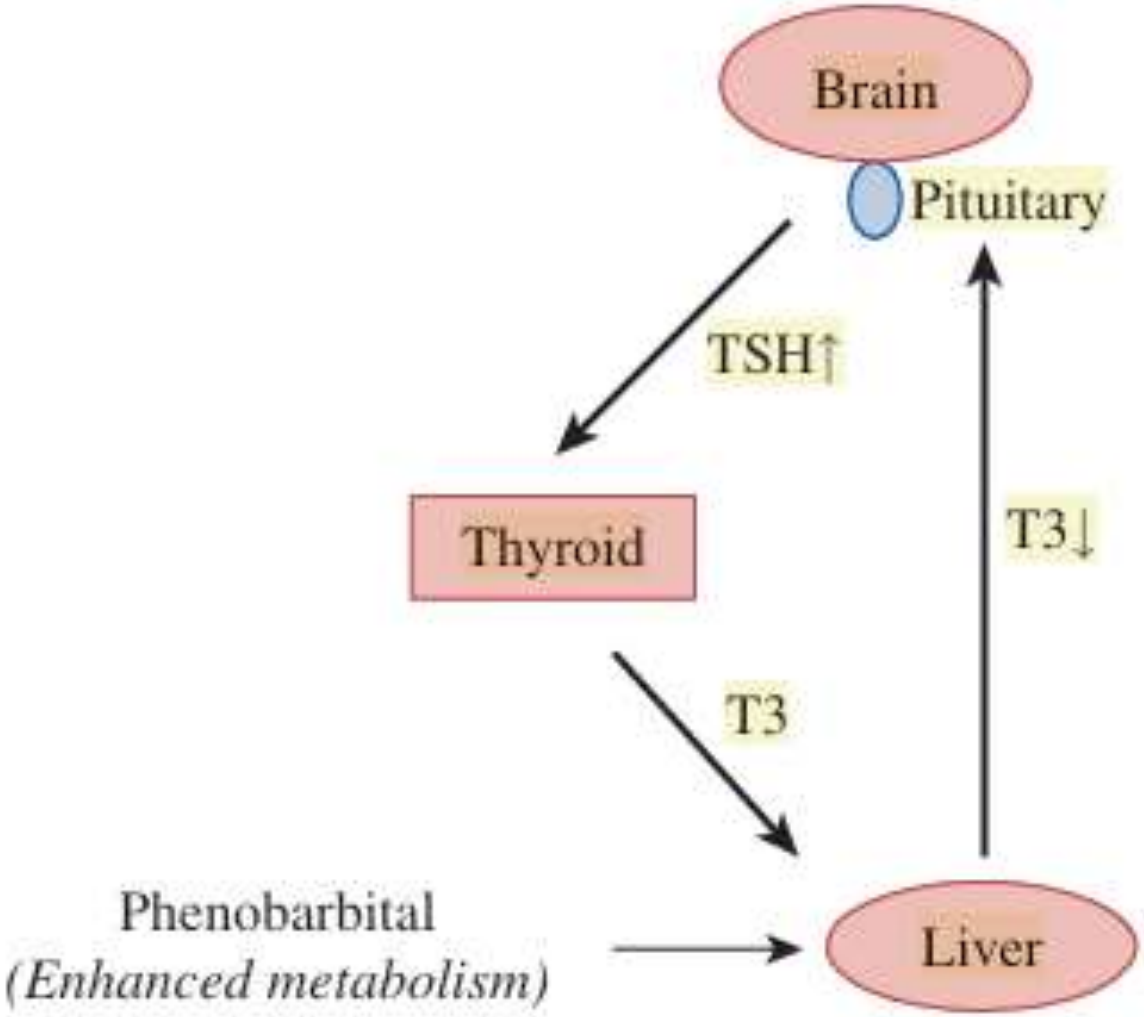
- Evidence that estrogenic chemicals are carcinogenic to humans comes from epidemiological data on breast and ovarian cancer, which indicates that individuals with higher circulating estrogen levels and those with exposure to the potent estrogenic chemical diethylstilbestrol (DES) are at increased risk for cancer development.

- Chronic exogenous administration of hormonally active chemicals including synthetic estrogens and anabolic steroids can increase hepatic adenoma incidence in rats and in humans.

Thyroid Hormone

- A reduction of thyroid hormone concentrations (T4 and/or T3) and increased thyroid-stimulating hormone (TSH) have been shown to induce neoplasia in the rodent thyroid.

- TSH increases proliferative activity in the thyroid. After chronic treatment chemical-induced increase in TSH leads to follicular cell hypertrophy, hyperplasia, and eventually neoplasia. Inducers of metabolic enzymes in the rat liver, for example with pheno barbital, results in increased thyroid hormone metabolism and leads to an increase in TSH levels.



Mechanism for phenobarbital-induced thyroid tumors. Through alteration of gene expression, phenobarbital enhances metabolism of thyroid hormone (T3) resulting in enhanced TSH production. Increased TSH then leads to increased cell proliferation in the thyroid.

DNA Methylation and Carcinogenesis

- Methylation of DNA occurs through an enzymatic reaction catalyzed by DNA methyltransferases (DNMTs). Under nor mal conditions, DNA is methylated symmetrically on both strands.

- Immediately following DNA replication, the newly synthesized double-stranded DNA contains hemimethylated sites that signal for DNA maintenance methylases to transfer methyl groups from S-adenosylmethionine to cytosine residues on the new DNA strand.

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

- hypermethylation of genes is associated with gene silencing, whereas hypomethylation results in an enhanced expression of genes. Several chemical carcinogens are known to modify DNA methylation, methyltransferase activity, and chromosomal structure. During carcinogenesis, both hypomethylation and hypermethylation of the genome have been observed.

- Choline and methionine, from dietary sources, are a com mon source of methyl groups used in methylation reactions.

- Rats exposed to choline and/or methionine-deficient diets displayed hepatocellular proliferation and neoplasia.

- Reactive oxygen species have also been shown to modify DNA methylation resulting in changes in DNA methylation profiles through interfering with the ability of methyltransferases to inter act with DNA, leading to hypomethylation.

Oxidative Stress and Chemical Carcinogenesis

- Experimental evidence has shown that increases in reactive oxygen in the cell, through either physiological modification or chemical carcinogen exposure, contribute to the carcinogenesis processes.

- Reactive oxygen species encompass a series of reactive compounds including the superoxide anion (•O2–), hydroperoxyl radical (HO2 •.), hydrogen peroxide (H2 O2), and the hydroxyl radical (•OH), all derived through the reduction of molecular oxygen.

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

- Antioxidant defenses are both enzymatic (e.g., superoxide dismutase, glutathione peroxidase, and catalase) and nonenzymatic (e.g., vitamin E, vitamin C, β-carotene, and glutathione); importantly, many of these antioxidants are provided through dietary intake.

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

- Ethanol, phenobarbital, and a number of chlorinated and nonchlorinated compounds such as dieldrin, TCDD, and lindane are among the xenobiotics shown to increase reactive oxygen species through P450-mediated mechanisms.

Oxidative DNA Damage and Carcinogenesis

- Reactive oxy gen species left unbalanced by antioxidants can result in damage to cellular macromolecules. Reactive oxygen species can produce single- or double-stranded DNA breaks, purine, pyrimidine, or deoxyribose modifications, and DNA cross-links.

- Oxidative damage to mitochondrial DNA and mutations in mitochondrial DNA have been identified in a number of cancers.

- Compared to nuclear DNA, the mitochondrial genome 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 and Cell growth Regulation

- Reactive oxygen species production and oxidative stress can affect both cell proliferation and apoptosis. H2 O2 and superoxide anion can induce cell proliferation in several mammalian cell types.

- Conversely, high concentrations of reactive oxygen species can initiate apoptosis.

- Many xenobiotics, by increasing cellular levels of oxidants, alter gene expression through activation of signaling pathways including cAMP-mediated cascades, calcium-calmodulin pathways, and transcription factors such as AP-1, Nrf2, Hif1, and NF-κB as well as signaling through mitogen-activated protein (MAP) kinases (extracellular signal-regulated kinases [ERK], c-Jun N-terminal kinases [JNK].

- Activation of these signaling cascades by reactive oxygen species induced by chemical carcinogens ultimately leads to altered gene expression for a number of genes including those affecting proliferation, differentiation, and apoptosis.

CHEMICAL CARCINOGENESIS IN HUMANS

- A number of factors have been implicated in the induction of cancer in humans. Infectious agents, lifestyle, medical treatments, environmental, and occupational exposure account either directly or indirectly to the majority of cancers seen in humans. Of these, the component that contributes the most to human cancer induction and progression is lifestyle: tobacco use, alcohol use, and poor diet.

- Tobacco usage either through smoking tobacco, chewing tobacco, or tobacco snuff-type products is estimated be responsible for 25% to 40% of all human cancers. In particular, a strong correlation between tobacco usage and mouth, larynx, lung, esophageal, and bladder cancer exists.

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

- Poor diets whether high-fat, low-protein, high-calories or diets lacking in needed antioxidants and minerals account for anywhere from 10% to 70% of human cancers. Diet contaminated by molds such as Aspergillus flavis (which produces aflatoxin B1) have been linked epidemiologically to a higher incidence of liver cancer.

- It also appears that aflatoxin B1 exposure coupled with hepatitis B virus infection produces an increased incidence of liver cancer compared to aflatoxin B1 or hepatitis B exposure individually. Mold-contaminated foodstuffs have also been shown to produce nitroso compounds.

- There is substantial evidence that over nutrition either through excess calories and/or high-fat diets contribute to a number of human cancers. In particular, high-fat and high-calorie diets have been linked to breast, colon, and gall bladder and liver cancer in humans.

- Diets poor in antioxidants and/ or vitamins such as vitamin A and vitamin E probably also con tribute to the onset of cancer. The method of cooking may also influence the production of carcinogens produced in the cooking process.

- Carcinogenic heterocyclic amines (HCAs) and PAHs are formed during broiling and grilling of meat. Acrylamide, a suspected human carcinogen, has been found in fried foods at low concentrations.

- A number of occupations have been associated with the development of specific cancers.

Occupational Human Carcinogens

AGENT	INDUSTRIAL PROCESS	NEOPLASMS
Asbestos	Construction, asbestos mining	Peritoneum, bronchus
Arsenic	Mining and smelting	Skin, bronchus, liver
Benzene	Chemical manufacturing	Bone marrow
Nickel	Nickel refining	Nasal sinus, bronchus
Wood dust	Cabinet making	Nasal sinus
Cadmium	Smelting	Bronchus

- A number of drugs and medical diagnostic tools have also been linked to the induction of human cancer.

Human Carcinogenic Chemicals Associated with Medical therapy and Diagnosis

CHEMICAL OR DRUG	ASSOCIATED NEOPLASMS
Alkylating agents cyclophosphamide, melphalan)	Bladder, leukemia
Azathioprine	Lymphoma, reticulum cell sarcoma, skin, Kaposi sarcoma
Chloramphenicol	Leukemia
Diethylstilbestrol	Vagina (clear cell carcinoma)
Estrogens	Liver cell adenoma, endometrium, skin

Thanks for your attention