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Role of Free Radicals, Oxidative Stress and Xenobiotics in Carcinogenesis by Environmental Pollutants
(Papel de los radicales libres, estrés oxidativo y xenobioticos en la carcinogénesis por contaminación ambiental)

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Abstract (english)

Carcinogenesis by many small molecular weight chemicals involves either a direct action of the chemical on cellular DNA or metabolism of the parent chemical to an active or ultimate form, which can than react with cellular DNA to produce a permanent chemical change in a DNA structure. A free radical is an atom or molecule that has one or more unpaired electron(s). These are highly reactive species capable of wide spread, indiscriminate oxidation and per oxidation of proteins, lipids and DNA which can lead to significant cellular damage and even tissue and/or organ failure. . Oxidative stress is a leading cause to damage cells by oxidation. The rate at which oxidative damage is induced (input) and the rate at which it is efficiently repaired and removed (output). Xenobiotics are a compound that is foreign to the body. Xenobiotics can produce a variety of biological effects, including pharmacologic responses, toxicity, genes, immunologic reactions and cancer. Oxidative stress is a leading cause to damage cells by oxidation. The rate at which oxidative damage is induced (input) and the rate at which it is efficiently repaired and removed (output). This communication highlights the role of carcinogens as environmental pollutants with the possible mechanism of free radicals, oxidative stress and xenobiotics.

Keywords (english)

Carcinogenesis, xenobiotics, oxidative stress, free radicals, environment, pollutants.

Carcinogenesis-at a glance

Carcinogenesis is a general term used to denote the development of cancer (figure 1). This is an active phenomenon induced by any one or several of a variety of agents i.e. physical, chemical, genetic or biological. Passive carcinogenesis may occur with spontaneous carcinogenesis occurring in organisms without any active introduction of a carcinogenic agent into the system under study.

Some characteristic features of the stages of carcinogenesis:

Initiation: Irreversible, requires fixation, Additive, No threshold.

Promotion: Reversible, Somatic aneuploidy, Progressive karyotypic instability.

Progression: Irreversible, Somentic aneuploidy, Progressive karyotypic instability.

Initiation is rapid and irreversible and involves direct carcinogenic binding and damage to DNA.

Promotion, the period between initiation and premalignnancy, is generally reversible and primarily occurs by epigenetic mechanisms.

Progression the period between pre-malignant and malignant disease, is generally irreversible and involves primary genetic mechanism (1).

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Carcinogenes as an environmental pollutant

Heterocyclic amines represent an important class of carcinogens in foods They are mutagens and carcinogens at numerous organ sites in experimental animals, are produced when meats are heated above 180 degrees C for long periods. Four of these compounds can consistently be identified in well-done meat products from the North American diet, and although a causal linkage has not been established, a majority of epidemiology studies have linked consumption of well-done meat products to cancer of the colon, breast and stomach. Studies employing molecular biomarkers suggest that individuals may differ in their susceptibility to these carcinogens, and genetic polymorphisms may contribute to this variability. Heterocyclic amines, like most other chemical carcinogens, are not carcinogenic per se but must be metabolized by a family of cytochrome P450 enzymes to chemically reactive electrophiles prior to reacting with DNA to initiate a carcinogenic response. These same cytochrome P450 enzymes--as well as enzymes that act on the metabolic products of the cytochromes P450 (e.g. glucuronyl transferase, glutathione S-transferase and others)--also metabolize chemicals by inactivation pathways, and the relative amounts of activation and detoxification will determine whether a chemical is carcinogenic. Because both genetic and environmental factors influence the levels of enzymes that metabolically activate and detoxify chemicals, they can also influence carcinogenic risk. Many of the phenotypes of cancer cells can be the result of mutations, i.e., changes in the nucleotide sequence of DNA that accumulate as tumors progress. These can arise as a result of DNA damage or by the incorporation of non-complementary nucleotides during DNA synthetic processes. Based upon the disparity between the infrequency of spontaneous mutations and the large numbers of mutations reported in human tumors, it has been postulated that cancers must exhibit a mutator phenotype, which would represent an early event in cancer progression (2). A mutator phenotype could be generated by mutations in genes that normally function to guarantee genetic stability. These mutations presumably arise via DNA damage by environmental or endogenous agents, but it remains to be determined whether the acquisition of a mutator phenotype is a necessary event during tumor progression. An integrative theory is proposed in which environmental carcinogenesis is viewed as a process by which the genetic control of cell division and differentiation is altered by carcinogens. In this

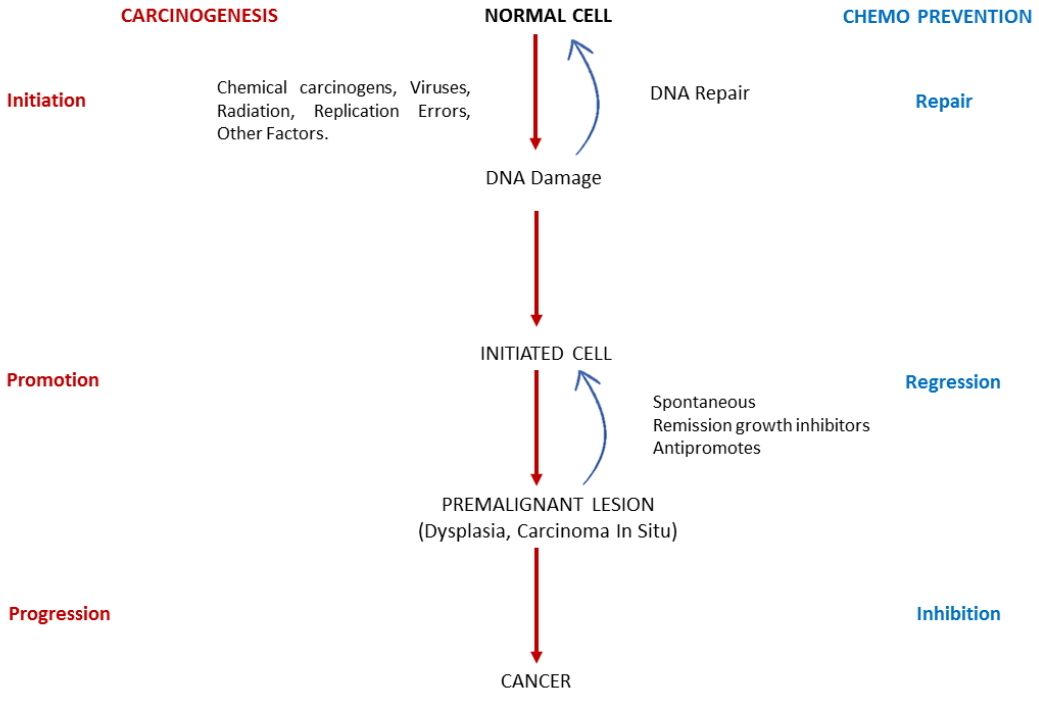

Figure 1. A Multistep Carcinogenesis Model

theory, carcinogens include physical, chemical, and viral "mutagens," as well as chemical and viral gene modulators. Existing explanations of carcinogenesis can be considered either as somatic mutation theories or as epigenetic theories. Evidence seems to support the hypothesis that both mutations and epigenetic processes are components of carcinogenesis. The mutational basis of cancer is suported by the clonal nature of tumors, the mutagenicity of most carcinogens, high mutation frequencies in cells of cancer-prone human fibroblasts lacking DNA repair enzymes, the correlation of in vitro DNA damage and in vitro mutation and transformation frequencies with in vivo tumor genesis, age-related incidences of various hereditary tumors, and the correlation between photo reactivation of DNA damage and the biological amelioration of UV-induced neoplasm's (3). Since both mutagens and gene modulators can be carcinogenic it may be that carcinogens affect genes which control cell division. An Integration of the mutation and epigenetic theories of cancer with the "two-stage" theory and Coming's general theory of carcinogenesis is proposed. This integrative theory postulates that carcinogens can affect regulatory genes which control a series of "transforming genes." A general hypothesis is advanced that involves a common mechanism of somatic mutagenesis via error-prone repair of DNA damage which links carcinogenesis, teratogenesis, atherosclerosis and aging (4). Various concepts are presented to provide a framework for evaluating the scientific, medical, and social implications of cancer.

The pathways of impact of the environment on the human body evidently are the systems that are exposed to hazardous materials, covering the external skin, and the internal respiratory and alimentary systems, each with an array of organs and functions, and with an ultimate bearing on the structures and organs of the body as a whole. While many ailments like asthma and allergies are known to be environment linked, cancer is the most significant in the environmental health profile (5). Tobacco is a known cause of cancer of the lungs, bladder, mouth, pharynx, pancreas, stomach, larynx, esophagus and possibly colon. In addition to tobacco use, certain chemicals can also cause cancer such as asbestos, benzene, vinyl chloride, arsenic , aflatoxin, DDT, formaldehyde and ionizing radiation (IR) such as X-rays, and radon have also been proven to cause cancer in humans. While tobacco and other environmental toxins are the causes of cancer, all smokers or those exposed to environmental hazards do not get cancer, indicating the importance of genetic alterations that occur in the DNA (6). Alterations in the sequences of certain genes, which are inherited, are equally responsible for carcinogenesis. A combination of tobacco exposure and genetic alterations will increase the risk for malignant transformation of normal cells.

Environmental carcinogens with examples

Environmental carcinogens mean any of the natural or synthetic substances that can cause cancer. Such agents may be divided into chemical agents, physical agents, hormones, and viruses. Some environmental carcinogens are arsenic, asbestos, uranium, vinyl chloride, ionizing radiation, ultraviolet rays, x-rays, and coal tar derivatives. Carcinogenic effects of chemicals may be delayed for as long as 30 years (7). Other carcinogens produce more immediate effects. Some studies indicate that the carcinogens in cigarette smoke are involved in 80% of all lung cancer. Most carcinogens are unreactive or secondary carcinogens but are converted to primary carcinogens in the body. Numerous factors, such as heredity, affect the susceptibilities of different individuals to cancer-causing agents (8).

Arsenic is a naturally occurring element. It is most commonly used as a wood preservative (in pressure treated wood) and can be found in building materials, industry, and water (inorganic) as well as fish and shellfish (organic compounds). Exposure is through inhalation or ingestion (intentional poisoning). Arsenic is linked to lung cancer, skin cancer, and urinary tract cancer. Arsenic is a known human carcinogen.

Asbestos is a group of naturally produced chemicals composed of silicon compounds. It is used in insulation materials due to heat resistance. Human exposure is through inhalation (from disruption of materials containing asbestos) and ingestion (contaminated food/water). Tiny asbestos fibers in the air can get trapped and accumulate in the lungs. Asbestos is linked to increased risk of lung cancer, and development of mesothelioma (cancer of the thin lining surrounding the lung (pleural membrane) or abdominal cavity (the peritoneum) and laryngeal cancer. Cancer may appear 30 to 50 years after exposure. Asbestos is a known human carcinogen.

Benzene is used as a solvent in chemical and pharmaceutical industry, and is released by oil refineries. It is one of the largest-volume petrochemical solvents in production; it is produced from coal and from petroleum. Exposure is through inhalation (smoke, gas emissions, etc.) or ingestion

(contaminated food/water). Exposure to benzene is linked to acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL); breast cancer; lymphatic and hematopoietic cancer. Benzene is a known human carcinogen.

Bisphenol A (BPA), a building block of polycarbonate plastic, is one of the most widely produced chemicals in the world. It is used in hard plastics, food cans, drink cans, receipts, and dental sealants. BPA is ubiquitous. CDC biomonitoring surveys indicate that more than 90% of Americans have the substance in their bodies. BPA is an endocrine disruptor linked to breast and prostate cancer. The International Agency for Research on Cancer has listed BPA as "not classifiable as to its carcinogenicity in humans."

Chromium Hexavalent compounds: Elemental chromium does not occur naturally; chromium (IV) compounds are highly corrosive and strong oxidizing agents rarely found in nature. Such compounds are also used as corrosion inhibitors in the leather tanning process, in the manufacture of dyes and pigments, and in wood preserving, chrome plating, and steel and other alloy production. Exposure is through inhalation, ingestion (chromium leached into soil and water), and dermal contact. They are linked to lung, nasal, and nasopharyngeal cancer. Chromium hexavalent compounds are a known human carcinogen.

Dioxins are a group of chemicals formed as unintentional byproducts of industrial processes involving chlorine, such as waste incineration, chemical manufacturing, and pulp and paper bleaching. Dioxins include polychlorinated dibenzo dioxins (PCDDs), polychlorinated dibenzo furans (PCDFs), and the polychlorinated biphenyls (PCBs). Exposure is through the ingestion of contaminated foods and, to a lesser extent, dermal contact. Dioxins accumulate in fat cells and degrade very slowly in the environment. The cancer classification depends on the dioxin: 2,3,7,8-TCDD (Agent Orange) is a known human carcinogen; some other dioxins are probable or possible human carcinogens.

Formaldehyde can be found in a variety of building and home decoration products (as urea-formaldehyde resins and phenol-formaldehyde resin). It is also used as a preservative and disinfectant. Exposure is through inhalation and dermal contact. Automobile exhaust is the greatest contributor to formaldehyde concentrations in ambient air. Construction materials, furnishings, and cigarettes account for most formaldehyde in indoor air. Formaldehyde has caused nasal cancer in rats after long term exposure; it is linked to leukemia and nasopharygeal cancer in humans. It is a known human carcinogen.

Polybrominated diphenylethers (PBDEs) are used as flame retardants in furniture, computers, electronics, medical equipment, and mattresses. Exposure is through inhalation, ingestion and dermal contact. Two of the common commercial formulations, penta- and octa-BDE, have been voluntarily phased out of US production. Deca-BDE continues to be produced. Highly persistent in the environment, they are endocrine disruptors. PBDEs are linked to liver cancer in laboratory animals, but are not classifiable as to carcinogenicity in people.

Polycyclic aromatic hydrocarbons (PAHs) form as a result of incomplete combustion of organic compounds: combustion from wood and fuel in residential heating, coal burners, automobiles, diesel-fueled engines, refuse fires, and grilled meats. They are found in coal tar and coal tar pitch, used for roofing and surface coatings. Exposure to these lipophilic substances results from inhalation of polluted air, wood smoke, and tobacco smoke, and ingestion of contaminated food and water. PAHs are reasonably anticipated to be a human carcinogen, according to the National Toxicology Program. IARC lists them as probably or possibly carcinogenic.

Vinyl Chloride is used by plastics companies in the production of PVCs and copolymers. Exposure is largely occupational, and results from inhalation, ingestion or dermal contact. Exposure is very low in the general population. Exposure to vinyl chloride is linked to the development of liver cancer and weakly associated with brain cancer. Vinyl chloride is a known human carcinogen.

Free radicals

Free radicals are atoms or molecules containing an odd number of electrons, which results in an odd electron in the external orbit (figure 2). Free

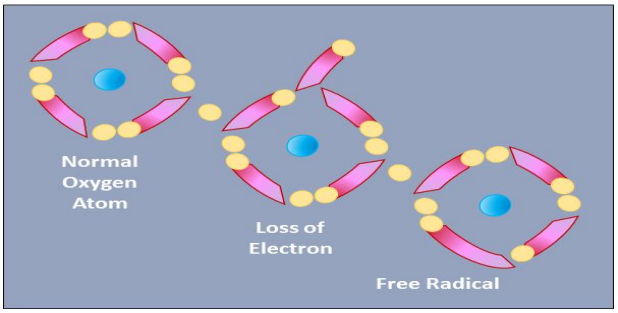

Figure 2. Free Radicals.

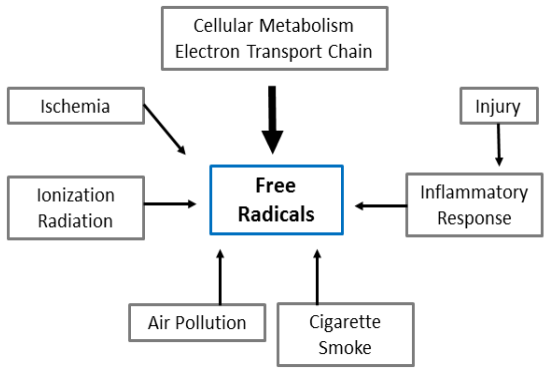

Figure 3. Exposure of Free Radicals in Environment

radicals frantically seek electrons in order to pair their unpaired electrons (Table 1). Free radicals cause a chain of reactions loading to consecutive oxidation (figure 3). These radicals attacks molecules like fat, proteins, DNA, sugar etc. the newly damaged molecule unfortunately becomes a free radicals and thus a chain reaction started (9)

Free Radicals Cause Oxidative Stress

- Superoxide anion radicals.
- Hydrogen peroxide.
- Hydroxyl radicals.
- Per-oxy radicals.
- Nitric oxide radicals.

Formation of Free Radicals

- Air pollution.
- Cigarette, pipe smoke.
- Injury & inflammatory response.
- Ionization radiation.
- Ischemia.

Table 1. Radicals and non-radicals

Radicals		Non-Radicals	
Hydroxyl	$OH^{\bullet}$	Peroxynitrite	ONOO-
Superoxide	$O_2^{\bullet-}$	Hypochloric acid	HOCl
Nitric Oxide	$NO^{\bullet}$	Hydrogen Peroxide	H_2O_2
Thyl	$RS^{\bullet}$	Singlet Oxygen	$^1\Delta_g$ ($^{-1}O_2$)
Peroxyl	$RO_2^{\bullet}$	Ozone	O_3
Lipid peroxyl	$LOO^{\bullet}$	Lipid peroxide	LOOH

- Cellular metabolism (electron transport chain).
- Exercise.
- Food additives.
- Food preparation.
- Ozone.
- Pesticides.
- Other pollution.
- Stress.
- Sunlight.
- X-rays.

Effect of carcinogen by modulating enzyme activation

Effect on Carcinogenic Activation by Modulating Phase I Enzyme Activation. The cytochrome p450 dependent mono oxygenase system was evolved as one of our primary defense against toxic chemical present in the environment. The multi-enzymes system functions as an adaptive response to environment challenge. In that exposure to specific agents induce the expression of cyp- 450 isozyme active in their metabolism (10). In most cases such metabolism lead to increase rate of detoxification, but in certain cases it can also lead to an increased rate of chemical activation of toxic products, as for example most of the chemical carcinogens in the environment induced tumors only after metabolic activation by CYP 450.

Effect on Carcinogen Detoxification by Modulating Phase II Enzymes. In addition to the phase II enzymes, mammalian system including humans possess a series of enzymes called phase II detoxification enzyme that are involved in the detoxification of activated carcinogens, thus preventing their binding to DNA and thus retard the initiation and progression of carcinogenesis. One unifying features of the metabolic activation of all procarcinogens is that the ultimate DNA reactive carcinogenic species is electrophilic. The electrophilic metabolites may themselves be reactive oxygen species (ROS), reactive nitrogen species (RNS), hydroxyl radicals (OH), malonldialdehyde (MDA) that directly or indirectly are involved in multistage carcinogenesis (11). They are mainly involved in DNA damage leading sometimes to mutation in tumor suppressor genes. They also act as initiator and / or promoter in carcinogenesis. Thus agents that can modulate body's antioxidant enzymes system (phase II enzymes) which can scavenge DNA reactive

intermediates constitute a plausible strategy for perturbing the entry stage of carcinogenesis.

Oxidative stress

Oxidative stress is a leading cause to damage cells by oxidation. All forms of life maintain a reducing environment within their cells. The cellular redox environment is preserved by enzymes that maintain the reduced state through a constant input of metabolic energy. The effects of oxidative stress depend upon the size of changes, with a cell being able to overcome small perturbations and regain its original state (12). A particularly aspect of oxidative stress is the production of reactive oxygen species, which include free radicals and peroxides.

Pathways:

- Oxidative stress – DNA damage.
- Oxidative stress – GSH depletion.
- Oxidative stress – Direct damage to proteins – Rises in intracellular free Ca^{2+} - Cytoskeletal damage.
- Oxidative stress – Rises in intracellular free iron – Membrane per-oxidation and destruction – Injury to adjacent cells.
- Oxidative stress – Increased lipid per-oxidation – Increased damage to DNA, proteins, lipids.

Oxidative stress is imposed on cells as a result of one of three factors:

- An increase in oxidant generation;
- A decrease in antioxidant protection;
- A failure to repair oxidative damage.

The determinants of oxidative stress are regulated by an individual's unique hereditary factors, as well as his/her environment and characteristic lifestyle. Unfortunately, under the present day life-style conditions many people run an abnormally high level of oxidative stress that could increase their probability of early incidence of decline in optimum body functions. Oxidative stress has been one of the prime factors in arsenic induced carcinogenicity. The reactive oxygen species (ROS) generated by arsenic causes damage to the genome, lipids and proteins in the vicinity. As III administration elevated both lipid peroxides and protein carbonyl level in the liver tissues of Swiss albino mice. ROS generation beyond the body's endogenous antioxidant balance caused a severe imbalance of the cellular antioxidant defense mechanism. This was evident from the depletion of antioxidant enzymes like CAT, SOD GPx, GST, GR and non enzymatic antioxidants like GSH (13). Tea was used as antioxidant against these oxidative damages and it was interesting to note that both black tea and green tea was efficient in reducing the lipid peroxidation and formation of protein carbonyl groups induced by As III in Swiss albino mice. The induction of the antioxidants like SOD, CAT GPx, GST, GR and GSH provided protection against the oxidative stress created by As III in mice liver tissue. The chronic arsenic affected showed that curcumin intervention for three months at a dose of 500mg twice daily gave significant recovery of DNA damage as evident from the results of comet assay and fluorimetric analysis of DNA unwinding. HPLC analysis exhibited that there was an increase in the level of curcumin in the plasma after one month of curcumin intake which remained unaltered throughout the study period. This consistency of curcumin level might have provided protection against arsenic induced DNA damage. The antioxidant enzymes catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, glutathione-s-transferase and the non enzymatic antioxidant glutathione which were depleted with chronic arsenic exposure were elevated with curcumin administration. Apart from this, curcumin also showed enhancement of DNA repair capacity which was evident from the profiles of protein expression and genetic activity of the DNA repair genes (14). The enzymes related with break excision repair pathway were studied in detail. Poly ADP ribose polymerase and DNA ligase III which were down regulated with arsenic were up regulated after curcumin administration. XRCC 1, another DNA repair enzyme which showed positive correlation with arsenic exposure was inhibited with curcumin intervention. Constitutive levels of various PKC isoforms (PKC α, βII, ε, and δ) were found high in tumor cells of human origin compared to normal lymphocytes isolated from healthy donor. However, expression of PKC δ, which is a pro-apoptotic isoform, was not overexpressed in tumors. Expression of PKC δ in PC-3 cell was very low. Telomerase, a reverse transcriptase, was found to get activated in all tumor cells. These observations clearly indicated that both PKC and telomerase can be considered as molecular markers of tumorigenesis, and their suppression will be a rational strategy in cancer therapy (15). Effect of some natural polyphenols like curcumin, EGCG, resveratrol, capsaicin, and isothiocyanates PEITC, sulphoraphane and sulphoraphene have been examined and the results indicated that these compounds efficiently modulated the expression levels of different PKC

isoforms as well as inhibited the activity of the enzyme telomerase (16). The concentration, in which these tumor markers were modulated, had been found to induce apoptosis in tumor cells, but not in normal lymphocytes. Although beneficial, it is accepted that oxygen, through ROS generation, can react with DNA, proteins and other cellular components and can become problematic (figure 4). The body is constantly trying to maintain homeostasis with the utilization of the immune system. The immune system is divided into two categories: adaptive and innate. In adaptive immunity, highly complex cells are deployed and recognize antigens on foreign cells. Innate immunity is much broader and is designed to recognize common features on foreign cells and ultimately release more expansive white blood cells such as macrophages and neutrophils. These cells are capable of releasing cytokines which are chemicals that signal other cells to a specific site of damage or injury and aid with the induction of inflammation. Typically most ROS have a short half-life and cause damage locally but for example H2O2 has a relatively long half-life and can travel long distances, causing DNA damage at distant sites. In addition, it may be pointed out that mostly hydroxyl radical (*OH) and to a lesser extent the lower-energy singlet molecular oxygen (1O2) through specific targets (guanine, histidine, tryptophan, tyrosine) may react with DNA and proteins. In contrast O2* is completely unreactive towards biomolecules while H2O2 requires the presence of reduced transition metals such as Fe2+ to promote the Fenton type reaction (17)

Xenobiotics

The principal classes of xenobiotics of medical relevance and drugs, chemical carcinogens, and various compounds that have found their way into our environment by one route or another, such as polychlorinated biphenyls and certain insecticides. Xenobiotics are chemical compounds foreign to the body, such as drugs, food additives, and environmental pollutants; more than 200,000 have been identified.

Xenobiotics are metabolized in two phases. The major reaction of phase 1 is hydroxylation catalyzed by a variety of monooxygenases, also known as cytochrome P450s. In phase 2, the hydroxylated species are conjugated with a variety of hydrophilic compounds such as glucuronic acid, sulfate or glutathione. The combined operation of these two phases renders lipophilic compounds into water soluble compounds that can be eliminated from the body (18). Cytochrome P450s catalyze reactions that introduce one atom oxygen delived from molecular oxygen into the substrate, yielding a hydroxylated product. NADPH and NADPH – cytochrome P450 reductase are involved in the complex reaction

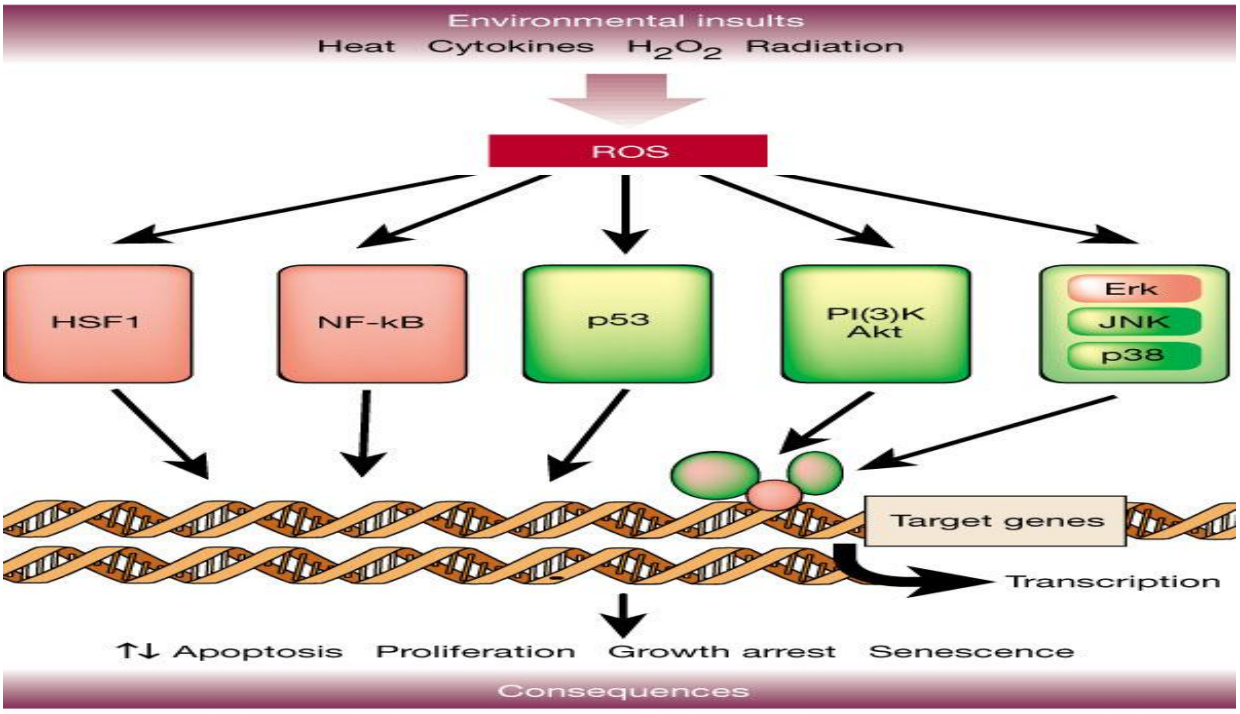

Figure 4. Apoptosis & oxidative stress

mechanism (figure 5). All cytochrome P450s are hemoproteins and generally have a wide substrate specificity, acting on many exogenous and endogenous substrates. They represent the most versatile biocatalyst known. Members of II families of cytochrome P450 are found in human tissue. Cytochrome P450s are generally located in the endoplasmic reticulum of cells and are particularly enriched in liver. Many cytochrome P450s are inducible. This has important implications in phenomena such drug interaction (19).

Conclusion

Exogenous sources include exposure to cigarette smoke, environmental pollutants such as emission from automobiles and industries, consumption of alcohol in excess, asbestos, and exposure to ionizing radiation, and bacterial, fungal or viral infections. Free radicals are generated during normal metabolism and exposure to environmental insults such as infections agents, pollution, UV light, radiation and so on. These are highly reactive species capable of wide spread, indiscriminate oxidation and per-oxidation of proteins, lipids and DNA which can lead to significant cellular damage and even tissue and/or organ failure. When these harmful free radicals cause damage to vital proteins, lipids and DNA (20). Oxidative stress can damage many biological molecules, indeed, proteins and DNA are obtain more significant targets of injury than are lipid and lipid peroxidation often occurs late been injury process. The disorders in lipid organization of biological membranes result in alterations in the activity of a number of membrane bound enzymes. Induction of apoptosis is evident from the release of mitochondrial cytochrome c to the cytosol and also by the induction of caspase 3 and 8. Based on these observations, ability of natural compounds in potentiating the efficacy of antitumor drugs in tumor cells was investigated. Results as obtained from MTT assay demonstrated that compounds especially curcumin, EGCG, PEITC, sulphoraphane and sulphoraphene were effective in reducing dose levels of chemotherapeutic drugs like adriamycin and etoposide when tumor cells were treated with these natural compounds before or during treatment with adriamycin etoposide. Mito chondrial cytochrome P450s also exist and are involved in cholesterol and steroid biosynthesis. They use a non heme iron containing sulfur protein, adrenodoxin, not required by microsomal isoforms. Cytochrome P450s, because of their catalytic activities, play major roles in the reactions of cells to chemical compounds and in chemical carcinogenesis (21). Phase 2 reactions are catalyzed by enzymes such as glucuronosyl transferases, sulfotrans ferases and

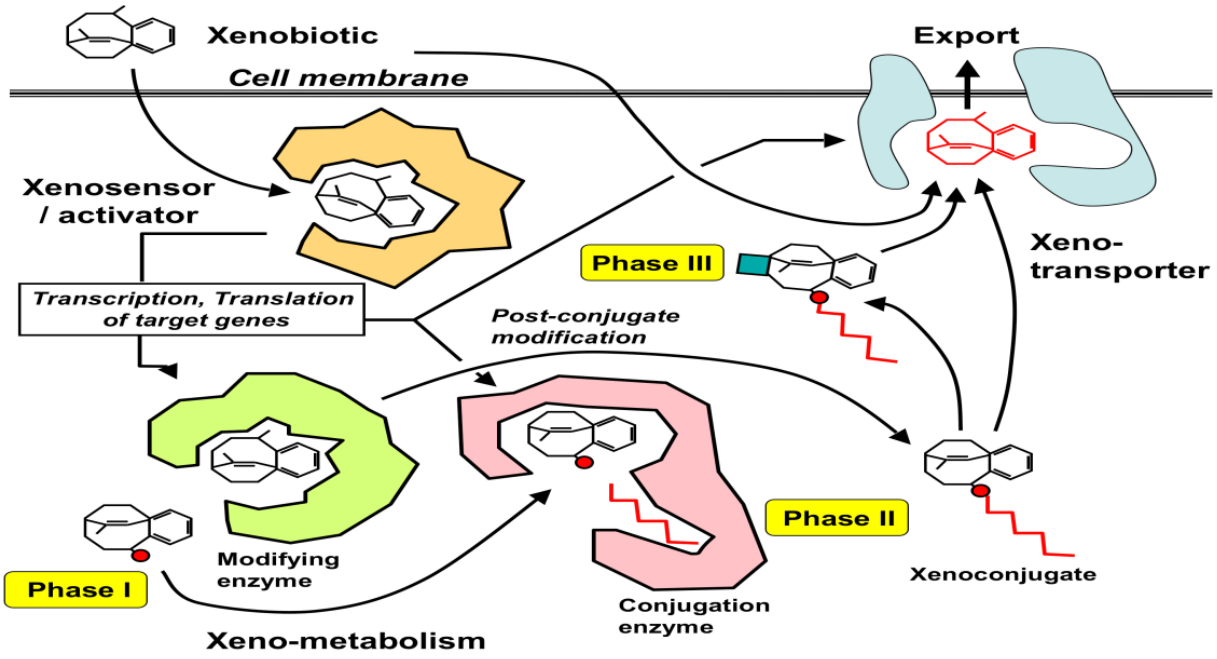

Figure 5. Xenobiotics mechanism

glutathione S – transferases, using UDP – glucuronic acid, PAPS (active sulfate), and glutathione, as donors. Glutathione not only plays an important role in phase 2 reactions but is also intracellular reducing agent and is involved in the transport of certain amino acids into cells.

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