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|  | |  | | --- | | **Carcinogenesis**   * The term *cancer* describes a subset of neoplastic lesions. * A *neoplasm* is an abnormal mass of tissue that results when cells divide more than they should or do not die when they should. * Neoplasms may be either *benign* or *malignant* (tumor)*.* * *Metastases* are secondary growths of cells from the primary neoplasm. * A *carcinogen* is any substance that has the potential to cause cancer in living tissues. |     Numerous chemicals and many other factors can alter the structure of the genome and/or the expression of genetic information, with the subsequent appearance of cancer. However, cancer as a disease usually develops slowly, with a long latent period between the first exposure to the chemical carcinogen and the ultimate development of malignant neoplasia, in which various biological structural and functional alterations are involved.  **The Pathogenesis of Neoplasia:**  The pathogenesis of neoplasia consists of three operationally defined stages, beginning with initiation, followed by an intermediate stage of promotion, from which evolves the stage of progression.  **Initiation:**  Initiation is the first irreversible step in the stages of cancer development; it is an immediate genetic change (mutation) in DNA that will be come after the exposure to a carcinogenic agent. The type of carcinogen, dose, and the duration of cells exposure to a carcinogen can influence on the series of multiple genetic alternations. Ideally, the failure to repair damaged DNA should trigger cell death via apoptosis to maintain the genomic stability of the entire cell population. The increased survival of cells that fail to repair damaged DNA can lead to the buildup of “initiated” cells harboring mutations in tumor suppressor genes and oncogenes essential for cell transformation.  **Promotion:**  At this step, cell proliferation will be arising, giving a large number of daughter cells containing the mutation created by the initiator. Tumor growth requires that mutant cells possess the ability to proliferate autonomously, a characteristic hallmark of cancer cells. The risk of tumor growth with promoter application is dose-dependent. Very low doses of promoters will not lead to tumor development and extremely high doses will not produce more risk than moderate levels of exposure. On the other hand, the microenvironment that consists of numerous cell types as well as non-cellular components such as the matrix surrounding the tumor also plays supportive roles for tumor growth by providing not only the “survival signal”, but also oxygen and nutrients.  **Progression:**  Progression is associated with stepwise transformation of a benign tumor to a neoplasm and to malignancy, which can be achieved by continuous progressive change and genomic instability. The accumulated tumor cells acquire more aggressiveness; they can escape from immune surveillance, resist apoptosis and the ability of the tumor to invade surrounding tissues and to metastasize to remote organs.  **The role of genes in cancer development:**  Many genes are involved in normal growth, and their nonlethal damage is associated with the development of cancer and they include:  **Oncogenes:**  Oncogenes are over-expressed in various human tumors, and might be a good target for developing diagnostic and therapeutic agents against many cancers. Oncogenes are derived from proto-oncogenes that are altered by any of the three structural changespoint mutation, chromosomal translocation or gene amplification. The normal signal transduction pathways are disrupted by oncogenic proteins; leading to futility in fundamental cell functions, including proliferation, cell cycle regulation, and apoptosis.  **Tumor suppressor genes**:  Tumor suppressor genes play an important role in the regulation of various cellular processes including development, differentiation, proliferation and apoptosis. Functional inactivation of these genes has been associated with cancer development and progression. Many different tumor suppressor genes have been found, including *p53.* Mutated *p53* is involved in colon, lung, and breast cancers, also in the pathophysiology of leukemias, lymphomas, sarcomas, and neurogenic tumors. These mutations can disable *p53* gene to trigger the cell to undergo apoptosis.  **DNA Repairing genes:**  DNA repair mechanisms are essential in preventing tumor initiation and progression. Mutations in DNA repair genes can be inherited from a parent or acquired over time as the result of aging and environmental exposures. Defects in DNA repairing genes can confer predisposition to several cancers, including skin, breast, bladder, oral, and gastric cancers.    **Apoptosis regulating genes:**  Transcriptional quieting of apoptosis-related genes associated with the exposure to a carcinogen may impair the apoptotic machinery, eventually leading to cancer development. In normal cells multiple genes are involved and display either pro- or anti-apoptotic effects. Impaired apoptosis can produce cells which have the potential to stay alive, and then contribute in the appearance of the malignant phenotype, tumor progression, and resistance to chemotherapy. Apoptosis bypass is considered a hallmark of cancer cells.  Many members of the *Bcl-2* family of apoptosis-related genes have been found to be differentially expressed in various malignancies including melanoma, breast, prostate, chronic lymphocytic leukemia, and lung cancer, and some are useful prognostic cancer biomarkers  **The cell cycle and cancer**  The connection between the cell cycle and cancer is obvious, cell cycle controls cell proliferation, and cancer is a disease of inappropriate cell proliferation. The cell cycle described by a series of steps at which the cell checks for the accuracy of the process and instructs itself to proceed to the next step. The cell cycle consists of the presynthetic growth phase 1 (G1), the DNA synthetic phase (S), the premitotic growth phase 2 (G2), and the mitotic phase (M). Non dividing cells are either in cell cycle arrest in G1 or they exit the cycle to enter a phase called G0. Proper progression through the cell cycle is monitored by checkpoints that sense possible defects during DNA synthesis and chromosome segregation. Activation of these checkpoints induces cell cycle arrest which allows cells to properly repair these defects. Defective cell cycle regulation and checkpoint mechanisms are hallmarks of cancer   |  |  | | --- | --- | |  |  | |  |  | | **Carcinogenesis by Chemicals**  **Organic Chemical Carcinogens**  Several organic compounds can cause cancer: polycyclic aromatic hydrocarbons (PAHs), dialkylnitrosamines, nitrite (which is metabolized into carcinogenic nitrosamines or nitrosamides), and aflatoxin B1.  **Inorganic Chemical Carcinogens**  A number of inorganic elements and their compounds are involved, including compounds of cadmium, chromium, nickel, lead, and arsenic.  **Hormonal Carcinogenesis**  Some cancers may result from abnormal internal production of specific hormones. Alternatively, excessive production or the derangement of the homeostatic mechanisms of an organism may result in neoplastic transformation, which may be produced by a manipulation that breaks the feedback loop between the pituitary and the target organ. Including testes, ovary, adrenal gland, mammary gland, and uterus.  **Chemical Carcinogenesis by Mixtures**  The most common environmental mixtures are those seen in tobacco smoke and other combustion products. Interactions between the chemicals in mixtures may be additive, synergistic, or inhibitory.  **Chemical Carcinogenesis by Diet**  Evidence indicates that many dietary components, including excessive caloric intake, excessive alcohol intake, and a variety of chemical contaminants of the diet, including aflatoxin B1, are carcinogenic. |  |      |  | | --- | | **Mechanisms of Chemical Carcinogenesis**  **Metabolism of Chemical Carcinogens in Relation to Carcinogenesis**  A critical step in the induction of cancer by chemicals is the covalent interaction of some form of the chemical with macromolecules. Some parent compounds require metabolic alteration to a metabolite that is capable of covalent binding directly with macromolecules. Chemical carcinogens that require metabolism for their carcinogenic effect are termed procarcinogens, whereas their highly reactive metabolites are termed ultimate carcinogens. A number of metabolic reactions are involved in the "activation" process.  **Free Radicals and the Metabolism of Chemical Carcinogens**  Free radical reactions also are involved in the formation of ultimate carcinogens. Free radicals are chemical elements or their compounds that possess a single unpaired electron. Free radicals may react directly with DNA to produce a variety of structural changes in bases.  **Mutagenesis and Carcinogenesis**  The process of mutagenesis consists of structural DNA alteration, cell proliferation that fixes the DNA damage, and DNA repair that either directly repairs the alkylated base or bases or results in the removal of larger segments of the DNA. Direct-acting alkylation agents induce preferential binding to highly nucleophilic centers such as the *N* 7 position of guanine. Mutagenesis can be the result of several different alterations in the physical and chemical nature of DNA. Methylating and ethylating agents result in mutations as a result of base mispairing. The active metabolites of numerous compounds, such as PAHs and aromatic amines, can form bulky DNA adducts that block DNA synthesis, resulting in a noncoding lesion. The role of DNA repair in protection of the genome and in the induction of mutations is an essential component in mutagenesis.  **Macromolecular Adducts Resulting from Reaction with Ultimate Carcinogens**  The most nucleophilic site in DNA is the *N* 7 position of guanine, and many carcinogens form covalent adducts at that site. Another common structural change in DNA is the hydroxylation of DNA bases. Such oxidative reactions, occurring either as a result of an endogenous oxidative phenomenon or from the administration of exogenous chemical and radiation carcinogens.  Chemical carcinogens may inhibit DNA methylation through several mechanisms. Therefore, the inhibition of DNA methylation by chemical carcinogens may represent a further potential mechanism for carcinogenesis induced by chemicals.  Structural changes in DNA of largely unknown character also have been reported. The exact role of structural adducts of DNA in carcinogenesis is not a simple one to characterize with adduct = mutation = carcinogenesis. Adducts of known carcinogens may play a significant role in carcinogenesis induced by their procarcinogenic forms, but the function of structurally undefined, endogenously produced adducts in the carcinogenic process is not as clear.  **Classification of Chemical Carcinogens in Relation to Their Action on One or More Stages of Carcinogenesis**  Initiating agent (incomplete carcinogen): a chemical capable only of initiating cells |   Promoting agent: a chemical capable of causing the expansion of initiated cell clones  Progressor agent: a chemical capable of converting an initiated cell or a cell in the stage of promotion to a potentially malignant cell  Complete carcinogen: a chemical possessing the capability of inducing cancer from normal cells, usually possessing properties of initiating, promoting, and progressor agents   |  |  |  | | --- | --- | --- | | **Chemical Carcinogenesis in Humans**  **Lifestyle Carcinogenesis**  Many chemical factors are involved in the development of cancer from lifestyle practices like alcoholic beverages, aflatoxins, and others. Elevated risks of several neoplasms in the human result from excessive intake of alcoholic beverages because ethanol is metabolized into acetaldehyde, an incomplete carcinogen that can contribute to the progression of cancer that already has been initiated or can act as a cocarcinogen when administered with another carcinogen. For example, cancer of the oral cavity and pharynx is markedly increased when an individual smokes tobacco as well as abuses alcoholic beverages.  Aflatoxins, especially aflatoxin B1, which are produced by some strains of the ubiquitous mold *Aspergillus flavus,* are potent hepatocarcinogens. Other dietary contaminants—produced directly by organisms such as molds, substances naturally occurring in plants such as the pyrrolizidine alkaloids, and products of the metabolism of dietary components by contaminating molds—have been demonstrated as carcinogenic in experimental systems.  The most common mechanism of diet-associated carcinogenesis in the human is the action of major dietary constituents (fat, carbohydrate, and protein) as promoting agents. Considerable experimental evidence has demonstrated that carbohydrate and lipid are effective promoting agents in the development of several tissue types of neoplasms.  There is substantial epidemiologic evidence that being overweight may increase the incidence of a variety of human cancers. Relatively high levels of dietary fat are associated with increased death rates from cancer of the prostate, colon, and breast in humans.  Endogenous hormone production probably also is related to the phenomenon of the enhanced risk of breast cancer in patients who wait until the fourth decade or more to have the first child. In addition to late first full-term pregnancy, early menarche and late menopause appear to increase the risk of breast cancer in humans.  Perhaps the most common exogenous cause of human cancer is tobacco smoking and other forms of tobacco abuse. The chewing of tobacco leads to cancer of the mouth. Smoking cessation decreases the incidence of lung cancer because the stage of tumor promotion occupies the longest time interval and poses the greatest risk in the development of cancer in smokers.  **Chemical Carcinogens Associated with Occupations**  Many chemicals are associated with cancer development related to some occupations for example: benzene, organochlorine pesticides and ethylene oxide which may be associated with bone marrow cancer, while cadmium and formaldehyde are associated with bronchus cancer.  Polychlorinated biphenyls are a causative agent of liver cancer.   |  | | --- | |  | |  |   **Chemical Carcinogenesis Resulting from Medical Therapy and Diagnosis**  There are risk–benefit considerations in the use of a number of drugs and hormones in humans, and the most striking is the utilization of known carcinogenic agents in chemotherapy for neoplasia. Immunosuppression as a result of genetic abnormalities, therapeutic immunosuppression (as in transplants), and immunosuppression resulting from diseases such as advanced cancer or the acquired immune deficiency syndrome (AIDS) are associated with increased incidences of a variety of different cancers. For example alkylating agents may be associated with bladder cancer and leukemia, azathioprine and phenytoin associated with lymphoma, chloramphenicol associated with leukemia, ultraviolet light associated with skin cancer, thorotrast associated with liver cancer |      |  | | --- | | **The Prevention of Human Cancer Induced by Chemicals**  Cancer prevention in humans in general may be grouped into two approaches: active and passive. Depicts an outline of various methods of cancer prevention with an indication of the stage of carcinogenesis toward which the preventive measure is directed. The passive prevention of cancer involves the cessation of smoking, dietary restrictions, and modification of other personal habits. Active prevention of cancer development usually is accomplished by the administration of an agent to prevent infection by carcinogenic viruses and other organisms or by the intake of chemicals, nutrients, or other factors that may modify or prevent the action of carcinogenic agents. |   **Cancer cell lines**  Marvelous progresses in our understanding of the cancer have been made over the past several decades using cancer cell lines.  Cancer cell line can be defined as a population of cells descended from a single cell and containing the same genetic makeup, these cells keep dividing and growing over time, under certain conditions in a laboratory. Cancer cell lines are used in research to study the biology of cancer and to test cancer treatments. Which can be considered as good experimental models for cancer study, and have the greatest impact on improving outcome for cancer patients. The use of cell lines has resulted in a wealth of information about the efforts to discover new anticancer drugs and predict their clinical activity. The availability of cancer cell lines is the fundamental basis for cancer research; without cell lines any progress in cancer treatment cannot evolve. The *in vitro* and *in vivo* methods were used to investigate the inhibitory effect of many plants on these cell lines. |  |

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