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DEPARTMENT OF BIOTECHNOLOGY
FACULTY OF ENGINEERING & TECHNOLOGY

Natural history of carcinogenesis & Target of chemical carcinogenesis

Content outline

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Natural History of carcinogenesis

From carcinogenesis, when cancers begin, until the time when, in many cases, they cause the death of the persons with them, cancers develop by stages over many years. This process of development, when uninterrupted by treatment, is the “natural history” of cancer. While the complete characteristics of the early period of cancer development are still under active investigation, these two major features stand out:

1.the natural history of cancer is clearly a *multistage* process; some characteristics of major stages are well described and unique; and

2.the natural history of a cancer occurs over a variable, but often long period of time; there is a period of *latency* — often many years in duration — during which early development occurs at the cellular and microscopic level.

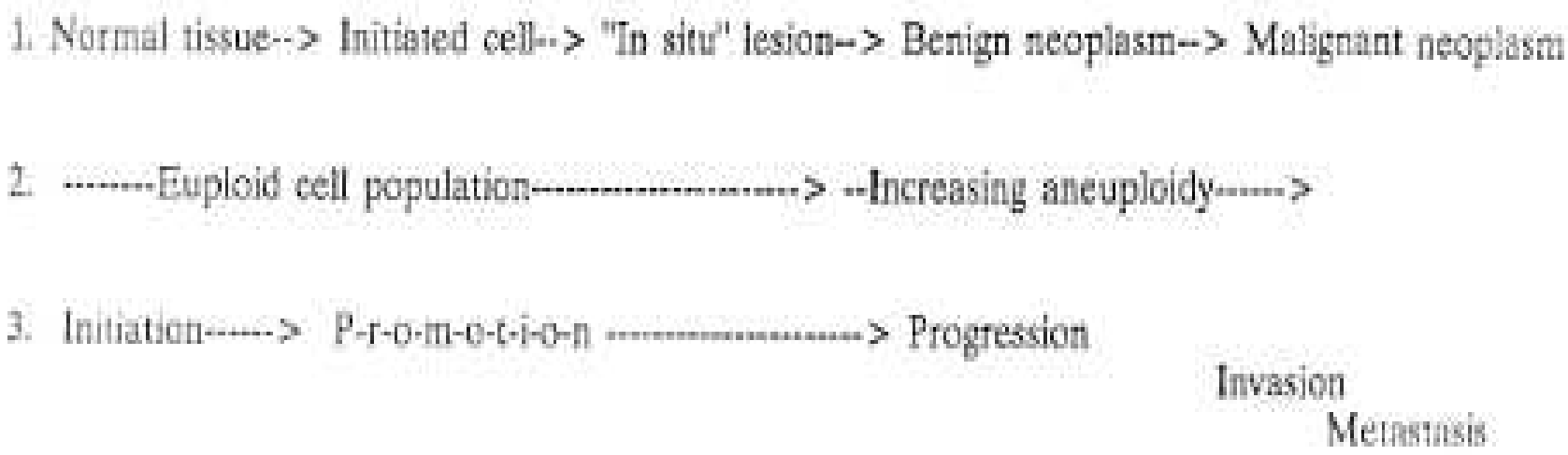
Stages in natural history of cancer is described by following three stages:

a. Initiation
b. Promotion
c. Progression

Initiation: It is a rapid and irreversible process caused by exposure to a carcinogenic agent.

Promotion: Prolonged process consequent to a repeated or continuous exposure to a substance which may not be carcinogenic or capable of initiating the process.

Progression: It refers to the stepwise transformation of a benign tumor to a neoplasm and to malignancy. Progression is associated with a karyotypic change since virtually all tumors that advance are aneuploid (have the wrong number of chromosomes). This karyotypic change is coupled with an increased growth rate, invasiveness, metastasis and an alteration in biochemistry and morphology.



The natural history of cancer: These three lines depict the sequence of simultaneous change which occur preclinically and then clinically (line 1), in karyotype (line 2), and in the individual stages (line 3) as cancer develops over time. Within the stages of promotion, the longest stage , the process is irreversible.

Target of chemical carcinogenesis

•Substances that cause cancer, called carcinogens, have been identified both by studies in experimental animals and by epidemiological analysis of cancer frequencies in human populations (e.g., the high incidence of lung cancer among cigarette smokers). Since the development of malignancy is a complex multistep process, many factors may affect the likelihood that cancer will develop, and it is overly simplistic to speak of single causes of most cancers. Nonetheless, many agents, including radiation, chemicals, and viruses, have been found to induce cancer in both experimental animals and humans.

Chemical carcinogens are of two distinct types

i. DNA-reactive ,

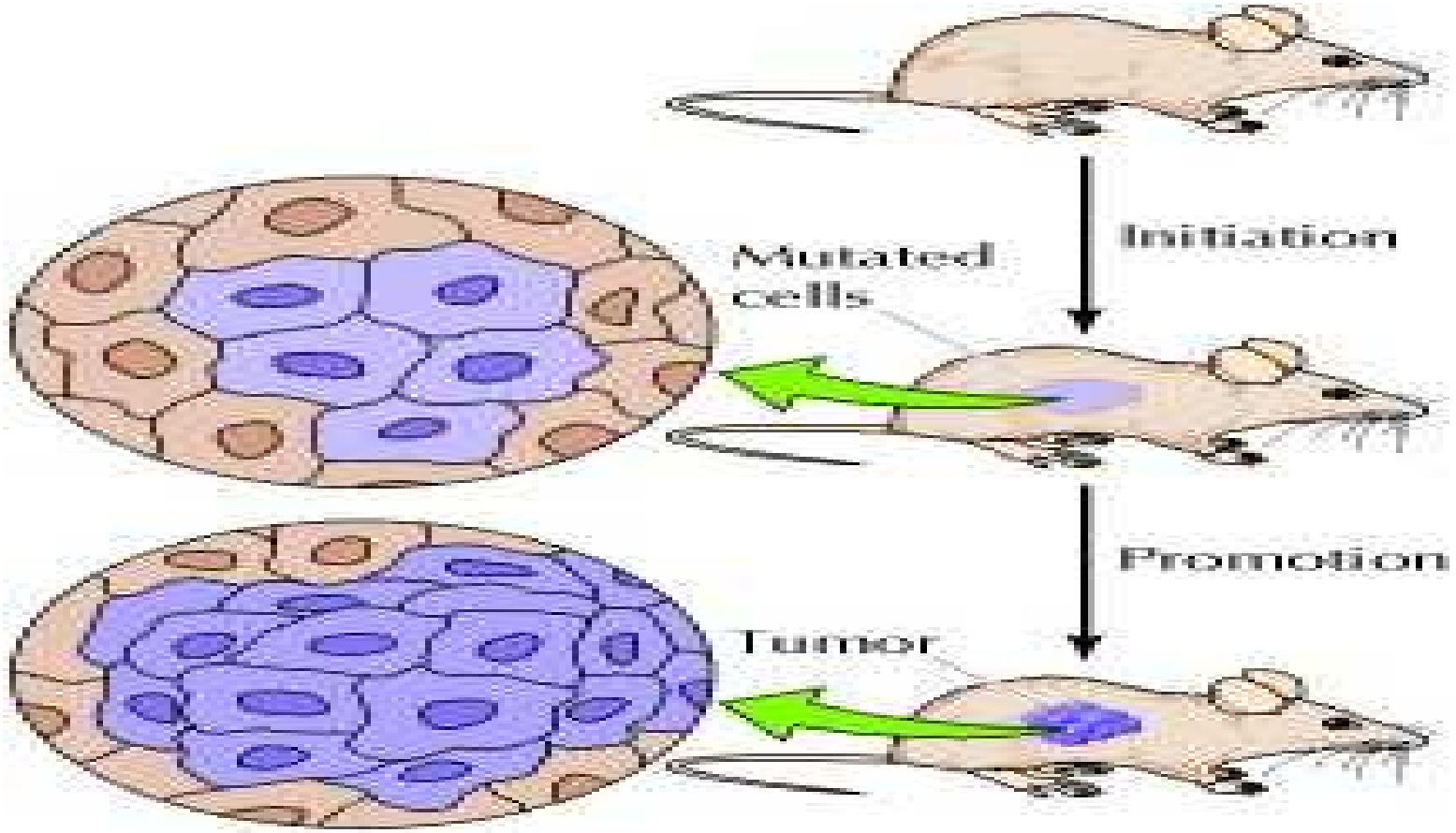
ii. epigenetic.

Carcinogens of the DNA-reactive type are defined by the formation of covalently bound DNA adducts. These chemicals have structures that yield electrophilic reactants either directly or after bioactivation. These agents cause genomic alteration in the structure or function of DNA in the target cell. In addition, these compounds can exert other cellular and tissue epigenetic effects, such as cell proliferation and growth promotion

•Carcinogens of the epigenetic (paragenetic) type, in contrast, do not react with DNA, but rather display cellular effects such as neoplasm growth promotion, cytotoxicity, inhibition of tissue growth regulation, peroxisome proliferation, endocrine modification, immunosuppression and/or sustained tissue ischemia that can be the basis for increases in neoplasia. Their chemical structure is such that they do not give rise to a reactive electrophile.

•Radiation and many chemical carcinogens act by damaging DNA and inducing mutations. These carcinogens are generally referred to as initiating agents, since the induction of mutations in key target genes is thought to be the initial event leading to cancer development.

•Some of the initiating agents that contribute to human cancers include solar ultraviolet radiation (the major cause of skin cancer), carcinogenic chemicals in tobacco smoke, and aflatoxin (a potent liver carcinogen produced by some molds that contaminate improperly stored supplies of peanuts and other grains). The carcinogens in tobacco smoke (including benzo(*a*)pyrene, dimethylnitrosamine, and nickel compounds) are the major identified causes of human cancer. Smoking is the undisputed cause of 80 to 90% of lung cancers, as well as being implicated in cancers of the oral cavity, pharynx, larynx, esophagus, and other sites. In total, it is estimated that smoking is responsible for nearly one-third of all cancer deaths—an impressive toll for a single carcinogenic agent.



➢Tumors are initiated by mutations induced by a carcinogen. Development of a tumor then requires treatment with a tumor promoter to stimulate proliferation of the mutated cells.

References & Further reading

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