Genetics

Biology Dept.3rd stage

Asst. Professor. Dr. Kazhal M. Sulaiman

Lec.12

Genotoxicity

Teratogenesis, mutagenesis and carcinogenesis :-

Genotoxic substances are known to be potentially mutagenic or carcinogenic, specifically those capable of causing genetic mutation and of contributing to the development of tumors.

Mutagenesis & Carcinogenesis & Teratogenesis

	Mutagenesis	Carcinogenesis	Teratogenesis
time between induction& diagnosis	next generation up to several generation	several months to many years	several weeks to month
reversibility	irreversible	irreversible	irreversible
sensitivity	no apparent difference between mature and immature tissue	some cancer type seem to affect especially younger individuals, in other type the opposite applies	only immature tissue is sensitive: the sensitivity decrease with development
characterization	changes in amount or quality of genetic material (molecular level)	uncontrolled proliferation at cellular level	change in pattern of development at tissue and organ level
target	genetic material is usually affected at random	usually there are specific target	often with high degree of specificity between nature of teratogen and type of malformation
basic toxicological characteristics	can be induced instantaneously or be caused by repeated exposure : probably no NOEL	chronic toxicity : probably no NOEL	acute toxicological phenomenon (rapid expression) :apparently no NOEL

Carcinogenesis :

The role of substances foreign to the body in causing uncontrolled cell

replication commonly known as cancer is termed as chemical carcinogenesis. Chemically induced carcinogenesis is thought to involve two distinct stages, referred to as **initiation and promotion**. In the initiation stage chemical carcinogens alter the DNA in a manner such that cells replicate uncontrollably and forms cancerous tissue

Carcinogenesis involves damage-induced genetic alterations (mutations) that **produce cancers**.

A carcinogen is any substance, radionuclide or radiation that is an agent directly involved in causing cancer. This may be due to the ability to damage the genome or to the disruption of cellular metabolic processes.

Carcinogens may increase the risk of cancer by altering cellular metabolism or damaging DNA directly in cells, which interferes with biological processes, and induces the uncontrolled, malignant division, ultimately leading to the formation of tumors.

2 major classes of gene are involved in carcinogenesis:

- **Proto-oncogenes**: promote cell cycle progression

eg. constitutive activity of growth factor tyrosine-kinase receptors can cause neoplastic transformation

- **Tumour-suppressor genes**: inhibit cell cycle progression

eg. mutations in tumour suppression gene product p53 (prevalent in smokers)

Carcinogenesis typically results from a series of mutations that affect regulation of proliferation.

m1: inactivation of a tumor suppressor gene results in cell proliferation

m2: mutation inactivates a DNA repair gene

m3: mutation of a proto-oncogene generates an oncogene

m4: mutation inactivates more cancer suppressor genes, resulting in cancerous proliferation

Cancers

Arise when cells escape normal controls on cellular proliferation. Cancer is not a single disease, rather the term encompasses a group of conditions that share the characteristic process of uncontrolled cellular proliferation of cells that are typicallly capable of local infiltration into other tissues (invasion). This propensity for invasion and migration is associated with the capacity to metastasize to sites distant from the point of origin. Benign tumors evidence as local overgrowth, but fortunately have minimal or no propensity for tissue infiltration and metastasis. Cancers originating in the same tissue/organ can vary considerably in degree of undifferentiation, sensitivity to chemotherapeutic agents, growth rate, invasiveness, and metastatic potential.

Mutation in a proto-oncogene, such as a gene which encodes an intracellular signaling protein that is normally activated only by extracellular growth factors, converts the proto-oncogene into an oncogene.

There is two types of tumours:-

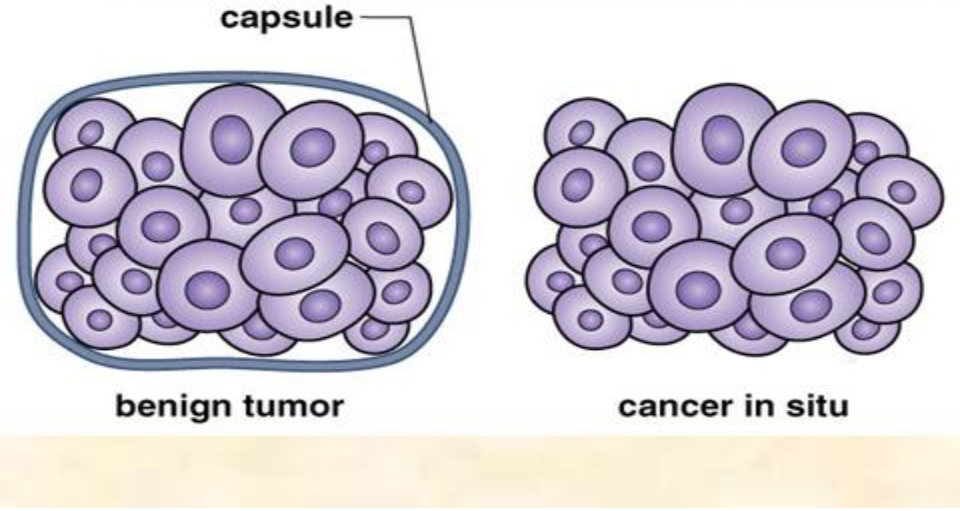
Benign tumours

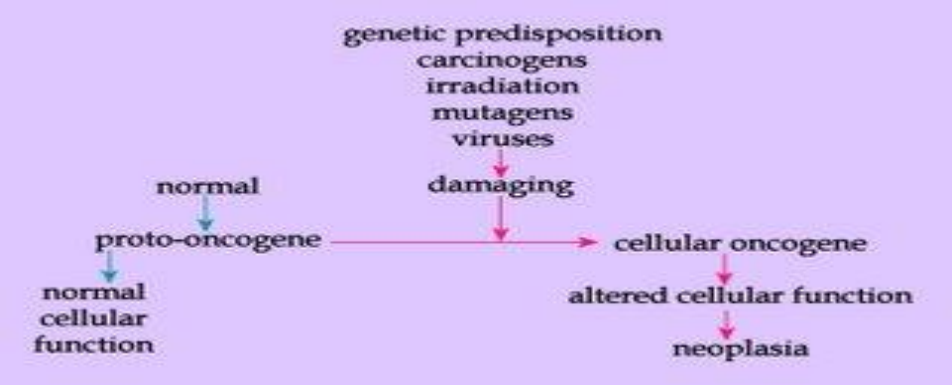
- are generally slow growing and enclosed in a fibrous capsule
- are relatively innocuous, although their location can make them serious (such as a tumour located in the brain)
- are not considered cancerous (that is, they are not malignant)
- are given names that usually end in "*oma*" (although a melanoma is a malignant skin cancer)

Malignant tumours

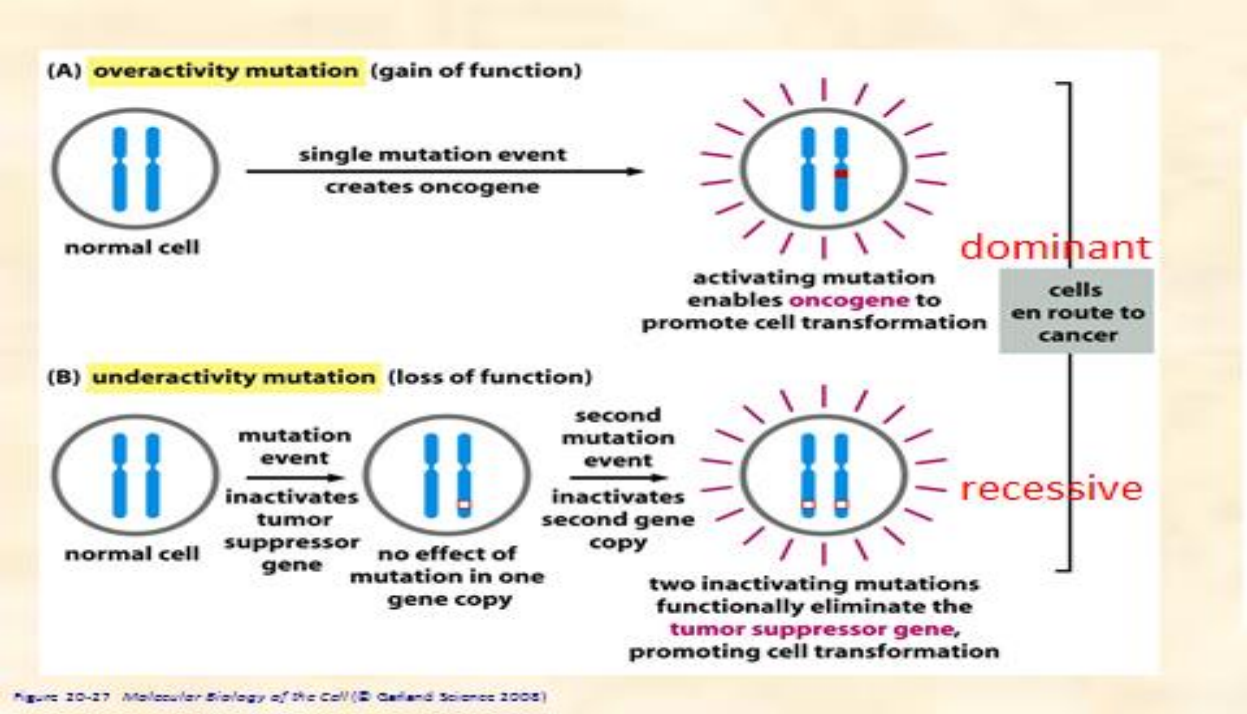
- proliferate rapidly, invading neighbouring tissues
- can metastasise, or spread, to other sites of the body
- are named using the conventions of tissue, cell type, and origin

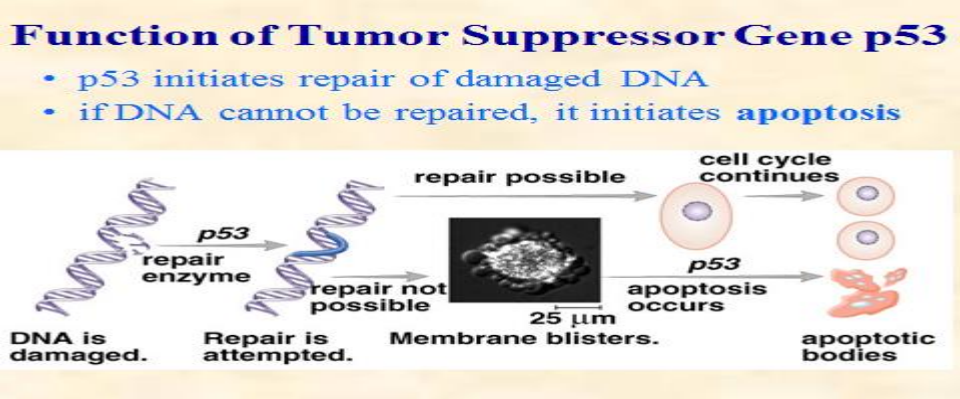
e.g. A tumour of the bone is an *osteoma* if benign and an *osteosarcoma* if malignant



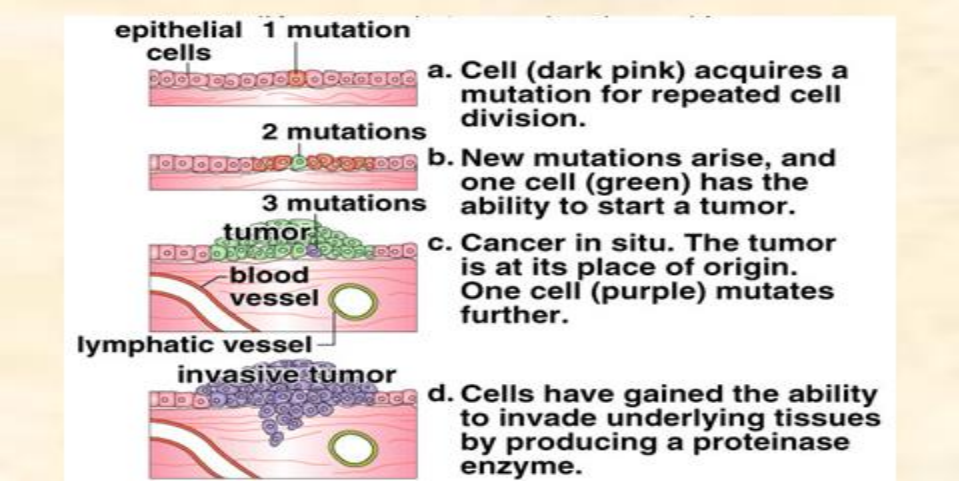


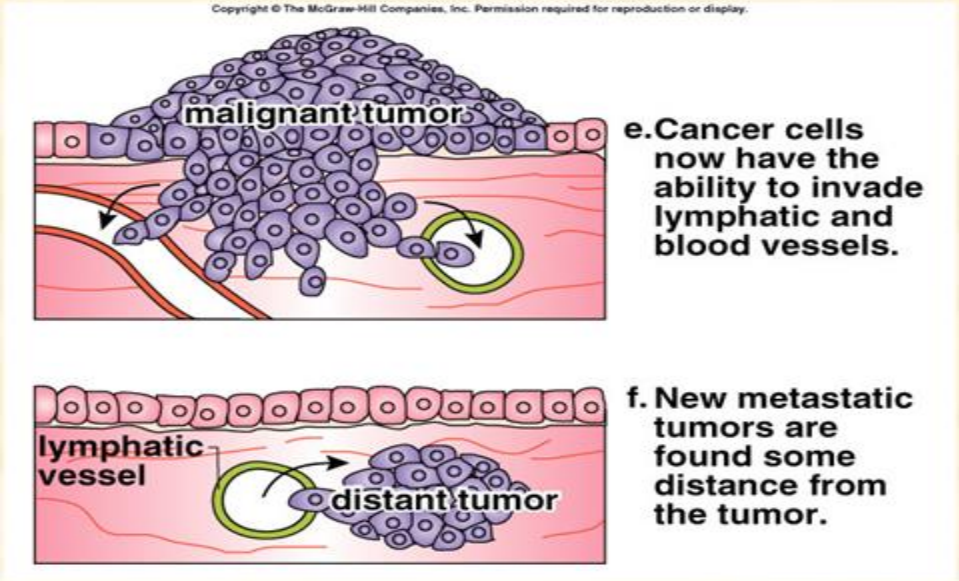
Alteration **of a gene that normally controls cell growth can promote the uncontrolled growth characteristic of cancer. The normal form of the gene is termed a proto-oncogene, and the malignantly transformed gene is termed an oncogene.**

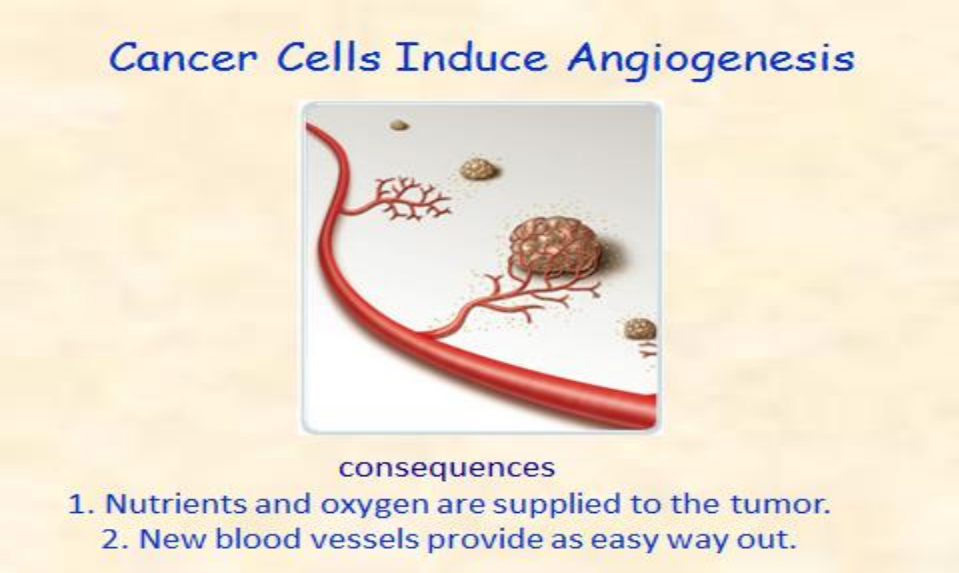




- **Cancer is a multistage process requiring an average of 10 mutations that lead to the development of a tumor**
  - loose control over the cell division process
  - do not adhere to each other
  - do not resemble normal cells
  - do not carry out functions of normal cells







Some environmental agents associated with cancer are:

- Viruses
- Tobacco smoke
- Food
- Radiation
- Chemicals

Pollution