Neoplasia

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Human neoplasia collectively represents a spectrum of diseases characterized by abnormal cell growth, loss of tissue homeostasis, and distorted architecture. Such new growth is called a **neoplasm** or **tumour.**

The term "**benign**" is often used to describe such low-effect tumours, which include many common growths such as dermal nevi, warts, and uterine fibroids. The term "**cancer**" or "**malignant** tumour" is used to describe a more advanced form of neoplasia that involves tissue invasion and destruction and defines that can terminate in systemic disease and host death.

Tumorigenesis: A pathologic process that involves the transformation of normal cells to a neoplastic state and results in polyclonal or monoclonal neoplastic cell proliferation.

The clinical phase of disease: The recognition of overt malignancy by symptoms or physical examination findings defines.

The preclinical phase is usually unknown to the patient but may sometimes be identified by screening interventions. Preclinical signs and potential precursors of colon cancer and breast cancer may consist of polyps in the colon and proliferative abnormalities of the breast.

Precursor lesions: defined as lesions earlier than in situ disease, although in some instances, carcinoma-in-situ and minimally invasive cancer are included in the term "precursor lesion".

THE CELLULAR & MOLECULAR BASIS OF NEOPLASIA

a. Cell **Hypertrophy:** Morphologic abnormalities, enlargement of the cell, reflecting too much protein and membrane synthesis.
b. Cell **Hyperplasia:** crowding due to too much cell division.
c. Cell **dysplasia** reflects a return to a more immature cell without a committed identity.
d. **Metaplasia**: which reflects abnormal cell reprogramming to appear and function like a cell of a different type.

this process of new growth, called **neoplasia**, is preceded by a years-long process of molecular evolution at the cellular DNA level, which is not apparent by microscopy.

GENETIC AND EPIGENETIC CHANGES IN NEOPLASIA

Mutagen: Anything that causes a mutation (a change in the DNA of a cell).

Epigenetics: the study of how the environment can cause changes that affect the way genes work. Unlike genetic changes, epigenetic changes are reversible and do not change the DNA sequence

Uncorrected errors lead to the accumulation of mutations in the genomic DNA in many cells throughout the human body. The accumulation of such mutations is subject to many influences including:

A. Inheritable genetic factors. Gene mutations inherited from parents are present in all the cells. Inherited defects in the genes involved in the machinery that guards the genome can greatly increase the spontaneous rate at which genomic mutations or structural alterations occur, accelerating the accumulation of mutations.
B. Environmental factors. Exposure to the environmental factors of ionizing radiation and chemical carcinogens may

initiate or accelerate the accumulation of genomic mutations.

Melanomas, lung and oropharyngeal cancers, and cancers of the gastrointestinal (GI) tract have the highest mutational burden of all cancers. This is due to the direct exposure of these tissues to the outside environment and exposure to mutagenic insults such as ultraviolet (UV) light (skin), inhaled carcinogens (lung and oropharynx), and ingested carcinogens and products of endogenous bacterial flora (GI tract).

1- Defects in DNA repair mechanisms :

The nucleotides in genome DNA can be chemically altered by exogenous or endogenous carcinogens, radiation, UV light, and other mutagens. Cells are able with a repertoire of DNA repair mechanisms, each designed for a specific type of damage, to repair and restore the DNA's nucleotide sequence. A malfunction in one or more of these DNA repair mechanisms is one of the fundamental hallmarks of cancer and is often an early event in tumorigenesis.

2- Defects in Chromatin Structure and Dynamics

In addition to the repertoire of DNA repair mechanisms available to correct errors, the integrity of the genome is also preserved and protected by a mega-structural framework consisting of a densely packaged complex of the genome DNA and histone proteins referred to as **chromatin**.

Loss of the epigenetic control of chromatin is commonly seen in cancer cells, leading to abnormal expression of many genes, increased susceptibility to DNA damage, and errors in mitotic separation.

3- Defects in Genome Content: Maintaining the integrity of the genome also requires preserving its entire content, even though the human genome is split into 46 fragments (46 chromosomes). As such, a complex cellular machinery is in place to preserve the integrity of each chromosome, to orchestrate the proper duplication of each of the chromosomes in every S phase, and to the proper allocation and distribution of a full set of chromosomes to each daughter cell during every mitosis. In neoplasia, these mechanisms can fail, leading to abnormalities in the structure or number of chromosomes, which is referred to as **chromosome instability**.

4- Defects in Protecting Chromosome Ends

The fact that the diploid human genome is fragmented into 46 chromosomes means that there are 92 ends in the human genomic DNA. There are cellular mechanisms in place to hide and protect these loose ends from the DNA repair machinery that would otherwise consider them damaged DNA and inappropriately attempt to fuse them. This protection is accomplished by highly repeated sequences at the ends of chromosomes called **telomeres** and an associated complex of proteins called **shelterin**. Since normal DNA replication is unable to proceed to the very end of the telomeres, telomeres shorten with every replication. With continuous cycles of replication, telomeres eventually shorten to nothing; a loss of protective telomeres leads to a **telomere crisis** consisting of inappropriate DNA damage response, chromosome fusion, and ultimately cell senescence or cell death. Indeed, most cells have

limited replicative potential.

The enzyme **telomerase** can lengthen telomeres. **An enzyme in cells that helps keep them alive by adding DNA to telomeres** (the ends of chromosomes). Each time a cell divides, the telomeres lose a small amount of DNA and become shorter. Over time, the chromosomes become damaged and the cell dies.

5- SPECIFIC GENE MUTATIONS IN NEOPLASIA

Tumour suppressor genes: or anti-oncogene, is a gene that regulates a cell during cell division and replication. If the cell grows uncontrollably, it will result in cancer. When a tumour suppressor gene is mutated, it results in a loss or reduction in its function.

proto-oncogenes: A gene involved in normal cell growth. Mutations (changes) in a proto-oncogene cause it to become an **oncogene**, which can cause the growth of cancer cells.

An inherited mutation in one allele of Tumor suppressor genes the ***TP53*** gene can be characterized by the early development of bone, breast, brain, and soft tissue tumours (sarcomas). Inherited mutations in single alleles of the ***BRCA1*** gene ((**BReast CAncer gene 1**) and BRCA2 (BReast CAncer gene 2) are genes that produce proteins that help repair damaged DNA) can cause a high risk for breast or ovarian cancers.

How PROTO-ONCOGENES & TUMOR SUPPRESSOR GENES IN NORMAL PHYSIOLOGY & NEOPLASIA

Proteins encoded by proto-oncogenes and tumour suppressor genes perform diverse cellular functions. Not surprisingly, they include proteins that recognize and repair DNA damage, proteins

that regulate the cell cycle, proteins that mediate growth factor signal transduction pathways and regulate programmed cell death, proteins involved in cell adhesion to the matrix or in cell-to-cell communication, and proteins that regulate the metabolic needs and biomass production of cells. The deregulation of these pathways through mutational events results in increased genomic instability, overactive growth factor signalling, unrestricted proliferation, inactivation of programmed cell death (apoptosis), decreased dependency on cell adhesion, increased energy supplies and protein synthesis, and extracellular proteolysis. Many of these functions may be altered simultaneously through the deregulation of transcription factors that regulate many genes.

Examples of tumour suppressor proteins include both the **retinoblastoma protein** and the **p16 cell cycle inhibitor**, which function in restricting proliferation at the G1 checkpoint of the cell cycle. Loss of the genes encoding these proteins can result in unchecked progression through the G1/S checkpoint. The *TP53* tumour suppressor gene encodes the **p53 protein**, which is a critical guardian of genomic integrity and serves to recognize DNA damage and consequently inhibit cell cycle progression and induce apoptosis. Loss of the p53 protein can result in continued cell replication despite DNA damage and failure to activate apoptosis.

7- HORMONES AND GROWTH FACTORS IN IN NEOPLASIA

The regulation of growth in complex organisms requires

specialized proteins for the normal growth, maturation, development, and function of cells and specialized tissues. The complexity of the human organism requires that these proteins be expressed at precisely coordinated points in space and time. An essential component of this regulation is the system of **hormones, growth factors, and growth inhibitors.** On binding to **specific receptor proteins** on the cell surface or in the cytoplasm, these factors lead to a complex set of signals that can result in a variety of cellular effects, including mitogenesis, growth inhibition, changes in cell cycle regulation, apoptosis, differentiation, and induction of a secondary set of genes.
a subset of **growth factor receptors** is proto-oncogenes. many **growth factors** and **growth factor receptors** appear important in tumour growth and progression.
For example, EGFR epidermal growth factor receptors and EGFR-targeted therapies are used to treat this type of cancer. Some growth factor signalling pathways function to inhibit cell growth and provide negative regulation in response to extracellular stimuli. An example of this is the **transforming growth factor-β** (**TGF-β**). In some tumour types, the anti-proliferative response to **TGF-β** is lost early on because of mutations in its downstream signalling components. Also, over-secretion, of **TGF-β** by the tumour leads to promoting the invasive and metastatic properties of tumours.

Another important class of receptors is the large superfamily of **nuclear hormone receptors**. These include the cellular receptors for a variety of hormones, among them estrogen and

progesterone, androgens, glucocorticoids, and thyroid hormone. The actions of estrogen are fundamentally important in the development of breast cancer. In women, oophorectomy early in life offers substantial protection against its development. More than half of all breast cancers are dependent on estrogen for proliferation. The **androgen receptor** (**AR**), plays a critical role in the development of prostate cancer.

8- CONTROL OF THE CELL CYCLE IN NEOPLASIA

Several molecular mechanisms contribute to the unrestricted proliferative capacity of tumour cells.

First, excessive growth factor or hormonal signalling stimulates proliferation. Second, telomerase gene activation lifts the natural replicative ceiling pre-existing in most cells.

Third, the orderly progression of the phases of the cell cycle is strictly regulated by a large family of cell cycle machinery proteins that can halt cell replication if precise conditions are not met. At the heart of cell cycle regulation are complexes of **cyclins and cyclin-dependent kinases (CDKs)** that drive the forward direction of cell cycle progression. These are under both positive and negative regulation by a plethora of other proteins and a highly complex, intertwined signalling network that functions to ensure that cell cycle progression proceeds in a desired and healthy manner.

9- CONTROL OF THE APOPTOTIC PROGRAM IN NEOPLASIA

Apoptosis: The process of programmed cell death, or apoptosis, is considered a vital component of various processes including

normal cell turnover, proper development and functioning of the immune system.

These are in communication with many input signals that function to report DNA damage, metabolic stress, or other malfunctioning programs. Some integral proteins of the apoptotic machinery are the protease family of **caspases** and the **Bcl-2 family proteins**. Whether apoptosis occurs depends greatly on the balance of these stimulatory and inhibitory proteins.

The loss of apoptotic control allows cancer cells to survive longer and gives more time for the accumulation of mutations which can increase invasiveness during tumour progression, stimulate angiogenesis, deregulate cell proliferation and interfere with differentiation.