Genetics of Cancer

Carcinogenesis: Under normal circumstances cells in the human body are under strict control in terms of growth and differentiation. This growth and differentiation of cells is stimulated by growth factors. Cell growth can temporarily cease (senescence), and cells can also undergo organized and programmed cell death (apoptosis). Apoptosis is a normal aspect of tissue health and maintenance. However, in cancer cells the control mechanisms have gone awry and cell growth goes out of control. The hallmark of cancer is uncontrolled growth of abnormal cells which consume nutrients and energy within the host. In addition, the cancer cells lose their ability to perform their normal functions. If the cancer cells are in tissues, they are commonly called "**solid tumors**". If they involve cells in the blood, they are called "**liquid tumors**". **Apoptosis is mediated by proteolytic enzymes called caspases, which trigger cell death by cleaving specific proteins in the cytoplasm and nucleus.**

Mutagenesis: Mutations are changes in genes of DNA. Mutations can occur in proto-oncogenes to create oncogenes (which promote cancer), or mutations can occur in tumor suppressor genes (which suppress cancer). Oncogenes promote cancers and regulate the communication between cells and their outside environment.

proto-oncogenes:
Genes are made of sequences of DNA that contain the information necessary for your cells to function and grow properly. Genes contain instructions that tell a cell to make a specific type of protein. Each protein has a specialized function in the body. A proto-oncogene is a healthy gene found in the cell.

After the mutations occur and generate oncogenes (or dysfunctional tumor suppressor genes), the cells that possess these mutations can be stimulated by chemical, hormonal, environmental, and viral mechanisms to promote the incorrect expression of specific proteins and the growth of the cancer cells

Tumor suppressor genes are the opposite of oncogenes. They exist to keep oncogenes in check. So, while the expression of oncogenes can induce cancer (gain-of-function), the inactivation or suppression of tumor suppressor genes can also induce cancer (loss-of-function). Two additional tumor suppressors are p*53* (protein 53) and p*Rb* (protein of retinoblastoma). Both of these proteins exert control over the cell cycle so that the cycle does not continue endlessly.

Oncogenes refer to those genes whose alterations cause gain-of-function effects, while tumor suppressor genes cause loss-of-function effects that contribute to the malignant phenotype.

Typically the genetic alterations in cancer can be said to include three major types of genes, oncogenes, tumor suppressor genes and genes that preserve the integrity of the genome. It must be kept in mind that cancer is a multi-step process and several genetic alterations are required for a full blown cancer phenotype.

Oncogenes

These are today known to be cellular genes that when mutated and/ or inappropriately expressed in a manner that increases their activity result in a malignant phenotype. Classical examples include *src*, *ras* and *myc* oncogenes. These genes are very much the key components of cellular regulatory processes eg. the *src* gene is codes for a tyrosine kinase, the *ras* gene for a G protein and the *myc* gene for a nuclear protein that is involved in DNA replication.

Tumour Suppresor Genes (TSG)

These genes can be compared to the brakes of a car, and functionin the cell to regulate cell division. Loss of genetic matter is also a key event in the generation of neoplasia, and the same can be demonstrated by cytogenetic techniques. Molecular tools have been able to further define the loss of genetic matter. Typically there is

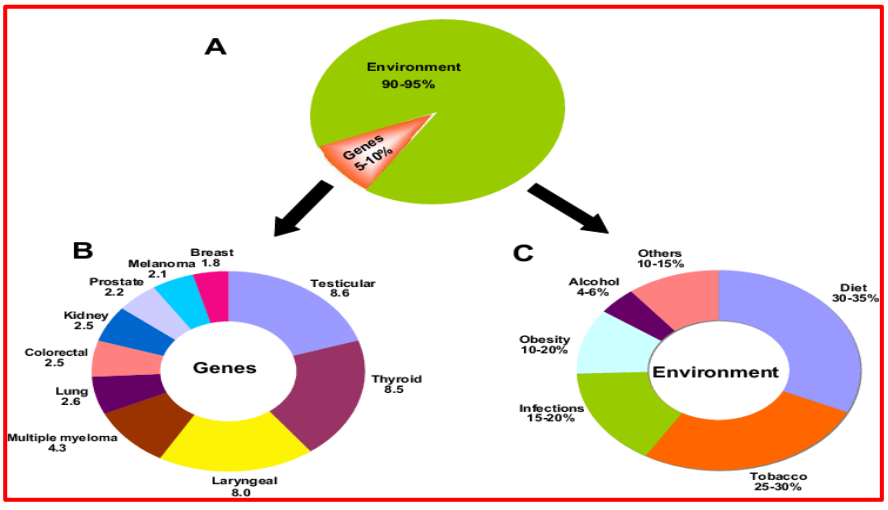
loss of one allele of a TSG while the other is inactivated by point mutation. The concepts of TSGs were demonstrated first with the Retinoblastoma gene (*RB*). Commonly affected TSGs include the p*53*gene (affected in almost half the human malignancies) .

Genes controlling genomic integrity

These have also been called caretaker genes. Inactivation of such genes leads to genomic instability and thus markedly increases the probability of alterations in the oncogenes and the TSGs. DNA mismatch repair genes have been extensively studied and include the h*MSH2* and h*MLH1* genes which are commonly affected in human malignancies.

Interaction of Cancer and environment

Cancer is a multifactorial disease. Most genetic factors and environmental factors such as viruses, bacteria, radiation and eating habits and chemicals increase the risk of developing cancer. 10-15% of all cancers are thought to be related to heredity, as for the rest, 85-90% of cancer have their roots in the environment and lifestyle.



The role of genes and environment in the development of cancer

It is known that approximately 25-30% of tobacco, 30-35% of diet, 15- 20% of infections and the remaining percentage of other factors like radiation, stress, physical activity, environmental pollutants, etc. cause cancer related mortality [9]. In terms of genetic factors, the mutations in multiples genes, including oncogenes, tumor suppressor genes and DNA repair genes can lead to cancer formation rather than a single gene. These genes cause cancer through three main biologic pathways [cell cycle, apoptosis and differentiation], which are normally, regulate tissue homeostasis and cell growth

***SRC* gene** this proto-oncogene may play a role in the **regulation of embryonic development and cell growth**. The protein encoded by this gene is a tyrosine-protein kinase whose activity can be inhibited by phosphorylation by c-SRC kinase. Mutations in this gene could be involved in the malignant progression of colon cancer.

Ras are **proto-oncogenes that are frequently mutated in human cancers**. They are encoded by three ubiquitously expressed genes: HRAS, KRAS and NRAS. These proteins are GTPases that function as molecular switches regulating pathways responsible for proliferation and cell survival.

Myc gene this gene is **a proto-oncogene and encodes a nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation**.

The retinoblastoma (RB) gene is the prototype tumor suppressor gene. It **encodes a nuclear protein that acts as a cell cycle control checkpoint at the G1 phase**.

The p35 gene **plays a key role in brain development**. In wildtype mice, the p35 protein participates in the signaling pathway involved in corticogenesis. It acts as a neuron-specific activator of cyclin-dependent kinase 5 (Cdk5).

What chromosomal events convert proto-oncogenes to dominantly acting oncogenes

•Point mutations (e.g., RAS)

• Partial deletion mutations (e.g., RTKs)

•Chromosomal translocations that produce novel fusion proteins (e.g., Bcr-Abl)

•Chromosomal translocation to juxtapose a strong promoter upstream and the protooncogene such that it is inappropriately expressed (e.g., cMyc, Bcl2)

• Gene amplification resulting in overexpression (e.g., N-Myc)