Disorder of cell growth and carcinogenic

Introduction

Cells are often lost through death (apoptosis and necrosis), sloughing (e.g., shedding of cells lining the gastrointestinal tract and skin), or injury (e.g., bleeding). New cells replace cells at the same rate they are lost, a highly regulated state of balance known as homeostasis. If normal cellular regulatory mechanisms malfunction, unregulated and unchecked cell division may result, a condition known as cancer. Proto-oncogenes regulate or produce proteins that regulate normal cell growth and development. Mutations that alter proto-oncogenes may convert them from regulatory genes into cancer-causing oncogenes. In addition, mutations that create a loss of function in genes known as tumor suppressor genes may also induce cancer.

Most genetic changes that occur during carcinogenesis (transformation of normal cells to cancer cells) are somatic mutations. Each time a cell divides, there is a chance of somatic mutation; therefore, there is always a low background risk for cancer. A far more prevalent cause of cancer is environmental exposure.

GENES AND CANCER

The regulation of cell cycle progression is controlled by proto-oncogenes, which promote cell cycle progression, and tumor suppressor genes, which function to control the rapid progression through the cell cycle.

A. Proto-oncogenes and oncogenes

Cell division is controlled by a number of cellular proteins. Because these proteins are the products of genes, genetic mutation may result in deregulated cellular proliferation. Proto-oncogenes are genes whose protein products control cell growth and differentiation. These genes undergo mutations causing qualitative and quantitative changes in gene products and are then called oncogenes. Our knowledge of proto-oncogenes stems from molecular genetic studies on the defective gene product.

1. Proto-oncogenes

Proto-oncogenes stimulate the cell cycle and have been identified at all levels of the various signal transduction cascades that control cell growth, proliferation, and

differentiation. As normal regulatory elements, proto-oncogenes function in a wide variety of cellular pathways (Figure 1). Mutations can occur in any of the steps involved in regulating cell growth and differentiation. When such mutations accumulate within a particular cell type, the progressive deregulation of growth eventually produces a cell whose progeny forms a tumor.

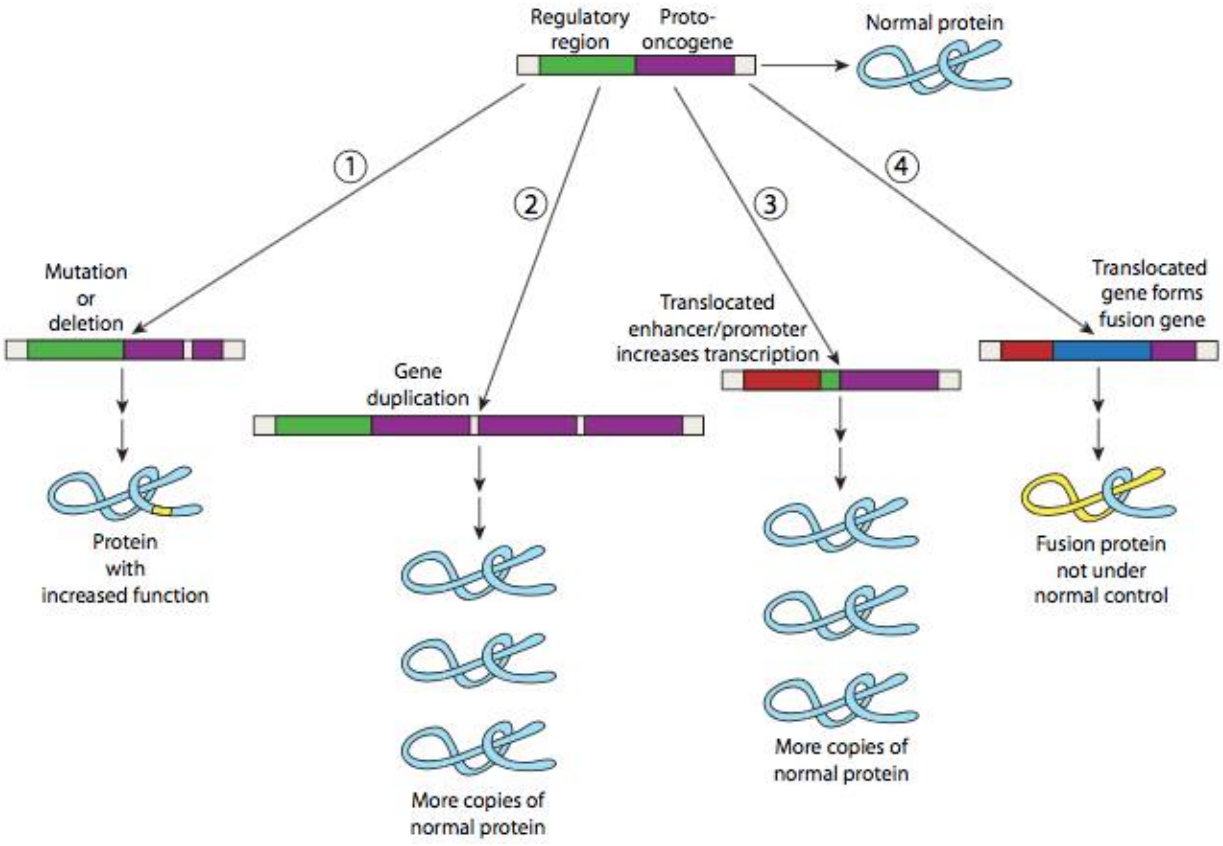


Figure 1: proto-oncogenes

2. Several ways of activating proto-oncogenes to oncogenes:

Point mutations, insertion mutations, gene amplification, chromosomal translocation (Chapter 8), and/or changes in expression of the oncoprotein can all result in deregulated activity of these genes (Figure 2).

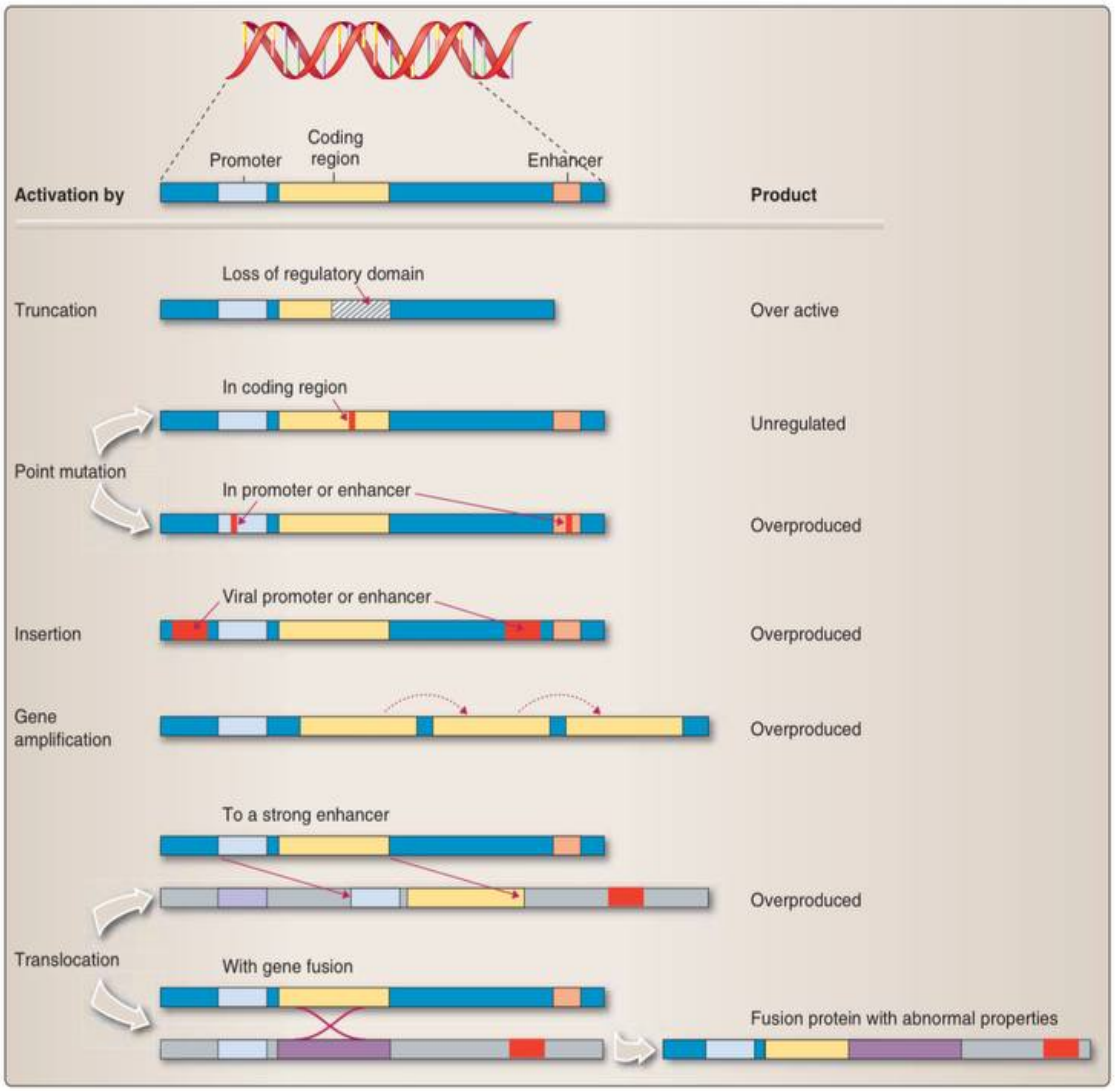


Figure 2: Activating proto-oncogenes to oncogenes

B. Tumor suppressor genes: Tumor suppressor genes are important for maintaining normal cell growth control by curtailing unregulated progression through the cell cycle. Situations that diminish tumor suppressor gene function may lead to neoplastic changes.

1. Loss of function: Loss of tumor suppressor genes predisposes cells to cancer. Protein products of proto-oncogenes are involved in growth stimulation; the protein products of tumor suppressor genes repress cell growth and division. Therefore, loss of gene function (through mutations and other alterations) can lead to cell trans- formation by removing the restraints that normally regulate cell growth.

2. p53—guardian of the genome: The most frequently inactivated tumor suppressor gene is the p53 gene, which encodes a pro- tein with a 53 kilodalton molecular mass, or p53, which is most often implicated in cancer development. More than half of human cancers show p53 mutations .Loss of p53 function can contribute to genomic instability within cells (Figure3). **p53** is important in preventing cancer because of its unique functional capabilities .

• p53 regulates gene expression and controls several key genes involved in growth regulation.

• facilitates DNA repair. When DNA damage is encountered, p53 senses the damage and causes G1 arrest of the cells, until the damage is repaired.

• activates apoptosis of damaged cells. When damage to DNA within cells is beyond repair, p53 functions to trigger apoptosis in these cells.

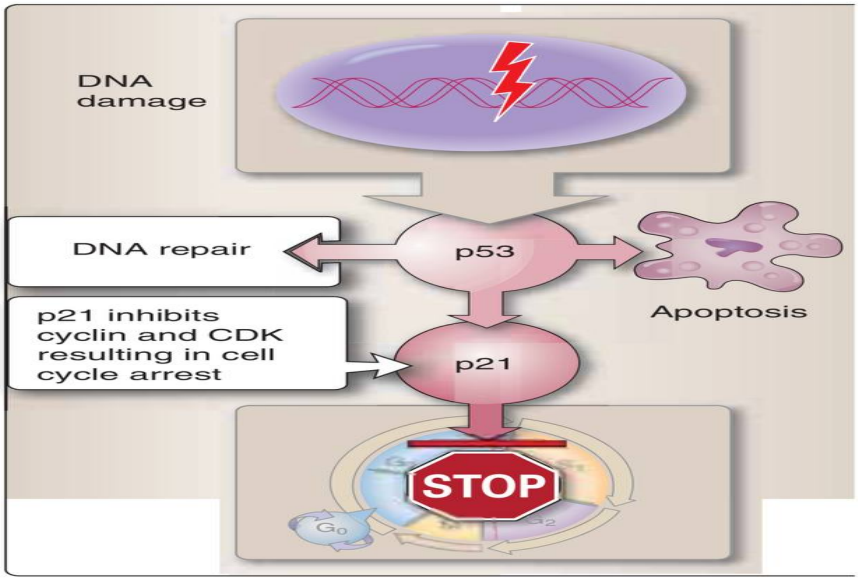


Figure 3: p53- gene function

- **C. Dominant and recessive nature of oncogenes and tumor suppressor genes**

Some genetic mutations confer a growth advantage to the cell that contains it, allowing selective growth of these cells. Therefore, when proto-oncogenes undergo mutations, they are "activated" to oncogenes (Figure 4). Because these genes normally regulate growth, mutations in them often favor the unregulated growth of cancer. Generally, tumor suppressor genes are "inactivated" by mutations and deletions,

resulting in the loss of function of the protein and in unregulated cell growth. Both copies of the tumor suppressor genes have to be mutated or lost for loss of growth control; therefore, these genes act recessively at cell level. Oncogenes, on the other hand, are dominant in action requiring mutation of only one copy of a proto-oncogene (Figure 4).

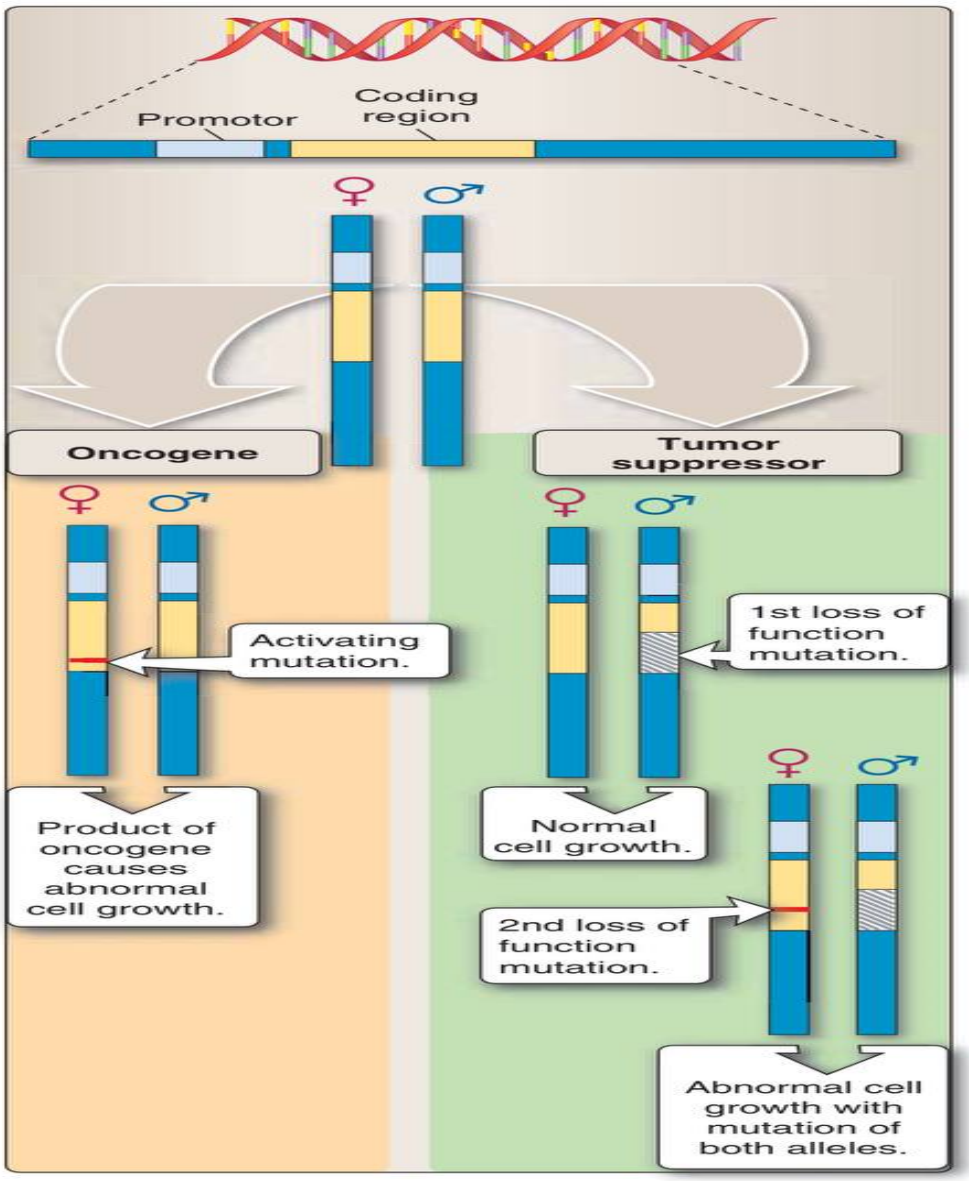


Figure 4: Dominant and recessive nature of oncogenes and tumor suppressor genes

MOLECULAR BASIS OF CANCER

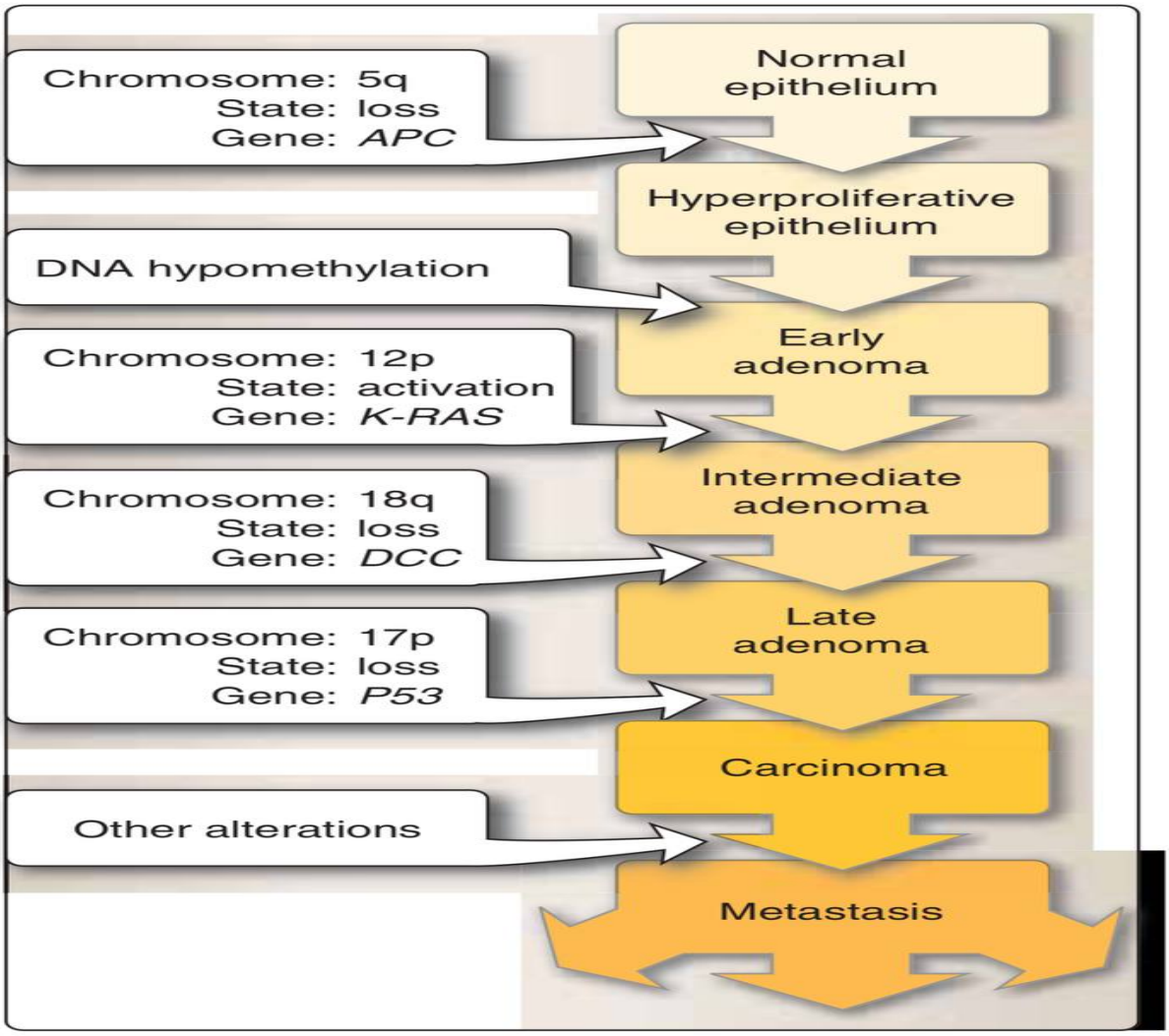
Cancer is a stepwise process. Often, several genetic alterations must occur at specific sites before malignant transformation is seen in most adult cancers. Cancers of childhood appear to require fewer mutations before manifestation of overt cancer. Rare inherited mutations can pre- dispose individuals to cancer at one or more sites. This type of mutation is present virtually in all somatic cells of the body.

A. Growth regulation

Normal cells respond to a complex set of biochemical signals, which allow them to develop, grow, differentiate, or die. Cancer results when any cell is freed from these types of restrictions and the resultant abnormal progeny of cells are allowed to proliferate.

B. Cancer genesis—a multistep process

Mutations in the key genes have to accumulate over time to create a progeny of cells that have lost most control over growth. Each individual mutation contributes in some way to eventually produc- ing the malignant state. The accumulation of these mutations spans several years and explains why cancers take a long time to develop in humans (Figure 5). Both exogenous (environmental insults) and endogenous processes (carcinogenic products generated by cellular reactions) may damage DNA. DNA damage that goes unrepaired may lead to mutations during mitosis. Increased errors during DNA replication or a decreased efficiency of DNA repair may favor increased frequency of genetic mutations. Cells become cancerous when mutations occur in proto-oncogenes and tumor suppressor genes.


Chromosome: 5q
State: loss
Gene: APC
DNA hypomethylation
Chromosome: 12p
State: activation
Gene: K-RAS
Chromosome: 18q
State: loss
Gene: DCC
Chromosome: 17p
State: loss
Gene: P53
Other alterations
Normal epithelium
Hyperproliferative epithelium
Early adenoma
Intermediate adenoma
Late adenoma
Carcinoma
Metastasis