

Applied Toxicology

NURS 735

Carcinogenesis

• Section 6: Molecular Basis of Cancer

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Etiology and Pathogenesis of Neoplasia Molecular Basis of Cancer

Learning Objectives

1. Understand the concepts underlying the molecular basis of neoplasia development
2. Understand the multi-stage process of carcinogenesis
3. Know the basic groups of regulatory genes that are the principal targets of genetic damage leading to carcinogenesis
4. Understand the role of damaged or defective DNA repair genes in carcinogenesis

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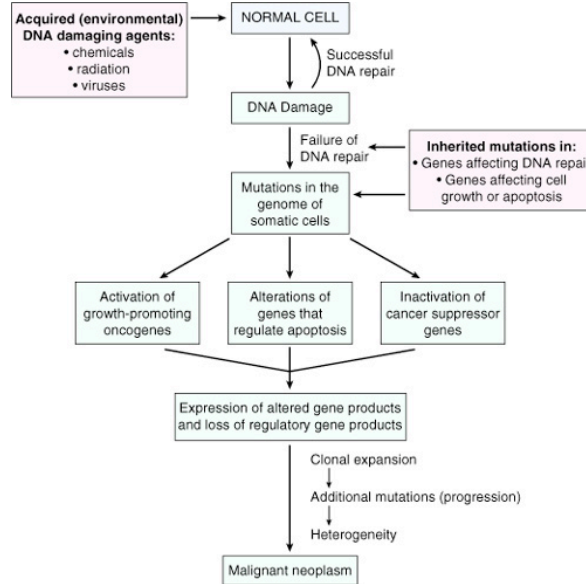
- The basic paradigm for carcinogenesis, irrespective of the carcinogenic agent, is illustrated in the next slide. Normal cells acquire basic genetic damage via somatic mutations to key regulatory genes or through inheritance. DNA repair must be circumvented for this to occur. Initiated cells bear alterations in 1 or more of these critical regulatory genes leading to altered gene expression and altered cell behavior. The initiated cells can undergo clonal expansion and act as a site for additional genetic alteration. Cell proliferation acts to push clonal expansion. This may increase the probability that additional mutations can occur.

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In the following sections we will examine the regulatory genes, oncogenes, tumor suppressor genes and apoptotic genes and how alterations in these genes push the carcinogenic process towards malignant neoplasia. We will develop the concept that it is the accumulation of multiple genetic defects in these critical classes of genes that ultimately confer on a cell the ability to invade and metastasize, the ultimate biological criteria of malignancy.

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- **Malignant development is a multi-step process at both the phenotypic and genetic levels.**
- Carcinogenesis is essentially the progression of initiated cells that acquire critical characteristics (such as autonomous growth, invasiveness, etc.) in a stepwise fashion. This is accompanied at the molecular level by the accumulation of multiple genetic lesions in critical classes of genes, in some cases facilitated by defective DNA repair.

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- **Carcinogenesis is built on a foundation of non-lethal genetic changes.**
- These could be acquired by any agent mentioned in previous lectures or any combination of these agents. The genetic hypothesis of cancer states that a neoplasm arises from the clonal expansion of a single progenitor cell that has incurred this genetic damage

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There are 3 basic groups of normal regulatory genes that are the principal targets of genetic damage in carcinogenesis.

Growth-promoting proto-oncogenes, growth-inhibiting tumor suppressor genes and genes that regulate programmed cell death are the critical targets. Alterations or deletions in these gene classes give cells the characteristics that lead to a malignant phenotype.

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In addition, DNA repair genes may affect cell proliferation and cell survival capabilities by influencing the ability of a tissue to repair non-lethal DNA damage.

Damage to DNA repair genes is a major predisposition factor leading to mutations in the genome and increasing the probability of neoplastic transformation. Like tumor suppressor genes both alleles of DNA repair genes must be inactivated to induce genomic instability.