

Carcinogenesis

What is cancer and what are the biochemical processes that facilitate the transformation of normal cells into those with cancerous properties? Cancer is a group of diseases in which genetically damaged cells proliferate autonomously. Such cells cannot respond to normal regulatory mechanisms that ensure the intercellular cooperation required in multicellular organisms. Consequently, they continue to proliferate, thereby robbing nearby normal cells of nutrients and eventually crowding surrounding healthy tissue. Depending on the damage they have sustained, abnormal cells may form either benign or malignant tumors. Benign tumors, which grow slowly and are limited to a specific location, are not considered cancerous and rarely cause death. In contrast, *malignant* tumors are often fatal because they can undergo *metastasis*, migration through blood or lymph vessels to distant locations throughout the body. Wherever new malignant tumors arise, they interfere with normal functions. When life-sustaining processes fail, patients die.

Cancers are classified by the tissues affected. The vast majority of cancerous tumors are carcinomas (tumors derived from epithelial tissue cells such as skin, various glands, breasts, and the lining of most internal organs). In the leukemias, which are cancers of the bone marrow, excessive leukocytes are produced. Similarly, the lymphocytes produced in the lymph nodes and spleen proliferate uncontrollably in the lymphomas. Tumors arising in connective tissue are called sarcomas. Despite the differences among the diseases in this diverse class, they also have several common characteristics, among which are the following.

1. **Cell culture properties.** When grown in culture, most tumor cells lack contact inhibition; that is, they grow to high density in highly disorganized masses. (Normal cells grow only in a single layer in culture and have defined borders.) In contrast to normal cells, growth and division in cancer cells tend to be growth factor-independent, and cancer cells often do not require attachment to a solid surface. The hallmark of cancer cells, however, is their immortality. Normal cells undergo cell division only a finite number of times, whereas cancer cells can proliferate indefinitely.
2. **Origin.** Each tumor originates from a single damaged cell. In other words, a tumor is a clone derived from a cell in which heritable changes have occurred. The genetic damage consists of mutations (e.g., point mutations, deletions, and inversions) and chromosomal rearrangements or losses. Such changes result in the loss or altered function

of molecules involved in cell growth or proliferation. Tumors typically develop over a long time and involve several independent types of genetic damage. (The risk of many types of cancer increases with age.)

The transformation process in which an apparently normal cell is converted or “transformed” into a malignant cell consists of three stages: initiation, promotion, and progression.

During the *initiation* phase of carcinogenesis, a permanent change in a cell’s genome provides it with a growth advantage over its neighbors. Most initiating mutations affect protooncogenes or tumor suppressor genes. Protooncogenes code for a variety of growth factors, growth factor receptors, enzymes, or transcription factors that promote cell growth and/or cell division. Mutated versions of protooncogenes that promote abnormal cell proliferation are called **oncogenes** (Table 1). Because tumor suppressor genes suppress carcinogenesis, their loss also facilitates tumor development. Recall that *Rb* and *p53* are tumor suppressors. Other examples are *FCC* and *DCC*, which are both associated with susceptibility to colon cancer. The functions of most tumor suppressor genes are unknown. However, it now appears that *p53* codes for a 53kD protein that normally inhibits Cdk enzymes. Recent evidence indicates that other damaged or deleted tumor suppressor genes may code for enzymes involved in DNA repair mechanisms. The damage that alters function

TABLE 1 Selected Oncogenes*

Oncogene	Protooncogene Function
<i>sis</i>	Platelet-derived growth factor
<i>erbB</i>	Epidermal growth factor receptor
<i>src</i>	Tyrosine-specific protein kinase
<i>raf</i>	Serine/threonine-specific protein kinase
<i>ras</i>	GTP-binding protein
<i>jun</i>	Transcription factor
<i>fos</i>	Transcription factor
<i>myc</i>	Transcription factor

*Abnormal versions of protooncogenes that mediate cancerous transformations.



of protooncogenes and tumor suppressor genes is caused by the following.

1. **Carcinogenic chemicals.** Most cancer-causing chemicals are mutagenic; that is, they alter DNA structure. Some carcinogens (e.g., nitrogen mustard) are highly reactive electrophiles that attack electron-rich groups in DNA (as well as RNA and protein). Other carcinogens (e.g., benzo[a]pyrene) are actually procarcinogens, which are converted to active carcinogens by one or more enzyme-catalyzed reactions.
2. **Radiation.** Some radiation (UV, X-rays, and γ -rays) is carcinogenic. As noted, the damage inflicted on DNA includes single- and double-strand breaks, pyrimidine dimer formation, and the loss of both purine and pyrimidine bases. Radiation exposure also causes the formation of ROS, which may be responsible for most of radiation's carcinogenic effects.
3. **Viruses.** Viruses appear to contribute to the transformation process in several ways. Some introduce oncogenes into a host cell chromosome as they insert their genome. (Viral oncogenes are now recognized as sequences that are similar to normal cellular genes that have been picked up accidentally from a previous host cell. To distinguish viral oncogenes and their cellular counterparts, they are referred to as *v-onc* and *c-onc*, respectively.) Viruses can also affect the expression of cellular protooncogenes through insertional mutagenesis, a random process in which viral genome insertion inactivates a regulatory site or alters the protooncogene's coding sequence. Most virus-associated cancers have been detected in animals. Only a few human cancers have been proven to be associated with viral infection.

Tumor development can also be promoted by chemicals that do not alter DNA structure. So-called **tumor promoters** contribute to carcinogenesis by two principal methods. By activating components of intracellular signaling pathways, some molecules (e.g., the phorbol esters) provide the cell a growth advantage over its neighbors. (Recall that phorbol esters activate PKC because they mimic the actions of DAG.) The effects of many other tumor promoters are unknown but may involve transient effects such as increasing cellular Ca^{2+} levels or increasing synthesis of the enzymes that convert procarcinogens into carcinogens. Unlike initiating agents, the effects of tumor promoters are reversible. They produce permanent damage only with prolonged exposure after an affected cell has undergone an initiating mutation.

Following initiation and promotion, cells go through a process referred to as progression. During *progression*, genetically vulnerable precancerous cells, which already possess significant growth advantages over normal cells, are further damaged. Eventually, the continued exposure to carcinogens and promoters makes further random mutations inevitable. If these mutations affect cellular proliferative or differentiating capacity, then an affected cell may become sufficiently malignant to produce a tumor. A proposed sequence of the events in the development of colorectal cancer is outlined in Figure 18I.

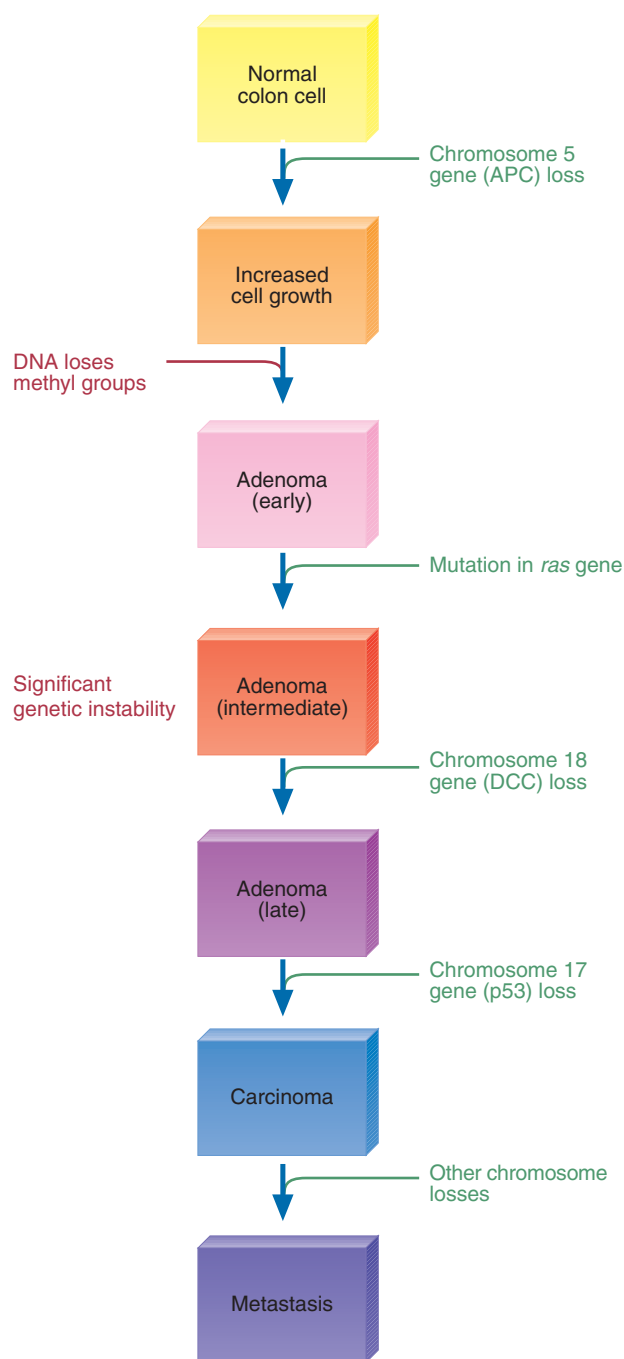


FIGURE 18I

The Development of Colorectal Cancer

Colorectal cancer develops over a long time. Because somatic cells are diploid, the loss of the tumor suppressor genes *APC*, *DCC*, and *p53* usually requires two mutations. Recent research suggests that mutations in genes involved in DNA repair processes may occur during the early stages of colon cancer. (An adenoma is a precancerous epithelial tumor.) Healthy diets that are high in folate, antioxidants, and certain polyunsaturated fatty acids found in fish provide significant protection against colorectal cancer.



Cancer is not only a genetic disease, it is presently appreciated as an epigenetic disease as well. Chromatin-associated gene silencing has been implicated in the progress of a number of cancers. Inappropriate silencing of tumor suppressor genes caused by abnormal methylation patterns in a regulatory sequence of these genes has been suggested as a contributing factor in carcinogenesis. Silencing of *MHL1*, a postreplication repair gene, by DNA methylation is seen in colorectal cancers. The CpG islands within these genes are normally unmethylated, and any level of methylation can inhibit transcription, or condense chromatin. (*CpG islands* are 1 to 2 kb sequences with a high density of 5'-CG-3'-dinucleotides. The cytosine residues in these sequences are often highly methylated.)

An Ounce of Prevention . . .

Because of the enormous cost and limited success of cancer therapy, it has become increasingly recognized that cancer prevention is cost-effective. Recent research indicates that the majority of cases of cancer are preventable. For example, over one-third of cancer mortality is directly caused by tobacco use, and another one-third of cancer deaths have been linked to inadequate diets. Tobacco smoke, which contains thousands of chemicals, many of which are either carcinogens or tumor promoters, is responsible

for most cases of lung cancer and contributes to cancers of the pancreas, bladder, and kidneys, among others. Diets that are high in fat and low in fiber content have been associated with increased incidence of cancers of the large bowel, breast, pancreas, and prostate. Other dietary risk factors include low consumption of fresh vegetables and fruit.

In addition to providing sufficient antioxidant vitamins, many vegetables (and fruits to a lesser extent) contain numerous non-nutritive components that actively inhibit carcinogenesis. Some carcinogenesis inhibitors (e.g., organosulfides), referred to as *blocking agents*, prevent carcinogens from reacting with DNA or inhibit the activity of tumor promoters. Other inhibitors, referred to as *suppressing agents* (e.g., inositol hexaphosphate), prevent the further development of neoplastic processes that are already in progress. Many nonnutritive food components (e.g., tannins and protease inhibitors) possess both blocking and suppressing effects. In general, these molecules very effectively protect against cancer because many of them inhibit the arachidonic acid cascade and oxidative damage. Apparently low-fat, high-fiber diets that are rich in raw or fresh vegetables that are leafy green (e.g., spinach), cruciferous (e.g., broccoli), and members of the allium family (e.g., onions), as well as fresh fruits, are a prudent choice for individuals seeking to reduce their risk of cancer.



SUMMARY: Carcinogenesis is the process whereby cells with a growth advantage over their neighbors are transformed by mutations in the genes that control cell division into cells that no longer respond to regulatory signals.