7.2: Carcinogenesis

Skills to Develop

- Describe the process by which a normal cell becomes a cancer cell.

The transformation of a normal cell into a cancer cell is a multi-step process that involves initiation, promotion, progression and finally malignancy (see Figure 7.2.1). This process takes years and starts with a single cell in which the right genes are mutated so the cell does not appropriately die and begins to proliferate abnormally. Then, additional mutations occur that select for more rapidly growing cells within this population leading to a tumor with rapid growth and malignancy. By the time the cells are cancerous, proto-oncogenes have been activated and tumor suppressor genes inactivated. Even within the same tumor type, like colon cancer, the specific genes mutated can vary from person to person making cancer a unique disease for each individual. Using measures of age-dependent cancer incidence, scientists have been able to determine at least four to six independent steps are needed. What drives initiation and progression?

Figure 7.2.1: Multistep process involved in carcinogenesis that transforms a normal cell into a malignant tumor.

Initiation

As you can see in the figure, both endogenous and exogenous substances can initiate DNA damage. Endogenous...
agents are substances that are in our body that can cause DNA damage directly or indirectly, for example, bile acids or reactive oxygen species. Exogenous agents are agents that are in our environment like cigarette smoke, radiation, or smog. Diet is an exogenous agent and consumption of certain foods, like processed meats, have been linked to a higher incidence of cancer while consumption of other foods, like fruits and vegetables, have been linked to a lower risk of developing a tumor. Doll and Peto estimated 35% of cancers could be contributed to diet alone with a range from 10 to 70% (Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 1981;66(6):1191–1308). They made their landmark observations thirty-five years ago and it has remained generally true since then.

Carcinogens are substances or exposures that can cause cancer in a living tissue. Not all carcinogens affect DNA directly. For example, they may cause cells to divide faster which increases the risk for DNA damage. Also, not all carcinogens cause cancer upon exposure because most have different levels of cancer-causing potential and the length of exposure is also critical. So, the risk of developing cancer depends on many factors including how you are exposed, how long you are exposed, and your genetic makeup.

Lab studies are used to determine if a substance is a carcinogen. Most studies expose lab animals to the potential carcinogen at much higher levels than common to human exposures. Then, scientists observe if the animal grows a tumor.

A carcinogen can modify the molecular structure of DNA in a variety of different ways, indirectly or directly. One common way is to form a new compound (adduct) between the chemical carcinogen, or one of its functional groups, and DNA. Usually, this adduct is recognized and broken down by our cells; but if it escapes detection or degradation, then it can go on and multiply.

**Promotion**

The next step in the multistep carcinogenesis model is the clonal expansion of the initiated cells. Promoters help speed this process but are not generally mutagenic so they do not initiate tumorigenesis but speed up the process. Also, promoters do not need metabolic activation; instead, they work by reducing the latency period for tumor formation after exposure of a tissue to a tumor initiator or they increase the number of tumors formed in that tissue. Examples of tumor promoters are alcohol, high estrogen, dietary fat, chronic irritation, ultraviolet light, and chemicals like dioxin, saccharin, tryptophan, polychlorinated biphenyl (PCBs) to name a few. Specific types of dietary fat have been linked to colon, breast and prostate cancer, and may promote tumor formation by causing the body to secrete more hormones favorable to cancer growth (ex. estrogen), promote the secretion of bile acid in the intestine which microorganisms convert to carcinogens, or are incorporated into cell membranes increasing the cells' susceptibility to carcinogens.

Dietary fiber and calorie restriction are two anti-carcinogen or anti-promoters that decrease the risk of tumor formation. Dietary fiber is both and is inversely associated with cancer, particularly colon cancer. So the more fiber you eat, the less risk you have of developing colon cancer. One mechanism by which fiber acts is hastening bile acid excretion. Fiber also increases the rate of passage of materials through the colon resulting in decreased production and exposure of the colon to cancer-causing agents, ie dilutes the concentration of carcinogens.

Animal studies have shown that restricting caloric intake by 30% reduces tumor growth and increases life span. The mechanism is not known but may be due to less oxidation thus damage to DNA.
Antioxidants can help block the action of initiators or promoters if their mode of action is to damage DNA by oxidation. Vitamin A, C, E, beta-carotene, and selenium are antioxidant nutrients. Some work locally, like vitamin E in the colon, while other work more globally like selenium and vitamin C. Vitamin A appears to work by keeping cells differentiated which slows the growth rate.

Other compounds in food, particularly fruits and vegetables, have been shown to slow tumor formation. Cruciferous vegetables (eg broccoli, cauliflower, cabbage, and Brussel sprouts to name a few) are rich in nutrients, fiber, glucosinolates which are sulfur-containing chemicals, indoles, and isothiocyanates. Animal studies have found these substances inhibit the development of cancer in several organs in rats and mice (Hecht SS. Inhibition of carcinogenesis by isothiocyanates. Drug Metabolism Reviews 2000;32(3-4):395-411; Murillo G, Mehta RG. Cruciferous vegetables and cancer prevention. Nutrition and Cancer 2001;41(1-2):17-28). Indoles and isothiocyanates help protect cells from DNA damage; help inactivate carcinogens; have antiviral and antibacterial effects; have anti-inflammatory effects; induce cell death (apoptosis); and inhibit tumor blood vessel formation (angiogenesis) and tumor cell migration (needed for metastasis) (National Cancer Insitute, Cruciferous Vegetables and Cancer Prevention, 2012, https://www.cancer.gov/about-cancer/...les-fact-sheet). Studies in humans, however, have shown mixed results.

Progression and Malignancy

Conversion of a preneoplastic cell into one that expresses the malignant phenotype is malignant conversion and requires more genetic changes. The rate of conversion can be increased by repeated exposure of preneoplastic cells to DNA-damaging agents which results in activation of proto-oncogenes and inactivation of tumor suppressor genes. Tumor progression is the expression of this malignant phenotype and the tendency for these cells to become more aggressive over time. A common characteristic of malignant cells is genomic instability and uncontrolled growth. It is the accumulation of genetic mutations and not the order or stage in which they occur that is important for tumor formation.