Mechanisms of Carcinogenesis

Initiation

Cancer is a complex group of diseases with many causes, including chemical carcinogens, radiation, hormones, dietary factors, infectious agents and oxidative stress. Animal studies have provided the basis for our understanding of how these diverse agents result in the production of a malignant tumor. A model for the multistage process of carcinogenesis divides it into three stages: initiation, promotion, and progression [1–4]. Initiation is the irreversible interaction of a carcinogen with tissue DNA. This DNA damage is necessary but not sufficient for tumorigenesis since other events must also take place. It cannot be detected pathologically but produces cells that are precursors of the future tumor.

Chemical carcinogens can be divided into several categories. Direct-acting carcinogens have inherent reactivity, due to their electrophilic nature, and react with nucleophilic residues in cellular proteins and with nucleic acids (RNA and DNA) to form adducts, covalent products resulting from binding of the carcinogen [5–8]. Examples of direct-acting chemical carcinogens include epoxides, such as ethylene oxide, and cytotoxic chemotherapeutic agents, such as cyclophosphamide. Radiation, another example of a direct-acting agent, is known to induce nucleotide base damage, cross links, and DNA single- and double-strand breaks [9].

Most chemical carcinogens present in the environment, however, exist as procarcinogens (Figure 1.1) and are not active in their native form. Examples include polycyclic aromatic hydrocarbons (PAHs) (produced during the combustion of organic material and present in cigarette smoke, polluted air, and various foods), aromatic amines (also present in cigarette smoke and the diet as well as in certain occupational settings), and aflatoxin B1 (a dietary carcinogen produced by a mold contaminant). Initiation by these agents is dependent upon their conversion to highly reactive electrophilic species (Figure 1.1). This process of metabolic activation of the procarcinogen to the “ultimate” carcinogen is carried out by a number of enzymes present in various human tissues [10,11]. The model PAH, benzo(a)pyrene (BP), for example, is not chemically reactive and does not bind to DNA. However, enzymes in the cytochrome P450 system, including CYP1A1, oxidatively metabolize BP and related PAHs to a variety of derivatives, including phenols and dihydrodiols. This process is part of the normal mechanism for conversion of xenobiotics to more watersoluble forms for excretion. Unfortunately, for PAH, highly reactive epoxides are one of the intermediates in this oxidative process. For BP, a specific diol epoxide has been identified as the critical reactive intermediate. This intermediate covalently binds DNA primarily at the N2 position of guanine, although adducts are also found on adenine. Adducts on RNA, and on proteins such as albumin, have also been
identified. Oxidative metabolism of exogenous chemicals such as BP also results in oxidative DNA damage, increasing the hazard of such exogenous chemicals. Further complicating the issue, many of the activation enzymes, such as CYP1A1, are inducible by PAH and other chemicals, enhancing the conversion of xenobiotics to toxic intermediates.

In addition to electrophilic intermediates, free radical derivatives of chemicals are implicated in carcinogenesis [5,12,13]. DNA damage also arises spontaneously from endogenous chemicals that arise during metabolism, oxidative stress, and chronic inflammation [14]. The types of damage produced include deaminations, alkylations, base loss, and oxidation. The level of these potentially mutagenic endogenous lesions is high, and they have been suggested to be major contributors to carcinogenesis and aging.

While chemical carcinogens are activated by a wide range of enzymes, there also exists a series of enzymes (phase II enzymes) that are involved in the detoxification of activated carcinogens, thus preventing their binding to DNA. These include epoxide hydrolase, N-acetyl transferases, glutathione S-transferases (GSTs), sulfotransferase, and glucuronide transferase [10]. The products of these reactions are generally more hydrophobic and thus more readily excreted. For example, the reactive diol epoxide of BP can be conjugated to glutathione and thus detoxified by both GST M1 and GST T1. However, in some relatively rare situations, phase II enzymes have also been shown to activate chemical carcinogens; GST activates 1,2-dihaloethanes [11].

Evidence that DNA is the critical target in carcinogenesis came from the increased incidence of cancer in individuals with genetic defects in DNA repair (e.g., xeroderma pigmentosa [15]). A relationship between the level of DNA adduct formation in animals and carcinogen potency has also been observed [16,17]. The association of particular mutations in specific genes (discussed later) with tumors provided additional evidence. But adducts also form in many tissues in which tumors do not