Indirect-Acting Carcinogens

The designation indirect-acting carcinogen refers to chemicals that require metabolic conversion to become active carcinogens; the carcinogenic product of metabolism is called an *ultimate carcinogen*. Some of the most potent indirect chemical carcinogens—the polycyclic hydrocarbons—are present in fossil fuels. Others, for example, benzo[*a*]pyrene (the active component of soot, which Potts showed to be carcinogenic), are formed during the high-temperature combustion of tobacco in cigarettes and are implicated in the causation of lung cancer. Polycyclic hydrocarbons may also be produced from animal fats during the process of broiling or grilling meats and are present in smoked meats and fish. The principal active products in many hydrocarbons are epoxides, which form covalent adducts (addition products) with molecules in the cell, principally DNA, but also with RNA and proteins.

The aromatic amines and azo dyes are another class of indirect-acting carcinogens that were widely used in the past in the aniline dye and rubber industries. Many other occupational carcinogens are listed in Table 7-10.

Most chemical carcinogens require metabolic activation for conversion into ultimate carcinogens (Fig. 7-44). Certain metabolic pathways may inactivate (detoxify) the procarcinogen or its derivatives. Most of the known carcinogens are metabolized by *cytochrome P-450-dependent mono-oxygenases*. The genes that encode these enzymes are polymorphic, and the activity and inducibility of these enzymes vary significantly among individuals (described further in Chapter 9). Because these enzymes are essential for the activation of procarcinogens, the susceptibility to carcinogenesis is related in part to the particular polymorphic variants that an individual inherits. Thus, it may be possible to assess cancer risk in a given individual by genetic analysis of such enzyme polymorphisms.

Table 7-10 Major Chemical Carcinogens

Direct-Acting Carcinogens
Alkylating Agents
β-Propiolactone
Dimethyl sulfate
Diepoxybutane
Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
Acylating Agents
1-Acetyl-imidazole
Dimethylcarbamyl chloride
Procarcinogens That Require Metabolic Activation
Polycyclic and Heterocyclic Aromatic Hydrocarbons
Benz[*a*]anthracene
Benzo[*a*]pyrene
Dibenz[*a,h*]anthracene
3-Methylcholanthrene
7,12-Dimethylbenz[*a*]anthracene
Aromatic Amines, Amides, Azo Dyes
2-Naphthylamine (β-naphthylamine)
Benzidine
2-Acetylaminofluorene
Dimethylaminoazobenzene (butter yellow)
Natural Plant and Microbial Products
Aflatoxin B_1
Griseofulvin
Cycasin
Safrole
Betel nuts
Others
Nitrosamine and amides
Vinyl chloride, nickel, chromium
Insecticides, fungicides
Polychlorinated biphenyls

The metabolism of polycyclic aromatic hydrocarbons, such as benzo[*a*]pyrene by the product of the P-450 gene, *CYP1A1*, provides an instructive example. Approximately 10% of the white population has a highly inducible form of this enzyme that is associated with an increased risk of lung cancer in smokers. Light smokers with the susceptible *CYP1A1* genotype have a sevenfold higher risk of developing lung cancer compared with smokers without the permissive genotype. It should be appreciated, however, that not all variation in the activation or detoxification of carcinogens is genetically determined. Age, sex, and nutritional status also influence the internal dose of toxicants produced and hence the risk of cancer development in a particular individual.

Molecular Targets of Chemical Carcinogens. Because malignant transformation results from mutations, it comes as no surprise that most chemical initiating agents target DNA and are mutagenic. There is no single or unique alteration associated with cancer initiation. Nor is there any apparent predisposition for initiators to cause mutations in particular genes; presumably, mutations occur throughout the genome and cells that by chance suffer damage to the "usual suspects", oncogenes and tumor suppressors such as *RAS* and *TP53*, gain a potential selective advantage and are at risk for subsequent transformation.

This is not to say that mutations induced by carcinogens occur in an entirely random fashion. Because of their chemical structures, some carcinogens interact preferentially with particular DNA sequences or bases, and thus produce mutations that are clustered at "hotspots" or that are enriched for particular base substitutions. One illustrative example of a chemical carcinogen associated with a mutational "hotspot" is *aflatoxin* B_1, a naturally occurring agent produced by some strains of a mold called *Aspergillus*. *Aspergillus* grows on improperly stored grains and nuts, and there is a strong correlation between the dietary level of this food contaminant and the incidence of hepatocellular carcinoma in parts of Africa and the Far East. Interestingly, aflatoxin B_1-associated hepatocellular carcinomas tend to have a particular mutation in *TP53*, a G:C→T:A transversion in codon 249 that produces an arginine to serine substitution in the p53 protein. In contrast, *TP53* mutations are infrequent in liver tumors from areas where aflatoxin contamination of food does not occur, and few of these mutations involve codon 249. Similarly, lung cancers associated with smoking have a 10-fold higher mutational burden on average than lung cancers in nonsmokers, and these excess mutations are strongly skewed toward particular base substitutions known to be caused by carcinogens in cigarette smoke (the proverbial "smoking gun"). With sequencing of cancer genomes becoming routine, it is likely that other "carcinogen signatures" will be discovered; these associations