

Mechanism-Based Cancer Prevention Approaches: Targets, Examples, and the Use of Transgenic Mice

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Humans are exposed to a wide variety of carcinogenic insults, including endogenous and man-made chemicals, radiation, physical agents, and viruses. The ultimate goal of carcinogenesis research is to elucidate the processes involved in the induction of human cancer so that interventions may be developed to prevent the disease, either in the general population or in susceptible subpopulations. Progress to date in the carcinogenesis field, particularly regarding the mechanisms of chemically induced cancer, has revealed several points along the carcinogenesis pathway that may be amenable to mechanism-based prevention strategies. The purpose of this review is to examine the basic mechanisms and stages of chemical carcinogenesis, with an emphasis on ways in which preventive interventions can modify those processes. Possible ways of interfering with tumor initiation events include the following: i) modifying carcinogen activation by inhibiting enzymes responsible for that activation or by direct scavenging of DNA-reactive electrophiles and free radicals; ii) enhancing carcinogen detoxification processes by altering the activity of the detoxifying enzymes; and iii) modulating certain DNA repair processes. Possible ways of blocking the processes involved in the promotion and progression stages of carcinogenesis include the following: i) scavenging of reactive oxygen species; ii) altering the expression of genes involved in cell signaling, particularly those regulating cell proliferation, apoptosis, and differentiation; and iii) decreasing inflammation. In addition, the utility for mechanism-based cancer prevention research of new animal models that are based on the overexpression or inactivation of specific cancer-related genes is examined. [J Natl Cancer Inst 1999;91:215-25]

The major stages of carcinogenesis were deduced over the past 50 years, primarily from animal model studies (particularly in the mouse skin); these stages are termed initiation, promotion, and progression (1,2) and are shown in Fig. 1. Tumor initiation begins when DNA in a cell or population of cells is damaged by exposure to exogenous or endogenous carcinogens. If this damage is not repaired, it can lead to genetic mutations. The responsiveness of the mutated cells to their microenvironment can be altered and may give them a growth advantage relative to normal cells. In the classic two-stage carcinogenesis system in the mouse skin, a low dose of 7,12-dimethylbenz[*a*]anthracene (DMBA) causes permanent DNA damage—the initiating event—but does not give rise to tumors over the lifespan of the mouse unless a tumor promoter, such as 12-*O*-tetradecanoylphorbol-13-acetate (TPA), is repeatedly applied (3). The tumor-promotion stage is characterized by selective clonal expansion

of the initiated cells, a result of the altered expression of genes whose products are associated with hyperproliferation, tissue remodeling, and inflammation (2). During tumor progression, preneoplastic cells develop into tumors through a process of clonal expansion that is facilitated by progressive genomic instability and altered gene expression (4).

The classic view of experimental carcinogenesis, in which tumor initiation is followed by tumor promotion and progression in a sequential fashion, remains conceptually important to experimental carcinogenesis research. However, while the processes involved in each stage of experimental carcinogenesis also appear to be involved in human carcinogenesis (5), the temporal nature of initiation, promotion, and progression events in the natural world is complex. For instance, we know from the work of Fearon and Vogelstein (6) and of Sugimura (7) that multiple mutational events are involved in the formation of a tumor. Humans are generally exposed to mixtures of agents that can simultaneously act at different stages of the carcinogenesis process, and it has become clear that promotional events—which frequently increase cellular proliferation or decrease apoptosis—can influence subsequent initiation events. It is also increasingly apparent that an individual's genetic background can dramatically affect his or her susceptibility to a carcinogen (8-10).

Thus, rather than occurring in three discrete stages in a predictable order, human carcinogenesis is best characterized as an accumulation of alterations in genes regulating cellular homeostasis, such as oncogenes, tumor suppressor genes, apoptosis-regulating genes, and DNA repair genes (11). Most animal models used in carcinogenesis research were developed before the identification of the major cancer-related genes, the recognition of the importance of host susceptibility to a carcinogenic insult, or the realization that mitogenesis and apoptosis together regulate cell number. Nonetheless, these animal models have contributed significantly to our current understanding of carcino-

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See "Note" following "References."