Diet and Cancer Prevention Studies in p53-Deficient Mice

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ABSTRACT Progress in mechanism-based cancer prevention research may be facilitated by the use of animal models displaying specific genetic susceptibilities for cancer such as mice deficient in the p53 tumor suppressor gene, the most frequently observed genetic lesion in human cancer. We observed in p53-deficient (p53-/-) mice that calorie restriction (CR; 60% of the control group’s intake of carbohydrate energy) increased the latency of spontaneous tumor development (mostly lymphomas) ~75%, decreased serum insulin-like growth factor (IGF)-1 and leptin levels, significantly slowed thymocyte cell cycle traverse and induced apoptosis in immature thymocytes. In heterozygous p53-deficient (p53+/−) mice, CR and 1 d/wk of food deprivation each significantly delayed spontaneous tumor development (a mix of lymphomas, sarcomas and epithelial tumors) and decreased serum IGF-1 and leptin levels even when begun late in life. We have also developed a rapid and relevant p53-/- mice mammary tumor model by crossing p53-deficient mice with MMTV-Wnt-1 transgenic mice, and found that CR and 1 d/wk food deprivation significantly increased mammary tumor latency (greater than twofold) and reduced the mean serum IGF-1 and leptin levels to <50% of that of control mice (P < 0.0001). In addition, fluasterone, fenretinide and soy each delayed tumor development but had little effect on IGF-1 or leptin levels. We have capitalized on the susceptibility of p53-/- mice to chronic, low dose, aromatic amine-induced bladder carcinogenesis to develop a useful model for evaluating bladder cancer prevention approaches such as cyclooxygenase-2 inhibition. As demonstrated by these examples, mice with specific (and human-like) genetic susceptibilities for cancer provide powerful new tools for testing and characterizing interventions that may inhibit the process of carcinogenesis in humans. J. Nutr. 131: 3092S–3094S, 2001.

KEY WORDS: • nutrition • chemoprevention • transgenic animals • calorie restriction • insulin-like growth factor-1 • leptin

The recent development of mouse strains with carcinogenesis-related genes overexpressed or inactivated provides investigators with new models for studying the carcinogenesis process and for testing preventive strategies that can offset highly relevant genetic susceptibilities to cancer in humans (1). Our work has focused on using mice deficient in the p53 tumor suppressor gene to ask the following question: can we offset increased cancer risk due to a genetic lesion such as loss of p53 suppressor activity by preventive (particularly nutritional) approaches? Mutation of the p53 tumor suppressor gene is the most frequently observed genetic lesion in human cancer; >50% of all human tumors examined to date have identifiable p53 gene point mutations or deletions (2). Donehower et al. (3) first reported in 1992 that homozygous p53-knockout (p53-/-) mice were viable but highly susceptible to spontaneous tumorigenesis (particularly lymphomas) at an early age. These p53-deficient mice have been useful tools for studying the role of p53 in carcinogenesis. For example, in response to the two-stage skin carcinogenesis protocol, p53-/- mice relative to wild-type (p53+/+) mice, showed no difference in benign papilloma formation but did display greatly accelerated progression to malignant carcinomas (4). Furthermore, the carcinomas formed in the p53-/- mice showed higher indices of malignancy as measured by histopathology, further confirming the importance of p53 loss in acceleration of tumor progression. These mice also provide an attractive and potentially relevant tumorigenesis model for studying cancer prevention strategies, given the frequency of p53 mutations in human tumors and the rapidity with which spontaneous tumors develop in these mice. The purpose of this article is to provide a summary of studies to date that have used p53-deficient models for cancer prevention studies.

Prevention studies in p53-/- mice

We evaluated the ability of several dietary and chemopreventive interventions to offset the increased susceptibility of p53-/- mice to spontaneous tumorigenesis (5–8). We chose...
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3 Abbreviations used: DHEA, dehydroepiandrosterone; CR, calorie restriction; fluasterone, 16α-fluoro-5-androsten-17-one; IGF, insulin-like growth factor.
dence by nearly 50% (Hursting, S. D. and Perkins, S. N., unpublished observations, 2001). Fenretinide had no effect. Despite the more modest degree of CR (20%) relative to our previous studies (40%), we still observed significant CR-induced reductions in serum IGF-1 and leptin levels, whereas indomethacin had no effect on these factors. Studies of the effects of selective cyclooxygenase inhibitors (i.e., MF Tricyclic; Merck, Whitehouse Station, NJ) as well as naturally occurring cyclooxygenase inhibitors (resveratrol and diallyl disulfide) are currently underway in this model.

P53-deficient mammary tumor model

We have been characterizing a rapid and spontaneous p53+/− mouse mammary tumor model developed by crossing p53+/− mice with MMTV-Wnt-1 transgenic mice (24). In these mice, CR, 1 d/wk food deprivation, the synthetic retinoid fenretinide, the chemopreventive steroid fluasterone and a high soy diet each delay spontaneous mammary tumor development (25,26). Mammary tumors from these mice are estrogen-receptor positive, overexpress cyclooxygenase-2 and show reduced BRCA-1 expression, suggesting that this model, which involves alterations in two critical carcinogenesis pathways, may be highly relevant for the development of breast cancer prevention strategies.

In summary, carcinogen-induced models of cancer in rodents have been crucial to advancing our understanding of the neoplastic process, and recent progress in the fields of toxicology, pathology and molecular carcinogenesis has revealed multiple targets for the nutritional modulation and chemoprevention of cancer. We must now capitalize on the availability of new tools such as transgenic mice to identify additional targets that can be modulated and make important progress toward one of the major goals in contemporary cancer research, i.e., the development of effective mechanism-based strategies for preventing human cancer. Successful attainment of this goal will require the integration of the very best science from multiple levels of investigation, including clinical and epidemiologic research, animal studies and basic molecular and cellular biologic research. In our view, the animal model studies play a critical central role in this endeavor. For example, animal studies are required to confirm (under controlled experimental conditions) potential leads from human studies that show associations between certain risk factors (both protective and harmful) and cancer risk. In addition, preclinical studies are critical in translating basic mechanistic findings from the bench to the clinic or population. Thus, the development and characterization of highly relevant animal models will greatly facilitate future progress in cancer prevention research. We have discussed examples of cancer prevention studies that have used p53-deficient mouse models. Taken together, these examples clearly indicate that mice with specific (and human-like) genetic susceptibilities for cancer provide powerful new tools for testing interventions that may inhibit the process of carcinogenesis in humans.

LITERATURE CITED