1. INTRODUCTION

Over the past few decades, the mouse has been established as the primary organism used to investigate the fundamental mechanisms of skin carcinogenesis and to model human neoplasia. Skin is the most important protective barrier against the harmful and lethal carcinogenic effects of physical (e.g., ultraviolet (UV) radiation), chemical (e.g., polycyclic aromatic hydrocarbons (PAHs)), and biological (e.g., oncogenic viruses) environmental factors. Carcinogenesis has been demonstrated by experimental and epidemiologic studies to be a multifactorial, multigenic, and multiphasic process composed of three major sequential stages: initiation, promotion, and progression (1). A single exposure of a carcinogenic agent such as 7,12-dimethylbenz(a)anthracene (DMBA), benzo(a)pyrene B(a)P to epidermal cells may result in a small subset of initiating cells carrying irreversible mutations in critical gene(s) such as proto-oncogenes and tumor-suppressor genes, which control normal cellular growth and differentiation (2). In the promotion stage, repeated applications of promoters such as phorbol esters that are generally nonmutagenic bring about many important epigenetic alterations in initiated cells, facilitating the clonal expansion of an initiated phenotype and leading to the formation of benign tumors or papillomas. The early stage of promotion is reversible, but promotion in late stage and progression represents the irreversible phases of carcinogenesis process (3). In progression stage, papillomas acquire additional aberrant genetic and epigenetic changes, and develop into a rapidly growing
invasive lesion known as carcinoma. Because of an increasing trend in the incidence of human skin cancer, many laboratories have been involved in the process of developing a suitable skin carcinogenesis model to investigate and understand the tumorigenic factors and the cellular, biochemical, and molecular mechanisms involved in the process of human skin tumorigenesis. The ongoing search effort for genetically sensitive mice with a shorter latency period, in addition to increased tumor incidence and tumor multiplicity, has led to the development of the SENCAR mouse, which is the best currently available skin carcinogenesis model. Study of this skin carcinogenesis model has greatly advanced planning strategies to reduce or avoid the risk factors and search for chemopreventive and anticancer agents (4).

2. DEVELOPMENT OF SENCAR MOUSE-SKIN TUMORIGENESIS MODEL

The most widely used skin-tumor-sensitive mouse is the outbred SENCAR (sensitive to skin carcinogen) mouse developed by Boutwell and Baird in early 1970s by the outbreeding method developed by Boutwell in the 1960s (2,5). These mice respond more rapidly and uniformly to the chemical induction of skin tumors than other available inbred and outbred strains. SENCAR mice were selectively bred for sensitivity to skin-tumor induction by the two-stage tumorigenesis protocol. Coincidently, they were also found to be extremely sensitive to complete carcinogenesis, which is accomplished by application of either repetitive small doses or a single large dose of a chemical carcinogen (6). The criteria employed for selection and breeding was the sensitivity of mice skin to DMBA-TPA (12-O-tetradecanoylphorbol-13-acetate) protocol. Skin-tumor-sensitive (STS) Rockland mice were obtained by selective breeding on the basis of tumor incidence and tumor multiplicity (100% tumor incidence and >12 papillomas per mouse at wk 12 of promotion in a classical DMBA-TPA skin carcinogenesis protocol) for eight generations. The resulted STS male mice were crossed with Charles CD-1 female mice and again selected for sensitivity to DMBA-TPA two-stage carcinogenesis for eight generations, leading to the development of the SENCAR mouse strain. In both cases, the mice developing the earliest and greatest number of papillomas after initiation-promotion treatment were selected for each breeding.

3. SENCAR MOUSE VS OTHER SKIN TUMORIGENESIS MODELS

A comparison of complete carcinogenesis and initiation-promotion protocols among the mouse, rat, and hamster has revealed that mice are more sensitive than rats and hamsters (7,8). The high incidence of papillomas in mice and their subsequent conversion to squamous-cell carcinomas (SCCs), especially in two-stage protocol, has made this a suitable experimental model for skin carcinogenesis. Rats mainly produce basal-cell carcinomas in both protocols, whereas hamsters mainly give rise to SCCs in complete carcinogenesis and melanomas in initiation-promotion protocol (8).

To date, several stocks and strains of mice have been used for skin tumorigenesis, but there is little data available for comparing the relative sensitivity of these stocks and strains of mice to various carcinogens. DiGiovanni and Colleagues have shown that for tumor initiation, SENCAR mice are 10–20 times more sensitive to DMBA and 3–5 times to B(a)P as compared to CD-1 mice (5). On the basis of available studies, the susceptibility of various strains of mice to DMBA and B(a)P-induced skin carcino-