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SENCAR Mouse Skin Tumorigenesis Model Versus Other Strains and Stocks of Mice

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The SENCAR mouse stock was selectively bred for eight generations for sensitivity to skin tumor induction by the two-stage tumorigenesis protocol using 7,12-dimethylbenz(a)anthracene (DMBA) as the initiator and 12-O-tetradecanoylphorbol-13-acetate (TPA) as the promoter. The SENCAR mouse was derived by crossing Charles River CD-1 mice with skin-tumor-sensitive mice (STS). The SENCAR mice are much more sensitive to both DMBA tumor initiation and TPA tumor promotion than CD-1, BALB/c, and DBA/2 mice. An even greater difference in the sensitivity to two-stage skin tumorigenesis is apparent between SENCAR and C57BL/6 mice when using DMBA-TPA treatment. However, the SENCAR and C57BL/6 mice have a similar tumor response to DMBA-benzoyl peroxide treatment, suggesting that TPA is not an effective promoter in C57BL/6 mice. The DBA/2 mice respond in a similar manner to the SENCAR mice when using *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG)-TPA treatment. The SENCAR mouse model provides a good dose-response relationship for many carcinogens used as tumor initiators and for many compounds used as tumor promoter. When compared to other stocks and strains of mice, the SENCAR mouse has one of the largest data bases for carcinogens and promoters.

Introduction

It is well known that skin tumors (papillomas, keratoacanthomas, and squamous cell carcinomas) can be induced in mice by a complete carcinogenesis protocol (carcinogen given repetitively) or by the sequential application of a subthreshold dose of a carcinogen (initiation stage) followed by repetitive treatment with a weak or noncarcinogenic tumor promoter (promotion stage). The initiation stage requires only a single application of either a direct or an indirect carcinogen at a subthreshold dose and is essentially irreversible, whereas the promotion stage is brought about by repetitive treatments after initiation and is reversible for a period of time but later becomes irreversible (*1,2*).

To provide a better understanding of the SENCAR mouse and its relative sensitivity to skin carcinogenesis when compared to other stocks and strains of mice, this paper first discusses the derivation of the SENCAR mouse.

Derivation

The SENCAR stock of mice was selectively bred for sensitivity to skin tumor induction by two-stage tumorigenesis. Consequently, the SENCAR mouse is extremely sensitive to two-stage carcinogenesis and coincidentally sensitive to complete carcinogenesis. The SENCAR mouse was derived from crossing Charles River CD-1 mice with skin tumor-sensitive mice (STS) and selected for sensitivity to 7,12-dimethylbenz(a)anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA) two-stage carcinogenesis for eight generations starting with the F_1 cross as originally described by Boutwell (*2*). Figure 1 outlines the method used by Boutwell to select for the STS mice. A similar selection procedure was used by Boutwell and coworkers to derive the SENCAR mice as outlined in Figure 2. In both cases, the mice developing the earliest and most numerous papillomas after initiation–promotion treatment were selected for each breeding.

Comparison of SENCAR Mice to Other Stocks and Strains of Mice

SENCAR mice are between 10 and 20 times more sensitive to DMBA tumor initiation than CD-1 mice (Table 1). However, as shown in Table 2, they are only between three and five times more sensitive to benzo(a)pyrene (B[a]P) tumor initiation than CD-1 mice (*3*). In addition, SENCAR mice are two to three times more sensitive to TPA promotion than CD-1 mice (*3*). BALB/c mice also appear to be consistently less sensitive to two-stage tumorigenesis than SENCAR mice (*4*).

Although several stocks and strains of mice have been used in skin tumor induction experiments very little dose-response data are available. In addition, with the exception of studies on SENCAR and C57BL/6 mice, very few comparative studies have been performed to determine the relative sensitivity of various stocks and strains of mice to carcinogens. An even greater differ-

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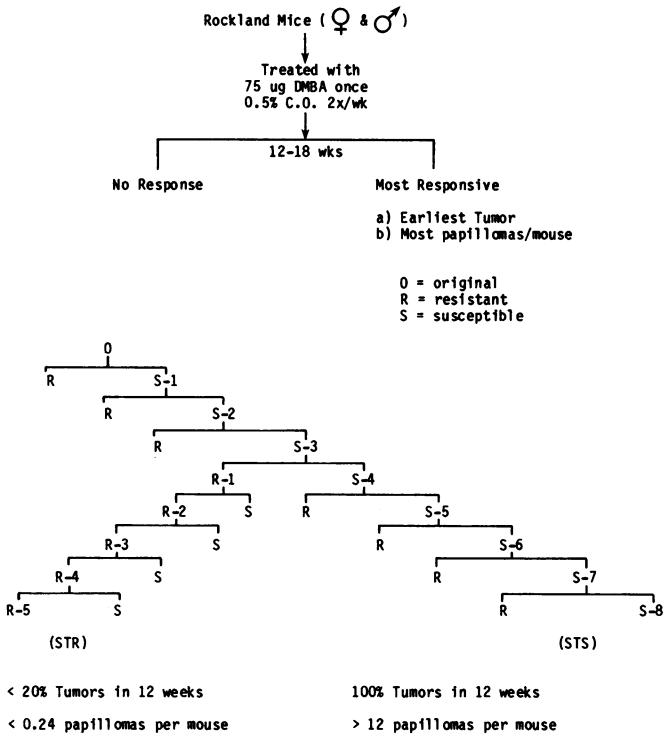

FIGURE 1. Outline of the method used in the selective breeding experiments for skin tumor-sensitive (STS) and resistant (STR) mice (Boutwell)

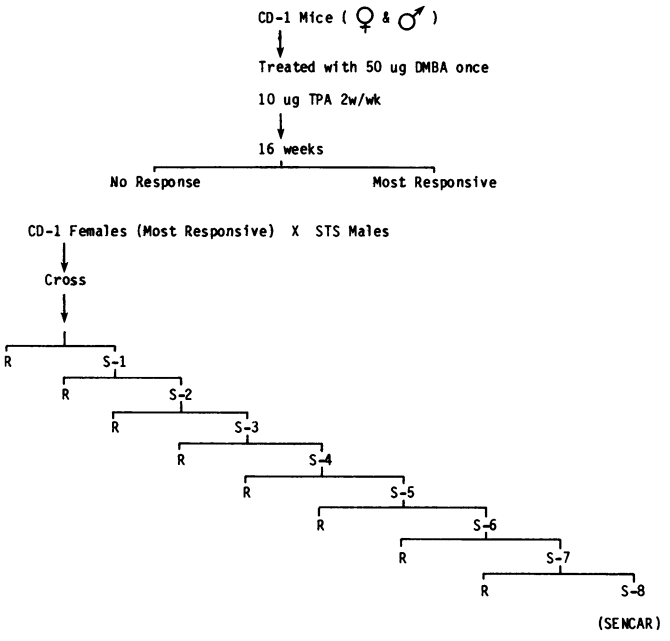

FIGURE 2. Outline of the method used in the selective breeding experiments for SENCAR mice (outbreeding)

Table 1. Comparison of the tumor-initiating activity of DMBA in SENCAR vs. CD-1 mice.[a]

Mice	DMBA dose, nmole	No. of papillomas per mouse at 15 wk	No. of mice with papillomas at 15 wk	No. of papillomas per mouse at 25 wk	% of mice with papillomas at 25 wk
SENCAR	100	22.0	100	24.0	100
SENCAR	10	6.4	100	7.0	100
SENCAR	1	3.2	90	3.8	95
SENCAR	0.1	0.3	15	0.6	20
SENCAR	0.0[b]	0	0	0.1	10
CD-1	100	4.8	75	5.6	90
CD-1	10	2.2	60	3.0	72
CD-1	1	0	0	0.2	10
CD-1	0.1	0	0	0	0
CD-1	0.0[c]	0	0	0.2	10

[a] Data taken from Slaga and Fischer (*33*). Each experimental group is an average of three experiments containing 30 mice per experiment. DMBA was applied topically once and followed 7 days later by twice weekly promoting applications of 8.5 nmole of TPA. The maximum percent standard deviation for all groups was 15%.

[b] TPA-only group; the mice received twice weekly applications of 8.5 nmole of TPA for 25 wk.

ence in the sensitivity to two-stage skin carcinogenesis is apparent between SENCAR and C57BL/6 mice than between the SENCAR and CD-1 mice. C57BL/6 mice are very refractory to two-stage skin carcinogenesis by B(a)P-TPA. As shown in Table 3, even high initiating doses of B(a)P (1600 nmole) and high promoting doses of TPA (10 μg) are quite ineffective in causing skin tumors in C57BL/6 mice. However, C57BL/6 mice do respond to complete carcinogenesis by B(a)P and, in this regard, they appear to be equal to or slightly more sensitive than SENCAR mice (*5*). This unequal susceptibility to complete and two-stage carcinogenesis within a stock or strain of mice strongly suggests that the promotional phases of complete and two-stage carcinogenesis are dissimilar. In addition, differences in sensitivity to initiation and promotion among mice may be caused by alterations in the promotional phase of two-stage carcinogenesis. In this regard, we have recently found that benzoyl peroxide is an effective promoter in

Table 2. Comparison of the tumor-initiating activity of B(a)P in SENCAR vs. CD-1 mice.[a]

Mice	DMBA dose, nmole	No. of papillomas per mouse at 15 wk	No. of mice with papillomas at 15 wk	No. of papillomas per mouse at 25 wk	% of mice with papillomas at 25 wk
SENCAR	200	7.6	100	8.2	100
SENCAR	100	3.4	78	3.8	80
SENCAR	50	1.4	56	1.6	60
SENCAR	10	0.6	36	0.9	42
SENCAR	0[b]	0	0	0.1	10
CD-1	200	1.4	56	3.8	72
CD-1	100	1.0	44	1.8	58
CD-1	50	0.5	36	0.7	40
CD-1	10	0	0	0.1	10
CD-1	0[c]	0	0	0.1	10

[a] Data taken from Slaga and Fischer (*33*). The maximum percent standard deviation for all groups was 18%.

[b] TPA-only groups; the mice received twice weekly applications of 8.5 nmole of TPA for 25 wk.

Table 3. Initiation-promotion in SENCAR and C57BL/6 mice.[a]

Treatment	Result: SENCAR mouse	Result: C57BL/6 mouse
Repetitive applications of TPA for 52 weeks without initiation	Low level of papillomas (5-20%) and carcinomas (<15%) No dose–response relationship	No tumors
Repetitive applications of benzoyl peroxide for 52 weeks without initiation	Less than 5% tumors	No tumors
Repetitive application of various levels of TPA peroxide after initiation with 50-1600 nmole B(a)P	Dose–response relationship in papillomas (early) and carcinomas (late)	Low level of papillomas (<5%) and carcinomas (<10%)
Repetitive applications of various levels of benzoyl peroxide after initiation	Dose–response relationship in papillomas (early) and carcinomas (late)	45% carcinoma incidence

[a] Data of Reiners et al. (*5*).

C57BL/6 and SENCAR mice (*5*). For some reason, TPA is not an effective promoter in C57BL/6 mice.

Recently, DiGiovanni and coworkers (*6*) have found that the DBA/2 mice are much less sensitive to DMBA-TPA two-stage tumorigenesis than the SENCAR mice. If high initiating doses (400 nmole/mouse) of DMBA are used on the DBA/2 mice followed by TPA promotion, they do respond with a high tumor yield. When DBA/2 mice are compared with SENCAR mice following initiation with *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG) and TPA promotion, the DBA/2 and SENCAR mice respond with a nearly identical tumor response (*6*).

Carcinogens and/or Initiators Used With the SENCAR Mouse Model

The SENCAR mouse model currently has one of the largest data bases for carcinogens and/or initiators. All the carcinogens and/or initiators that have been tested in both the CD-1 and SENCAR mice have been found to be positive in both stocks of mice. The major difference is related to the increased sensitivity to and shorter latent period for tumor development in the SENCAR mice. As was the case in CD-1 mice, DMBA and B(a)P show a good dose-response relationship in SENCAR mice (Table 4). As can be seen, a good correlation exists between the number of papillomas per mouse at 15 weeks and the final carcinoma incidence at 50 weeks. The percentage of mice with papillomas also has a reasonable correlation, but the dose response relationship is very narrow (Table 4).

The carcinogenicity of many polycyclic aromatic hydrocarbons (PAHs), metabolites, and derivatives has been determined in the SENCAR mouse skin tumorigenesis model (*4,7–27*). Besides the PAHs, a number of other classes of chemical carcinogens have been found to be positive in a dose-response relationship as skin carcinogens and/or initiators in the SENCAR mouse. These classes include sterigmatocystin, urethane, 1,3-propanesultone, 4-nitroquinoline-*N*-oxide, MNNG, *N*-nitrosoethylurea (ENU), *N*-nitrosomethylurea, epichlorohydrin, and β-naphthylamine (Slaga et al., unpublished data). In this regard, both MNNG and ENU have been found to be very potent skin carcinogens and tumor initiators, which suggests that these compounds will be useful, direct-acting carcinogens in the skin model (Slaga and Nesnow, unpublished data). Several other chemicals (dimethylnitrosamine, dimethylhydrazine, acetylaminofluorine, and 4-aminobiphenyl), which have been found to be positive as carcinogens in certain tissues, have been extensively studied in SENCAR mouse skin and found to be negative as carcinogens (Slaga et al., unpublished data). A possible explanation may be the lack of metabolic activation of these compounds in the skin. In addition, several compounds such as chloroform and malonaldehyde were also found to be negative as carcinogens in the SENCAR mouse skin tumorigenesis model (Slaga and coworkers, unpublished data).

Table 4. Dose-response studies on the ability of DMBA and B(a)P to initiate skin tumors in SENCAR mice.[a]

Initiator	Dose, nmole	No. of papillomas per mouse at 15 wk	% of mice with papillomas at 15 wk	% of mice with carcinomas at 50 wk
DMBA	100	22.0	100	100
DMBA	10	6.8	100	40
DMBA	1	3.2	93	22
DMBA	0.1	0.5	20	5
B(a)P	200	7.5	100	55
B(a)P	100	3.2	78	30
B(a)P	50	1.4	60	18

[a] Data taken from Slaga and Fischer (*33*). The mice were treated one week after initiation with twice weekly applications of 5 μg of TPA.

A number of environmentally important complex mixtures have also been extensively studied for skin-carcinogenic and/or tumor-initiating activity in the SENCAR mouse (*28–32*). Of the complex mixtures tested, coke oven main and roofing tar both had strong skin carcinogenic and tumor-initiating activity, whereas the Nissan diesel exhaust sample was only a strong tumor initiator.

Promoters Used With the SENCAR Mouse Model

As in the case with carcinogens and/or tumor initiators, not all the various skin tumor promoters tested have been assayed in SENCAR mice. As shown in Table 5, a good dose-response relationship exists for TPA skin tumor promotion after DMBA initiation when considering either the number of papillomas per mouse at 15 weeks or the percentage of mice with squamous cell

Table 5. Dose-response studies on the ability of TPA to promote tumors after DMBA initiation.[a]

Promoter	TPA dose, μg	Time to first papilloma, wk	No. of papillomas per mouse at 15 wk	% with papillomas at 15 wk	% with carcinomas at 50 wk
TPA	10	8	3.0	100	32
TPA	5	6	7.2	100	46
TPA	2	7	6.5	100	45
TPA	1	8	3.6	80	25
TPA	0.1	11	0.4	5	8

[a] See Slaga and Fischer (*33*) for details. The mice were initiated with 10 nmole of DMBA and promoted one week later with various dose levels of TPA.

carcinomas at 50 weeks. The repetitive application of the promoter TPA without initiation by DMBA in general gives rise to a few tumors, but a dose-response relationship has never been noted (Table 6). The maximum response observed after 50 weeks of treatment with TPA was a 22% incidence of mice with papillomas and 5% with carcinomas.

Although the initiation stage appears to be irreversible, the promotion stage is reversible, requiring a certain frequency of promoter application to induce tumors. Table 7 compares the promoting activity of various doses of TPA when given either three times, two times, or one time per week. In general, as the frequency of TPA application decreases, the promoting activity also decreases. It should be pointed out, however, that one application per week of TPA after initiation by 20 nmoles of DMBA is still fairly effective in tumor promotion. In constrast, high doses of TPA given once every 2 weeks or once every 3 weeks are ineffective in tumor promotion (*33*).

Besides TPA, several other phorbol ester tumor promoters have been assayed in SENCAR mice. Phorbol 12,13-dibutyrate and 12-deoxyphorbol-13-decanoate both show a good dose-response relationship (Slaga et al., unpublished data). Although 4-O-methyl-TPA is generally not considered a tumor promoter, it does have some promoting activity at doses greater than 200 μg per application. 12-O-Retinylphorbol-13-acetate was also found to have skin tumor promoting activity but less than that of TPA. In general, mezerein can be considered a weak skin tumor promoter in SENCAR mice (*33,34*).

Table 6. Dose-response studies on the ability of TPA to act as a complete carcinogen in SENCAR mice.[a]

TPA dose, μg	No. of papillomas per mouse at 50 wk	% of mice with papillomas at 50 wk	% of mice with carcinomas at 50 wk
0	0	0	0
1	0.09	8	0
2	0.07	7	0
4	0.20	22	5
6	0.15	12	0

[a] The mice (80 per group) were treated twice weekly with various dose levels of TPA.

Table 7. Comparison of the frequency of application and dose of TPA on skin tumor promotion.[a]

DMBA initiation, dose, nmole	TPA dose, μg	Frequency of application, times per week	No. of papillomas per mouse at 16 wk	% of mice with papillomas at 16 wk
10	1	3	7.8	100
10	1	2	3.6	80
10	2	2	6.5	100
10	5	2	10.2	100
10	10	2	4.6	100
10	0.5	1	1.0	40
10	1	1	1.8	66
10	2	1	3.2	74
10	3	1	4.3	78
10	4	1	5.1	82
10	5	1	6.4	86
20	1	1	4.2	76
20	2	1	6.0	96
20	4	1	9.0	100

[a] Thirty female SENCAR mice were used for each group. Data of Slaga et al. (unpublished results).

A number of other chemicals have been found to promote skin tumors in SENCAR mice. These chemicals include telecidin, retinoic acid, benzoyl peroxide, lauryl peroxide, cumene peroxide, decanoyl peroxide, cumene hydroperoxide, *tert*-butyl hydroxperoxide, butylated hydroxytoluene hydroperoxide, 1-fluoro-2,4-dinitrobenzene, benzo(e)pyrene, anthralin, and chrysarobin (*1,33,35* and Slaga et al., unpublished data). A number of chemicals have been found to be negative or very weak as skin tumor promoters in SENCAR mice. These chemicals include hydrogen peroxide, hydroquinone, butylated hydroxyanisole, butylated hydroxytoluene, calcium ionophore A23187, chloroquine, ouabain, chlorpromazine, epichlorohydrin, chloroform, malonaldehyde, phenanthrene, 2-aminoanthracene, 1-aminoanthracene, phenanthrenequinone, and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (Slaga et al., unpublished data).

In terms of complex mixtures, diesel fuel was found to have a moderate skin-tumor-promoting activity, but was found to be negative as a carcinogen in SENCAR mice (Slaga et al., unpublished data).

Conclusion

The SENCAR mouse is, in general, one of the most sensitive stocks and strains of mice currently available for both complete and two-stage carcinogenesis studies. The SENCAR mouse skin tumorigenesis model has one of the largest data bases for skin carcinogens, tumor initiators, tumor promoters, and anticarcinogens (antiinitiators and antipromoters). The model provides excellent data on dose-response relationships when both pure substances and complex mixtures are tested. The two-stage tumorigenesis protocol can be considered a reliable and relatively short-term bioassay for carcinogens and promoters. This model has also been very

important in determining the mechanism of action of carcinogens, promoters, and anticarcinogens.

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