Increased susceptibility to mammary carcinogenesis and an opposite trend in endometrium in Trp53 heterozygous knockout female mice by backcrossing the BALB/c strain onto the background C3H strain

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Abstract: Patients with dominantly inherited Li-Fraumeni syndrome have a loss-of-function mutation in TP53 and develop diverse mesenchymal and epithelial neoplasms at multiple sites. Trp53+/- female mice with the BALB/c background provide unique characteristics for the study of breast cancer in Li-Fraumeni syndrome; however, we previously found that female C3H-Trp53−/− mice did not spontaneously develop mammary tumors. Therefore, we obtained F1 and N2-N4 female mice by backcrossing the BALB/c strain and examined the incidence of mammary and other tumors in lifetime studies. Malignant lymphomas, osteosarcomas, and uterine adenocarcinomas spontaneously developed in approximately 20% or more of Trp53−/− mice with the C3H background. In contrast, the incidence of uterine adenocarcinomas showed a tendency to decrease, while that of mammary adenocarcinomas gradually increased in mice with the BALB/c strain backcross. Wild-type BALB/c female mice are predisposed to a wide spectrum of neoplasms, including mammary tumors, partly due to genetic factors, whereas uterine tumors are uncommon not only in BALB/c mice but also C3H mice. Thus, genetic factors appear to contribute to a strain-specific predisposition to malignant neoplasms in Trp53−/− mice, and further studies are needed to clarify the detailed mechanisms. (DOI: 10.1293/tox.2018-0057; J Toxicol Pathol 2019; 32: 197–203)

Key words: Trp53, BALB/c, C3H, backcrossing, mammary carcinoma, uterine carcinoma

Patients with dominantly inherited Li-Fraumeni syndrome have a loss-of-function mutation in codon 245 (GGC to GAC) of TP53 and develop diverse mesenchymal and epithelial neoplasms at multiple sites, e.g., the breast, soft tissue, brain, bone, leukocytes, and adrenal cortex1,2. This mutation does not produce a mutant TP53 protein with a dominant negative effect, is expected to exert a trans-dominant loss-of-function effect on the wild-type TP53 protein, and is considered to increase susceptibilities to various tumors3. In Trp53-deficient mouse models, homozygotes (Trp53−/−) are highly susceptible to early onset spontaneous tumors. The most frequent tumor type was found to be malignant lymphoma in homozygotes, with an estimated background of ~75% C57BL/6 (B6) and ~25% 129/Sv strains3,4, followed by several testicular tumors, e.g., seminomas, Leydig cell tumors, and solid embryonal carcinomas of the testis, reflecting B6 and 129/Sv characteristics, respectively3.

The incidence of neoplastic lesions in various organs, predominantly including soft tissue sarcomas, is also high in Trp53−/− heterodeficient (Trp53+/−) mice, but with a slower onset than in homozygotes4. Furthermore, Trp53−/− mice with the BALB/c background provide unique characteristics for the study of breast cancer5.

Previous studies using Trp53−/− mice with the BALB/c background demonstrated a greater susceptibility to mammary carcinomas than those with the B6 or 129/Sv background4,6. In BALB/c-Trp53−/− mice, the incidence of lymphomas and hemangiosarcomas was higher than that of mammary carcinomas5. Furthermore, the incidence of mammary carcinomas was lower in BALB/c-Trp53+/− mice than in BALB/c-Trp53−/− mice4. Less than 1% of wild-type and Trp53−/− B6 mice developed mammary tumors8,9. Blackburn et al. reported that Trp53−/− F1 mice with a 50% B6 and 50% BALB/c background developed mammary tumors at an incidence of 32%, while N2 mice with a 75% BALB/c background developed mammary tumors at a significantly lower incidence (45%) than BALB/c-Trp53−/− mice (65%) after long latency periods, suggesting that dominant and recessive BALB/c alleles contribute to spontaneous mammary tumor susceptibility in Trp53−/− mice6. Blackburn et al. also indicated that a strong interaction between two BALB/c alleles for the DNA-dependent protein kinase catalytic subunit (Prkdc) and cyclin dependent kinase inhibitor
2A (Cdkn2a) increased the incidence of mammary tumors, while the effects of these recessive alleles were restricted as major loci contributing to mammary tumor susceptibility.

Mice with the C3H strain background exhibit different spectra of spontaneous tumors from BALB/c, B6, or 129/Sv strains. For example, male C3H/HeN mice exhibited high susceptibilities to spontaneous hepatocarcinogenesis. Spontaneous mammary and ovary tumors were introduced in female C3H/HeN mice, and the contribution of an exogenous mouse mammary tumor virus to mammary tumors was demonstrated. To the best of our knowledge, limited information is currently available on the incidence of tumors in C3H-Trp53+/− mice. Therefore, the purpose of the present study was to characterize the susceptibilities of the C3H and BALB/c strains to carcinogenesis in Trp53+/− mice and investigate the incidence of spontaneous tumor development in C3H F0, as well as F1 and N2-N4 crossed with BALB/c mice in lifetime studies.

Frozen sperm of C3H-Trp53+/− mice, in which the Nco I site in exon 2 of the Trp53 gene was heterozygously inserted by a neomycin phosphotransferase gene, were obtained from Riken RBC (RBRC 01361, Tsukuba, Ibaraki, Japan). In vitro fertilization (IVF) was performed with C3H/HeN and BALB/c mouse oocytes, and F0 and F1 pups, respectively, were delivered from ICR surrogate dams. N2-N4 mice were obtained by crossing with BALB/c mice, which were purchased from CLEA Japan, Inc. (Tokyo, Japan). They were given free access to the standard chow diet CE2 (CLEA Japan) and filtered tap water and were housed up to 5 per plastic cage with woodchip bedding in an air-conditioned animal room maintained at 22°C (fluctuation range: within 1°C) and 55% relative humidity (fluctuation range: within 10%) with a 12:12-h light-dark cycle. In the experiment, palpations of the cervix, thorax, and abdomen of awake mice were conducted weekly in order to detect subcutaneous, intrathoracic, or intraperitoneal nodules. When nodules accounted for more than 10% of the body weight of mice (the longest diameter of nodules was regularly greater than 10 mm), the animals gained weight less than 0.5% with most (11 out of 18, 61%) arising in the inguinal or glutheal areas and in subcutaneous tissues with macroscopic abnormalities in the abdominal, thoracic, and cranial cavities were excised. All animal experiments were performed under protocols approved by the Committee for the Ethics of Animal Experimentation at the National Cancer Center. Seventy virgin female Trp53+/− mice of the following backgrounds were included: 16 recipient inbred C3H (F0), 14 of the initial outcross of C3H and BALB/c (F1), 15 of the first backcross BALB/c onto C3H (N2), 12 of the second backcross (N3), and 13 of the third backcross (N4).

Genotyping was performed as described previously. The primers used were mixtures of (1) intron 1 upstream of exon 2, 5'-AATTGACAAGGTATGCATCACAAGTAGCA-3'; (2) exon 4, 5'-ACTCTCAACATCTGGGCGAGCAACAGAT-3'; and (3) the neo sequence, 5'-GAACCTGCGTGCATCCATCTT-3'. Samples were fixed in 10% neutral buffered formalin, processed routinely, and embedded in paraffin wax. Sections (thickness of 3 μm) were stained with hematoxylin and eosin (HE) and histopathologically diagnosed. Paraffin-embedded sections were also used for immunohistochemistry for human ERα (Leica, Newcastle, UK; clone, 6F11; 1:100 dilution). Antigen retrieval for sections was conducted in an autoclave at 121°C for 10 min in 10 mM citrate buffer (pH 6.0). The streptavidin-biotin-peroxidase complex method (StreptABComplex/HRP, DAKO, Glostrup Denmark) was used to assess the expression and localization of each antigen, and sections were lightly counterstained with hematoxylin for microscopic examinations. Negative controls without primary antibody reactions were set using serial sections. ER-positive mammary tumors were defined by the presence of more than 10% ER-positive tumor cells.

The Log-rank test was used to evaluate overall survival. Regarding the incidence of histopathologically diagnosed tumors, the 2×5 chi-squared test was performed among all 5 groups, and this was followed by Fisher’s exact test between F0 and the remaining four groups when a significant difference was observed.

Survival rates were lower in N3 and N4 mice than in F0 mice (p=0.012 and 0.028, respectively; Fig. 1A–1E). Mammary tumors, which are described in detail below, sporadically developed in mice aged 38 to 82 weeks, and survival rates in N3 and N4 mice markedly decreased after approximately 40–50 weeks of age. The shorter survival rates in N3 and N4 mice than in F0 mice were partly attributed to increased susceptibility to mammary carcinogenesis by backcrossing the BALB/c strain onto the background C3H strain.

No mammary tumors (0%) were detected in C3H-Trp53+/− mice, whereas the incidence of mammary tumors in mice with the BALB/c strain backcross gradually increased (p=0.038; Table 1, Fig. 2A). The incidence of mammary tumors was significantly higher in N2, N3, and N4 mice than in C3H (F0) mice (p=0.043, 0.008, and 0.004, respectively). All mammary tumors were adenocarcinomas, with most (11 out of 18, 61%) arising in the inguinal or gluteal areas, though 4 out of 18 (22%) and 3 out of 18 (17%) were detected in the thoracic or axillary areas and in submaxillary areas, respectively, in the remaining four groups. The cut surfaces of histopathologically diagnosed mammary adenocarcinomas macroscopically showed a lobular appearance and were opaque with a light yellow-white color. The histological types of all cases were ductal and lobular adenocarcinomas in F1, N2, and N3 mice. In adenocarcinomas with ductal/lobular differentiation, tumor cells mainly showed tubular, papillary, and/or solid patterns, sometimes grew with ribbon-like patterns, and were middle- to high-grade malignancies (Fig. 2B). In N4 mice, 4 out of the 6 (67%) mammary tumors were ductal and lobular adenocarcinomas, while 2 (33%) exhibited adenosquamous characteristics. ERα-positive tumors were detected in 1 out of 3 F1 mice, 2 out of 4 N2 mice, 0 out of 4 N3 mice, and 2 out of 5 N4 mice (Fig. 2C).

The incidence of endometrial adenocarcinomas histopathologically showing the growth of malignant epithelia in
ductal and/or solid patterns (Fig. 2D) appeared to decrease with the crossing of C3H-\textit{Trp53}\textsuperscript{+/−} mice with BALB/c mice; however, no significant differences were observed among the groups (Table 1). Other endometrial lesions were rare (Fig. 2A).

The incidence of adrenal subcapsular cell carcinomas is shown in Table 1. The total incidence of these carcinomas was higher in F1, N2, N3, and N4 mice (20/54, 37%) than in C3H (F0) mice, with no significant differences being observed among F0, F1, N2, N3, and N4 mice or marked increases with the crossing of C3H-\textit{Trp53}\textsuperscript{+/−} mice with BALB/c mice.

![Survival curves](image)

**Fig. 1.** Survival curves of (A) F0, (B) F1, (C) N2, (D) N3, and (E) N4 mice.

**Table 1.** Incidence of Mammary, Uterine, and Adrenal Tumors

| Organ (tumor) | Finding | F0       | F1       | N2       | N3       | N4       | Chi-squared test |
|---------------|---------|----------|----------|----------|----------|----------|-----------------|
| Mammary gland | Adenocarcinoma | 0/16 (0.0) | 3/14 (21.4) | 4/15 (26.7) | \* | 5/12 (41.7) | b | 6/13 (46.2) | b | \( p=0.038 \) |
| Uterus (endometrial epithelia) | Adenocarcinoma | 3/16 (18.8) | 1/14 (7.1) | 1/15 (6.7) | 0/12 (0.0) | 0/13 (0.0) | \( p=0.269 \) |
| | Adenoma | 0/16 (0.0) | 0/14 (0.0) | 0/15 (0.0) | 0/12 (0.0) | 1/13 (7.7) | NT |
| Adrenal | Subcapsular cell carcinoma | 2/16 (12.5) | 7/14 (50.0) | \* | 6/15 (40.0) | 2/12 (16.7) | 5/13 (38.5) | \( p=0.140 \) |
| | Subcapsular adenoma | 0/16 (0.0) | 1/14 (7.1) | 0/15 (0.0) | 1/12 (8.3) | 0/13 (0.0) | NT |
| | Cortex adenocarcinoma | 0/16 (0.0) | 1/14 (7.1) | 0/15 (0.0) | 0/12 (0.0) | 0/13 (0.0) | NT |

\* \( p<0.05 \) vs. F0 (Fisher’s exact test); \* \( p<0.01 \) vs. F0 (Fisher’s exact test); NT, not tested.
All cohorts also developed the other expected types of tumors, including lymphomas, osteosarcomas, and some mesenchymal and epithelial tumors (Fig. 2A), as reported previously in Trp53<sup>−/−</sup> mice with other strain backgrounds<sup>4</sup>. The most common spontaneous tumors observed in all cohorts were malignant lymphomas followed by osteosarcomas (Fig. 2A, 2E). Lung adenocarcinomas were observed in F1, N2, and N3 mice, but not in F0 or N4 mice. As nonneo-
plastic lesions, cystic hyperplasia of the uterus and ovaries was noted in the present study, which was consistent with previous findings obtained from BALB/c-Trp53+/− mice.

In the present study, F1, N2, N3, and N4 mice showed a gradually increasing incidence of mammary tumors, from 21% in F1 mice to 46% in N4 mice, and these results were consistent with previous findings. The reason for this may be the unique functional polymorphism of Ptkdc, which encodes a subunit of a DNA-dependent protein kinase involved in DNA double-strand break repair. We did not elucidate the mechanisms underlying mammary tumorigenesis in mice with the BALB/c background in the present study; however, BALB/c may have a germ line-specific factor that contributes to mammary tumor development, as discussed in the Introduction section. The C3H parent strain was developed from a cross of a Bagg albino (which later produced BALB/c by inbreeding) female with a DBA male mouse, and they were genetically close. Therefore, the use of these strains is advantageous for clarifying dominant genetic factors in mammary tumorigenesis and may lead to the development of better breast cancer mouse models.

Mouse models of estrogen receptor-positive (ER+) breast cancer have been reviewed. Esr1, Cnd1, Prl, Tgfa, Ncoa3, Espll, and Wnt1 overexpression, Pik3ca gain-of-function, and the loss of Stal were shown to be associated with mouse ER+ mammary carcinogenesis. Based on the phenotypes of the mammary tumors that developed, FVB-Tg(C3-1-TAg)cJeg (C3-TAg) mice have genetic drivers for tumorigenesis, which is very relevant to the human basal-like disease. On the other hand, FVB/N-Tg(MMTVneu)202Mul/J (MMTV-Neu) mice develop mammary tumors that represent a human luminal subtype but do not express ER. Under these conditions, BALB/c-Trp53+/− mice are regarded as a typical ER+ mammary carcinoma model with acinar-type adenocarcinoma or adenoacanthoma phenotypes and occasional poorly differentiated carcinomas. The Trp53-related model developed in BALB/c mice uses implants of the mammary epithelium from eight-week-old female mice with the germ-line loss of Trp53 that are placed into the cleared mammary fat pads of three-week-old mice in order to generate a mouse model of human ductal carcinoma in situ. Implanted mice develop disease at an incidence of between 24 and 55% 11 or 12 months after implantation, and 21% of lesions are ER+. These findings are consistent with the present results showing that the incidence of spontaneously induced ER+ mammary tumors was approximately 30%.

There are currently only a few animal models of uterine carcinogenesis, e.g., Donryu rats treated with or without N-ethyl-N’-nitro-N-nitrosoguanidine. In Donryu rats, poorly differentiated adenocarcinomas were found to be positive for the Trp53 protein, suggesting the accumulation of mutated Trp53. Furthermore, Mitumori et al. generated a uterine carcinogenesis model that was useful for identifying the tumor-modifying effects of endocrine-disrupting chemicals following the administration of N-ethyl-N-nitrosourea to female CBA-Trp53+/− mice. In the present study, uterine adenocarcinomas were spontaneously detected in approximately 19% (3/16) of Trp53+/− mice with the C3H background. Donehower et al. reported that the loss of Trp53 function was sufficient to genetically predispose mice to the spontaneous development of tumors, e.g., malignant lymphomas and testicular tumors in Trp53+/− mice with the C57BL6 and 129/Sv backgrounds, respectively. Szyman-ka et al. recently showed that wild-type BALB/c female mice developed a wide spectrum of neoplasms, including mammary tumors, which is consistent with the present results as well as previous findings. On the other hand, wild-type DBA mice frequently (~25%) developed uterine tumors, which are uncommon not only in BALB/c mice but also in C3H wild-type mice. The C3H parent strain was developed from a cross of a Bagg albino female with a DBA male mice, and C3H and DBA strains are genetically close. In addition, Wall et al. reported clear strain differences in uterine physiological factors between C57BL6 and C3H female mice, e.g., cell proliferation/apoptosis indicators and gene transcripts under conditions with and without estrogen. Therefore, the uterine tumors observed in Trp53+/− mice with the C3H background in the present study are considered to be of biological significance and may have been influenced by C3H-specific genetic factors in addition to uterine environment factors.

In conclusion, backcrossing the BALB/c strain onto the background C3H strain resulted in a slight decrease in the incidence of uterine adenocarcinomas but also a gradual increase in mammary adenocarcinomas in Trp53+/− mice. The present results suggest that genetic factors partly contribute to a strain-specific predisposition to malignant neoplasms in Trp53+/− mice, and further studies are needed to clarify the detailed mechanisms.

Disclosure of Potential Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgments: We thank the Animal Core Facility of the National Cancer Center Research Institute for maintaining mice and for their technical support with histopathological evaluations. The Core Facility was supported by the National Cancer Center Research and Development Fund (26-A-8) and a Health and Labor Sciences Research Grant from the Ministry of Health, Labor and Welfare of Japan.

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