Short Communication

Spontaneous Tumors in p53-Deficient Mice

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Abstract: The p53-deficient mice (Riken mice) were examined for tumors occurring spontaneously histopathologically and hematologically. Histopathologically, 87% of the males with tumors and 86% of the females with tumors had malignant lymphomas or lymphatic hyperplasia. It must be safe to say that more marked tendency to have spontaneous malignant lymphomas is seen in the p53-deficient mouse. (J Toxicol Pathol 1997; 10: 239~242)

Key words: Spontaneous tumor, p53-deficient mouse, Homozygote, Malignant lymphoma

The mouse deficient for p53 tumor-suppressor gene was produced for the first time by a homologous gene recombination method in 1992¹. According to the report on the production of the p53-deficient mouse, mice homozygous for the null allele appear normal but are prone to the spontaneous development of a variety of neoplasms, for example, malignant lymphoma and sarcoma. The report also disclosed that the spectrums of occurrences of the various kinds of tumors were similar to the spectrum of Li-Fraumeni syndrome, a hereditary disease in humans, so that the p53-deficient mouse has peculiar phenotypes, which differ from those of transgenic mice to which other tumor-suppressor genes, WT-1 and APC, for example, have been introduced². However, it has been reported that malignant lymphomas considerably tend to occur in the p53-deficient mice, which was also produced by the homologous gene recombination method³. Thus, there are few differences in incidence of

malignant lymphomas among these transgenic mice. To study the differences, the authors used more deficient for p53 (abbreviated name: Riken mice) than those used in 1992¹ and examined the tumors occurring spontaneously in the mice histopathologically as well as hematologically.

Riken mice, established as SPF mice, are being kept and bred in an SPF animal room, Nihon Bioresearch Inc. Thirty mice of each sex, which had been obtained from homozygotes, served as animals in the test group. The animals were fed commercialized feed (CRF-1, Oriental Yeast Co., Ltd., Tokyo) and water *ad libitum*. Dead animals were necropsied immediately after they were discovered. Moribund animals and animals surviving for 41 weeks after birth were necropsied after being subjected to blood collection under anesthesia with aqueous pentobarbital sodium. Blood samples were subjected to hematological examination. Tissue samples were fixed in 10% phosphate buffered forma-

Fig. 1. Life span of p53-deficient mice.

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Fig. 2. Survival curves of p53-deficient mice.

Fig. 3. Hematological analysis of p53-deficient mice.

lin and then embedded in paraffin to prepare sections. The paraffin-embedded sections were stained with hematoxylin and eosin (HE) and then subjected to histopathological examination. Meanwhile, ten CBA mice (Atsugi Breeding Center, Charles River Japan, Inc., Kanagawa) of each sex served as animals in the control group. The control animals were sacrificed and necropsied at 25 weeks of age, which is the estimated average longevity of mice deficient for p53, and subjected to hematological and histopathological examinations in the same way as that employed for the animals in the test group.

Postnatally both sexes of p53-deficient animals normally grew and did not take abnormal behavior. However, decrease in locomotor activity was seen at three months of age and thereafter, and moribund animals began to be seen. The average longevity was 22 weeks in the males ($n=27$) and 24 weeks in the females ($n=29$) (Fig. 1), and the survival curve in the males was almost the same as that in the females (Fig. 2). According to necropsy findings, 85% (23/27) of the males and 100% (29/29) of the females had tumors, and markedly hypertrophic spleen, thymus, and lymphatic organs, including lymph nodes (Fig. 4) were seen in most of the

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Fig. 6. Malignant lymphoma of lymph node. HE $\times 250$.

Fig. 5. Malignant lymphoma of thymus. HE $\times 100$.

animals with tumors.

Upon the hematological examination (Fig. 3), abnormally increased white blood cell count was observed in 12 of the 22 males and 14 of the 21 females, and large, atypical lymphocytes increased in the 12 males and 14 females. The red blood cell count, hemoglobin concentration, and hematocrit level were decreased or lowered in four to seven of the 26 males and eight to ten of the 22 females. The animals in which the hematological changes were seen showed indications of anemia.

Upon the histopathological examination (Table 1), 87% of the males with tumors and 86% of the females with tumors had malignant lymphomas (Figs 5 and 6) or lymphatic hyperplasia. When the results of the hematological examination are considered, these findings suggest that most of the animals with tumors had leukemic conditions. Some of the males and females with tumors also had a few kinds of non-epithelial tumors, but only one animal each of both sexes had epithelial tumors, specifically, bronchiolar/alveolar adenoma.

According to Donehower *et al.*'s report¹ malignant lymphomas occurred in 77% (20/26) of both sexes of animals, and the organs in which the tumors were found were the thymus and other visceral organs, including the heart, lungs, spleen, kidneys, and brain. The malignant lymphomas observed were diagnosed as lymphoblastic tumors. Compared with Donehower *et al.*'s results, ours indicate that the incidence of tumors was higher, but both were alike in respect to the organs in which tumors occurred and types of cells. In general, spontaneous lymphatic tumors markedly occur in mice⁴. It must be safe to say that spontaneous malignant lymphomas are more apt to be seen in the p53-deficient mouse.

Table 1. Histopathology of p53-deficient Mice

Tumors in homozygous p53-deficient mice	
27 males	29 females
tumors ; 23/27 (85%)	tumors ; 29/29 (100%)
malignant lymphoma ; 17/23 (74%)	malignant lymphoma ; 20/29 (69%)
lymphoid hyperplasia ; 3/23 (13%)	lymphoid hyperplasia ; 5/29 (17%)
bronchiolar/alveolar adenoma ; 1/23 (4%)	bronchiolar/alveolar adenoma ; 1/29 (3%)
malignant fibrous histiocyoma ; 1/23 (4%)	malignant fibrous histiocyoma ; 1/29 (3%)
glioma ; 1/23 (4%)	adenocarcinoma ; 1/29 (3%)
hemangioma ; 1/23 (4%)	salivary gland tumor ; 1/29 (3%)
sarcoma ; 4/23 (17%)	sarcoma ; 4/29 (14%)
non-tumors ; 2/27 (7%)	non-tumors ; 0/29 (0%)
bronchopneumonia ; 1/27 (4%)	
abscess ; 1/27 (4%)	
Of 27 p53 males examined, 4 died from unknown (non-tumor) cases.	

The authors will attempt to study further the usefulness of the p53-deficient mouse to examine mutagens in homozygotes, elucidate the phenomena of aging, and to examine carcinogens in heterozygotes.

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