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低線量・低線量率放射線のリスク評価について

Carcinogenic risk assessment of low-dose and low-dose rate gamma-rays

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1. Introduction

The present manned space missions operate at International Space Station (ISS) in low earth orbit for six months to a year. One of the health effects that must be considered for the long-term stays in the space environment such as these manned flights and ISS is carcinogenesis due to long-term space radiation exposure. Exposure to radiation is known to increase the risk of carcinogenesis. However, it is difficult to accurately assess carcinogenic risk after exposure to low-dose / low-dose-rate radiation. Radiation-induced cancer cannot be evaluated directly because cancer is caused by variety of environmental factors, not just (radiation) exposure. Therefore, we attempted to evaluate the carcinogenic risk of radiation exposure at low-dose and low-dose-rate using model mice that can detect radiation-induced cancer by molecular analysis.

2. *Ptch1* heterozygous mouse

Ptch1 heterozygous mouse (*Ptch1*$^{+/-}$ mouse) carry a defective copy of a tumor suppressor gene *Ptch1*. *Ptch1*$^{+/-}$ mice develop spontaneous medulloblastoma, a tumor of cerebellum, by loss-of-function *Ptch1* gene. We have previously reported that medulloblastomas developed after radiation exposure exhibited an interstitial chromosomal deletion on the wild-type *Ptch1* allele (designated as "radiation-induced" or R-type tumor), while almost all of spontaneously developed medulloblastomas exhibited loss entire chromosomal regions distal to the wild-type *Ptch1* (designated as "spontaneous" or S-type tumor) (Figure.1) [1].

3. Materials and Methods

2.1 Mice and Irradiation

Male C57BL/6J *Ptch1*$^{+/-}$ and female C3H/HeCrl mice were intercrossed to obtain both male and female F1 hybrid C3B6F1 *Ptch1*$^{+/-}$ mice. Two irradiation regimes were used: acute (high-dose-rate) postnatal and protracted (low-dose-rate) postnatal. For acute postnatal exposure, the C3B6F1 pups were irradiated on postnatal day 1 (P1) with 0.1 or 0.5 Gy of ^{137}Cs gamma-

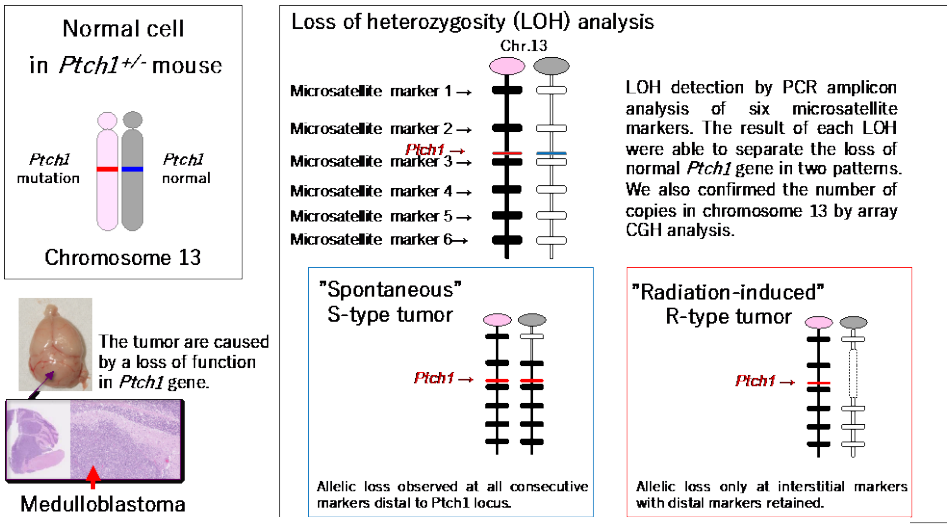

Fig 1. The characteristic of *Ptch1* heterozygous mouse

rays from 57.35TBq source at an acute dose rate of 540 mGy/min in an acrylic irradiation enclosure, before they were returned to their mother in their normal cage until weaning. For the protracted postnatal exposure, the C3H mothers carrying C3B6F1 litters were transferred to acrylic cages for the birth of their pups, and on P1 the cages were transferred to the low-dose-rate irradiation room equipped with a 111 GBq 137Cs source, which delivered 0.018 mGy/min [25 mGy over 23 h/day for 4 days (total dose: 0.1 Gy) or 11.1 TBq 137Cs source, which delivered 0.09 mGy/min [125 mGy over 23h/day for 4 days (total dose: 0.5 Gy)].

After the irradiations, the *Ptch1* genotype of pup was determined by PCR using DNA from mouse ear punch, and C3B6F1 *Ptch1*$^{+/-}$ mice were observed daily until moribund, at which point they were euthanized by venesection and were autopsied. Portions of cerebellar tumors were snap frozen in liquid nitrogen and tail tissue as a normal tissue control. The remaining whole brain fixed in 10% natural-buffered formalin for histology analysis.

2.2 Molecular analysis to separate radiation-induced tumor

Genomic DNA was isolated from medulloblastoma and ear samples. Detection of loss of heterozygosity (LOH) was analyzed for six microsatellite markers on chromosome 13, including *Ptch1* gene, and sequencing of single-nucleotide polymorphism (SNP) in exon 23 of the murine *Ptch1* gene. We also confirmed change in DNA copy number on chromosome 13 by array-CGH analysis. After LOH and array-CGH analyses, medulloblastomas are classified into two molecular subtypes, that is R-type tumors with interstitial deletion of the wild-type *Ptch1* allele or S-type tumor with loss of entire chromosomal region distal to the wild-type *Ptch1* allele (Figure 1).

3. Results and Conclusion

Mice were monitored for medulloblastoma development until 500 days of age. In acute exposure group, the incidence of medulloblastoma at 0.5 Gy-irradiated group was higher than that in non-irradiated control group, and the incidence of R-type medulloblastoma increased dose-dependent manner (Figure 2). On the other hand, the incidence of medulloblastoma in protracted exposed *Ptch1*$^{+/-}$ mice was the same as in the non-irradiated group. Surprisingly, R-type medulloblastoma was observed with protracted exposure of 0.5 Gy, but the incidence was lower than in the acute exposure group at the same dose. The incidence of R-type medulloblastoma with protracted exposure of 0.1 Gy was at the same level as in the non-irradiated group. That is, it was shown that exposure-induced tumors are induced even in protracted exposure in which the incidence does not increase significantly.

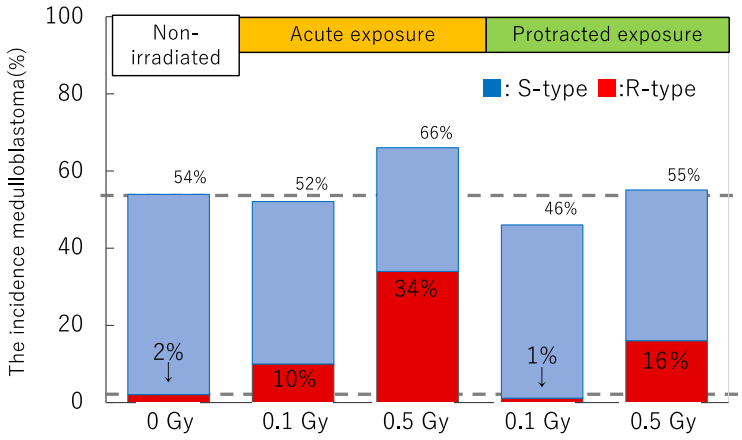

Fig 2. The incidence of medulloblastoma in *Ptch1*$^{+/-}$ mice

Acknowledgement

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