

【Grant-in-Aid for Scientific Research(S)】

Integrated Disciplines (Environmental science)



Title of Project: *In vivo*, *in situ* assessment of the mutagenic risk of radiation and environmental chemicals, using newly developed animal systems

Asao Noda

(Radiation Effects Research Foundation, Department of Genetics, Assistant Department Chief)

Research Area: Environmental science, risk sciences of radiation and chemicals

Keyword: Health effects, somatic mutation

【Purpose and Background of the Research】

Radiation and environmental chemicals affect every cell and tissue in our body, but detailed risk assessment is not currently available. In this study, we develop model animal systems in which living mutant cells arising in the body become fluorescent (GFP positive) to allow the detection of mutant cells in an intact tissue structure. Apart from examination of preexisting systems, this approach enables measurement of the mutant frequencies in self-renewing somatic stem cells, as well as differentiation committed cell populations and functionally differentiated cells *in situ* after genotoxic insult. Thus the study provides a novel opportunity to estimate mutational risk in cancer-susceptible cell populations.

【Research Methods】

- (1) The systems we use resemble a higher-animal version of the Ames Test. We develop cell systems in which reversion, or forward mutation, at a specific gene locus turns the cells “green” in mice and *medaka* killifish. The reversion system consists of partial duplication of the HPRT gene in conjunction with the GFP gene, so that deletion of one segment from the tandem duplicate produces HPRT-GFP fusion protein. The forward mutation system turns cells “green” with inactivating or dominant negative (gain-of-function) mutations at the oncogene or tumor suppressor gene.
- (2) The effects of fetal and childhood exposure are examined in various tissues in relation to different doses and the timing of individual development. Also, the genetic effects of radiation are monitored with germ cell mutations (spermatogonia cells and mature oocyte mutations).

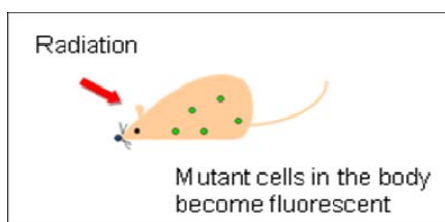
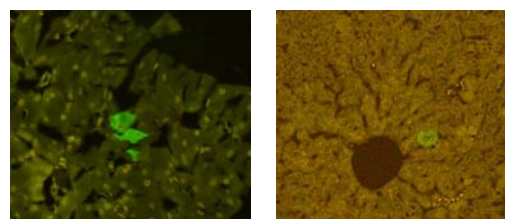


Figure 1. Model animals

(3) The effects of genetic background and somatic cell instability on offspring born to irradiated parents are examined. The molecular mechanisms of stem cell mutation in regenerating tissues are analyzed.



Pancreas

Liver

Figure 2. *In vivo* arising mutant cells

【Expected Research Achievements and Scientific Significance】

Detection and measurement of the mutagenic risk of somatic cells *in vivo*, in a spatio-temporal manner, are prerequisites for contemporary risk assessment of environmental radiation and chemicals. For example, the risk of breast cancer development should be evaluated in mammary gland cells *in vivo*. Our model system will make such assessment possible. It should also be noted that genetic effects, i.e. transgenerational effects, are evaluated easily by measuring germ cell mutations. Low-dose and life-time chronic exposures, or the effects of internal exposure by radionuclides, are also challenging issues that this study addresses.

【Publications Relevant to the Project】

- Noda A. et al., *Mutat. Res.* 721:101-107, 2011.
- Noda A. et al., *J. Cell Sci.* 125:5280-5287, 2012.
- Nakamura N. et al., *Ann. Rev. Genet.*, in press.

【Term of Project】 FY2013-2017

【Budget Allocation】 140,500 Thousand Yen

【Homepage Address and Other Contact Information】

<http://www.rerf.jp/>