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Division of Radiation and Regeneration Control Department of Cellular Biology

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Hiromitsu Watanabe held a seminar about 2nd Mibyou Foram in Hiroshima. He presented papers entitled "Protection of radiation damages and chemical carcinogenesis by using different term fermented miso in animals" at Health Forum of Human on 21st Century, Harbin, China and "Acquisition of a gastric or duodenal phenotype on heterotrophic transplantation of esophagus diaphragm, trachea and bladder tissues in F344 rats" at JSTP/IFSTP (IATP) 2004, Kobe. He received by Grants-in-Aid for Science Promotion Fund of the Ministry of Education, Culture, Sports, Science and Technology (Chief Y. Ichimasa, Ibaragi Univ.) and Cancer Research for Ministry of Health, Lobour and Welfare of Japan (Chief K. Wakabayashi, National Cancer Center Res. Inst.). He took mandatory retirement on March 31 2004. Shuneki Shoji, research associate presented a paper entitled "Abnormal vasculogenesis and embryonic development induced by maternal radiation exposure." at the First International Symposium of 21st Century COE Program—Cellular Responses to Genome Damage and Chromatin Dynamics-Hiroshima, on February 13, 2004. He has also been serving as part time lecturer to teach graduate students at Graduate School of Medicine, University of Tokushima. Toshihiro Uesaka, research associate received by a Grant-in-Aid for Young Scientists (B) (KAKENHI 14780424), and Grant-in-Aid of Cancer Research for Ministry of Health, Labour and Welfare of Japan (Chief M. Fukushima, Osaka City Univ.) and Dawn Research for Japanese Atomic Energy Institute. He moved to the Center for Developmental Biology, RIKEN CDB at Kobe on Apr 1st 2004. Shoji Kashiwabara, graduate students have been researching. He presented 2 papers entitled "Tumor induction by colon carcinogenesis in rat gastric mucosa featuring intestinal metaplasia caused by X-irradiation." and "Incidence of cardiomyopathy in rats treated with PhIP varies with the rat strain." at JSTP/IFSTP (IATP), Kobe, 2004.

Takahiro Ochiya, Department of Cancer Metastesis, National Institute Cancer, Res. Inst. is scientific advisors in this department from 2003 to 2004.

The main research projects of this department, which were carried out in 2003-2004 and are being planned for the following years, are summarized as follows.

1. Factors influencing on experimental carcinogenesis in stomach.

Participants: Kashiwabara, S., Kashimoto, N., Watanabe, H.

We have already confirmed that sex hormones, especially progesterone have an influence on the development of gastric tumors. Ten % NaCl, growth hormone, progesteron and androgen worked promotive and alcohol or Miso, reduced salt Miso inhibitory for gastric tumorigenesis. The 180 day fermented miso was decreased size of gastric tumor induced by MNNG in SD rats as compared with same amount of NaCl. One- day old SD rats were treated with MNU nursed by SD or ACI mothers and retreated with MNNG from 6 weeks old. There were no increased tumor induction, but cumulative incidence of tumor in ACl

surrogate mothers group was later as compared to that in SD mother group. Occurrence of signet ring cell carcinomas was noted in hypocatalasemic mice by X-irradiation. Signet ring cell carcinomas of the glandular stomach in mice are not promoted by H_2O_2 or NaCl. It is our scope to find out the substances which are influencing for the occurrence of gastric tumors.

2. Induction of intestinal metaplasia and its role of tumorigenesis in the stomach.

Participants: Kashiwabara, S., Kashimoto, N., Watanabe, H.

Gastric region of rats was locally irradiated and intestinal metaplasia was numerated by staining, alkaline phosphatase and PAS staining. The induction of intestinal metaplasia by X-irradiation in rat is greatly influence by sexes and by the rat strains. Subtotal resection of the fundus combined with X-ray irradiation in Donryu rats was an effective induction protocol for intestinal metaplasia. However, there are no induction of intestinal metaplasia in Mongolian gerbil (*Meriones meridianus*) by X-irradiation. Also development and maintenance of intestinal metaplasia was influenced by a changes of pH valve in stomach. There was no genetic changed in X-ray induced intestinal metaplasia. Twenty-two months after the first X-irradiation the insulinoma and kidney tumors were induced in SD and F344 rats.

Based on investigations in humans, intestinal metaplastic changes in the stomach have been considered as precancerous lesions or a predisposing condition for differentiated gastric carcinoma development. However, we have experimentally reported an inverse relationship between quantity of intestinal metaplasia, with or without Paneth cells, and gastric tumor development and have established that its presence does not exert a positive influence on induction of gastric neoplasia by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) or N-methylnitorsoure (MNU) in rats. Colorectal mucosa implanted into the glandular stomach, like the intrinsic large intestine, is sensitive to tumorigenesis caused by 1, 2-dimethylhydrazine (DMH), in contrast to the normal gastric mucosa. Male 5-week-old Crj: CD, Crj: Wistar and F344/DuCrj rats were X-irradiated with a total of 20 Gy in two equal fractions with a 3-day interval. Beginning 16 weeks after the first dose, DMH was injected i.m. at a dose of 20mg/kg body weight weekly for 10 times in CD and Wistar rats. Azoxymethane (AOM) was injected i.m. at a dose of 15mg/kg body weight weekly for 3 weeks and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) was given every 2 days, 3 times per week, for a total 10 doses of 75 mg/kg body weight by intragastric intubation in F344 rats. Twelve months after the initial carcinogen treatment, tumors in pylorus of the glandular stomach were observed in 2(3 lesions) of 30 animals in CD rats, 5 of 23 in Wistar rats and 4 of 29 animals in the X-rays+AOM groups and 4 of 25 animals receiving X-rays+PhIP in F344 rats. No such lesions were found in the DMH, AOM, PhIP or X-ray alone or nontreated groups. Large intestinal tumors appeared in colon carcinogen treated groups. Skin, pancreatic and kidney tumors appeared in X-irradiated groups. While we must consider the alternative possibility that the effects of irradiation and DMH and other colon carcinogens on glandular stomach epithelial cells are additive or synergistic, it appears likely that intestinal mucosal stem cell(s) are susceptible to colon carcinogenesis, independently of the administration route or their location. The presence of intestinal metaplasia, with or without Paneth cells, may increase the sensitivity of the stomach to the induction of tumors by carcinogens like DMH, AOM or PhIP, but not MNNG or MNU.

3. Cell differentiation of heterotopically transplanted tissues into different locus of the gastrointestinal tract in rats.

Participants: Kominami, Y., Gon, R., Hayashi, M., Nishiki, M., Sasaki, A., Shiraishi, M., Kashimoto, N., Ochiya, T., Watanabe, H.

Colonic tissues were implanted into the glandular stomach, and gastric mucosa into the duodenum. Colorectal mucosa implanted in the glandular stomach would be stable or be new-differentiated to the gastric mucosa in the recipient environment.

Gastric mucosa, esophagus and bladder were transplanted into the duodenum, and the esophagus was implanted into the glandular stomach. In case of gastric mucosa implanted into the duodenum pepsinogen positive chimeric glands with goblet cells appeared in the graft. Esophagus grafts transplanted into the glandular stomach or duodenum, newly-differentiated into gastric on duodenal mucosa, respectively. GFP transgenic rats were produced by Dr. Ochiya. Skin of ear, trachea and bladder in GFP

rats were transplanted into the duodenum in normal F344 rats. One month after the transplanted the grafts were stained with GFP antigen and had GFP gene. It was suggested that the grafts might be differentiated into duodenum.

4. Modifying factors for the colonic tumorigenecity.

Participants: Ouchi, Y., Kashimoto, N., Watanabe, H.

Various environmental factors influencing on colonic tumorigenicity in rodents will be tested. So far, we have studied the effect of limonene, imuran and Miso diet. Twenty ppm of imuran containing diet was promotive for the DMH induced colonic tumors in mice, but 5% of limonene and lactosucrose were decreased dose dependently tendent in colon tumor incidence. Miso was not inhibited DMH-induced colon tumors in mice. However, ACF induced by AOM was decreased in dose dependent manner by miso in F344 rats. ACF was not inhibited by pure salt but was inhibited by crude salts. The strongest inhibition of ACF and colon cancer in 180 day fermented miso was shown as compared with early or 120 day fermented-stage miso. Moreover ACF was inhibited by hot water extract from culture medium of *Ganoderma lucidum* (Rei-shi) mycelia (MAK) and also tumor size was deceased in mice. and rats . Recently we found that sericine, buckwheat protein and vitamin B_6 were prohibited induction of colon tumor and that dietary Ca markedly suppresses colon ACF and lowers colonic cell proliferation and fecal deoxycholic acid in fecal and that the enhancement of colon cell proliferation and carcinogenesis by high fat diet is mediated through elevating serum leptin.

5. Cardiomyopathy induced by heterocyclic amines.

Participants: Kashiwabara, S., Kashimoto, N., Shokawa, T., Yoshizumi, M., Kawamata, S., Wakabayashi, K., Watanabe, H.

Heterocyclic amines were induced tumors of various site in experimental animals. Hyperglysimia was induced by PhIP in F344 male rats. but cardiapathy was not induced in this strain. On the other hand, cardiomyopathy was induced by PhIP in 18-months-old Donryu male rats but not 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and in F344 rats. There was no induction of cardiomyopatty in 6-week-old both sex in Donryu rats.

The following seven strains and two of F_1 rats were used in this study, i.e., 18 months-old male Crj: Donryu, Crj: CD, Crj: Wistar, WKY/NCrj, SHR/NCrj, LEW/Crj, BN/Crj, and both sexes of F344 x Donryu, Donryu x F344. Each strain was divided into two groups. One was used as PhIP treatment group, and the other was as non-treatment group. PhIP (75mg/kg/day) was administered by gavage 10 times on 3 time per week for two day intervals and saline instead of PhIP. Animals in a moribund state were killed and autopsied, and the others were killed 53 weeks after the initial treatment. The incidence of cardiomyopathy in each strain was investigated. No significant difference of mean survival except Donryu was observed among the groups. Donryu was begun to die by cardiomyopathy the first PhIP treatment to 45% at 98 days and up to 80% at 310 days.

It is well known that 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) , is a heterocyclic amine derived from cooked meat and a potent environmental carcinogen for rat colon, prostate and mammary glands. We have reported that the cardiomyophathy was induced in Donryu rats treated with PhIP. The aim of this study is to clarify the rate of cardiomyopathy induced by PhIP in several strains of rats.

6. Anticancer effect and inhibition of melanin synthesis of blue light-emitting diode irradiation

Participants: Ohara, M., Watanabe, H.

Although a number of studies have been carried out to examine the biological effects of radiation and ultraviolet rays (UV), little is known of the effects of visible light. The effects of components of visible light on the growth of cancer cells using light-emitting diodes (LEDs), which have specific light-emission spectra, and found that blue light suppressed the growth of B16 melanoma cells in a time-dependent manner. We suggested that this effect of blue light could be due to the inhibition of DNA synthesis and cell division. When the blood of rats with 1-ethyl-1-nitrosourea-induced leukemia was exposed to blue light for 3 h

during extracorporeal circulation, the growth of leukemic cells was suppressed, but the growth of normal lymphocytes was not affected significantly. Additionally, when B16 melanoma cells exposed to blue light and incubated for 7 days were injected intravenously into mice, metastasis of the B16 melanoma cells to the lung was significantly inhibited. The suppressing effect of blue light on the proliferation of B16 melanoma cells continued to be present even after the passage of cells over several generations, and exposure to blue light resulted in marked alterations in morphology of the cell colonies, with the formation of relatively low-density colonies of long and large striated cells. These findings suggest that exposure to blue light modifies the functions of B16 melanoma cells. Melanin-producing capacity is one of the main functions of B16 melanoma cells. The effects of blue light on the melanin-producing capacity of B16 melanoma 4A5 cells (a melanin-producing cell line) and Weiser-Maple guinea-pigs (a melanin-producing species) to confirm the biological effect of blue light on melanin formation. Melanin synthesis in B16 melanoma 4A5 cells was selectively suppressed by blue light, but blue light did not induce decolorization of previously produced melanin. In the back skin of brown guinea-pigs, the brightness of the sites exposed to UVB began to decrease on the fifth day of the experiment, decreasing further from the 12th day to the 18th day after UVB exposure. The brightness of the sites exposed to UVB and blue light decreased in a manner similar during the UVB exposure, but remained relatively unchanged from the 12th day to the 30th day. These results suggest that blue light suppresses melanin formation following repeated UVB exposure. Further investigation with various light such as blue light may lead to a new approach to the care of ultraviolet-affected skin such as hyperpigmentation.

7. Protective mechanisms of radiation injuries

Participants: Myojin, Y., Kubo, N., Yokoyama, H., Uesaka, T., Katoh, O., Watanabe, H.

With the JCO Company Ltd. accident two victims received bone marrow transplants and skin grafts but death due to gastrointestinal problems could not be prevented. How to protect the gastrointestinal tract from irradiation is a very severe problem. Moreover, A-bomb survivors who had frequently consumed miso (Japanese soybean fermented paste) demonstrated decreased radiation damage. Because of this report, Europeans were recommended to eat miso after the Chernobyl Accident. However, there have been few reports on animal experiments to confirm these beneficial effects. If gastrointestinal cell death were indeed ameliorated, miso would be very useful for prevention of radiation damage. The response of crypt stem cells to a variety of genotoxic and cytotoxic agents has been primarily studied using microcolony formation assays based on the capacity of surviving stem cells to regenerate crypt like foci that can be scored histologically 3-4 days after irradiation.

The radioprotective effect of miso, a fermentation product from soy bean, was investigated with reference to the survival time, crypt survival and jejunum crypt length in male B6C3F1 mice. Miso at three different fermentation stages (3-4 days, 120 days- and 180 days fermented miso) was mixed in MF diet into biscuits at 10% and was administered from 1 week before irradiation. Animal survival in the 180 days fermented miso group was significantly prolonged as compared with the short-term fermented miso and MF cases after 8 Gy of ^{60}Co-γ-ray irradiation at a dose rate of 2Gy min^{-1}. Delay in mortality was evident in all three miso groups, with significantly increased survival. At doses of 10 and 12 Gy X-irradiation at a dose rate of 4 Gy min^{-1}, the treatment with long-term fermented miso significantly increased crypt survival. Also the protective influence against irradiation in terms of crypt lengths in the long-term fermented miso group was significantly greater than in the short-term or medium-term fermented miso and MF diet groups. Thus, prolonged fermentation appears to be very important for protection against radiation effects Supplementation of a nucleotide-free diet with NS inhibited the development of nonneoplastic lesions, such as those associated with amyloidosis, without promoting the carcinogenesis induced by ^{252}Cf irradiation.

8. Effects of testis on environmental factors.

Participants: Kashiwabara, S., Watanabe, H.

Tritiated water was injected by C3H, B57BL and B6C3F1 mice, then one months after the injection testis was examined paghologicallly. The most sensitive strain of testis lesion atrophy was in B57BL mice. Testis atrophy in B6C3F1 male mice was

tested by estrogen or their derivatives in B6C3F1 male mace. Testis atrophy was appeared by i.p. injection of 2.5mCi tritiated water. Further investigations are required induction of testis atrophy by doses of triated water and their derivatives.

Tritiated water at 23.2, 46.3 or 92.5 MBq/animal and ^{137}Cs-γ rays at 9.5 Gy (equivalent 370MBq) or lower doses were administered to 6-week old male C3H/HeNCrj and C57BL/6NCrj mice, as well as F_1 Crj: B6C3F1 (C3H x C57BL) progeny. Animals were autopsied 30 days after the first irradiation. Testis weights were decreased dose dependently, relative values being highest in the C3H and lowest in the C57BL case, with B6C3F1 intermediate. Vacuolization in seminiferous tubules appeared in the 23.2 MBq group and increased with the dose. Focal pyknosis and karyomegaly were found at 46.3 MBq, while primary and secondary spermatocytes and spermatids disappeared with 92.5 MBq. Only a few spermatogonia and Sertoli cells remained after exposure to 9.5 Gy ^{137}Cs-γ rays. Sizes of seminiferous tubules were decreased dose dependently, with no strain differences. When male B6C3F1 mice were irradiated with Cs-γ rays at 0.119 (equivalent 4.63 MBq tritiated water) or 2.38Gy (equivalent 92.5 MBq tritiated water), body weights and size of the seminiferous tubules were decreased at both doses and the larger dose also caused reduction of testis weight and abnormal sperm. However, all the changes except for alteration in weights had disappeared 1 month after the final irradiation. It is considered that 0.119 Gy of Cs-γ rays (equivalent to 4.63 MBq tritiated water) may be a no effect level for testis changes.

9. Animal model of abnormal vasculogenesis and conotruncal anomalies in Neurocristopathy syndrome induced by environmental factors.

Participants: Shoji, S.

Our studies suggested that environmental factor, protein synthesis inhibitor Fertilysin, induced Bis-diamine syndrome in rat offspring, producing coronary arterial origin in conotruncal anomalies with aortic arch anomalies and craniofacial, as well as thymic, defects that are resembled in DiGeorge and Velocardiofacial (CATCH22) syndromes. Neurocristopathy syndrome such as Bis-diamine syndrome represents an interesting model for studying the cellular and molecular basis. We indicated that Fertilysin-induced Bis-diamine syndrome are caused by disruption of proliferation and migration of the neural crest cells or of mesenchymal cell development, apoptosis as well as reduction in synthesis of the extracellular matrix, and neurocristopathy of the pharyngeal arches in surviving offspring. To clarify the vasculogenesis of coronary arterial origin in cardiac outflow tract and conotruncal anomalies, we investigated the pathogenesis of these abnormalities and compared them to those reported in humans in this study. The environmental factors and several transcription factors and genes may play important roles in this process.

10. Radiation or environment agent-induced teratogenesis and tumorigenesis in the offspring following exposures.

Participants: Shoji, S.

The present study was conducted to determine whether following genetic damage induced by ionizing radiation or environmental agents leads to lethality, teratogenesis and tumorigenesis among the progeny and to compare them to those reported in humans.

11. Cdx2 gene transfer to the intestine: Gene therapy clinical trial for intestinal damage by radiation.

Participants: Uesaka, T., Watanabe, H.

Non-viral vectors are thought to have several advantages over viral vectors, since they are simpler to use, less immunogenic and able to transfer high molecular weight DNA molecules. For gene therapy trial for intestinal damage by radiation, we evaluated the non-vial vectors transfer based on cationic lipids into mice. Primary results confirmed the safety of these compounds, but showed low transgene expression levels. In order to develop improved gene transfer to intestine, we have evaluated gene transfer efficiency of hemagglutinating virus of Japan (HVJ) envelope vector. In the mouse intestine, green fluorescent protein (GFP) staining analysis suggested that epithelial cell transfection and foreign gene expression may have

occurred in the crypts. Cdx2 gene delivery given before 12 Gy of irradiation resulted in a 2.5-fold increase in the number of surviving crypts 3 days after irradiation ($p<0.05$).

12. Molecular biological analysis for mechanism of epithelial cell survival and regeneration after radiation injury in the intestine.

Participants: Uesaka, T.

Homeostasis of the normal intestinal epithelium is maintained by continuous and rapid replacement by cell replication within the crypt. The actively dividing epithelial cells within the crypt are the most sensitive to radiation injury. However, direct evaluation of cellular function in gastrointestinal tract damage by radiation is not feasible since there is not marker specific for intestinal stem cells. In this study, we focused on target genes for intestinal Cdx2 homeobox gene, which is critical in intestinal proliferation and differentiation. We identified several genes, including heparin-binding epidermal growth factor-like growth factor (HB-EGF) induced its expression by Cdx2 in rat intestinal epithelial cell line, IEC-6. In addition, oligonucleotide microarray analysis revealed that over 10 genes expression was induced directly by Cdx2 induction. We have been analyzing molecular mechanisms for their function in the cellular proliferation, differentiation and survival.

Original Papers

1. Kashiwabara, S., Kashimoto, N.[*1], Sanoh, S., Uesaka, T., Katoh, O., Watanabe, H. ([*1]Dept Exp Oncol): Damage of mouse testis by tritiated water and ^{137}Cs-γ-rays. Hiroshima J. Med. Sci., 52, 53-58, 2003.

2. Watanabe, H., Kinoshita, K., Katayama, M., Kin, Y., Kominami, Y., Gon, R., Nishiki, M., Sasaki, A., Shiraishi, M., Uesaka, T., Katoh, O.: Acquisition of a gastric or duodenal phenotype on heterotrophic transplantation of esophagus and bldder tissues in F344 rats. J.Exp. Clin. Cancer Res. 21, 421-424, 2003.

3. Watanabe, H.: Cancer prevention by life style-related diseases by used miso. J. Jpn. Mibyo Sys. Ass., 9,59-62, 2003. (*in Japanese*)

4. Watanabe, H.: Cancer prevention by adult lifestyle habits.. J. Jpn. Mibyo Sys. Ass., 9,99-108, 2003. (*in Japanese*)

5. Kashimoto, N.[*1], Kyo, E.[*2], Uesaka, T., Katoh, O., Watanabe, H. ([*1]Dept Exp Oncol, [*2]Wakunaga Pharm. Co. Healthcare): Immunoadjuvant effect by a water-soluble extract from cultured medium of *Ganoderma lucidum* (Reishi) mycelia.J. Jpn. Mibyo Sys. Ass., 9, 293-296, 2003. (*in Japanese*)

6. Shiraki, K., Kashiwabara, S., Kashimoto, N.[*1], Une, K., Yano, R., Ootani, S., Mineoka, A., Hashimoto, K., Kageyama, N., Nishioka, T., Kominami, Y., Sasaki, A., Shiraishi, M., Uesaka, T., Katoh, O., Watanabe, H. ([*1]Dept Exp Oncol): Inhibition by long-term fermented miso of induction of pulmonary adenocarcinoma by diisopropanolnitrosamine in Wistar rats. Miso Sci Tech.,51, 391-397, 2003. (*in Japanese*)

7. Kawano, K.[*1], Matuda, S., Kashiwabara, S., Kashimoto, N.[*2], Kageyama, N., Hashimoto, K., Nishioka, T., Uesaka, T., Katoh, S. Watanabe,H. ([*1]Dept Exp Oncol, [*2]Hiroshima Pref. Food Tech. Res. Center): Effects of each fractions extracted from miso on the protection against radiation damage and aberrant crypt foci. Miso Sci Tech., 51, 429-434, 2003. (*in Japanese*)

8. Zhaorigetu, S.[*1], Yanaka, Y.[*1], Sasaki, M.[*1], Watanabe, H., Kato, N. ([*1]Fac. Appl. Biochem) Inhibitory effects of

silk protein, sericin on UVB-induced acute damage and tumor promotion by reducing oxidative stress in the skin of hairless mouse. Photochem. Photobiol. B: Biol., 71, 11-17, 2003.

9. Ohara, M.[*1], Kobayashi, M.[*1], Fujiwara, H.[*1], Kitajima, S.[*1], Mitsuoka, C.[*1], Watanabe, H. ([*1]Otsuka Pharm Fac): Blue light inhibits melanin synthesis in B16 melanoma 4A5 cells and melanin production induced by utltaviolet B in guinea pigs. Photodermatol. Photoimmunol. Photomed., 17, 25-30 2004.

10. Yokoyama, H.[*1], Fujiwara, H.[*1], Watanabe, H. ([*1]Otsuka Pharm Fac): Dietary nucleoside-nucleotide does not affect the incidence of tumor but reduces the incidence of amyloidosis in B6C3F1 mice irradiated with Californium-252. Nutrition, 20, 383-389, 2004.

11. Kashiwabara, S., Kin, K., Sugihara K.[*1], Kitamura, S.[*1], Kashimoto, N.[*2], Uesaka, T., Katoh, O., Watanabe, H.: ([*1]Grad Scl Biomed Sci, [*1]Dept Exp Oncol): Spontaneous tumors in hypocatalasemic C3H/C$^{b}_{s}$/Gen and C3H Mice. J. Toxicol. Pathol., 17, 25-30, 2004.

12. Shoji, S.: The long term effects of ^{137}Cs γ rays and tritiated water (tritium β-rays) on induction of teratogenesis in rats. in Proceedings of the International Symposium on Biological Effects of Low Dose Radiation: Molecular Mechanisms for Radiation-induced Cellular Response and Cancer Development. pp343-347, Published by Institute for Environmental Sciences, Rokkasho, Aomori, Japan, 2003. (A, R)

13. Shoji, S.: Neutron induced teratogenesis and Protein synthesis inhibitor Fertilysin induced fetal Bis-diamine syndrome in the rat: an animal model for CATCH-22 and DiGeorge syndrome. in Proceedings of the International Symposium on Biological Effects of Low Dose Radiation: Molecular Mechanisms for Radiation-induced Cellular Response and Cancer Development. pp348-354, Published by Institute for Environmental Sciences, Rokkasho, Aomori, Japan, 2003. (A, R)

14. Uesaka T., Kageyama N., Watanabe H.: Identifying target genes regulated downstream of Cdx2 by microarray analysis. J. Mol. Biol., 337, 647-660,. 2004.

15. Myojin, Y.[*1], Ouchi, Y.[*1], Kubo, N.[*1], Shimamoto, F.[*1], Shirahata, S, Uesaka, T., Katoh, O.,Watanabe, H. ([*1]Dept of Fac Hum Life Environ Sci Hiroshima Prif Women's Univ., Dept. Genetic Resource Technol Fac of Agr, Kyusyu Univ. The protection effect of fermented milk Kefir on radiation. Hiroshima Med. Ass., 57, 396-398, 2004. (*in Japanese*)

Meeting Presentations

1. Watanabe, H.: Gastric cancer and daily diets such as miso and sodium chloride. Meeting of Risk Factor for Gastric Carcinogenesis, Tokyo, 2003.

2. Watanabe, H., Radiation induced intestinal metaplasia. in Workshop 16, Pathological Studies for Radiation Damages. 92th Annual Meeting of the Japanese Society of Patholgy, Fukuoka, 2003. (*Proc Jpn Soc Pathol 92, 173, 2003.*)

3. Myojin, Y.[*1], Ouchi, Y.[*1], Kubo, N.[*1], Shimamoto, F[*1]., Shirahata, S.[*2], Uesaka, T., Katoh, O.,Watanabe, H. ([*1]Dept of Fac Hum Life Environ Sci Hiroshima Pref Women's Univ., [*2]Dept Genetic Resource Technol Fac. Agr., Kyusyu

Univ): The protection effect of fermented milk Kefir on radiation. 44th Annual Meeting on Late Effects of Atomic Bomb, Hiroshima, 2003. (*Abstracts 33, 2003.*)

4. Watanabe, H., Shiraki, K., Kashiwabara, S., Kashimoto, N.[*1], Uesaka, T., Katoh, O. ([*1]Dept Exp Oncol): Inhibition by long-term fermented miso of induction of pulmonary adenocarcinoma by diisopropanolnitrosamine in Wistar rats.10th Japanese Society for Cancer prevention, Sapporo, 2003. (*Abstract 119, 2003*) .

5. Watanabe, H: Development of radiation protection by using fermented foods and growth factors. Japan Atomic Energy Research Institute-Conference, 2003-21, Tokaimura, 2003. (*Abstracts 44*)

6. Watanabe, H., Ochiya, T.[*1], Kawamata, S.[*2], Kominami, Y.[*2], Gon, R., Sasaki, A., Shiraishi, M., Mishiki, M., Hayashi, M., Uesaka, T., Katoh, O. ([*1]National Cancer Center Res. Inst., [*2]Med Scl): Cell differentiation in gastrointestinal tract. 18th Carcinogenesis Semina, Takayama, 2003. (*Abstracts 28, 2003.*)

7. Watanabe, H.: Protection of radiation damages and chemical carcinogenesis by using different term fermented miso in animals. Health Forum of Human in 21st Century, Harbin, China, 2003.

8. Kashiwabara, S., Kashimoto, N.[*1], Uesaka, T., Katoh, O., Wakabayashi, K.[*2], Watanabe, H. ([*1]Dept Exp Oncol, [*2]National Cancer Center Inst): Tumor induction by colon carcinogenesis by azoxymethane and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in rat gastric mucosa featuring intestinal metaplasia caused by X-irradiation. 62nd Anuual Meeting of Japanese Cancer Association, Nagoya 2003. (*Jpn J Cancer Res 62, suppl 469, 2003.*)

9. Watanabe, H., Kashiwabara, S., Kashimoto, N.[*1], Uesaka, T., Katoh, O., Ishikawa, M.[*2] ([*1]Dept Exp Oncol, [*2]Res Cent Nuc Sci Techinol Univ Tokyo): Tumorigenesis by monoenergetic neutron.in B6C3F1 mice. Symposium Biological Effects in neutron, present and prospective 46th Annual Meeting of Japanese Radiation Research, Kyoto, 2003. (*J. Radiat. Res., 44, 373, 2003*)

10. Watanabe, H.: Protection of chemical carcinogenesis by using different term fermented miso in rats Symposium 1. Soybeans and Health.. The 6th Annual Meeting of the Japanese Society for Complementary and Alterative Medicine, Sendai, 2003.

11. Watanabe, H.: Gastric tumorigenesis from intestinal metaplasia in rat model. 3rd Meeting of Risk Factors for Gastric Carcinogenesis, Tokyo, 2003.

12. Kubo, N.[*1], Ouchi, Y.[*1], Myoujin, Y.[*1], Shimamoto, F.[*1], Kashimoto, N.[*2], Kyo, E.[*3], Katoh, O., Watanabe, H.([*1]Dept of Fac Hum Life Environ Sci Hiroshima Pref Women's Univ., [*2]Dept Exp Oncol, [*3]Wakunaga Pharm. Co. Healthcare): Radiation protection using mycelia and fruit body. 10th Annual Meeting of Japanese Mibyo System Association, Kawasaka, 2004, (Incentive Award 10th Annual Meeting of Japanese Mibyo System Association)

13. Kashimoto, N.[*1], Ueno, Y.[*2], Kyo, E.[*3], Tanaka, N.[*2], Watanabe, H. ([*1]Dept Exp Oncol, [*2]1st Dep. Int. Med., Sch. Med., [*3]Wakunaga Parm. Co.): The protection of dextran sulfate sodium induced chronic ulcerative colitis model of *Panax notoginseng* F.H.Chen.. 10th Annual Meeting of Japanese Mibyo System Association, Kawasaka, 2004,

14. Watanabe, H., Ochiya, T[*1], Kawamata, S.[*2], Kurose, T.[*2], Kominami, Y., Nishiki, M., Sasaki, A., Shiraishi M., Gon, R., Hayashi, M., Kashiwabara, S., Kashimoto, [*3]N., Uesaka, T., Katoh, O.: ([*1]National Cancer Center Res. Inst.,

[*2]Med Sch, [*3]Dept Exp Oncol) Acquisition of a gastric or duodenal phenotype on heterotrophic transplantation of esophagus diaphragm, trachea and bladder tissues in F344 rats. JSTP/IFSTP (IATP) 2004, Kobe, 2004. (*Abstract 238*)

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(R) Report on the using Radiation Facilities, (A): Study conducted at Research Laboratory for Radiation Experimented Animals, (G): Gene Technology Facilites, (C): Studies established at the International Information Center, (I): Publication listed in Current Contents.