Epidemiological study demonstrated that the risk of solid tumors in atomic bomb survivors is still higher even today, with more than 65 years having passed since the atomic bombing. The purpose of this research group is to elucidate the molecular mechanisms of DNA double-strand break repair and chromosomal stability maintenance, which are involved in the radiation-induced carcinogenesis.

Professor Matsuura worked on the support efforts for reconstruction of Fukushima as a member of the radiation emergency medicine assistance team (REM AT) of Hiroshima University, and was awarded a special prize from the vice-president of Hiroshima University. Assistant professor Miyamoto studied the molecular function of a spindle assembly checkpoint regulator BUBR1, and the findings were written up in the Kagaku Shinbun (Japan) and Nature Japan Homepage. Dr. Ochiai joined the lab as a postdoctoral fellow of the Japan Society for the Promotion of Science and started studying the genome editing. Postgraduate students, Mr. Hosoba and Mr. Hayashi, joined the lab, and Mr. Hosoba was awarded an excellent student scholarship. Ms. Royba from Orenburg University (Russia) stayed in Hiroshima University for 6 months as a visiting research fellow, and worked on the mechanism of DNA damage response. Ms. Tonouchi provided technical support and office work for the lab, and also office work for the Radiation Research Society of the Chugoku area.

1. Interphase function of a spindle assembly checkpoint protein BUBR1

Miyamoto T., Matsuura S.

Constitutional mutations in the BUB1B gene encoding BUBR1 cause a human disorder—premature chromatid separation (PCS) syndrome, also known as mosaic variegated aneuploidy (MVA) syndrome. About 40 patients were reported worldwide, and most patients developed childhood cancers. The clinical findings in the patients included Dandy-Walker complex, postcerebellar cyst, hypoplasia of the cerebellar vermis, lissencephaly, polycystic, often bilateral, nephroblastoma, polycystic kidney, and infantile obesity. These clinical features imply a critical role of BUBR1 in morphogenesis. However, little is known about the function of BUBR1 other than mitotic control. Using cell lines from the patients with the syndrome, we demonstrated that BUBR1 is essential for the formation of primary cilium: a microtubule-based organelle on the surface of most vertebrate cells in G0 phase, and that PCS (MVA) syndrome is a novel ciliopathy. Morpholino antisense oligonucleotide mediated knockdown of bubr1 in medaka fish also caused ciliary dysfunction characterized by defects in cerebellar development and perturbed left-right asymmetry of the embryo. Biochemical analyses demonstrated that BUBR1 is required for ubiquitin-mediated proteasomal degradation of CDC20 in the G0 phase and maintains APC/C(Cdh1) activity that regulates the optimal level of Dishevelled for ciliogenesis. At present, we are trying to identify novel downstream molecules of BUBR1 for ciliogenesis.
2. Regulation of primary cilium formation by kinesin family proteins

Miyamoto T., Hosoba K., Matsuura S.

It was reported that the kinesin-13 subfamily motor protein Kif24 specifically interacts with CP110 and Cep97, preferentially localizes to mother centrioles, and is involved in negative regulation of cilia assembly (Kobayashi T. et al. Cell 2011). We recently reported that Kif2a, another protein of the kinesin-13 subfamily, localizes to centrioles. We are studying molecular basis of the kinesin-13 subfamily proteins in primary cilium formation.

3. Regulation of bipolar spindle formation by Kinesin family proteins

Miyamoto T., Matsuura S.

Treatment of monastrol, a specific inhibitor of bipolar kinesin Eg5, in normal cells induces mitotic cell death with monopolar spindles. We found that cells with high Plk1 activity show monastrol-resistant bipolar spindle formation. We reasoned that another kinesin(s) might be regulated by Plk1 and involved in the monastrol-resistant bipolar spindle formation, and so functional analyses of candidate proteins are in progress.

4. Identification of BUB1B mutation in the second allele of the patients using next generation sequencer and genome-editing technology

Ochiai H., Miyamoto T., Hayashi K., Matsuura S.

Premature chromatid separation (PCS) syndrome is a rare autosomal recessive disorder, which is caused by mutations in the BUB1B gene. Both monoallelic and biallelic mutations have been found in individuals with the PCS (MVA) syndrome. Patients outside Japan had biallelic mutations and showed a moderate phenotype. On the other hand, all Japanese patients had monoallelic mutations and were severely affected with Dandy-Walker complex, polycystic nephroblastoma, and rhabdomyosarcoma. No mutation was found in the second allele in each of the Japanese patients. We are trying to identify the underlying mutation deeply embedded in the second alleles of the PCS patients using a next generation DNA sequencer and evaluate candidate alterations by reverse genetics using genome-editing technology.

5. Identification of the genes for Seckel syndrome and primary microcephaly

Miyamoto T., Matsuura S.

Seckel syndrome and primary microcephaly (head circumference <-4 SD) are heterogeneous genetic disorders with autosomal recessive inheritance. Although the incidence is extremely rare, the disorders are considered very important because there is a causal link between impaired DNA damage signaling response and severe microcephaly. We are trying to identify underlying genes for Seckel syndrome and primary microcephaly using Japanese microcephalic patients using whole-exome sequencing.

6. Molecular pathology of genetic disorders with impaired ATR-signaling

Royba E., Miyamoto T., Matsuura S.

DNA damage results in genome-wide suppression of transcription. It was reported that chromatin dissociation of Chk1 and subsequent reduced H3-T11 phosphorylation is responsible for DNA-damage-induced transcriptional repression (Shimada et al. Cell 2008). We recently showed that ATR Seckel syndrome cells show 50% reduction of H3-T11 phosphorylation even in a steady state. Therefore we try to evaluate accurately the translational level of a large number of genes in the cells after targeted disruption of the ATR gene.

7. Identification of the SNPs responsible for individual difference of radiation sensitivity

Ochiai H., Miyamoto T., Matsuru S.

It is generally thought that radiation sensitivity may vary among individuals. Therefore, it is important to establish the new standard for radiation protection based on the individual radiation sensitivity. We try to identify the novel SNPs responsible for individual difference of radiation sensitivity by the genome wide association study, and functional analysis will be performed using artificial nucleases.
8. Development of practice guideline and medical treatment for congenital anomalies

Matsuura S., Ochiai H., Miyamoto T.

We will participate in a clinical research network consisting of medical genetician to develop new practice guideline and medical treatment for congenital anomalies. We will specifically collect DNA samples from patients with premature senescence, DNA repair deficiency or CNS anomalies.

A. Original Papers


B. Meeting Presentations


8. Miyamoto, T., Porazinski, S.\textsuperscript{,1}, Huijia, W.\textsuperscript{,1}, Shimizu, A.\textsuperscript{,2}, Kajii, T.\textsuperscript{,3}, Kikuchi, A.\textsuperscript{,4}, Furutani-Seiki M.\textsuperscript{,1}, Matsuura, S. (*Dept. Mol. Biol. and Biochem., Univ. of Bath, U.K., \textsuperscript{2}Dept. Mol. Biol., School of Med., Keio Univ., \textsuperscript{3}Hachioji, \textsuperscript{4}Dept. Mol. Biol., Biochem., Grad. School of Med., Osaka Univ.): BUBR1, a mitotic spindle checkpoint regulator, plays a role of ciliogenesis in G0 phase. The 34th Annual Meeting of the Molecular Biology Society of Japan. December 13-16, 2011 Kobe (G)


13. Miyamoto, T., Kikuchi, A.\textsuperscript{,1}, Furutani-Seiki, M.\textsuperscript{,2}, Matsuura, S. (*Department of Molecular Biology and Biochemistry, Graduate School of School of Medicine, Osaka Univ., \textsuperscript{2}Department of Biology and Biochemistry, University of Bath U.K.): Insufficiency of BUBR1, a mitotic spindle checkpoint regulator, causes a ciliopathy with chromosomal instability. International symposium 50th anniversary of RIRBM, Hiroshima University. February 20-21, 2012 Hiroshima (G)


15. Tauchi, H.\textsuperscript{,1}, Ohara, M.\textsuperscript{,1}, Abe, H.\textsuperscript{,1}, Matsuura, S., Komatsu, K.\textsuperscript{,2} (*Department of Biological Sciences, Ibaraki Univ., \textsuperscript{2}Radiation Biology Center, Kyoto Univ.): Functional link between Nbs1 and Ku70 protein in cellular response to DNA damage induced by ionizing radiation. International symposium 50th anniversary of RIRBM, Hiroshima University. February 20-21, 2012 Hiroshima

16. Sakuma, T.\textsuperscript{,1}, Hosoi, S.\textsuperscript{,1}, Ochiai, H., Miyamoto, T., Matsuura, S., Sakamoto, N.\textsuperscript{,1}, Yamamoto, T.\textsuperscript{,1} (*Department of Mathematical and Life Sciences, Graduate School of Science, Hiroshima Univ.): Targeted genome editing using transcription activator-like effector nucleases (TALENs). International symposium 50th anniversary of RIRBM, Hiroshima University. February 20-21, 2012 Hiroshima

intergenic region, which is likely a candidate mutation for human genetic disorder. The 1st Meeting of the Genome Editing. February 28-29, 2012 Hiroshima


C. Others


(R), (A), (G) and (C) are reports on the study using Radiation Experiments, Animal Experiments, Gene Technology Facilities and Studies established at Division of Radiation Information Registry, respectively. (I) indicates reports printed in the scientific journals listed in Current Contents.