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Division of Genome Biology
Department of Radiation Biology

Professor	Shinya MATSUURA, M.D., Ph.D.	
Assistant Professor	Hideki IZUMI, Ph.D.	
Research Associate	Kenichi MORISHIMA, M. Sci.	(～August 31, 2007)
Postgraduate Student	Yoshiyuki MATSUMOTO, M. Med. Sci.	
Postgraduate Student	Junya KAWADA	(～March 31, 2008)

The purpose of our research group is to elucidate the molecular mechanisms of chromosome instability by using human cell lines from the patients with cancer-prone genetic disorder. We are studying the molecular basis of the radiation-hypersensitive genetic disorders, including NBS, AT, LIG4 syndrome, Seckel syndrome, and hyper-IgM syndrome. We are also studying the molecular mechanism of chromosome segregation, using the cells with premature chromatid separation (PCS) syndrome patients. These studies will be useful to uncover the regulation of the cell-cycle checkpoints and DNA double strand break repair. Following research projects were carried out during the fiscal year of 2006.

1. Genetic and functional analysis of cancer-prone genetic disorder, PCS syndrome.
2. Isolation of the gene that regulates the inhibition of centrosome re-duplication.
3. Analysis of radiation-induced TopBP1 focus formation.
4. Molecular analysis of the cells from the patients with Seckel syndrome.

Research projects

1. Genetic and functional analysis of cancer-prone genetic disorder, PCS syndrome.

Kawada, J., Matsumoto, Y. Izumi, H., Suda, T., Ikeuchi, T. (Tokyo Med. Dent. Univ.), Kajii, T. (Hachioji), Matsuura, S.

A chromosomal instability syndrome of premature chromatid separation (PCS syndrome) is a mitotic-spindle checkpoint disorder, characterized by “mosaic variegated aneuploidy (MVA)” and “premature chromatid separation (PCS)”. We found that PCS syndrome patients were compound heterozygote for a null mutation and a cryptic hypomorphic mutation, and had reduced level of BubR1 protein, less than 50% of normal control. This is the first demonstration to confirm functionally that BubR1 insufficiency is the cause of abnormal mitotic checkpoint in PCS syndrome. We are trying to identify the BubR1 mutation that results in reduced protein expression. We performed chromosomal and SNPs-chip analysis in Wilms tumor and rhabdomyosarcoma samples from two PCS patients. Hyperdiploidy with uniparental disomy of chromosome 11 was detected in all the samples, suggesting that chromosome instability directly involved in carcinogenesis of PCS syndrome patients.

2. Isolation of the gene that regulates the inhibition of centrosome re-duplication.

Izumi H., Matsumoto, Y., Matsuura S.

Centrosome is a small nonmembranous organelle, consisting of a pair of centrioles and a number of different proteins surrounding the centriole pair, which localizes at nearby nucleus in animal cells. In interphase cell, centrosome functions as microtubule organizing center (MTOC) that stabilizes cell polarity. In mitotic phase, centrosome plays a key role in establishing bipolar spindle, which is essential for equal segregation of chromosomes into two daughter cells. Centrosome duplication occurs at G1/S transition and must do only once in a single cell cycle. Dysfunction of such control mechanism results in abnormal number of centrosomes (centrosome amplification). The presence of amplified centrosomes leads to in high frequencies of aberrant mitotic spindle formation, which in turn increases the unequal segregation of chromosomes, resulting in chromosome instability. It is reported that normal cells dominantly inhibit centrosome re-duplication. However, the centrosome re-duplication mechanism is still enigma. We analyzed the frequency of centrosome re-duplication in mouse A9 hybrid cells, and found that a transfer of some specific human chromosomes suppressed centrosome re-duplication in a series of mouse A9 cells. Now, we are narrowing down the candidate chromosomal regions by a technique of radiation hybrid mapping.

3. Analysis of radiation-induced TopBP1 focus formation.

Morishima, K., Kobayashi, J. (Kyoto Univ.), Komatsu, K. (Kyoto Univ.), Tauchi, H. (Ibaraki Univ.), Matsuura, S

Human TopBP1 shares sequence homology with Cut5/Rad4 identified in fission yeast, suggesting that TopBP1 is involved in damaged DNA repair and DNA replication. Recently, we found that formation of TopBP1 foci was significantly inhibited in AT cells or in the cells with an NBS1 phosphorylation mutant. On the other hand, NBS1 focus formation was not affected in the TopBP1 siRNA cells. We also found that the TopBP1 siRNA cells showed a high frequency of premature chromatin condensation (PCC), which is a hallmark of ATR deficient cells. These results suggested that TopBP1 localizes to damaged DNA in a manner of ATM/NBS1 dependence and regulates ATR activity.

4. Molecular analysis of the cells from the patients with Seckel syndrome.

Matsumoto, Y., Izumi, H., Matsuura, S.

Seckel syndrome is an autosomal recessive disorder of bird-like facial appearance, severe microcephaly, severe proportionate short stature, and severe developmental delay. The ATR or PCNT gene is mutated in some individuals with Seckel syndrome. We found that two out of five Japanese patients had mutations in Mre11 gene. A 6-year-old boy had biallelic splice site mutations, and a 33-year-old man had a missense and a splice site mutation in the Mre11 gene. There was a marked decrease in the levels of Mre11, Nbs1 and Rad50 in the two patients cells. The patents'cells showed hypersensitivity to ionizing radiation. The cells also showed increased numbers of centrosomes during interphase, suggesting dysregulation of centrosome re-duplication. Our data demonstrated that mutation of the Mre11 gene is responsible for Seckel syndrome.

List of Contributions

A. Original Papers

1. Haruta, M.*[1], Matsumoto, Y., Izumi, H., Watanabe, N., Fukuzawa, M.*[2], Matsuura, S., Kaneko, Y.*[1,2] (*[1]Res. Inst. Clin. Oncol., Saitama Cancer Ctr., *[2]Japan Wilms Tumor Study Group): Combined BubR1 protein down-regulation and RASSF1A hypermethylation in Wilms tumors with diverse cytogenetic changes. Mol Carcinog (in press) （Ⅰ）

2. Saito, T.*[1], Hama, S.*[1], Izumi, H., Yamasaki, F.*[1], Kajiwara, Y.*[1], Matsuura, S., Morishima, K., Hidaka, T.*[1], shrestha, P.*[1], Sugiyama, K.*[1], Kurisu, K.*[1] (*[1]Dept. Neurosurgery, Hiroshima Univ.): Centrosome amplification induced by survivin suppression enhances both chromosome instability and radiosensitivity in glioma cells. Br J Cancer 98, 345-355, 2008（Ⅰ）

3. Morishima, K., Sakamoto, S.*[1], Kobayashi, J.*[1], Izumi, H., Suda, T., Matsumoto, Y., Tauchi, H.*[2], Ide, H.*[3], Komatsu, K.*[1], Matsuura, S. (*[1]RBC, Kyoto Univ., *[2]Dept. Environ. Sci., Ibaraki Univ., *[3]Graduate School of Sci., Hiroshima Univ.): TopBP1 associates with NBS1 and is involved in homologous recombination repair. Biochem Biophys Res Commun 362, 872-879, 2007（Ⅰ）

4. Matsuura, S., Izumi, H., Ikeuchi, T.*[1], Kajii, T.*[2] (*[1]Tokyo Medical and Dental Univ., *[2]Hachioji): PCS (MVA) syndrome: The disorder supporting the theory that aneuploidy is the cause of cancer. Jikken-Igaku 25: 2925-2931, 2007

B. Meeting Presentations

1. Hideki Izumi, Yoshiyuki Matsumoto, Tatsuro Ikeuchi*[1], Hideyuki Saya*[2], Tadashi Kajii*[3], Shinya Matsuura (*[1]Tokyo Medical and Dental Univ., *[2]Inst. Adv. Med. Res., Keio Univ., *[3]Hachioji) : BubR1 localize to centrosome and suppress centrosome amplification via regulating Plk1 activity. 52nd Annual Meeting of the Japan Society of Human Genetics. September 12-15, 2007 Tokyo（G）

2. Hideki Izumi: Cancer-prone PCS syndrome: the abnormal chromosome segregation and centrosome amplification. 59th Annual Meeting of Chromosome Research Society and 17th Chromosome Colloquium. November 26-28, 2007 Kanagawa (invited)

3. Kenta Iijima*[1], Chizuko Muranaka*[1], Junya Kobayashi*[2], Shuichi Sakamoto*[2], Kenshi Komatsu*[2], Shinya Matsuura, Hiroshi Tauchi*[1] (*[1]Dept. Environ. Sci., Ibaraki Univ., *[2]Rad. Biol. Center, Kyoto Univ.): Regulation of DNA damage-induced apoptosis by NBS1 protein 30th Annual Meeting of the Molecular Biology Society of Japan. December 11-15, 2007 Yokohama

4. Junya Kobayashi*[1], Shuichi Sakamoto*[1], Kenichi Morishima, Kenta Iijima*[2] , Shinya Matsuura, Hiroshi Tauchi*[2], Kenshi Komatsu*[1] (*[1]Rad. Biol. Center, Kyoto Univ., *[2]Dept. Environ. Sci. Ibaraki Univ.): Role of NBS1 and ATM in DNA double-strand break repair. 30th Annual Meeting of the Molecular Biology Society of Japan. December 11-15, 2007 Yokohama

5. Hideki Izumi, Yoshiyuki Matsumoto, Tatsuro Ikeuchi*[1], Hideyuki Saya*[2], Tadashi Kajii*[3], Shinya Matsuura (*[1]Tokyo Medical and Dental University, *[2]Keio University, *[3]Hachioji): BubR1 localizes to centrosomes and suppresses centrosome amplification via regulating Plk1 activity in interphase cell 30th Annual Meeting of the Molecular Biology Society of Japan. December 11-15, 2007 Yokohama（G）

6. Hideki Izumi, Yoshiyuki Matsumoto, Tatsuro Ikeuchi*[1], Tadashi Kajii*[2], Shinya Matsuura (*[1]Tokyo Medical and Dental Univ., *[2]Hachioji) : BubR1 localizes to centrosomes and suppresses centrosome amplification via regulating Plk1 activity in interphase cells. 48th Annual meeting of Research

Society for Delayed Effects of Atomic Bomb Detonation. June 3, 2007 Hiroshima（G）

7. Hideki Izumi : BuR1 localises to centrosomes and suppresses centrosome amplification via regulating Plk1 activity in interphase cells. The 2007 meeting of Kyoto University Research Reactor Institute. September 28, 2007 Osaka (invited)

8. Hiroshi Matsumoto, Yoshiyuki Matsumoto, Kenichi Morishima, Shinya Matsuura : A patient with chromosomal instability syndrome of variegated translocation mosaicism. Annual Meeting of Research Society for Helicase. November 24, 2007 Kaga（G）

9. Shinya Matsuura : Cancer-prone genetic disorders and molecular mechanisms for chromosome maintenance. 12th meeting of Research Society for Molecular carginogenesis. February 19, 2008 Yokohama (invited)

10. Hiroteru Hatsumura [*1], Akihiro Kato [*1], Shinya Matsuura, Kenshi Komatsu[*1] ([*1]Rad. Biol. Center, Kyoto Univ.) : Analysis of NBS patient's cells and Nbs1 knockout mouse cells. 50th Annual Meeting of the Japan Radiation Research Society. November 14-17, 2007 Chiba

11. Kyosuke Nakamura[*1], Shuichi Sakamoto[*1], Kenta Iijima[*2], Daisuke Mochizuki[*2], Keisuke Teshigawara[*3], Junya Kobayashi[*1], Shinya Matsuura, Hiroshi Tauchi[*2], Kenshi Komtsu[*1] ([*1]Rad. Biol. Center, Kyoto Univ., [*2]Dept. Environ. Sci. Ibaraki Univ., [*3]Lymphocyte bank Co., Ltd.) : Role of NBS1 and ATM for DNA double strand break repair. 50th Annual Meeting of the Japan Radiation Research Society. November 14-17, 2007 Chiba

12. Yuki Okamoto[*1], Hiroko Fujimoto[*1], Junya Kobayashi[*1], Shinya Matsuura, Kenshi Komatsu[*1] ([*1]Rad. Biol. Center, Kyoto Univ.) : Role of NBS1 for DNA repair against alkylating reagents. 50th Annual Meeting of the Japan Radiation Research Society. November 14-17, 2007 Chiba

13. Junya Kobayashi[*1], Shuichi Sakamoto [*1], Kenta Iijima[*2], Kenichi Morishima, Kyosuke Nakamura [*1], Shinya Matsuura, Hiroshi Tauchi[*2], Kenshi Komatsu[*1] ([*1]Rad. Biol. Center, Kyoto Univ., [*2]Dept. Environ. Sci. Ibaraki Univ.) : Roles of NBS1 and Histone-H2AX for DNA double strand break repair. 50th Annual Meeting of the Japan Radiation Research Society. November 14-17, 2007 Chiba

14. Hiromi Yanagihara[*1], Ken Tsuchida[*1], Junya Kobayashi[*1], Toshio Mori[*2], Shinya Matsuura, Kenshi Komatsu[*1] ([*1]Rad. Biol. Center, Kyoto Univ., [*2]Nara Med. Univ.) : Functional analysis of NBS1 in UV-induced DNA damage repair. 50th Annual Meeting of the Japan Radiation Research Society. November 14-17, 2007 Chiba

15. Shinya Matsuura, Hideki Izumi, Yoshiyuki Matsumoto, Tatsuro Ikeuchi[*1], Hideyuki Saya[*2], Tadashi Kajii[*3] ([*1]Tokyo Med.& Dent. Univ., [*2] Inst. for Advanced Med. Res. Keio Univ., [*3]Hachiohji) : Dual roles of BubR1-the underlying protein for cancer-prone PCS syndrome-in chromosome segregation. 66th Annual Meeting of the Japanese Cancer Association. October 3-5, 2007 Yokohama (invited) （G）

16. Hideki Izumi, Yoshiyuki Matsumoto, Tatsuro Ikeuchi[*1], Hideuki Saya[*2], Tadashi Kajii[*3], Shinya Matsuura ([*1]Tokyo Med. & Dent. Univ., [*2]Inst. Adv. Med. Res., Keio Univ., [*3]Hachioji) : BubR1 localizes to centrosomes and suppresses centrosomes amplification via regulating Plk1 activity in interphase cells. 66th Annual Meeting of the Japanese Cancer Association. October 3-5, 2007 Yokohama（G）

17. Ahikiro Kato[*1], Hiromi Yanagihara[*1], Shinya Matsuura[*2], Tstsuo Noda[*3], Kenshi Komatsu[*1] ([*1]RBC, Kyoto Univ., [*2]Dept. Rad. Biol., RIRMB, Hiroshima Univ., [*3]Dept. Cell Biol., The JFCR-Cancer

Inst.): Domain analysis of the Nbs1 gene in murine cells. 66th Annual Meeting of the Japanese Cancer Association. October 3-5, 2007 Yokohama

18. Hiroshi Tauchi[*1], Junya Kobayashi[*2], Shuichi Sakamoto[*2], Shinya Matsuura, Kenshi Komatsu[*2] ([*1]Dept. Environ. Sci., ibaraki Univ., [*2]Rad. Biol. Ctr., Kyoto Univ., RIVRBM, Hiroshima Univ.): NBS1 is required for DNA damage-induced apoptosis. 66th Annual Meeting of the Japanese Cancer Association. October 3-5, 2007 Yokohama

19. Shinya Matsuura, Hideki Izumi, Yoshiyuki Matsumoto, Tatsuro Ikeuchi[*1], Hideyuki Saya[*2], Tadashi Kajii[*3] ([*1]MRI, Tokyo Med. Dent. Univ., Tokyo, [*2]IAMR, Keio Univ., Tokyo, [*3]Hachioji) : BubR1 deficiency causes centrosome amplification in PCS (MVA) syndrome. 57th Annual Meeting of the American Society of Human Genetics. October 23-27, 2007 San Diego (concurrent platform sessions) （G）

20. Hideki Izumi, Yoshiyuki Matsumoto, Tatsuro Ikeuchi[*1], Saya Hideyuki[*2], Tadashi Kajii[*3], Shinya Matsuura ([*1]Tokyo Med. Dent. Univ., [*2]Inst. Adv. Med. Res., Keio Univ., [*3]Hachioji): New role of BubR1: BubR1 localizes to centrosomes and suppresses centrosome amplification via regulating Plk1 activity in interphase cells. The Fifth International Symposium, Radiation and Cancer, Hiroshima, January 23-24, 2008（G）

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