

## Meeting report

# "Challenge to Conquer Cancer—New Trends in Mutation Research" JEMS Open Symposium 2011

Tatsuo Nunoshiba<sup>1,5</sup>, Isao Kuraoka<sup>2</sup>, Yuko Ibuki<sup>3</sup> and Issay Narumi<sup>4</sup>

<sup>1</sup>International Christian University, Tokyo, Japan

<sup>2</sup>Graduate School of Engineering Science, Osaka University, Osaka, Japan

<sup>3</sup>Graduate School of Nutrition and Environmental Science, University of Shizuoka, Shizuoka, Japan

<sup>4</sup>Quantum Beam Science Directorate, Japan Atomic Energy Agency, Gunma, Japan

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Conquering cancer is one of the most crucial missions for researchers of environmental mutagenesis and carcinogenesis. One effective approach to understanding carcinogenesis involves elucidating how mutations are fixed from DNA lesions induced by environmental mutagens and carcinogens and how DNA polymerases and intracellular functions related to these polymerases are involved in the mutation fixation. These are rather old-fashioned but still critical questions that should be clarified. Recent analyses using novel molecular biology and genome epidemiology techniques could be powerful weapons to make open this "black box." Seven scientists who were working to elucidate the molecular mechanisms for environmental mutagenesis and carcinogenesis were invited to the Public Symposium of the Japanese Environmental Mutagen Society (JEMS) held on May 28, 2011; they discussed the aims of mutation research in the next generation to conquer cancer.

**Key words:** translesion DNA polymerase, post-replication repair, lesion bypass, Hsp90, genome-wide association study (GWAS)

Conquering cancer is one of the most crucial missions that should be immediately accomplished by researchers of environmental mutagenesis and carcinogenesis to solve this serious worldwide health problem. One important approach to understanding carcinogenesis involves elucidating how mutations are fixed from DNA lesions induced by environmental mutagens and carcinogens and how DNA polymerases and intracellular functions in which these polymerases participate are involved in the mutation fixation. These are long-term crucial questions that have lingered since we first faced this health problem. Therefore, these would be rather old-fashioned but still critical questions that should be clarified. Since the advent of novel molecular biology to genome analysis techniques, we have been able to disclose various enzymes and functions that contribute to genome integrity and mutation fixation. For example,

during this decade, a number of DNA polymerases have been found in various model biological organisms ranging from bacteria to humans. DNA polymerases that stimulate the mismatched incorporation of bases opposite damaged bases, the so-called translesion (Y-family) polymerases (1), have recently been identified. Understanding the action of these translesion DNA polymerases and their regulation could be a clue for elucidating carcinogenesis.

The Public Symposium of the Japanese Environmental Mutagen Society (JEMS), entitled "Challenge to Conquer Cancer: New Trend in Mutation Research," was held on May 28, 2011, at the Shiba Kyoritsu Campus of Keio University in Tokyo. At this symposium, JEMS President Dr. Yamazoe gave a short opening speech, Dr. Kuraoka (Osaka University) delivered the introduction, and 3 sessions were presented by the 7 invited scientists. The symposium program has been reproduced below:

Yasushi Yamazoe (President of JEMS, Tohoku University): Opening Speech

Isao Kuraoka (Osaka University): Introduction

Session I (Chaired by Isao Kuraoka)

- Takehiko Nohmi (National Institute of Health Science): Mutation induced by environmental mutagens—Roles of translesion DNA polymerases
- Masanobu Kawanishi (Osaka Prefecture University): Molecular mechanisms of mutation induction by polyaromatic hydrocarbons—Structure of DNA lesions and mutagenesis

Session II (Chaired by Issay Narumi)

- Chikahide Masutani (Nagoya University): Regulation mechanisms for Pol $\eta$  encoded by the XPV gene
- Yuji Masuda (Hiroshima University): Regulation of

<sup>5</sup>Correspondence to: Tatsuo Nunoshiba, International Christian University, 3-10-2 Osawa, Mitaka, Tokyo 181-8585, Japan. Tel: +81-422-33-3723, E-mail: nunoshiba@icu.ac.jp

post-replication repair pathways—Through biochemical analysis on the ubiquitination of PCNA

- Yasukazu Daigaku (University of Sussex): The study of mutagenesis in *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*—Timing of DNA lesion bypass and its regulation

#### Session III (Chaired by Yuko Ibuki)

- Takayuki Yamashita (Gunma University): Regulation of replication stress response by molecular chaperone Hsp90
- Takashi Kohno (National Cancer Institute): Genetic polymorphisms on human cancer—Impacts of large scale genome-wide studies on environmental mutagenesis and cancer treatment

Tatsuo Nunoshiba (Chair of the planning committee, JEMS, International Christian University): Closing speech

Dr. Nohmi focused on determining which types of DNA polymerases were involved in mutagenesis induced by environmental mutagens (2). Dr. Nohmi pointed out the important roles of Y family DNA polymerases on mutagenesis based on *in vivo* mutation analysis using *Salmonella* strains deficient in different DNA polymerases and *in vitro* analysis for the incorporation of oxidative nucleotides by various DNA polymerases.

Dr. Kawanishi reported the molecular mechanism of mutations induced by polyaromatic hydrocarbons, particularly 3-nitrobenzanthrone (3-NBA) (3). Dr. Kawanishi analyzed DNA adducts in a human cell line treated with 3-NBA and identified 3 different DNA adducts, dG-(N2-C2)-ABA predominantly, and also found that repair of this adduct occurred more slowly than the others. He then site-specifically introduced these adducts into the target gene for mutation analysis and analyzed inhibition of DNA synthesis and induced mutations resulting from translesion synthesis (TLS). Based on these analyses, Dr. Kawanishi discussed the molecular mechanism of mutation fixation from DNA adducts produced by polyaromatic hydrocarbons.

Dr. Masutani proposed that TLS by human DNA polymerase Pol $\eta$  encoded by the XPV gene, which is responsible for the xeroderma pigmentosum variant, was involved in the prevention of carcinogenesis (4). In addition, recent research indicated that Pol $\eta$  interacted with several proteins involved in TLS, DNA replication, and DNA repair, and that interaction of Rev1 with Pol $\eta$  stimulated localization of Rev1 on damaged DNA sites and then prevented spontaneous mutagenesis. Based on these analyses, Dr. Masutani discussed the mechanisms of regulating TLS mediated by interaction of Pol $\eta$  with other proteins and post-translational modification of Pol $\eta$ .

Dr. Masuda proposed a study on the mechanism of post-replication repair (PRR). He described two path-

ways of PRR: TLS tightly related to mutagenesis, in which nucleotides were frequently misincorporated opposite a DNA lesion and extended DNA synthesis; and template switching (TS) with high fidelity, an error-free pathway mediated by insertion of a daughter strand into the strand with stalled synthesis by the DNA lesion. Through *in vitro* reconstitution of PRR using purified proteins, Dr. Masuda identified a novel mechanism for the polyubiquitination of the proliferating cell nuclear antigen (PCNA) and then discussed the roles of this polyubiquitination on the regulation of TLS and TS (5).

Dr. Daigaku proposed how the ubiquitination of PCNA was involved in regulation of normal replicative DNA synthesis and TLS and how these functions regulated mutagenesis using genetic analysis in *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*. In eukaryotes, DNA lesion bypass is induced by PCNA ubiquitination, which occurs at the site of the stalled replication fork. However, Dr. Daigaku recently found that even after DNA replication, the gap produced during replication at a DNA lesion could be filled in *Saccharomyces cerevisiae* (6). In addition, Dr. Daigaku also found that in the S phase of *Schizosaccharomyces pombe*, PCNA was ubiquitinated independent of the DNA lesion. Based on these new findings, Dr. Daigaku discussed how DNA lesion bypass and DNA replication were regulated by PCNA ubiquitination and how this regulation was involved in mutagenesis.

Dr. Yamashita reported that translesion DNA polymerases, particularly Pol $\eta$  and REV1, were regulated by heat shock protein Hsp90, which—even in non-stress conditions—provided quality control for proteins such as receptors and protein kinases, whose functions were tightly involved in cell proliferation (7). Based on these findings, Dr. Yamashita discussed the important roles of Hsp90 on the regulation of the replicative stress response as well as the possibility of an Hsp90 inhibitor for cancer treatment.

Dr. Kohno finally reported one example of a new type of cancer research by using a newly developed technique, a genome-wide association study (GWAS), which could detect genetic polymorphisms (8). Using GWAS, certain genes involved in the metabolism of carcinogens containing cigarette smoke and in DNA repair function have been identified as candidates for genes prescribed to risk of lung cancer. A newly developed high-speed DNA sequencing technique has also provided whole genome DNA sequences from various patients with lung, breast, skin, and liver cancers as well as healthy persons to indicate the somatic mutations specific to each cancer. Based on these examples, Dr. Kohno discussed the validity of these new techniques for cancer research including its prevention, diagnosis, and treatment.

More than 110 scientists researching mutagenesis and

carcinogenesis attended this symposium to listen to presentations, exchange new information, and actively discuss the current state of research. Most of the presentations and discussions have been summarized as review articles in this special issue of *Genes and Environment* edited by Tatsuo Nunoshiba, the planning committee chair, and Isao Kuraoka, the symposium organizer.

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