Possible role of WRN protein in low dose of DNA damage-induced cellular response

J. Kobayashi[a,*], M. Okui[b], K. Komatsu[a] and D. J. Chen[c]

[a] *Radiation Biology Center, Kyoto University, Kyoto 606-0025 Japan*

[b] *Biomedical Engineering Center, Toin University of Yokohama, Yokohama 225-8502, Japan*

[c] *University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390-9187, USA*

Ionizing radiation (IR) generates DNA double-strand breaks (DSBs) in genome DNA. Low energy of β-ray by tritium decay could generate a small amount of DSBs or cause stall of DNA replication (replication stress). As remain of such DNA damage might lead to mutagenesis or cell death, cells repair DNA damage immediately. Werner syndrome (WS) is an autosomal recessive disorder associated with premature aging and cancer predisposition caused by mutation of WRN gene. Several recent reports suggest that accumulation of DNA damage could lead to premature cellular aging. Therefore, WRN may function in DNA damage response and be important for the repair of DNA damage induced by tritium. Here, we investigated the role of WRN in DNA repair and genome integrity.

WRN rapidly accumulated at DNA damage sites and formed discrete nuclear foci. DNA damage-dependent focus formation of was detected only during S phase, but not in G1 phase. WRN-defective WS cells showed the spontaneous accumulation of γ-H2AX (DSB marker) and DNA polymerase eta foci. WS cells also showed the spontaneous ubiquitination of PCNA, which is essential to translesion DNA synthesis (TLS) by DNA polymerase eta. Further, WS cells displayed the interaction between PCNA and Rad18 E3 ligase without DNA damage. Furthermore, WRN interact with PCNA without DNA damage, but the generation of DNA damage let WRN dissociate from PCNA, suggesting that WRN dissociation might be important for PCNA ubiquitination. Taken together, WRN could participate DNA polymerase eta-related TLS pathway through regulation of PCNA ubiquitination. WRN may work in tritium-induced replication stress or subsequent DNA damage response via TLS pathway.