Title of Research:

16_PT01-01

Establishment of a comprehends test for identifying mutagenic chemical compounds and molecular mechanisms underlying mutagenesis

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Summary of Research:

(1) Creation of TK6 cells deficient in individual DNA repair proteins

The OECD countries have employed the human TK6 B lymphoid cells as a standard cell line for evaluating the genotoxicity of industrial chemical compounds. However, quick accurate repair of DNA damage induced by chemicals in DNA-repair proficient TK6 cells significantly limits the sensitive identification of mutagenic chemicals. To overcome this problem, we have disrupted genes encoding various DNA repair factors and shown the list of 119 DNA-repair mutants generated from TK6 cells in the web site (http://www.nihs.go.jp/dgm/tk6.html). The DNA-sensitivity profile of various DNA-repair mutants to given chemicals would allow for assessing the type of DNA lesion induced by them.

(2) Analysis of molecular mechanisms for mutagenesis induced by nucleoside analogs

Nucleoside analogs have been used for anti-viral and cancer therapies. We created a bioassay for comprehensively analyzing various mechanisms for mutagenesis caused by nucleoside analogs. This analysis will be published in *OncoTarget.*

(3) Establishment of micro nucleus (MN) assay using DNA repair deficient TK6 cells

We established XRCC1-deficient (*XRCC1*$^{-/-}$) TK6 cells, and conducted the MN assay using typical DNA damaging agents, such as X-rays and mitomycin-C. MN analyses with *XRCC1*$^{-/-}$ cells showed several times higher sensitivity than conventional MN analyses with wild-type TK6 cells.

(4) Generation of *XPA*$^{-/-}$*/XRCC1*$^{-/-}$ TK6 cells

We created *XPA*$^{-/-}$*/XRCC1*$^{-/-}$ TK6 cells.

Timeline:

March 1, 2016-

Topics:

ICCA-LRI and NIHS Workshop, “Establishment of method of characterizing DNA lesions caused by industrial chemical compounds”

Publications:

Masataka Tsuda, Kazuhiro Terada, Masato Ooka, Koji Kobayashi, Hiroyuki Sasanuma, Ryo Fujisawa, Toshiki Tsurimoto, Junpei Yamamoto, Shigenori Iwai, Kei Kadoda, Remi Akagawa, Shar-yin Naomi Huang, Yves Pommier, Julian E. Sale, Shunichi Takeda, and Kouji Hirota.
“The Dominant Role of Proofreading Exonuclease Activity of Replicative Polymerase □ in Cellular Tolerance to Cytarabine (Ara-C).” *Oncotarget (in press)*
(The first author belongs to Takeda lab.)