【Grant-in-Aid for Scientific Research (S)】

Integrated Disciplines (Environmental Science)

Title of Project : Mechanism of Genome Integrity Maintenance in Tissue Stem Cell

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Research Area : Biological Effects of Radiation and Chemicals
Keyword : Damage Response

【Purpose and Background of the Research】

Maintenance of genome integrity is crucial for all organisms. However genome stability is continuously challenged by a diverse array of mutagenic forces. To maintain the genome integrity several mechanisms have evolved. Multiple DNA repair pathways minimize the mutagenic consequences of DNA damage and erroneous DNA replication. Cell cycle checkpoint assures the efficient elimination of errors during DNA replication and chromosome segregation. Apoptosis is the most effective way to eliminate potentially deleterious cells carrying DNA damage. Each process has been well characterized at molecular level. However, how each process contributes to the induction of genome instability is still unclear. In this study we will clarify the role of each process on mutagenesis.

Another important issue for the study of damage response is the type of target cell. Tissues of our body consist of heterogenous population of cells, which include slowly dividing stem cells, extensively proliferating cells and differentiated function cells. Communication between these cells and the niche surrounding the stem cell play an important role on the maintenance of each tissues as well as the damage response. Among these cells, tissue stem cell is exceptional because it stays on the tissue for long time, and thus has strong impact on the late effects of genome damage, carcinogenesis and aging. In this study we will focus on tissue stem cells, and damage response in these cells will be studied *in vitro* and *in vivo*. Culture cell provides a uniform population of cells, thus suitable for the precise study of the gene function. On the other hand, *in situ* study of cell in tissue provides a lot of information about cell-cell interaction. In this study, we use rat mesenchymal stem cell or tissues of small fish medaka *Oryzias latipes* as *in vitro* or *in vivo* system, respectively.

【Research Methods】

Basic tool for the present study is genome analysis by Next Generation Sequencer (NGS). Rapid progress in NGS diffusion enables a direct approach to the genome stability. Rearrangement induced *in vitro* and/or *in vivo* cells will be determined by NGS. Another novel approach is mosaic analysis. The mosaic tissue, consisting of cells in which gene of the interest is either on or off, will provide a system for precise analysis of gene function. Two methods will be used for establishing mosaic tissues, IR-Lego (Infrared laser-Evoked Gene Operator) and transposon mediated efficient trans-genesis.

【Expected Research Achievements and Scientific Significance】

Maintenance of genome integrity is indispensable for the tissue stem cells. This study will clarify the nature of damage response expressed in stem cells. Another expected result is the quality control of stem cells. Recently stem cell competition has been noticed as a stem cell quality control system. Whether or how this system play a role on damage response will be clarified.

【Publications Relevant to the Project】

・Kamei Y, Suzuki M, Watanabe K, Fujimori K, Kawasaki T, Deguchi T, Yoneda Y, Todo T, Takagi S, Funatsu T, Yuba S. Infrared laser-mediated gene induction in targeted single cells in vivo. *Nature Methods*. (2009) 6(1):79-81.
・Ishikawa T, Kamei Y, Otozai S, Kim J, Sato A, Kuwahara Y, Tanaka M, Deguchi T, Inohara H, Tsujimura T, Todo T. High-resolution melting curve analysis for rapid detection of mutations in a Medaka TILLING library. *BMC Mol Biol.* 2010 15;11(1):70

【Term of Project】 FY2015-2019

【Budget Allocation】 153,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.med.osaka-u.ac.jp/pub/radbio/www/index.html