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

Biological Sciences (Medicine, dentistry, and pharmacy)

Title of Project : Integrative study for functional analyses of stem cell maintenance factors and visualization of stem cells

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Research Area : Medicine

Keyword : Cell proliferation and death

【Purpose and Background of the Research】

Purification and characterization of tissue stem cells are not successful at present, except hematopoietic, nervous, and intestinal systems. Identification of tissue stem cells is essential not only for the functional analysis of these cells but also for studies of cancer stem cells. We have studied hematopoietic stem cells as well as leukemia-initiating cells and found that three conditions (low proliferation, low metabolism, and low oxidation) are required for the maintenance of stem cell function.

We identified p57, Fbw7, and Fbxl5 in hetatopoietic stem cells as key factors that are responsible for low proliferation, low metabolism, and low oxidation, respectively. We thus hypothesized that these three factors might also be essential commonly for all tissue stem cells in the body. To validate our hypothesis, we would propose to examine the expression of p57, Fbw7, and Fbxl5 carefully in many tissues and to generate mice lacking one of these factors in tissue stem cells.

Furthermore, we plan to visualize all tissue stem cells by monitoring the expression of these three factors. Identification and characterization of tissue stem cells will contribute to the establishment of fundamentals for regenerative medicine.

【Research Methods】

In stem cells of many tissues, we will investigate the expression pattern of p57, Fbw7, and Fbxl5. We will next study the status of cell proliferation, metabolism, and oxidation in a various tissue stem cells prepared from conditional knockout mice for p57, Fbw7, and Fbxl5. Cis-elements that is integral to the gene expression in the promoter region of p57, Fbw7, and Fbxl5 will be identified, and tras-elements that bind to the identified cis-elements will also studied in depth. Both cis- an trans-elements will be evaluated for the impact on the function and maintenance of the tissue stem cells. We will generate knockin mice or transgenic mice that can monitor the expression of p57, Fbw7, or Fbxl5 to visualize tissue stem cells in the mice.

On the other hand, lineage-tracing experiments will be carried out with the use of these genetically engineered mice.

【Expected Research Achievements and Scientific Significance】

Identification and characterization of all tissue stem cells in mice will lead to understanding the mechanisms by which tissue stem cells in human are maintained and to the establishment of medical application.

Understanding of the mechanisms how normal stem cells are maintained is also important for anti-cancer therapy, given that cancer stem cells are thought to share many characteristics with normal stem cells and that cancer stem cells are resistant to anti-cancer drugs or gamma-ray irradiation. Such resistance of cancer stem cells to genotoxic insults will be explained by the hidden mechanisms underlying stem cell maintenance.

【Publications Relevant to the Project】

- Takeishi, S., et al., Nakayama, K. I.: Ablation of Fbxw7 eliminates leukemia-initiating cells by preventing quiescence. ***Cancer Cell***, 23: 347-361 (2013).
- Matsumoto, A., et al., Nakayama, K. I.: p57 is required for quiescence and maintenance of adult hematopoietic stem cells. ***Cell Stem Cell***, 9: 262-271 (2011).
- Moroishi, T., et al., Nakayama, K. I.: The FBXL5-IRP2 axis is integral to control of iron metabolism in vivo. ***Cell Metab.***, 14: 339-351 (2011).

【Term of Project】 FY2013-2017

【Budget Allocation】 166, 500 Thousand Yen

【Homepage Address and Other Contact Information】

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