課題番号（Project number）31

Roles of KEAP1-NRF2 system in long-term hematopoietic stem cells

［1］組織（Research group）
代表者（Principal Investigator (PI)）：
Paul-Henri Romeo
(Inserm, France)
対応者（Host researcher at IDAC）：
Hozumi Motohashi
(IDAC Tohoku University)

研究費（Expenditure report of research funds）：
Travel cost, 370,074 YEN
Consumables, 23,969 YEN,
Charge for IDAC Research Core, 5,957 YEN,

［2］研究経過（Research setup）
KEAP1-NRF2 system plays a central role in the defense mechanisms against oxidative and xenobiotic stresses. We recently found that long-term hematopoietic stem cells (LT-HSCs) are very sensitive to low dose irradiation, and clarified that generation of oxidative stress is the major cause of the loss of LT-HSCs after the low-dose irradiation rather than provoking DNA damage. We also found that, in LT-HSCs, NRF2 accumulation is triggered after the low-dose irradiation and that NRF2 target genes are induced, suggesting that NRF2 contributes to the protection of the LT-HSCs from the low-dose irradiation-induced oxidative stress. Based on these results, we aimed at testing whether constitutive enhancement of NRF2 activity in LT-HSCs is beneficial for maintaining the stemness and delay the senescent phenotype of LT-HSCs. Our goal is to establish a new therapeutic target for the prevention of tissue damage, particularly loss of tissue stem cells, from low-dose irradiation.

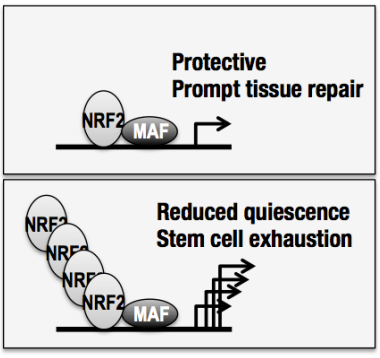
To achieve this goal, I visited Prof. Motohashi's lab last May and had intensive discussion with her lab members.

［3］成果（Research outcomes）
（3－1）研究成果（Results）
We clarified that LT-HSCs are hypersensitive to low-dose irradiation and that the hypersensitivity is not associated with DNA damage but with increase in the reactive oxygen species (ROS) levels. The low dose irradiation induced NRF2, which is beneficial for the protection of LT-HSCs.

On the side of Prof. Motohashi's group, they examined LT-HSCs in which NRF2 is genetically activated by disruption of *Keap1*. They found that continuous activation of NRF2 by *Keap1* disruption expands progenitor population and promotes cell cycle entry of LT-HSCs in steady state hematopoiesis, and impairs bone marrow reconstitution ability of LT-HSCs in hematopoietic regeneration.

These results suggest that appropriate control of NRF2 by KEAP1 is essential for protecting LT-HSCs from oxidative damages and saving LT-HSCs by avoiding unnecessary activation and differentiation.

（３－２）波及効果と発展性など（Future perspectives）
Outcomes of this joint research will establish a new concept regarding the environmental response of LT-HSCs and their aging phenotypes that develop after repetitive exposure to the environmental stresses.



［4］成果資料（List of Papers）

（1）Shohei Murakami, Takuma Suzuki, Paul-Henri Romeo, Masayuki Yamamoto, Hozumi Motohashi. NRF2 activation impairs quiescence and bone marrow reconstitution capacity of hematopoietic stem cells. Submitted.

（2）Shohei Murakami, Hozumi Motohashi. Recent advances in elucidating KEAP1-NRF2 functions in hematopoietic/immune cells and leukemic cells. Rinsho Ketsuoki 57, 1860-1868, 2016.

（3）Shohei Murakami, Masayuki Yamamoto, Hozumi Motohashi. KEAP1-NRF2 function in hematopoietic stem cells. The 89th JBS annual meeting. Sendai International Conference Center, Snedai, Sep. 25-27, 2016.