Elucidation of molecular pathogenesis and therapeutic targets for refractory hematological malignancies

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【Outline of survey】

Molecular pathogenesis of refractory hematological malignancies including acute leukemia is largely unknown. It has been advocated that, as with normal hematopoiesis, hierarchical organization exists among leukemic cells that includes a rare population of leukemic stem cells (LCSc) with self-renewal capacity. Understanding the characteristics of LSCs will provide important clues to the development of targeted therapies that can cure refractory leukemia. We have revealed several functions of leukemia-associated genes, including AML1 and Evi-1, in normal hematopoiesis and leukemogenesis. Of note, these genes are involved in the self-renewal process of hematopoietic stem cells and pathogenesis of refractory leukemia, which suggests their potential roles in the regulation of LSCs. We plan to elucidate functional significance of those genes for establishment of refractory leukemia and LSCs. We will also seek to identify novel genes that contribute to the development of refractory leukemia from clinical samples.

【Expected results】

This project will reveal the functional property of LSCs and promote understanding of molecular pathogenesis of refractory leukemia. These findings will provide a basis for establishment of novel and effective targeted therapies for those diseases. Furthermore, the results from this study will help to elucidate a role for cancer stem cells in other malignancies including solid tumors.

【References】

1. Ichikawa M, Asai T, Kurokawa M, Hirai H, et al. AML-1 is required for megakaryocytic maturation and lymphocytic differentiation, but not for maintenance of hematopoietic stem cells in adult hematopoiesis. Nature Medicine 10: 299-304, 2004.
2. Kurokawa M, Mitani K, Hirai H, et al. The oncoprotien Evi-1 represses TGF-β signalling by inhibiting Smad3. Nature 394:92-96, 1998.

【Term of project】 FY2007－2011	【Budget allocation】 15,400,000 yen (2007 direct cost)

【Homepage address】 http://www.h.u-tokyo.ac.jp/hematology/