【Grant-in-Aid for Scientific Research (S)】
Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Exploring Genetic Basis of Myelodysplastic Syndromes (MDS)

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Research Area : Medicine, dentistry, and pharmacy
Keyword : Myelodysplastic syndromes, RNA splicing, Clonal evolution

【Purpose and Background of the Research】

Myelodysplastic syndromes (MDS) and related disorders are a highly heterogeneous group of chronic myeloid neoplasms, characterized by varying degrees of cytopenias and/or abnormal myeloproliferation with bone marrow dysplasia, as well as a high propensity of acute myeloid leukemia (AML). As for their pathogenesis, substantial advances have been made in our understanding of MDS pathogenesis during the past decade through identification of a number of gene mutations frequently found in MDS. Especially, the discovery of frequent mutations in RNA splicing factors by our and other groups, provide a novel clue to understand MDS pathogenesis.

The purpose of the current study is to extend these findings of recent years, obtaining a better understanding of the molecular pathogenesis of MDS. Specifically we will elucidate clonal architecture and its chronological behavior during course of MDS in terms of gene mutations especially of RNA splicing factors and understand the functional/molecular basis of these relevant mutations during the development of MDS. We will also try to identify lead compounds amenable for targeting RNA splicing factor mutations.

【Research Methods】

Combining the state-of-the-art genomics /genetics and functional studies using mice models, as well as high throughput screening of chemical compounds, we will be extensively analyzed chronological behavior of MDS clones using deep whole exome sequencing of carefully collected/fractionated MDS samples over time to reveal fine structure of MDS clones, and thereafter, we will directly tested/translated the obtained knowledge in mice model. Clonal evolution in AA patients after immunosuppressive therapies and normal population in elderly, to obtain an insight into the origin of MDS clones. Finally, we will try to screen those chemical compounds that selectively kills MDS cells having splicing factor mutations. I believe these studies will certainly contribute to substantially expand our understanding of MDS, based on which we could finally contrive better diagnostics and therapeutics for MDS patients.

【Expected Research Achievements and Scientific Significance】

Through the project, the molecular pathogenesis of MDS in terms of clonal evolution and its difference from related myeloid neoplasms will be clarified. Especially the role of RNA splicing factor mutations will be delineated. The obtained knowledge will be applied to the improvement of the management of patients with MDS.

【Publications Relevant to the Project】

・Yoshida K, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. ***Nature*** 478(7367):64-69. 2011
・ Kon A, et al. Recurrent mutations in multiple components of the cohesin complex in myeloid neoplasms. ***Nature genetics*** 45(10):1232-1237. 2013
・ Makishima H, et.al, Maciejewski JP. Somatic SETBP1 mutations in myeloid malignancies. ***Nature genetics*** 45(8):942-946. 2013
・ Haferlach T, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. ***Leukemia*** 28(2):241-247. 2014

【Term of Project】 FY2014-2018

【Budget Allocation】 149,900 Thousand Yen

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