Analysis of Methylome of Cancer by high throughput sequencer

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【Outline of survey】

Myelodysplasia syndrome(MDS) comprise of a diverse set of abnormalities in which both anamia and leukemia coexist. In most cases, MDS is discovered as anemia but eventually develop to leukemia. Currently, the radical cure of MDS is only attained by bone marrow transplantation, which is usually difficult to apply for an aged population. As its incidence increase as aging, MDS is an important problem in such rapidly aging countries as Japan. Recently, it was reported that a group of drugs that inhibit DNA methylation is effective for a significant proportion of MDS. As DNA methylation is an epigenetic mechanism to inhibit gene expression, this observation suggests that abnormal DNA methylation is involved in development of MDS. However, which genes are methylated during MDS development remains unclear. This is due to a technological difficulty in genome-wide analysis of DNA methylation in a quantitative manner. Recently, this problem was overcomed by a technology based on DNA array bearing entire human genome. Moreover, development of next-generation sequencer that allows sequencing of 10-100 milion base pars at one run is expected to boost the genome-wide analysis of epigenome. The major purpose of this project is to apply a high-throughput sequencers for genome-wide analysis of methylome of MDS cells who respond to the treatment with drugs inhibiting DNA methylation.Likewise, we will try to define tumor specific methylome of malignant melanoma cells.

【Expected results】

That some MDS patients undergoes remission in response to inhibitors of DNA methylation is the evidence for that abnormal methylation is involved in MDS development. Thus, comparison of the methylome of MDS cells and normal hematopoietic cells will allow us to define genes that are involved in MDS development. Through this analysis,

1) The oncogenic process of MDS and melanoma will be elucidated.
2) Genes that are involved in the development of these two tumors will be defined, which will lead to discovery of target molecules for tumor treatment.
3) The basic mechanisms underlying maintenance of stem cell systems will be elucidated.

【References by the principal investigator】

For all participants including the principal investigator, this is the first time of studying genome-wide epigenome of tumors. Hence, there is no papers directly related to this projects. However, the PI has been working on the developmental biology of hematopoietic and melanocyte stem cell systems. Followings are examples of contributions.

Samokhvalov, I.M., N.I. Samokhvalova, and S. Nishikawa. 2007. Cell tracing shows the contribution of the yolk sac to adult haematopoiesis. *Nature* 446:1056-1061.
Nishimura, E.K., S.A. Jordan, H. Oshima, H. Yoshida, M. Osawa, M. Moriyama, I.J. Jackson, Y. Barrandon, Y. Miyachi, and S. Nishikawa. 2002. Dominant role of the niche in melanocyte stem-cell fate determination. *Nature* 416:854-860.

【Term of project】 FY2008－2012	【Budget allocation】 148,700,000 yen (direct cost)

【Homepage address】 http://www.cdb.riken.go.jp/scb/