General Summary of Division of Functional Genomics

Division of Functional Genomics has been started at April 2007 as one of the laboratories of Molecular and Cellular Targeting Translational Oncology Center. To develop the novel target-based cancer therapeutics, a detailed knowledge of the genes and signaling pathways mutated in cancer will be required. However, the heterogeneity and complexity of genomic alterations in most human cancers hamper straightforward identification of cancer-causing mutations. We use the retrovirus-infected mice as a model system for identifying novel cancer genes efficiently. Retroviruses induce tumors through activation of proto-oncogenes or inactivation of tumor suppressor genes as a consequence of retroviral integrations into host genome. Thus the viral integration sites provide powerful genetic tags for cancer gene identification. We are exploring the novel molecular targets for cancer treatment based on functional characterization of the cancer genes isolated by high-throughput screens using retroviral insertional mutagenesis. Once these genes are identified, we use gene knockout and transgenic mice to understand how these genes function in tumorigenesis, and to develop new animal models for human cancer.

A) Identification of novel tumor suppressor genes using retroviral insertional mutagenesis in mice with genomic instability

Generally, most retroviral integrations tagged proto-oncogenes rather than tumor suppressor genes. In order to isolate tumor suppressor genes efficiently, we utilized the Bloom syndrome model mice that have a high rate of mitotic recombination and LOH so that viral integrations could be efficiently homozygous. More than 20 candidate tumor suppressor genes were isolated in the screen, and they included the known tumor suppressor genes (Rb family, Cdk inhibitors etc.) and also novel interesting candidates (JmjC domain family).

B) Involvement of protein methyltransferases and demethylases in oncogenesis

We have so far identified 17 histone methyltransferase genes and 11 histone demethylase genes as potential oncogenes or tumor suppressor genes by retroviral tagging. Among histone modifications, acetylation has been unambiguously associated with cancer, and the inhibitor of histone deacetylases has been developed as an anti-cancer drug. However, a clear correlation of histone methylation and cancer has not been conclusively demonstrated yet. Our findings provide a unique opportunity to explore the novel relationship between the regulation of protein methylation and oncogenesis.