Core Research Facilities for Basic Science (Division of Molecular Genetics)

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General Summary

We can now analyze a person's whole genome within a week. Moreover, we can sequence the whole genome from a single cell. If we could perform sequencing without considering its ethical aspects, we could predict diseases that might affect the entire life of a new born baby. These technological developments have started a new era of medicine. The etiology and therapy of disease will be studied on the basis of genetics. As physicians of today, our research fields are the epigenetic control of cancers and neurodegenerative disorders.

Research Activities

Cancer Molecular Biology

Cancers develop when mutations in specific genes accumulate in normal cells. Recent cancer research has disclosed that the disruption of epigenetic regulation in normal cells can also elicit cancers. Studying the changes of mutations in a patient's cancer during therapy, we can see how cancer cells acquire more malignant characteristics. We are studying the effects of anticancer agents on patients' cancer cells to detect mutations with the next generation of the high-throughput sequencer. We have applied this technique to a pediatric patient with double cancers, and were able to estimate the affected stem cells of both cancers. These findings will help reveal the etiology of cancer and lead to new treatments. This method was also applied for detecting genetic abnormality of mixed lineage leukemia-related leukemias, which are a group of leukemias with poor prognoses. By comparing the characteristics of several mixed lineage leukemia-related cell lines, we are studying the relation between drug-sensitivity and mutations.

Molecular pharmacology of anticancer agents

We are investigating the pharmacological actions of inhibitors (bromodomain and extra terminal inhibitor 151 [I-BET151] and JQ1) of bromodomain and extraterminal domain proteins. Proteins containing bromodomain connect transcription-related proteins to target genes through binding to acetylated histones. They also recruit disruptor of telomeric silencing-1-like histone H3 methyltransferase (DOT1L1) to facilitate the transcription of RNA-polymerase II. This megaprotein complex forms active transcriptional machinery that regulates genes for cell proliferation and survival. However, the sensitivity of leukemia cells to I-BET151 differs among cell lines. The reason, why only a few cancers are sensitive to I-BET151 remains unclear. To answer this question, we compared messenger-RNA expression patterns before and after treatment with I-BET151 in the most sensitive cell line, JAM911. We found that the genes related to the immune system were markedly down-regulated after treatment with I-BET151. We are now attempting to identify

the gene that is substantially involved in this sensitivity.
Acquisition of drug resistance by cancer cells is inevitable in clinical cancer treatment; we are studying the resistance to I-BET151 in leukemia cells. First, we established U937 cells that are 100 times more resistant to I-BET151 than are parental cells. Using the resistant cells, we are now searching among candidates for genes that are responsible for the resistance.

Molecular genetical approach to neurological diseases
The homozygous deletion and mutation of the survival of motor neuron 1 gene (*SMN1*) causes the hereditary neurodegenerative disorder, Spinal Muscular Atrophy (SMA), which is characterized by progressive loss of alpha-motor neurons in the spinal cord. Recently, we found that the translation of SMN protein is inexplicably regulated by the heterogeneous nuclear ribonucleoproteins which control protein production through several steps. One step is stabilizing the full length of SMN messenger RNA, and another step is enhancing the translation of SMN protein. As a result, SMN protein production is regulated through a highly sophisticated manner, and these findings will provide new avenues for developing drugs to treat SMA.
Alzheimer's disease (AD) is a progressive and incurable degenerative condition. We studied the genetic risk factors of AD, and found that the single-nucleotide polymorphisms of genes for brain-derived neurotrophic factor (*BDNF*) and nerve growth factor (*NGF*) are related to the progression of AD. We are now studying the DNA methylation status of the promoter region of these 2 genes. The *BDNF* promoter seems to be associated with the manifestation and clinical presentation of AD. The DNA methylation of the *BDNF* promoter may be significantly related to the manifestation of AD and might be associated with its neurocognitive presentation.

Publications

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