Institute of DNA Medicine
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General Summary

The etiology of illness is based on the relationship between individual intrinsic factors and external environmental factors. Recently, the value of genetic factors has been assessed. The genetic involvement in disease occurs through DNA alignment disorders and epigenetic deregulation. The diseases we are interested in are cancers and neurodegenerative disorders. Many approaches have been taken to overcome these intractable diseases; we are now studying these diseases from the view-point of epigentical control.

Research Activities

Cancer Molecular Biology

In the past 3 decades, the genetic analysis of cancer cells has made remarkabl progress. Cancers develop when mutations accumulate in normal cells. Our previous research disclosed many mutations in each cancer by studying candidate genes, one at a time. However, the mutations of many candidate genes can be studied at one time with the high-throughput sequencer. By applying this method for a pediatric patient with double cancer, we could speculate that an affected stem cell was the cause of both cancers. These findings will help reveal the etiology of cancer and lead to new treatments.

Molecular pharmacology of anticancer agents

We are investigating the actions of bromodomain and extraterminal domain inhibitors (I-BET151 and JQ1). Bromodomain-containing proteins attach transcription-related proteins to acetylated histones. This megaprotein complex forms a set of active transcriptional machinery that regulates genes for cell proliferation and survival. However, the sensitivity of leukemia cells to I-BET151 differs markedly among cell lines. The reason, why only a few cancers are sensitive for 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.

Molecular genetical approach to neurological diseases

The homozygous deletion and mutation of the survival motor neuron (*SMN*) 1 gene causes the hereditary neurodegenerative disorder, Spinal Muscular Atrophy (SMA), which is characterized by progressive loss of alpha-motor neurons in the spinal cord. Initially we found that the heterogeneous nuclear ribonucleoprotein (hnRNP)

A2-specific knock-down repressed SMN synthesis (but increasing full-length transcripts of SMN2 gene) rather than increasing SMN by knock-down for hnRNP A1 (also increasing full-length transcripts by enhancing exon 7 splicing). The aim of this study was to characterize the molecular mechanism of hnRNP A2 specific RNA interference-mediated SMN reduction.

With the reverse transcriptase-polymerase chain reaction (RT-PCR) and the pulse-labeling and analysis of newly synthesized RNA and proteins, we found that this regulation was controlled at the translation level. Sucrose-gradient ultracentrifuge studies showed that SMN mRNA interacted less with polyribosomes after hnRNP A2 depletion. Pull-down analysis of RNA-protein complexes by RT-PCR, matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF) and immunoblots analyses showed that hnRNP A2 directly interacted with SMN mRNA and with other RNA binding proteins, hnRNP C1/2 and M dependent on RNA binding. The RNA pull-down assay revealed the interaction between hnRNP A2 and SMN mRNA via a UUUAGG A2 binding consensus motif at 3′-UTR. Our findings define a new regulatory mechanism for controlling SMN protein production provide new insight into cellular hnRNP A2 function in translation, and suggest new avenues for developing drugs to treat SMA.

Alzheimer disease is a progressive and incurable degenerative condition. We 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 Alzheimer disease. We are now studying the epigenetic regulation of these 2 genes.

Publications

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