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General Summary

Most biological phenomena are explained as a sequence of molecular genetic events. Molecular genetics is also revealing the causes of many diseases. Based on this knowledge, clinical medicine is also markedly changing. The diseases we are focusing on are malignant tumors, including hematological and pediatric malignancies. We are also investigating spinal muscular atrophy, Alzheimer's disease, and retinal diseases. Molecular pharmacological studies of anticancer agents are another part of our research. We are investigating these subjects from the viewpoint of molecular genetics to develop new diagnostic processes and treatments.

Research Activities

Exploring hematopoietic and pediatric malignancies

Most clinical events of cancers are explained on the basis of cancer stem cell theory, which assumes cancer stem cells are at the top of a cancer hierarchy. According to the classical understanding of this theory, cancer stem cells are never replaced by other cells that belong to a group beneath stem cells. However, our data poses a question about this point. We believe that cancer cells can change their phenotype under the influence of their growth environment.

The concept of cancer stem cells was initially suggested by a study of leukemia. The existence of leukemia stem cells (LSCs) explained many clinical issues, for example, why leukemic cells can acquire resistance against intensive chemotherapies. Initially, the characteristics of LSCs were considered to resemble those of normal hematopoietic stem cells. However, it has been becoming clear that leukemic cells have high ability of plasticity. This means that leukemic cells, other than LSCs, may occasionally de-differentiate to LSCs and may even differentiate to mesenchymal cells. We are studying this plasticity using JAS-R megakaryocytic leukemia cells, which we established, by changing the culture conditions that mimic the microenvironment of bone marrow.

Molecular pharmacology of anticancer agents

Radiation and chemotherapy are the main choices for comprehensive cancer treatment. In our laboratory, we are investigating the anticancer activity of the following chemicals: telomerase inhibitors, histone deacetylase (HDAC) inhibitors, tyrosine kinase inhibitors, and DNA topoisomerase I (Top1) inhibitors.

We recently found that HDAC inhibitors were suitable agents for combination therapy with radiation and tyrosine kinase inhibitors. The dose of radiation to induce apoptosis was reduced to 20% by simultaneous treatment with HDAC inhibitors. This augmenta-

tion was due to the stabilization of p53-tumor suppressor protein through the acetylation of p53 protein. This increased acetylation of p53 seems to interfere with the binding of p53 with an ubiquitin kinase.

Top1 inhibitors are key drugs for the treatment of solid tumors, especially colon cancers. We have successfully isolated several clones resistant to SN38 (an active compound of irinotecan) and analyzed their DNA sequences. Three independent mutations of the Top1 gene were found. Each mutation site is closely related to the degree of resistance to Top1 inhibitors in colon cancer cells. To further study the relation between the mutations and resistance, the function of each mutated Top1 gene is being studied using a Top1-defective yeast.

Molecular genetic approach to neurological diseases

Spinal muscular atrophy (SMA) is a degenerative disorder leading to muscular atrophy. A mutation of survival of motor neuron 1 (SMN1) is responsible for the onset of the disease. Unlike other mammals, human beings have SMN2, a member of the same family as SMN1. It remains unclear why intact SMN2 cannot compensate for the function of SMN1 in patients with SMA. SMN2 has several nucleic acid substitutions compared with SMN1. One substitution located in exon 7 seems to play an important role in the disturbance of intact SMN2 production. The RNA-binding heterogeneous nuclear ribonucleoproteins A1 and A2 may be involved in this disturbance through the splicing and translation of SMN2. These findings may contribute to the development of new treatments for SMA.

Alzheimer's disease (AD) is an incurable degenerative disease that ultimately leads to dementia. The signs and symptoms of AD are variable, and the clinical outcome of an individual patient can be difficult to predict at disease onset. To evaluate the pathogenesis of AD more accurately, we are studying the relationship between the clinical subtypes and single nucleotide polymorphisms of brain-derived neurotrophic factor. We have recently found that a single nucleotide polymorphism of brain-derived neurotrophic factor was useful for predicting frontal lobe functional impairment during disease progression.

Publications

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