Institute of DNA Medicine
Department of Molecular Genetics

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General Summary

With molecular genetics methods, the pathogenesis of many diseases has been revealed. To identify the genes responsible for each disease opens the door to the development of new treatments. The diseases that we are focusing on are malignant tumors, including hematological and pediatric malignancies. We are also investigating the molecular etiology of spinal muscular atrophy, Alzheimer's disease, and retinal diseases. Molecular pharmacological studies of anticancer agents are another part of our research. In particular, we are investigating histone deacetylase inhibitors (HDACIs), telomerase inhibitors, and DNA topoisomerase I inhibitors.

Research Activities

Exploring leukemogenesis

Leukemic stem cells (LSCs) and the structure of the hematopoietic stem cell niche have been vigorously studied in the past decade, and many discoveries have clarified how leukemic cells acquire resistance to intensive chemotherapy. We had initially thought that the characteristics of LSCs are similar to those of normal hematopoietic stem cells. It has been become clear that leukemic cells have high plasticity. Therefore, general leukemic cells, on occasion, may de-differentiate to LSCs and may even transdifferentiate into mesenchymal stem cells.

We are attempting to confirm this plasticity of leukemic cells by using JAS-R megakaryocytic leukemia cells, which were established by us. We are now studying the plasticity of JAS-R cells by changing the culture conditions that mimic the microenvironment of bone marrow.

Molecular pharmacology of anticancer agents

Most cancers are managed with comprehensive therapeutic strategies. Radiation and chemotherapy are the main choices for medical oncologists to treat cancers. In our laboratory, we are studying the anticancer activities of telomerase inhibitors, HDACIs, and a DNA topoisomerase I inhibitors. In general, telomerase inhibitors express anticancer effects by inducing telomere shortening. For this reason, a long time is needed for a telomerase inhibitor to show anticancer effects. We used 5,10,15,20-tetrakis(*N*-methyl-4-pyridyl)porphyrin (TMPyP4) as a telomerase inhibitor. Unexpectedly, we found that TMPyP4 inhibited the telomerase activity but that its cytotoxic effects were observed within a few days without the shortening of telomeres. Instead, c-Myc was markedly downregulated in treated cells. Moreover, TMPyP4 directly induced DNA damage in treated cells. We propose that TMPyP4 has telomerase

inhibitory activity but can also induce apoptosis through the induction of DNA damage. We are also studying the anticancer effect of HDACIs. Our previous studies demonstrated that HDACIs are suitable drugs for combining with radiation. The dose of radiation to induce apoptosis of irradiated cells was reduced to 20% by simultaneous treatment with an HDACI. This augmentation 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 to an ubiquitin kinase.

Molecular genetical approach of neurological diseases

Spinal muscular atrophy is a degenerative disorder that leads to muscular atrophy. The mutation of survival of motor neuron (SMN) 1 is responsible for the onset of the disease. However, unlike other mammals, human beings have SMN2, a member of the same family as SMN1. We are studying why intact SMN2 cannot compensate for the function of SMN1 protein in patients with spinal muscular atrophy.

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 is often difficult to predict at the onset of the disease. 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.

Publications

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