Institute of DNA Medicine
Department of Molecular Genetics

Hisashi Yamada, *Professor and Director* Takeshi Kawano, *Assistant Professor*

General Summary

The fates of most cells are genetically and epigenetically regulated. Therefore, we intend to study the pathogenesis and therapy of diseases based on this knowledge. The diseases we are interested in are hematological malignancies, pediatric cancers, spinal muscular atrophy, and Alzheimer's disease (AD). We believe that these intractable diseases will eventually be conquered through the harmonization of basic science and clinical medicine.

Research Activities

Cancer Molecular Biology

Leukemia consists of 2 types of cell. One type is rapidly growing mature leukemia cells, and the other type is slowly growing leukemia stem cells. Mature leukemia cells are highly sensitive to antileukemia drugs. In contrast, leukemic stem cells are resistant to drugs and remain alive during the ordinary induction therapy, resulting in the relapse of leukemia. However, the definition of leukemia stem cells is not concrete, and leukemic cells change their phenotype under the influence of their growth environment. We are studying the mechanism of leukemic cell plasticity using JAS-R megakaryocytic leukemia cells. We have found that hypoxia and cellular attachment to the environmental matrix are critical factors for leukemic cell plasticity.

Molecular pharmacology of anticancer agents

We are investigating the action of the following anticancer agents: telomerase inhibitors, histone deacetylase inhibitors, tyrosine kinase inhibitors, and DNA topoisomerase I inhibitors. In addition, we are studying the molecular mechanism of new agents called bromodomain inhibitors. Bromodomain proteins link acetylated histones to a set of transcriptional machinery proteins that are important for initiating cell proliferation. Bromodomain inhibitors inhibit proliferation of a small number of cancers. However, why only a few cancers are vulnerable to the inhibitors remains unclear. Bromodomain inhibitors and other epigenetic modifiers may be ideal anticancer agents, because of their new mechanisms of actions and because they do not directly damage DNA. These drugs will reduce the rate of therapy-related malignancies.

Molecular genetic approach to neurological diseases

The homozygous deletion and mutation of survival motor neuron (SMN) 1 gene causes the hereditary neurodegenerative disorder spinal muscular atrophy (SMA). A nearly identical gene, SMN2, also exists but cannot prevent SMA. We have previously shown

that a single-base difference in exon 7 of SMN2 creates a heterogeneous nuclear ribonucleoprotein (hnRNP) A1/A2-dependent exonic splicing silencer and that the specific knock-down of A1/A2 in cells effectively rescues exon 7 splicing in SMN2. However, we also found that A2-specific knock-down represses SMN synthesis.

The aim of this study was the molecular characterization of the above hnRNP A2-specific RNA interference-mediated SMN reduction and to find a molecular target as the basis of a new agent for treating SMA. We found that hnRNP A2 plays a significant role in the efficient translation of SMN2 messenger (m) RNA under ubiquitous conditions. Thus, the reduction of hnRNP A2 in cells decreases this activity, such that SMN is not efficiently translated. Additionally, we propose that the hnRNP A2-binding sequence at SMN 3′-UTR functions as a translational enhancer to efficiently activate translation from SMN1/2 mRNA. Our findings define a new regulatory mechanism to control SMN protein production, provide new insights into the function of cellular hnRNP A2 in translation, and suggest a pathway to new agents for treating SMA.

AD is a progressive, degenerative disease for which there is no cure. Both patients with amnestic mild cognitive impairment and patients with mild AD show memory impairment and executive dysfunction as core symptoms. Moreover, some cases of amnestic mild cognitive impairment will eventually progress to AD. We are investigating the differences between mild AD and amnestic mild cognitive impairment by studying the single nucleotide polymorphism of brain-derived neurotrophic factor and nerve growth factor. The *BDNF* gene may significantly influence the executive function of mild AD.

Publications

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