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General Summary

Development, growth, and aging in humans are tightly controlled by genetics and epigenetics. The pathogenesis of many diseases is also thought to be a result of either a mutation of genes or a dysregulation of epigenetics. On the basis of this knowledge, clinical medicine is markedly changing. Further understanding of molecular pathogenesis will lead to more sophisticated treatment strategies. The diseases we are focusing on are hematological malignancies and pediatric cancers. We are also investigating spinal muscular atrophy (SMA), Alzheimer's disease, and retinal diseases. Molecular pharmacological studies of anticancer agents are another part of our research.

Research Activities

Exploring hematological and pediatric malignancies

Resistance of cancers to chemotherapy is explained with the cancer stem cell theory, which assumes that 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 cells lower within the hierarchy. However, our data raise a question about this point. Cancer cells may change their phenotypes because of factors of their growth environment, including exposure to chemotherapeutic drugs. From this point of view, we are studying chemoresistance as a result of the plasticity of cancer cells. Eliminating cancer stem cells is required for successful treatment. However, the plasticity of cancer cells may change their vulnerabilities. We are studying this plasticity with JAS-R megakaryocytic leukemia cells. So-called cancer stem cells may consist of variable cells that change their characteristics and chemoresistance according to their growth conditions.

Molecular pharmacology of anticancer agents

Comprehensive cancer treatment often includes radiation therapy and chemotherapy. In our laboratory, we are investigating the anticancer activity of the following chemicals: telomerase inhibitors, histone deacetylase inhibitors, tyrosine kinase inhibitors, and DNA topoisomerase I inhibitors. We have found that these agents are suitable drugs for combination treatment. In particular, drugs that modulate epigenetic regulation may be ideal basal medicines, because many cancers have mutations of genes that regulate epigenetic control. Moreover, these drugs will reduce the risk of therapy-related malignancies, because they do not directly attack genomic DNA.

Molecular genetic approach to neurological diseases

SMA is degenerative disorder leading to muscular atrophy. Mutation of the survival

motor neuron 1 (SMN1) gene is responsible for the onset of SMA. Unlike other mammals, humans also have SMN2, a member of the same family as SMN1. Why intact SMN2 cannot compensate for the function of SMN1 in patients with SMA remains unclear. Our study found that RNA-binding proteins heterogeneous nuclear ribonucleoprotein A1 and A2 are involved in this obstruction through the splicing and translation of SMN2. These findings may contribute to new treatments for SMA.

Alzheimer's disease is an incurable degenerative disease that ultimately leads to dementia. It is occasionally difficult to predict the individual disease progression at the time of disease onset. We are investigating the relationship between the clinical characteristics of Alzheimer's disease and single-nucleotide polymorphisms of brain-derived neurotrophic factor and nerve growth factor. We believe that some of these single-nucleotide polymorphisms are useful for predicting disease progression.

Publications

Yamada O[1], Ozaki K, Furukawa T[1], Machida M[1], Wang YH[1], Motoji T[1], Mitsuishi T[1], Akiyama M, Yamada H, Kawauchi K[1], Matsuoka R[1] ([1]Tokyo Women's Med Coll). Activation of STAT5 confers imatinib resistance on leukemic cells through the transcription of TERT and MDR1. *Cell Signal.* 2011; **23:** 1119-27.

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