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General Summary

Over the last few decades, many genes involved in the etiology of cancers have been found. These findings must contribute to the improvement of cancer therapy, but cancer is still the leading cause of death in Japan. Our goal is to advance cancer medicine on the basis of molecular genetics.

Research Activities

Exploring human leukemic stem cells and the development of anticancer therapy
Leukemic stem cells represent a small percentage of human leukemia cells *in vivo* but play a critical role in prognosis. In general, leukemic stem cells are resistant to chemotherapeutic drugs and support the production of leukemic cells *in vivo*. The ability of leukemic stem cells to be transferred sequentially from mouse to mouse has been demonstrated, but the genetic and biochemical natures of these cells remain largely unknown. To address these issues we first studied how the growth environment affects leukemic cells. Cells of the megakaryocytic-erythroid leukemic cell line JAS-R show a lineage shift depending on culture conditions. The interaction between fibronectin and integrin elicits the megakaryocytic phenotype and leads to the loss of erythroid characteristics in JAS-R cells. Moreover, adherent cells express CD34 and CD9, which are markers of hematopoietic stem cells. These findings demonstrate that the growth microenvironment controls the leukemic phenotype. We are now studying, by means of a microarray method, the regulatory mechanism that determines the lineage of the two groups. The results will provide useful information about the nature of leukemic stem cells and the mechanisms of chemoresistance.

Pharmacology of anticancer drugs
The telomere is a protein-DNA complex that protects the ends of double-stranded DNA. Its shortening accelerates aging and cell senescence. Generally, somatic cells do not have telomerase activity, while most cancers do. Therefore, telomerase is a promising molecular target for cancer therapy. 5,10,15,20-Tetrakis(*N*-methyl-4-pyridyl)porphyrin (TMPyP4) is a compound that binds to telomere DNA stably and tightly and blocks telomerase. Thus, we studied the anticancer activity of TMPyP4 in cells over-expressing the telomerase catalytic gene human telomerase reverse transcriptase (hTERT). A short-term growth inhibition assay showed that the anticancer activity of TMPyP4 was not related to telomerase activity, but transcriptional dysregulation of growth-related genes, including the c-Myc oncogene, might play a critical role in cell death. These finding may lead to the appropriate application of TMPyP4 as an anticancer agent.

Publications

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