Oncogene (2004) 23, 4196–4197
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www.nature.com/onc

Obituary

Oncogene (2004) **23,** 4196–4197. doi:10.1038/sj.onc.1207626

Dr Hisamaru Hirai

We regret to inform all our colleagues that Dr Hisamaru Hirai, Professor of the Department of Hematology and Oncology at the Graduate School of Medicine, University of Tokyo, Japan, passed away unexpectedly on 23 August 2003. He was just 51. An autopsy confirmed the cause of his sudden death as myocardial infarction.

Dr Hirai was born in Tokyo, in 1952. In 1979, he graduated with an MD degree from the Faculty of Medicine, University of Tokyo. Following 2 years' postgraduate medical training, he started to study the molecular mechanisms of human leukemias at the Third Department of Internal Medicine at University of Tokyo. From 1987 to 1990, Dr Hirai worked in Professor Harold Varmus' laboratory at the University of California, San Francisco, USA. In 1990, he became a lecturer in the Third Department of Internal Medicine, University of Tokyo, and in 1996 he was appointed Associate Professor of the Department of Cell Therapy and Transplantation Medicine. In May 2003, he was promoted to Professor of Department of Hematology and Oncology, University of Tokyo.

One of Dr Hirai's major research projects was elucidation of the mechanisms of action of the *AML1/Runx1* gene product. Through the study of certain leukemias with *t*(12;21)(p13;q22), including myelodysplastic syndrome (MDS) or progression of chronic myelogenous leukemia to blastic crisis, he and his colleagues identified the AML1-Evi-1 fusion gene. This finding was reported in the EMBO Journal (1994). Subsequently, the group studied the function of the *AML1* gene, and found that the AML1-Evi-1 fusion protein binds to the promoters of AML1-target genes, but that it interferes with the transcriptional activity of native AML1. Although its functional importance is still not fully understood, the research team also found that AML1 is phosphorylated by ERK upon stimulation by growth factors. Recently, Dr Hirai became interested in the *in vivo* function of AML1 during the process of hematopoiesis. Despite his untimely death, some interesting studies using tissue-specific gene targeting in mice are continuing.

In addition to his studies on AML1/Runx1, Dr Hirai is noted for identifying a mutation of the N-*ras* gene in MDS. This work was published in Nature (1987) and is now considered to be a landmark in MDS research, because it led to a firm conclusion that MDS is a disease similar to acute leukemia. Since that breakthrough, research into MDS has been one of his life works.

Dr Hirai and his colleagues also reported that Evi-1 plays a critical role in malignant transformation of hematopoietic cells as a dominant oncogene. They reported in Nature (1998) that Evi-1 physically interacts with Smad3 and inhibits TGF-β signaling. Thus, Evi-1 may interfere with growth inhibitory activity of TGF-β, leading to aberrant growth of the *t*(3;21) leukemia cells. The group also showed that Evi-1 prevents stress-induced cell death by inhibiting JNK.

Dr Hirai also cloned a novel tyrosine kinase from an 'erythropoietin-producing hepatoma', known as *eph* (published in Science, 1987). The Eph and Eph-ligand system is now widely understood to play critical roles in various biological processes. He and his colleagues also isolated Crk-interacting protein, $p130^{Cas}$ (published in the EMBO Journal, 1994), which plays important roles in cell adhesion and migration (published in Nature Genetics, 1998).

As expanding the bone marrow transplantation team at University of Tokyo Hospital since 1995, Dr Hirai began to develop an interest in the field of hematopoietic stem cell biology. He and his colleagues chose the Notch system as an entry into this field, and they have published several important papers describing the characterization of ligand–receptor interactions and

cellular signaling through Notch receptors. More recently, they found that Notch1 is an important regulator for the conversion from bipotent endothelial cells (or hemangioblasts) to hematopoietic stem cells during embryonic development, and that Notch2 is essential for the development of splenic marginal zone B cells (published in Immunity, 2003).

While heading the department, Dr Hirai would often work from early morning to midnight, as both a clinician and a researcher. He devoted himself to the care of patients with hematological diseases, and developed a strong bone marrow transplantation team at the University of Tokyo Hospital. When he was promoted to Professor of the Department of Hematology and Oncology in May 2003, we all expected him to go on to become a global leader in the sciences of hematology and oncology. But tragedy befell him within only 3 months of this elevation.

At Dr Hirai's funeral in Tokyo, on 27 August 2003, more than 1500 mourners, including staff members, his colleagues in the Department of Hematology and Oncology, and many other associates, former teachers, collaborators, friends and acquaintances, expressed their deepest sorrow. To his students, fellows and colleagues, he was not only an inspirational group leader, but also an energetic and nurturing teacher. In his private life, he was a good husband and a loving father of two daughters. To us, he always felt like a supportive and encouraging elder brother. We will all miss him.

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