

Principal Investigator

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Employment History

2005 Yong Loo Lin Professor of Oncology, National Univ. of Singapore, Singapore
2002 Director, Oncology Research Institute, NUS, Singapore
2002 Principal Investigator, Institute of Molecular & Cell Biology, Singapore
1995 - 2001 Director, Inst. for Virus Research, Kyoto Univ., Japan
1984 – 2002 Professor, Kyoto University, Japan
1983 – 1984 Head, Cell Transformation Section, NCI, USA

Research Interests

Cancer/Oncology, Cell Biology, Signal Transduction, Gastroenterology, Structural Biology, Virology, Molecular Biology

Summary

RUNX genes, developmental regulators and major targets of TGF- β /Bone Morphogenetic Protein (BMP), are often involved in carcinogenesis. The research objectives of Prof Ito's laboratory have been to elucidate the molecular mechanisms of carcinogenesis. To this end, they have been studying the transcription factor PEBP2/CBF and the RUNX genes which encode the α subunits and PEBP2B/CBFB encoding the β subunit. RUNX genes are becoming more and more important in the oncology field and they are primarily responsible for identification of genes. RUNX1 is essential for definitive hematopoiesis and malfunction of RUNX1 is responsible for 30% of human acute leukemia. RUNX1 is the most frequent target of chromosome translocations but they also found sporadic and hereditary point mutations in RUNX1. These observations have led to the conclusion that heterozygous loss-of-function mutations in RUNX1 are leukemogenic. RUNX2 is essential for osteogenesis, and haploinsufficiency of the gene causes the autosomal dominant bone disease, cleidocranial dysplasia. Prof Ito's group showed that a mutation in RUNX2 found in the disease blocked the signal from BMP to inhibit osteogenesis. RUNX2 cooperates with c-myc to induce mouse T cell lymphoma. Recently, they found that RUNX3 is a major growth regulator of gastric epithelial cells and functions as a tumor suppressor of gastric cancer. In addition, RUNX3 was found to have multiple roles in many tissues, probably reflecting the fact that it is one of the major targets of the multi-functional TGF- β /BMP signaling cascades. Consistent with this notion, RUNX3 has been found to be involved in many types of cancers. RUNX proteins are unstable, since they are ubiquitinated and degraded by proteasome enzymes. The β -subunit blocks the ubiquitination and stabilizes RUNX proteins to become functional transcription factors. Regulation of heterodimerization, therefore, is important for the function of RUNX proteins.

Academic Qualifications

PhD 1968 Tohoku University, Japan

MD 1964 Tohoku University School of Medicine, Japan

Selected Publications

1. Kosei Ito, Qiang Liu, Manuel Salto-Tellez, Takashi Yano, Kotaro Tada, Hiroshi Ida, Canhua Huang, Nilesh Shah, Masafumi Inoue, Adnrea Rajnakova, Kum Chew Hiong, Bee Keow Peh, Hwan Chour Han, Tomoko Ito, Ming Teh, Khay Guan Yeoh and Yoshiaki Ito (2005) RUNX3, a novel tumor suppressor, is highly inactivated in gastric cancer by protein mislocalization. *CANCER RESEARCH* (in press)
2. Yoshida, C., Yamamoto, H., Fujita, T., Furuichi, T., Ito, K., Inoue, K., Yamana, K., Zannma, A., Tanaka, K., Ito, Y., and Toshihisa Komori. (2004) Runx2 and Runx3 are essential for chondrocyte maturation and Runx2 regulates limb growth through induction of Indian hedgehog. *GENES & DEVELOPMENT* 18, 952-963
3. Li, Q.L., Ito, K., Sakakura, C., Fukumachi, H., Inoue, K., Chi, X.Z., Lee, K.Y., Nomura, S., Lee, C.W., Han, S.B., Kim, H.M., Kim, W.J., Yamamoto, H, (2002), Casual Relationship between the Loss of RUNX3 Expression and Gastric Cancer. *CELL*, 109, 113-124
4. Inoue, K., Ozaki, S., Shiga, T., Ito, K., Masuda, T., Okado, N., Iseda, T., Kawaguchi, S., Ogawa, M., Bae, S.C., (2002), RUNX 3 controls the axonal projection of proprioceptive dorsal root ganglion neurons. *NATURE NEUROSCIENCE*, 5, 946-954
5. Taniuchi, I., Osato, M., Egawa, T., Sunshine, M.J., Komori, T., Ito, Y. and Littman D.R. (2002), Requirement for Runx proteins in CD4 silencing at different stages of T lymphocyte development. *CELL*. 111, 621-633
6. Nagata, T., Gupta V., Damian, S., Kim, W.-Y., Sali, A., Chait, B., Shigesada, K., Ito, Y., and Werner, M. (1999), Immunoglobulin motif DNA recognition and heterodimerization for the PEBP2/CBF Runt domain. *NATURE STRUC. BIOL*, 6, 615-619
7. Osato, M., Asou, N., Abdalla, E., Hoshino, K., Yamasaki, H., Okubo, T., Suzushima, H., Takatsuki, K., Kanno, T., Shigesada, K., and Ito, Y. (1999). Biallelic and heterozygous point mutations in the Runt domain of the AML1/PEBP2aB gene associated with myeloblastic leukemias. *BLOOD*, 93, 1817-1824
8. Ogawa, E., Maruyama, M., Kagoshima, H., Inuzuka, M., Lu, J., Satake, M., Shigesada, K., and Ito, Y. (1993). PEBP2/PEA2 represents a family of transcription factors homologous to the products of the *Drosophila runt* gene and the human AML1 gene. *PROC NAT ACAD SCI USA*. 90, 6859-6863
9. Segawa, K., and Ito, Y. (1983) Enhancement of polyoma virus middle T antigen tyrosine phosphorylation by epidermal growth factor. *NATURE*. 304, 742-747
10. Smart, J. E., and Ito, Y. (1978). Three species of polyoma virus tumor antigens share common peptides probably near the amino termini of the proteins. *CELL*. 15, 1427-1437
11. Ito, Y., Brocklehurst, J. R., and Dulbecco, R. (1977). Virus-specific proteins in the plasma membrane of cells lytically infected or transformed by polyomavirus. *PROC NAT ACAD SCI USA*. 74, 4666-4670

Honors and Awards

2003 Tomizo Yoshida Prize , Japanese Cancer Association, Japan

1995 Princess Takamatsu Cancer Research Award, Japanese Government, Japan

1968 Kuroya Award, Japanese Government, Japan

International Editorship/Advisorship

- 2005 Editorial Board Member, Critical Reviews in Eukaryotic Gene Expression, USA
- 2004 Editorial Board Member, Journal of Molecular Medicine
- 2003 Associate Editor, Cancer Research, USA
- 2003 Editorial Board Member, Oncogene, UK
- 2003 Editorial Board Member, Genes to Cell, USA
- 2003 Editorial Board Member, Seminars in Cancer Biology, USA
- 2003 Editorial Board Member, Journal of Cellular Biochemistry, USA