Chemical Epigenetics

Minoru Yoshida

Chemical Genomics Research Group, RIKEN Advanced Science Institute, Japan

Chromatin modifications serve as the important epigenetic marks responsible for inheritable changes in gene expression without changes in the DNA sequence, which ensure the unique gene expression patterns in differentiated tissues. The aberrant chromatin modifications, which are caused by the deregulation of factors that mediate the modification installation, removal and/or interpretation, actively contribute to human cancer. Indeed, histone deacetylase (HDAC) has been shown to associate with a variety of oncogenic factors that downregulate differentiation or tumor suppressor functions at the specific genetic loci. HDAC inhibitors can reverse the aberrant gene expression, and have been shown to have a therapeutic activity in cancer treatment. During the course of our mode-of-action studies on anticancer natural products, we have identified trichostatin A (TSA), trapoxin (TPX), and FK228 (Romidepsin) as the potent and specific HDAC inhibitors.

The long-term goal would be reversal or tuning of aberrant epigenetics occurring in the cancer tissues by the combined use of the small molecules that modulate chromatin modifications. To this end, we are currently making great effort to establish novel systems for detecting and evaluating the activity of cellular factors that regulate writing, reading and erasing of the epigenetic chromatin marks. These include *in vivo* imaging probes for monitoring dynamic changes in histone acetylation in living cells, which allows detection of not only HDAC inhibitory activity but also activity to interfere with bromodomain binding to histones acetylated at specific sites. Furthermore, we constructed *in vitro* fluorescent assays that enable high-throughput screening for histone methyltransferases and demethylases.

Minoru Yoshida Group Director, Chemical Genomics Research Group, RIKEN Advanced Science Institute; B.S. 1981, University of Tokyo; Ph.D. 1986, University of Tokyo (advisor: Teruhiko Beppu); Assistant and Associate Professor, 1986-2002, University of Tokyo; Chief Scientist, 2002-present, RIKEN; *Chemical genetics*; *Discovery and target identification of bioactive small molecules*; Tel: 81-48-467-9516, Fax: 81-48-462-4676, E-mail: yoshidam@riken.jp