Center for Stem Cell Biology and Regenerative Medicine

Division of Stem Cell and Molecular Medicine
幹細胞分子医学分野

Professor	Atsushi Iwama, M.D., Ph.D.	教　授	博士(医学)	岩　間　厚　志
Senior Assistant Professor	Motohiko Oshima, Ph.D.	講　師	博士(医学)	大　島　基　彦
Assistant Professor	Yaeko Nakajima, Ph.D.	助　教	博士(医学)	中　島　やえ子
Assistant Professor	Masayuki Yamashita, M.D., Ph.D.	助　教	博士(医学)	山　下　真　幸
Project Assistant Professor	Takako Yokomizo, Ph.D.	特任助教	博士(薬学)	横　溝　貴　子
Project Assistant Professor	Kazumasa Aoyama, Ph.D.	特任助教	博士(薬学)	青　山　和　正
Project Assistant Professor	Shuhei Koide, Ph.D.	特任助教	博士(薬学)	小　出　周　平

Stem cells have the remarkable capacity to both self-renew and give rise to many types of more specialized cells in the body, which explains their great therapeutic potential in regenerative medicine. But that's not the only reason stem cells have become such a hotbed of scientific inquiry. These cellular transformers also offer an invaluable research tool for probing the disease mechanisms that underpin cancer, aging and a host of other health problems. Our major interest is to elucidate the mechanisms of self-renewal and multi-lineage differentiation of hematopoietic stem cells (HSCs). We are also interested in how the deregulated HSC functions are associated with aging of our body and the development of age-related hematological malignancies. We approach these issues mainly from the view point of epigenetics.

1. Polycomb repressive complex 1.1 coordinates homeostatic and emergency myelopoiesis

Yaeko Nakajima-Takagi[1], Motohiko Oshima[1], Junichiro Takano[2], Shuhei Koide[1], Naoki Itokawa[1], Shun Uemura[1], Masayuki Yamashita[1], Shohei Andoh[1], Kazumasa Aoyama[1], Yusuke Isshiki[4], Daisuke Shinoda[1], Atsunori Saraya[4], Fumio Arai[5], Kiyoshi Yamaguchi[6], Yoichi Furukawa[6], Haruhiko Koseki[2], Tomokatsu Ikawa[3], and Atsushi Iwama[1,7,8]

[1]Division of Stem Cell and Molecular Medicine, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Tokyo 108-8639, Japan. [2]Laboratory for Developmental Genetics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. [3]Division of Immunobiology, Research Institute for Biomedical Sciences, Tokyo University of Science, Chiba 278-0022, Japan [4]Department of Cellular and Molecular Medicine, Graduate School of Medicine, Chiba University, Chiba 260-8670, Japan [5]Department of Stem Cell Biology and Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan [6]Division of Clinical Genome Research, Advanced Clinical Research Center, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan. [7]Laboratoty of Cellular and Molecular Chemistry, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan

Polycomb repressive complex (PRC) 1 regulates stem cell fate by mediating mono-ubiquitination of histone H2A at lysine 119. While canonical PRC1 is critical for hematopoietic stem and progenitor cell (HSPC) maintenance, the role of non-canonical PRC1 in hematopoiesis remains elusive. PRC1.1, a non-canonical PRC1, consists of PCGF1, RING1B, KDM2B,

and BCOR. We recently showed that PRC1.1 insufficiency induced by the loss of PCGF1 or BCOR causes myeloid-biased hematopoiesis and promotes transformation of hematopoietic cells in mice. Here we show that PRC1.1 serves as an epigenetic switch that coordinates homeostatic and emergency hematopoiesis. PRC1.1 maintains balanced output of steady-state hematopoiesis by restricting C/EBPαa-dependent precocious myeloid differentiation of HSPCs and the HOXA9- and β-catenin-driven self-renewing network in myeloid progenitors. Upon regeneration, PRC1.1 is transiently inhibited to facilitate formation of granulocyte-macrophage progenitor (GMP) clusters, thereby promoting emergency myelopoiesis. Moreover, constitutive inactivation of PRC1.1 results in unchecked expansion of GMPs and eventual transformation. Collectively, our results define PRC1.1 as a novel critical regulator of emergency myelopoiesis, dysregulation of which leads to myeloid transformation.

2. UTX inactivation in germinal center B cells promotes the development of multiple myeloma with extramedullary disease

Ola Rizq[1,2,3,4], Naoya Mimura[3,5], Motohiko Oshima[1,2], Shuji Momose[6], Naoya Takayama[7], Naoki Itokawa[1], Shuhei Koide[1], Asuka Shibamiya,[3] Yurie Miyamoto-Nagai[3], Mohamed Rizk[1,2], Yaeko Nakajima-Takagi[1,2], Kazumasa Aoyama[1,2], Changshan Wang[2,8], Atsunori Saraya[2], Ryoji Ito[9], Masanori Seimiya[10], Mariko Watanabe[11], Satoshi Yamasaki[12], Tatsuhiro Shibata[12], Kiyoshi Yamaguchi[13], Yoichi Furukawa[13], Tetsuhiro Chiba[14], Emiko Sakaida[3,5], Chiaki Nakaseko[15], Jun-ichi Tamaru[6], Yu-Tzu Tai[4], Kenneth C. Anderson[4], Hiroaki Honda[16], and Atsushi Iwama[1,2,17]

[1]Division of Stem Cell and Molecular Medicine, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan. [2]Department of Cellular and Molecular Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan. [3]Department of Hematology, Chiba University Hospital, Chiba, Japan [4]Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA. [5]Department of Transfusion Medicine and Cell Therapy, Chiba University Hospital, Chiba, Japan. [6]Department of Pathology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan. [7]Department of Regenerative Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan. [8]The State Key Laboratory of Reproductive Regulation and Breeding of Grassland Livestock, School of Life Sciences, Inner Mongolia University, Hohhot, China [9]Central Institute for Experimental Animals, Kanagawa, Japan [10]Department of Medical Technology and Sciences, School of Health Sciences at Narita, International University of Health and Welfare, Narita, Japan. [11]Department of Clinical Laboratory, Chiba University Hospital, Chiba, Japan. [12]Laboratory of Molecular Medicine, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan [13]Division of Clinical Genome Research, Advanced Clinical Research Center, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan [14]Department of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan [15]Department of Hematology, International University of Health and Welfare, Narita, Japan. [16]Field of Human Disease Models, Major in Advanced Life Sciences and Medicine, Institute of Laboratory Animals, Tokyo Women's Medical University, Tokyo, Japan. [17]Laboratoty of Cellular and Molecular Chemistry, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan

UTX/KDM6A, a histone H3K27 demethylase and a key component of the COMPASS complex, is frequently lost or mutated in cancer; however, its tumor suppressor function remains largely uncharacterized in multiple myeloma (MM). Here, we show that the conditional deletion of the X-linked *Utx* in germinal center (GC) derived cells collaborates with the activating $Braf^{V600E}$ mutation and promotes induction of lethal GC/post-GC B cell malignancies with MM-like plasma cell neoplasms being the most frequent. Mice that developed MM-like neoplasms showed expansion of clonal plasma cells in the bone marrow and extramedullary organs, serum M proteins, and anemia. Add-back of either wild-type *UTX* or a series of mutants revealed that cIDR domain, that forms phase-separated liquid condensates, is largely responsible for the catalytic activity-independent tumor suppressor function of UTX in MM cells. *Utx* loss in concert with $Braf^{V600E}$ only slightly induced MM-like profiles of transcriptome, chromatin accessibility, and H3K27 acetylation, however, it allowed plasma cells to gradually undergo full transformation through activation of transcriptional networks specific to MM that induce high levels of *Myc* expression. Our results reveal a tumor suppressor function of UTX in MM and implicate its insufficiency in the transcriptional reprogramming of plasma cells in the pathogenesis of MM.

Publications

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