

The nutrient sensing signaling pathways in the hematopoietic stem cells and leukemia

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Hematopoietic stem cells (HSCs) are maintained in an undifferentiated quiescent state within a bone marrow niche. Although appropriate intrinsic and extrinsic controls are required for HSC homeostasis, the underlying molecular mechanisms are still unknown. Since we hypothesized that HSC fate may be controlled by molecules that are involved in longevity, we focused on mTOR complex 1 (mTORC1) and forkhead transcription factor FOXO, which function in nutrient sensing signaling pathways. In the quiescent HSCs, the phosphorylation of AKT is down-regulated, associated with activation of FOXO3a. We found that FoxO3a is critical for HSC self-renewal. FoxO3a-deficient HSCs showed increased phosphorylation of p38MAPK, an elevation of ROS, defective maintenance of quiescence, and heightened sensitivity to cell-cycle-specific myelotoxic injury. In addition, it was reported that dysregulation of mTORC1 causes abnormality in HSC behavior. We also found that deficiency of Tsc1, a negative regulator of mTORC1, led to defective maintenance of the quiescence, associated with reduced HSC function. Thus, appropriate controls of these signaling pathways play a pivotal role in maintaining the HSC pool. Furthermore, we have investigated roles of FOXO/mTORC1 in the proliferation, survival and differentiation of leukemia cells, since it has been suggested that the molecular mechanisms known to govern the fate of normal HSCs may also be involved in regulating leukemia stem cells. In this symposium, I present common and distinct functions of these molecules in HSCs and leukemia.

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EDUCATIONS/TRAINING

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1994 University of Tokushima, Japan (PhD)
1995-1998 Postdoctoral fellow, Japan Society for the Promotion of Science (Kumamoto University School of Medicine), Japan
1997-2001 Postdoctoral fellow, Ontario Cancer Institute, Departments of Medical biophysics and Immunology, University of Toronto, Canada

POSITIONS AND HONORS

- 2001-2002 Assistant professor, Department of Cell Differentiation, Institute of Molecular Embryology and Genetics, Kumamoto University
2002-2004 Assistant professor, The Sakaguchi Laboratory of Developmental Biology, Keio University School of Medicine
2004-2005 Associate professor, The Sakaguchi Laboratory of Developmental Biology, Keio University School of Medicine
2005-present Professor, Division of Molecular Genetics, Cancer Research Institute, Kanazawa University
2011-present: Associate Editor, Cancer Science

2007 The JSPS PRIZE
2011 The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology

RECENT PUBLICATIONS

1. Hoshii T, Tadokoro Y, Naka K, Ooshio T, Muraguchi T, Sugiyama N, Soga T, Araki K, Yamamura K, Hirao A. mTORC1 is essential for leukemia-propagation but not stem cell self-renewal. *J Clin Invest.* 122:2114-29, 2012.
2. Muraguchi T, Tanaka S, Yamada D, Tamase A, Nakada M, Nakamura H, Hoshii T, Ooshio T, Tadokoro Y, Naka K, Ino Y, Todo T, Kuratsu J, Saya H, Hamada J, Hirao A. NKX2.2 suppresses self-renewal of glioma-initiating cells. *Cancer Res.* 71:1135-45, 2011
3. Naka K, Hoshii T, Muraguchi T, Tadokoro Y, Ooshio T, Kondo Y, Nakao S, Motoyama N, Hirao A. TGF β -FOXO signalling maintains leukaemia-initiating cells in chronic myeloid leukaemia. *Nature*, 463:676-80, 2010
4. Tamase A, Muraguchi T, Naka K, Tanaka S, Kinoshita M, Hoshii T, Ohmura M, Shugo H, Ooshio T, Nakada M, Sawamoto K, Onodera M, Matsumoto K, Oshima M, Asano M, Saya H, Okano H, Suda T, Hamada JI, Hirao A. Identification of tumor-initiating cells in a highly aggressive brain tumor using promoter activity of nucleostemin. *Proc Natl Acad Sci USA.* 106:17163-8, 2009
5. Ohmura M, Naka K, Hoshii T, Muraguchi T, Shugo H, Tamase A, Uema N, Ooshio T, Arai F, Takubo K, Nagamatsu G, Hamaguchi I, Takagi M, Ishihara M, Sakurada K, Miyaji H, Suda T, Hirao A. Identification of Stem Cells During Prepubertal Spermatogenesis Via Monitoring of Nucleostemin Promoter Activity. *Stem Cells.* 26:3237-46, 2008
6. Miyamoto K, Araki YK, Naka K, Arai F, Takubo K, Yamazaki S, Matsuoka S, Miyamoto T, Ito K, Ohmura M, Chen C, Hosokawa K, Nakauchi H, Nakayama K, Nakayama KI, Harada M, Motoyama N, Suda T, and Hirao A. Foxo3a is essential for maintenance of the hematopoietic stem cell pool. *Cell Stem Cell.* 1:101-112: 2007