"The 83rd of Stem Cell Biology and Regenerative Medicine Forum"

Date：Jul 31st (Fri) 2015
Time : 18:00 ～ 19:30
Place：8th fl of New Hospital Building

（Internal Speaker）

18:00-18:30 Kana Tominaga (Division of Molecular Therapy, IMSUT. Division of Internal medicine, Graduate School of Medicine, University of Tokyo, JSPS Research Fellow DC2)
Dependence on the HER2/3-NF□B-IGF2-ID1 circuit as a fundamental mechanism for stabilization of the stemness of breast cancer cells

（External Speaker）

18:30-19:30 Atsushi Hirao (Division of Molecular Genetics, Cancer Research Institute, Kanazawa University)
Molecular mechanisms of the maintenance of stem cells in normal and malignant hematopoiesis

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Hosted by Center for Stem Cell Biology and Regenerative Medicine

---Information---

＊ Please register attendance at the reception desk.
＊ Next forum (the84th) will be held on Sep. 15th (Tue) 13:00～ at Auditorium
＊ Please contact tatsu-m@ims.u-tokyo.ac.jp, for Forum speaker recommendations

Dependence on the HER2/3-NF□B-IGF2-ID1 circuit as a fundamental mechanism for stabilization of the stemness of breast cancer cells

Kana Tominaga (Division of Molecular Therapy, IMSUT. Division of Internal medicine, Graduate School of Medicine, University of Tokyo, JSPS Research Fellow DC2)

Many breast cancer patients suffer from relapse, which is potentially due to cancer stem cells that were not eliminated by treatment. Not only is it difficult to eradicate cancer stem cells, but the cancer cells themselves even appear to have plasticity by which they can acquire cancer stem cell properties. There may be unknown mechanisms to stabilize cancer stemness. Since the HER2/3—PI3K—NF□B pathway contributes to cancer stemness, we examined expression of downstream molecules in this pathway by comprehensive analysis of gene expression profiles over time. Insulin-like growth factor 2 (IGF2) was identified as a key downstream molecule, since anti-IGF2 antibody treatment blocked tumor sphere formation, characteristic of stemness, even in the presence of other growth factors/cytokines. IGF2—PI3K signaling induced tumor sphere formation and enhanced the expression of genes favoring stemness, including the transcription regulator *ID1* and *IGF2* itself. ID1 and the IGF2 receptor IGF-1R were specifically expressed at high levels in cancer stem cell-enriched populations in freshly obtained primary breast cancer cells derived from patients and patient-derived xenografts (PDXs). Moreover, *ID1* knockdown suppressed IGF2-induced expression of *IGF2*. Thus, HER2/3—PI3K—NF□B signaling may trigger IGF2—PI3K—ID1—IGF2 positive feedback circuits and PI3K-mediated feed-forward circuits that stabilize the stemness of cancer cells, and on which they are dependent. It would be critical to target these stemness circuits for eradication of cancer stem cells, irrespective of breast cancer subtypes.

Molecular mechanisms of the maintenance of stem cells in normal and malignant hematopoiesis

Atsushi Hirao (Division of Molecular Genetics, Cancer Research Institute, Kanazawa University)

Hematopoietic stem cells (HSCs) are able to reproduce themselves, a property known as self-renewal, and to give rise to mature hematopoietic cells. Under steady-state conditions, HSCs are maintained as a quiescent population and their numbers in the BM and circulation are tightly regulated by microenvironment components. In order to maintain HSC homeostasis over the life of an animal, HSCs must either be long-lived or self-renew. In either case, the quality of HSCs must be sustained during aging. Although aging is a complicated phenomenon, its effects on HSCs have been dissected by examining DNA damage response processes, cellular senescence, and metabolism. Recent studies have suggested that shared mechanisms regulate stem cell properties ”stemness” in both HSCs and leukemia stem cells (LSCs). Despite the differing origins of LSCs among different leukemias, there appears to be a common regulatory mechanism governing “stemness” and thus the behavior of LSCs.

We have been focusing on mTOR complex (mTORC) and forkhead transcription factor FOXO family members, which function in nutrient sensing signaling pathways. We revealed that FOXO activity is essential for maintaining self-renewal of HSCs and contributes to blockade of differentiation programs in leukemia, suggesting that the nutrient pathways may be commonly critical for normal and malignant stem cell systems. We have also found that modulation of cell-cell interaction controls HSC function and that actin polymerization may be involved in HSC aging. Thus, identification of stemness regulators would lead to deep understanding of mechanisms of aging and tumorigenesis.