



CDB SEMINAR

Yoku Hayakawa

Graduate School of Medicine, Department of Gastroenterology, The University of Tokyo

Wednesday, December 7, 2016

16:00~17:00 C1F Auditorium

The regulatory mechanism of gastric stem cell and its malignant transformation

Summary

The gastrointestinal epithelium is maintained by gastrointestinal stem cells and their niches. The stomach comprises two major parts, the proximal corpus and the distal antrum. These two parts have distinct gland structures and are maintained by different stem cells. However, gastric stem cells and their niche have not been characterized in detail. During carcinogenesis, various niche factors, such as immune cells and fibroblasts, stimulate and activate stem cells in the glands. Indeed, Lgr5+ antral stem cells have been reported to give rise to cancer following loss of the Apc gene. We recently identified new gastric stem cell populations that serve as a cellular origin of cancer, and discovered unique niches that support gastric stem cells and facilitate cancer development.

We performed lineage-tracing experiments with Mist1-CreERT mice. We found that Mist1 is expressed in the isthmus of the corpus, and that Mist1+ isthmus cells are quiescent, long-lived stem cells. Mist1+ corpus stem cells can give rise to intestinal metaplasia due to expression of mutant Kras, and to intestinal-type cancer with additional loss of the Apc gene. Moreover, Mist1+ stem cells convert to signet ring cancer cells following loss of the Cdh1 gene, but for progression to diffuse-type cancer, chronic inflammation is required. In the corpus isthmus, we discovered a perivascular stem cell niche comprising Cxcl12-expressing endothelial cells and Cxcr4-expressing innate lymphoid cells (ILCs). During chronic inflammation, Cxcr4+ ILCs are recruited to the gastric isthmus by the Cxcl12+ endothelium, where they produce Wnt5a within the stem cell niche. Finally, Wnt5a activates RhoA signaling in Cdh1-depleted cancer cells derived from Mist1+ stem cells, resulting in expansion of Mist1-derived signet ring cells due to inhibition of anoikis.

We further determined that multiple gastric stem cells are regulated by unique stromal niches—including endothelial cells, nerves, and tuft cells—in a manner dependent on the cell type and location in the stomach. These interactions may affect tissue homeostasis and tumor development from stem cells.

Host:

Mitsuru Morimoto

Lung Development, CDB

mmorimoto@cdb.riken.jp

Tel: 078-306-3199

(ext:1602)

Cell Stem Cell. 2015 Jun 4;16(6):627-38.

Cancer Cell. 2015 Dec 14;28(6):800-14.

RIKEN CENTER for DEVELOPMENTAL BIOLOGY (CDB)