＊＊平成 26 年度医学・生命科学セミナー／D1"Medical & Life Science Seminar, 2014" ＊＊

Mob1a/1b control cell differentiation and cancer suppression in mice

●Lecturer: Prof. Akira Suzuki

Division of Cancer Genetics, Medical Institute of Bioregulation, Kyushu University

鈴木 聡 教授 ＜九州大学生体防御医学研究所 ゲノム腫瘍学分野＞

●Date: January 21st (WED), 2015 from 17:30. ／1 月 21 日（水）17：30～

●Place: Lecture Room 2, Medical Education & Library Building 3F.
医学教育図書棟 3 階、第 2 講義室

今回のセミナーは日本語にて開催します。（スライドは英語表記有り）

This seminar will be held in Japanese. (Slide data will be written in English)

Most components of the mammalian Hippo pathway have been implicated as tumor suppressors, including neurofibromin-2 (NF2), the mammalian STE20-like protein (MST) kinases, the large tumor suppressor homolog (LATS) kinases, and the adaptor proteins Salvador Homolog-1 (SAV1) and Mps One Binder Kinase Activator (MOB). Downstream of these components are two paralogous transcriptional coactivators: Yes-Associated Protein-1 (YAP1) and transcriptional co-activator with PDZ-binding motif (TAZ). Activation of the Hippo pathway occurs in response to increased cell density and decreased extracellular matrix rigidity. In the presence of MOB1, LATS1/2 strongly phosphorylates YAP1/TAZ, which binds to 14-3-3 protein. This binding draws phosphorylated YAP1/TAZ into the cytoplasm, preventing it from activating TEAD-mediated transcription of *CTGF*, *Birc5*, *FGF*, *SPP1*, *TGFβ,* and *JAG1*. Phosphorylated YAP1/TAZ also binds to E3-ubiquitin ligase $SCF^{\beta TRCP}$ and is degraded**.** Thus, YAP1/TAZ are positive regulators of cell proliferation that are suppressed by Hippo signaling.

The precise roles of mammalian Hippo signaling components have been difficult to identify. Because multiple homologues of each element exist, and deficiency for almost any one of them is embryonic lethal in mice. In addition, the function of a given Hippo component may differ in different tissues. For example, the liver phenotype of $Nf2^{-/-}$ mice depends on NF2-EGFR signaling rather than on the NF2-MOB1-YAP1 pathway, and the skin phenotype associated with abnormal Hippo signaling depends on SAV1-YAP1 but is independent of MST1/2. Therefore, the *in vivo* function of each mammalian Hippo pathway component in each tissue must be clarified separately.

We generated Mob1A/1B double homozygous mutant mice but they died at gastrulation. Mob1A/1B partially mutant mice or tissue-specific double homozygous mutant mice resulted in the development of a variety of tumors including skin and liver. MOB1A/1B-deficient cells exhibited hyperproliferation, apoptotic resistance, impaired contact inhibition, enhanced progenitor self-renewal, defective terminal differentiation. Thus Hippo pathway is important for the tissue homeostasis and contributes to organ size control and tumor suppression. Therapeutic strategies able to control Hippo signaling might benefit many cancer patients.

Inviter: Prof. Katabuchi (Dept. of Obstetrics & Gynecology) / 産科婦人科学分野 片渕教授

Essay/レポート宛先(To Prof. Katabuchi)：buchi@kumamoto-u.ac.jp

Essay/レポート宛先(CC: Student Affairs Sec.／医学教務)：iyg-igaku@jimu.kumamoto-u.ac.jp