"The 81th of Stem Cell Biology and Regenerative Medicine Forum"

Date：May 22nd (Fri) 2015
Time : 18:00 ～ 19:30
Place：8th fl of New Hospital Building

（Internal Speaker）

18:00-18:30 Munakata Shinya (Laboratory of Stem Cell Regulation, Center for Stem Cell Biology and Regenerative Medicine, IMUST/ Department of Coloproctological Surgery, Juntendo University Faculty of Medicine)
Inhibition of plasmin protects against experimental colitis by suppressing inflammatory cytokine release

（External Speaker）

18:30-19:30 Katsuhiko Asanuma (Associate Professor Kyoto University Graduate School of Medicine Medical Innovation Center, TMK Project)
The role of Notch2 activation in injured kidney podocytes

Hosted by Center for Stem Cell Biology and Regenerative Medicine

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＊ Please register attendance at the reception desk.
＊ Next forum (the82st) will be held on Jun. 24nd (Wed) 18:00～ at Auditorium in 1st Building.
＊ Please contact tatsu-m@ims.u-tokyo.ac.jp, for Forum speaker recommendations

Inhibition of plasmin protects against experimental colitis by suppressing inflammatory cytokine release

Munakata Shinya (Laboratory of Stem Cell Regulation, Center for Stem Cell Biology and Regenerative Medicine, IMUST/Department of Coloproctological Surgery, Juntendo University Faculty of Medicine)

BACKGROUND & AIMS: Activated proteases such as plasmin and matrix metalloproteinases (MMPs) are activated in intestinal tissues of patients with active inflammatory bowel diseases. We investigated the effect of plasmin on progression of acute colitis.

METHODS: Colitis was induced in *Mmp9–/–*, *Plg–/–*, and C57BL/6 (control) mice by administration of dextran sulfate sodium, trinitrobenzene sulfonic acid, or CD40 antibody. Plasmin was inhibited in control mice by intraperitoneal injection of YO-2, which blocks its active site. Mucosal and blood samples were collected and analyzed by reverse transcription polymerase chain reaction and immunohistochemical analyses, as well as for mucosal inflammation and levels of cytokines and chemokines.

RESULTS: Circulating levels of plasmin were increased in mice with colitis, compared with controls. Colitis did not develop in control mice injected with YO-2 or in *Plg–/–* mice. Colons from these mice had reduced infiltration of Gr1+ neutrophils and F4/80+ macrophages, and reduced levels of inflammatory cytokines and chemokines. Colonic inflammation and colitis induction required activation of endogenous MMP9. Following colitis induction, mice given YO-2, *Plg–/–* mice, and *Mmp9–/–* mice had reduced serum levels of tumor necrosis factor and CXCL5, compared to control mice.

CONCLUSIONS: In mice, plasmin induces a feedback mechanism in which activation of the fibrinolytic system promotes development of colitis, via activation of MMP9 or proteolytic enzymes. The proteolytic environment stimulates influx of myeloid cells into the colonic epithelium and production of tumor necrosis factor and CXCL5. In turn, myeloid CD11b+ cells release the urokinase plasminogen activator, which accelerates plasmin production. Disruption of the plasmin-induced chronic inflammatory circuit might therefore be a strategy for treatment of colitis.

The role of Notch2 activation in injured kidney podocytes

Katsuhiko Asanuma (Associate Professor Kyoto University Graduate School of Medicine Medical Innovation Center, TMK Project)

Kidneys serve the body by filtering blood and removing water-soluble wastes. The glomerulus filters waste products from the blood and initiates urine formation. Glomerular visceral epithelial cells, also called podocytes, are highly specialized epithelial cells that attach to the outer layer of the glomerular basement membrane (GBM). Podocytes form the final barrier to protein loss, and this explains why podocyte injury is typically associated with marked proteinuria. Chronic podocyte injury may cause podocyte detachment from the GBM, leading to glomerulosclerosis and chronic kidney disease (CKD). Notch signaling pathway is an evolutionarily conserved intracellular signaling pathway that regulates cell fate. Recently, it was reported that the regulation of Notch2 activation plays an important role in the development of proximal nephron structure including podocytes. However, details of the Notch2 signaling pathway in injured podocytes remain unclear. In this seminar, I would like to talk about the role of Notch2 activation in injured podocytes and propose the possibility of using a Notch2 agonistic antibody as a new target for the treatment of glomerular diseases.