"The 85th of Stem Cell Biology and Regenerative Medicine Forum"

Date：Sep 16th (Wed) 2015
Time : 18:00 ～ 19:30
Place：Auditorium in 1st Building at Institute of Medical Science in Univ. of Tokyo

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（Internal Speaker）

18:00-18:30 Beate Heissig (Department of Stem Cell Dynamics, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo)
The fibrinolytic system controls the niche composition and function during cancer progression and inflammation

（External Speaker）

18:30-19:30 Shahin Rafii (Weill Cornell Medical College, Angiocrine Bioscience, Ansary Stem Cell Institute, HHMI, New York, NY)
Executive functions of tissue-specific vascular niche in stem cell self-renewal and organ regeneration

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Hosted by Center for Stem Cell Biology and Regenerative Medicine

---Information---

* Please register attendance at the reception desk.
* Next forum (the86th) will be held on Oct. 22th (Thurs) 18:00～ at Tommy Hall
* Please contact tatsu-m@ims.u-tokyo.ac.jp, for Forum speaker recommendations

The fibrinolytic system controls the niche composition and function during cancer progression and inflammation

Beate Heissig (Department of Stem Cell Dynamics, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo)

The serine protease plasmin generated from its zymogen plasminogen is best known for its function as a key enzyme of the fibrinolytic cascade. However, beyond fibrinolysis, plasmin has a number of crucial functions in wound healing, inflammation and cancer.

Tumors are formed of cancer cells, extracellular matrix and cells of the tumor microenvironment: inflammatory cells, endothelial and stromal cells, fibroblasts and mesenchymal stem cells (MSC). We found that the fibrinolytic factor tissue-type plasminogen activator (tPA) expands murine MSC *in vivo* through a growth factor-driven crosstalk between MSC and endothelial cells in the bone marrow and tumor niche. Since MSC are known to protect cancer cells from the toxic effect of immune cells through their immune modulatory potential, controlling the recruitment and function of MSC in the cancer microenvironment seems a promising approach to control cancer growth and progression.

Inflammatory cells are another component of the tumor microenvironment and chronic inflammation is known to enhance cancer development. We showed that excessive plasmin activation occurs in inflammatory bowel disease (IBD), and during tumor progression. Genetic or pharmacological plasmin inhibition improved clinical signs of IBD and tumor cell progression. Mechanistically, plasmin regulates the recruitment of myelomonocytic cells into diseased tissues by altering the biological activity of chemokines/growth factors, which are known to enhance myeloid cell migration. The altered biological activity of chemokines/growth factors was either a direct result of plasmin's proteolytic potential or was due to the ability of plasmin to activate proteases like matrix metalloproteinases.

We propose that plasmin by modulating the proteolytic environment changes the cellular and cytokine composition of tissues, and thereby controls cancer progression and chronic inflammatory diseases.

Executive functions of tissue-specific vascular niche in stem cell self-renewal and organ regeneration

Shahin Rafii (Weill Cornell Medical College, Angiocrine Bioscience, Ansary Stem Cell Institute, HHMI, New York, NY)

Organ specific endothelial cells (ECs) are not just passive conduits to deliver oxygen and nutrients, but also establish an instructive vascular niche, which by elaboration of specific paracrine trophogens, (known as angiocrine factors), directly balance the rate of stem cell self-renewal and differentiation. For example, activation of Akt-mTOR pathway in the sinusoidal ECs (SECs) stimulates expression of angiocrine factors, including Notch-ligands, Wnts, FGFs and TGF-modulators, that induce expansion of authentic hematopoietic stem cells (1). While MAPkinase induces expression of angiocrine factors, that support differentiation of the stem cells into lineage-committed progenitors.

Furthermore, after partial hepatectomy, SECs within the liver stimulated regeneration by angiocrine expression of Wnt2 and HGF (2). Pulmonary capillary ECs (PCECs) by deploying MMP14 and release of EGF-ligands sustain lung regeneration. Notably, transplantation of SECs or PCECs into mice restores organ regeneration (3). These data establish the remarkable tissue-specific vascular heterogeneity in orchestrating organ regeneration. Indeed, we have recently shown that each organ is arborized with specialized capillary ECs endowed with unique repertoire of angiocrine factors (4,5). Therefore, to capitalize on the potential of vascular cells for organ regeneration, we need to engineer tissue-specific ECs that can home and engraft in tissues promoting organ regeneration and repair. Most importantly, as ECs can be provoked to instigate pro- fibrotic changes, we need to manufacture tissue-specific ECs that drive organ regeneration without promoting maladaptive fibrosis (6, 7).

To translate these findings to the clinical setting, we have differentiated human and mouse embryonic stem and iPSC cells into induced vascular endothelial cells (iVECs) (4). However, iVECs are unstable and have limited expansion potential. Most importantly, iVECs are plastic and tend to drift into other non-vascular, such as smooth muscle cells. To circumvent this hurdle, we have developed new strategies by transcriptional (short term ETV2+Fli1+Erg1+TGFβ inhibition) reprogramming of amniotic cells into vascular ECs (rAC-VECs) without employing pluripotent transcription factors (4). rAC-VECs phenocopy the specialized tissue-specific function of ECs, supporting long-term expansion of repopulating cells (5), such as hematopoietic stem cells in xenobiotic-free conditions.

We show that once transplanted intravenously, rAC-VECs can home to the regenerating tissues and by production of specific angiocrine factors promote organ regeneration and repair without provoking aberrant fibrosis. Given that rAC-VECs can be HLA-typed, cryopreserved, and publicly banked, these cells could establish an inventory for generating abundant tissue-specific vascular niche cells for promoting angiocrine-dependent organ regeneration (4,5,7).