"The 77th of Stem Cell Biology and Regenerative Medicine Forum"

Date：Jan 29th (Thu) 2015
Time : 18:30 ～ 20:00
Place：Auditorium in 1st Building at Institute of Medical Science in Univ. of Tokyo

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（Internal Speaker）

18:30-19:00 Yukie Tanaka (Division of Molecular Therapy, IMSUT, Division of Hematology, Saitama Medical Center, Jichi Medical University)
Investigation of redirected T-cell immunotherapy against HTLV-1 Tax

（External Speaker）

19:00-20:00 Yoshinobu Maeda (Department of Hematology and Oncology, Okayama University Hospital)
Mouse Models for Understanding the Pathogenesis of Chronic Graft-versus-Host Disease

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Hosted by Center for Stem Cell Biology and Regenerative Medicine

---Information---

＊ Please register attendance at the reception desk.
＊ Next forum(the78th)will be held on Mar. 4th(Wed)17:00～ at Auditorium in 1st Building.
＊ Please contact tatsu-m@ims.u-tokyo.ac.jp, for Forum speaker recommendations

Investigation of redirected T-cell immunotherapy against HTLV-1 Tax

Yukie Tanaka (Division of Molecular Therapy, IMSUT, Division of Hematology, Saitama Medical Center, Jichi Medical University)

Adult T-cell leukemia (ATL) is an aggressive T-cell malignancy caused by human T cell lymphotropic virus type 1 (HTLV-1) infection. Tax is the most important regulatory protein of HTLV-1, and is also a major target antigen for $CD8^+$ cytotoxic T-cells (CTLs). Immunological studies of ATL patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) showed that donor Tax-specific CTL might contribute to control of HTLV-1 replication after allo-HSCT. We previously analyzed T cell receptor (TCR) repertoire of HTLV-1 $Tax_{301\text{-}309}$-specific CTLs of ATL patients underwent allo-HSCT at single-cell levels, and reported that a particular amino acid sequence motif (P-D-R) in CDR3 of TCR-β was conserved among predominant Tax-specific CTLs. Moreover, the PDR-motif$^+$ Tax-specific CTLs with sufficient activities persistently existed in long-term ATL survivors after HSCT. Based on these observations, we considered that PDR-motif$^+$ TCR-gene could be a promising candidate for TCR-gene immunotherapy against HTLV-1 Tax. Therefore, PDR-motif$^+$ TCRα/β gene was introduced into donor T-cells by retroviral vector system. The redirected T-cells selectively killed HTLV-1 infected-cells without any reaction against normal cells *in vitro*. Now, we are testing the cytotoxic performances *in vivo* using mouse models.

Mouse Models for Understanding the Pathogenesis of Chronic Graft-versus-Host Disease

Yoshinobu Maeda (Department of Hematology and Oncology, Okayama University Hospital)

Allogeneic stem cell transplantation (SCT) is a widely performed therapy for many hematologic malignancies, although graft-versus-host disease (GVHD) remains potentially lethal complications after allogeneic SCT. Based on differences in clinical manifestations and histopathology, GVHD can be divided into acute and chronic types. The clinical manifestations of acute GVHD occur in the skin, gastrointestinal tract, and liver. Several convergent lines of experimental data have demonstrated that donor T cells and donor and/or host antigen-presenting cells are important in the induction of acute GVHD.

Chronic GVHD often presents with clinical manifestations that resemble those observed in autoimmune diseases, and is a major cause of late death and morbidity after allogeneic SCT. However, the pathophysiology and treatment strategy of chronic GVHD remain poorly defined. Initially, chronic GVHD was considered to be a Th2-mediated disease, based on results from the non-irradiated parent into F1 mouse GVHD model. However, chronic GVHD has not fit neatly into the Th2 paradigm. Firstly, we evaluated the kinetics of regulatory T cell (Treg) reconstitution in mouse allogeneic SCT model. Next, we showed that Th1 cell and Th17 cell expansion occurred during chronic GVHD and contributed to chronic GVHD progression using a mouse model. We also identified a population of donor-derived IFN-□/IL-17 double-positive cells following only allogeneic transplantation, not syngeneic transplantation, suggesting that this population is generated by allogeneic stimulation.

In this talk, we discuss the pathophysiology of chronic GVHD, focusing on four aspects: (a) Tregs, (b) Th1 cell and Th17 cell, (c) the IL-12/IL-23 pathway and (d) the PD-1 pathway. Finally, we present a new strategy for the treatment of chronic GVHD.