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Toward the realization of cell therapy
The advent of MAIT cells from iPSCs

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Mucosal-associated invariant T (MAIT) cells are a subset of the innate type T cells and are characterized for the expression of an invariant T cell receptor (TCR) Vα7.2-Jα33, CD161 as a marker for natural killer cells, and the interleukin (IL)-18 receptor chain α (IL-18Rα) for T helper (Th)17 cells. MAIT cells are rare in mouse but are abundant in human, occupying up to 10% of the T cells in the peripheral blood mononuclear cells, 10% of the T cells in the lamina propria lymphocytes, and 50% of the liver-resident T cells. The development of MAIT cells depends on the major histocompatibility complex-related molecule 1 (MR1) as well as on the commensal flora in the gut. MAIT cells play a pivotal role in host defense against a wide range of bacterial and fungal infection.[1] Indeed MAIT cells have been identified as *Mycobacteria tuberculosis (Mtb)*-reacting nonconventional human $CD8^+$ T cell clones. MAIT cells may also be involved in inflammatory disorders in the liver and joints and are supposed to be pathogenic in multiple sclerosis owing to a tight correlation between $CD8^+CD161^{hi}$ cells and MAIT cells.[2,3] It is thus conceivable that functional analyses of MAIT cells in health and disease would shed light on the cause of immune-related diseases and allow exploiting causal treatments against the diseases as well as developing a novel vaccine against multidrug-resistant bacterial infections. Nevertheless, the rarity of MAIT cells in mice and their poor ability for expansion have hindered the progress. In the recent work, we have reported the reprogramming of MAIT cells into iPSCs, highly selective redifferentiation of MAIT cells from iPSCs (reMAIT cells), and characterization of reMAIT cells[4] (**Fig. 1**).

MAIT cells from cord blood (CB) were infected with a Sendai virus harboring a standard set of the reprogramming factors, and more than 55 iPSC clones were isolated. These iPSCs conformed to be pluripotent cells in that they harbored ES cell markers, telomerase activity, as well as potential to differentiate into three germ layers both in vitro and in vivo.

Of note is that there was no need to expand the cell to be reprogrammed to iPSC state. This finding argues against the present dogma in T cell reprogramming in that the stimulation of cell cycling is prerequisite for iPSC generation. Gene expression analyses revealed that the overall expression profile of iPSCs from MAIT cells was similar to that of iPSCs from human fibroblasts or to that of ESCs. When MAIT cells-derived iPSCs (MAIT-iPSCs) were cultured under the T cell-permissive conditions, more than 98% of the lymphocytes were recognized as MAIT cells expressing Vα7.2, TCRαβ, CD161, IL-18Rα, and CD45RA (reMAIT cells). This highly efficient rediferentiation of reMAIT cells from iPSCs is reminiscent to that of NKT cells from the cloned mice and ESCs.[5,6] Given that antigen-specific T cell's redifferentiation from iPSCs is not as efficient as reMAIT cells, it is plausible that the in-frame rearranged invariant *TCR*α loci plays a crucial role in blocking the further rearrangement of the *TCR*. MAIT cells are distinguished from the conventional T cells in their ability to produce interferon gamma (IFN-γ) in response to the bacterial-fed monocytes. reMAIT cells exhibited the activity and produced other inflammatory cytokines and chemokines, including IL-17 and IL-22. reMAIT cells also produced tumor necrosis factor (TNF)-α and IL-10. Given that reMAIT cells represented Th17 phenotype harboring CCR6, IL-18Rα, and RORC at the end of in vitro differentiation and further acquired IL-12Rβ2 and IL-23R upon adoptive transfer, MAIT cells may possess a unique developmental pathway in the thymus. Concomitant with the acquisition of Th17 cell markers, reMAIT cells matured in mice, as evidenced by downregulation of naïve markers CD45RA and CD62L as well as by the appearance of chemokine receptors that had been absent at the end of in vitro differentiation. reMAIT cells produced a similar array of cytokines and chemokines upon incubation with the bacteria-fed monocytes as did MAIT cells prepared from CB. Experiments using mouse MAIT cell-specific TCR transgenic mice and mice deficient for MR1 (no MAIT cells) suggest that MAIT cells would play a protective role against mycobacterial burden. When reMAIT cells were transferred in mice, they protected the host from mycobacterial infection. Granulysin was identified as an effector molecule for combating against the bacteria. It is noteworthy that *GRANULYSIN* or its homolog is absent in mice. Intriguingly, reMAIT cells expanded in vivo, while they did not during in vitro differentiation from the precursor cells. The expansion may be due to the presence of commensal flora in the mouse gut.

Our data open the avenue for the realization of cell therapy with reMAIT cells in the near future, as reMAIT cells are

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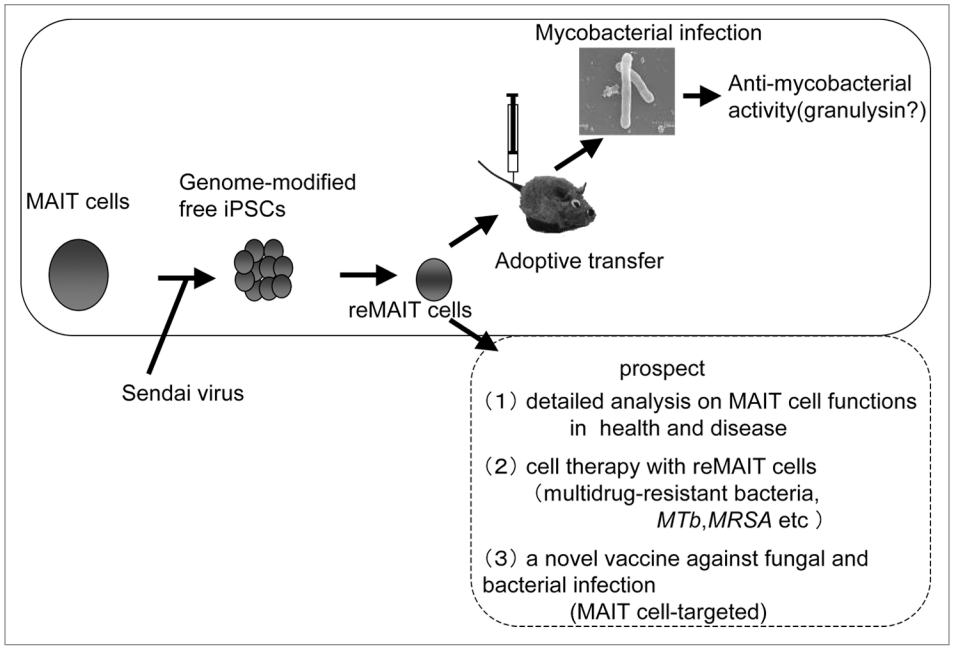

Figure 1. Schematic representation of the MAIT cell reprogramming to iPSC and redifferentiation of MAIT cells from iPSCs (reMAIT cells) and the function of reMAIT cells. Cord blood-derived MAIT cells are induced to be iPSCs by transducing with a Sendai virus harboring Yamanaka factors. Then iPSCs are differentiated under the T cell-permissive conditions to generate 3C10 (Vα7.2) $^{+}$TCRαβ^{+}CD161^{+}IL-18Rα^{+}CCR6^{+}CD45RA^{+} cells (reMAIT cells). Upon adoptive transfer, reMAIT cells establish in the immunocompromised mice and exert anti-mycobacterial activity most likely via granulysin release (plain line). The potential usefulness of reMAIT cells is summarized as a prospect (dotted line).

generated without any ectopic gene expression from iPSCs that are also free from the genomic modification. reMAIT cells would be useful against the opportunistic infection caused by non-*Mtb* mycobacterium or the multidrug-resistant *Mtb*, often observed at a later stage of HIV infection.[7] Alternatively, armed with granulysin reMAIT cells could fight against the multidrug-resistant nosocomial infections.

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