

Mucosal-associated invariant T cells from induced pluripotent stem cells: A novel approach for modeling human diseases

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Abstract

Mice have frequently been used to model human diseases involving immune dysregulation such as autoimmune and inflammatory diseases. These models help elucidate

the mechanisms underlying the disease and in the development of novel therapies. However, if mice are deficient in certain cells and/or effectors associated with human diseases, how can their functions be investigated in this species? Mucosal-associated invariant T (MAIT) cells, a novel innate-like T cell family member, are a good example. MAIT cells are abundant in humans but scarce in laboratory mice. MAIT cells harbor an invariant T cell receptor and recognize nonpeptidic antigens vitamin B2 metabolites from bacteria and yeasts. Recent studies have shown that MAIT cells play a pivotal role in human diseases such as bacterial infections and autoimmune and inflammatory diseases. MAIT cells possess granulysin, a human-specific effector molecule, but granulysin and its homologue are absent in mice. Furthermore, MAIT cells show poor proliferation *in vitro*. To overcome these problems and further our knowledge of MAIT cells, we have established a method to expand MAIT cells via induced pluripotent stem cells (iPSCs). In this review, we describe recent advances in the field of MAIT cell research and our approach for human disease modeling with iPSC-derived MAIT cells.

Key words: Mucosal-associated invariant T cells; Induced pluripotent stem cells; Differentiation; Adoptive transfer; Inflammatory diseases; Autoimmune diseases; Disease modeling; Infectious diseases; Immunocompromised mouse

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Core tip: Mucosal-associated invariant T (MAIT) cells, a novel innate-like T cell subset abundant in humans, play a pivotal role in immune-dysregulated diseases. However, MAIT cells are quite rare in laboratory mice and show poor proliferation *in vitro*. This makes it difficult to delineate their physiological functions in health and disease. Therefore, we developed a method to generate

human MAIT cells from induced pluripotent stem cells [redifferentiation of MAIT (reMAIT) cells]. Given that reMAIT cells harbor characteristics quasi-identical to those found in MAIT cells from human peripheral blood, they will be useful to model human diseases in animals.

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INTRODUCTION

T cells are distinguished from other lymphocytes, such as B cells and natural killer cells, by the expression of T cell receptors (TCRs) on the cell surface. T cells have been well-characterized as central players in adaptive immunity, so-called conventional T cells. The TCRs in conventional T cells consist of a heterodimer of α -chain and β -chain and are highly diverse owing to gene rearrangement together with insertion and/or deletion of nucleotides at the junctions between the gene segments, enabling them to recognize a wide variety of peptide antigens presented on major histocompatibility complex (MHC) molecules, which are also highly polymorphic^[1]. In recent years, however, non-conventional type T cells termed "innate-like" T cells have received keen attention in immune homeostasis and diseases^[2]. In contrast to conventional T cells, innate-like T cells express a limited set (semi-invariant) of TCRs and recognize nonpeptidic antigens presented on evolutionarily conserved non-classical MHC molecules^[3,4]. Innate-like T cells develop in the thymus, similar to conventional T cells^[5]. There is a time lag between the initial antigen exposure and execution of the maximum effector function in conventional T cell responses. Given that conventional T cells transit from naïve to effector/memory stage through the recognition of peptidic antigens, these T cells are ready to be activated and to expand upon receiving secondary stimuli to exert effector functions. In marked contrast, innate-like T cells have already acquired such immune competence when leave the thymus. This may be relevant to the fact that innate-like T cells, but not conventional T cells, express the transcription factor promyelocytic leukemia zinc finger (PLZF), which directs effector differentiation of these cells during thymic development^[5-7]. Thus far, it has been appreciated that the *raison-d'être* of innate-like T cells consists in filling a gap between innate and adaptive immunity^[8].

Mucosal-associated invariant T (MAIT) cells and natural killer T (NKT) cells are representatives of innate-like T cells expressing semi-invariant $\alpha\beta$ TCR in mammals^[2]. Because the discovery of NKT cell ligands has preceded that of MAIT cells, most of our knowledge on diseases has been made with NKT cells abundant in laboratory mice (but quite few in humans). NKT cells play a pivotal role in the suppression

of tumor growth and/or metastasis, and in ameliorating or aggravating autoimmune diseases^[9,10]. NKT cells produce a plethora of cytokines, including Th1-, Th2- and Th17-cytokines, upon stimulation, and MAIT cells also have a similar potential^[11,12]. Although they are different in many aspects such as antigens, restriction molecules for development and/or differentiation, and abundance, they are common in that they play a critical role in infectious diseases and autoimmune and inflammatory diseases. Regardless of their importance, it was not until recently that some information on MAIT cells has become available. In the last couple of years, there has been exciting progress regarding the functions of MAIT cells in the immunology field and in clinical settings. There are, however, some difficulties in studying MAIT cells, in that the frequency of MAIT cells is much lower in laboratory mice than in humans, and that MAIT cells show extremely poor proliferation *in vitro* with any T cell stimulants tested to date. Here, we provide an overview of recent advances in the study on MAIT cells and introduce our approach with induced pluripotent stem cell (iPSC) technology to overcome the experimental difficulties in MAIT cell study.

PHENOTYPIC FEATURES OF MAIT CELLS

MAIT cells are probably one of the most abundant T cell subsets in humans^[13]. However, until quite recently, MAIT cells had been hidden behind conventional T cells because they are indistinguishable from other T cell populations by standard T cell phenotyping using cell surface markers such as CD3, CD4 and CD8. MAIT cells are distinguished from conventional T cells and other T cell subsets such as NKT cells and $\gamma\delta$ T cells by the expression of an invariant TCR α chain, V α 7.2-J α 33 in humans and V α 19-J α 33 in mice, paired with a limited repertoire of TCR β chains; V β 13 and V β 2 are preferentially used in humans and homologous V β 8 and V β 6 in mice (Figure 1)^[13,14]. Together with invariant TCR α V α 7.2, human MAIT cells express a C-type lectin CD161 and interleukin (IL)-18 receptor α chain (IL-18R α) as specific markers^[15,16]. Primarily, MAIT cells are defined as CD3⁺, V α 7.2⁺, CD161⁺ and IL-18R α ⁺. MAIT cells can further be classified into CD8⁺ (most abundant), CD4⁻CD8⁻ [double negative (DN)] and CD4⁺ phenotypes (very few) in healthy human subjects^[13,17]. In addition, MAIT cells display CD45RA⁻, CD45RO⁺, CD95^{high}, and CD62L^{low} as their effector/memory T cell phenotype, and α 4 β 7 integrin⁺, CCR9^{int}, CCR7⁻, CCR5^{high}, CXCR6^{high}, and CCR6^{high}, suggesting MAIT cells home to the intestines and liver^[11,18,19]. High expression levels of CD161 in MAIT cells are accompanied by ROR γ t, IL-23R and IL-21R, markers associated with Th17/Tc17 type T cells^[11,19,20]. Furthermore, MAIT cells possess PLZF, indicating the capacity to promptly produce cytokines upon stimulation without priming^[7,17] and CD26⁺, a serine exodipeptidase, which processes chemokines in the extracellular matrix^[20,21]. Accordingly, MAIT cells have the potential to release a variety of cytokines under various conditions: Interferon (IFN)- γ , tumor necrosis factor (TNF)- α , IL-2, IL-4, IL-10, IL-17, IL-22, granzymes, and

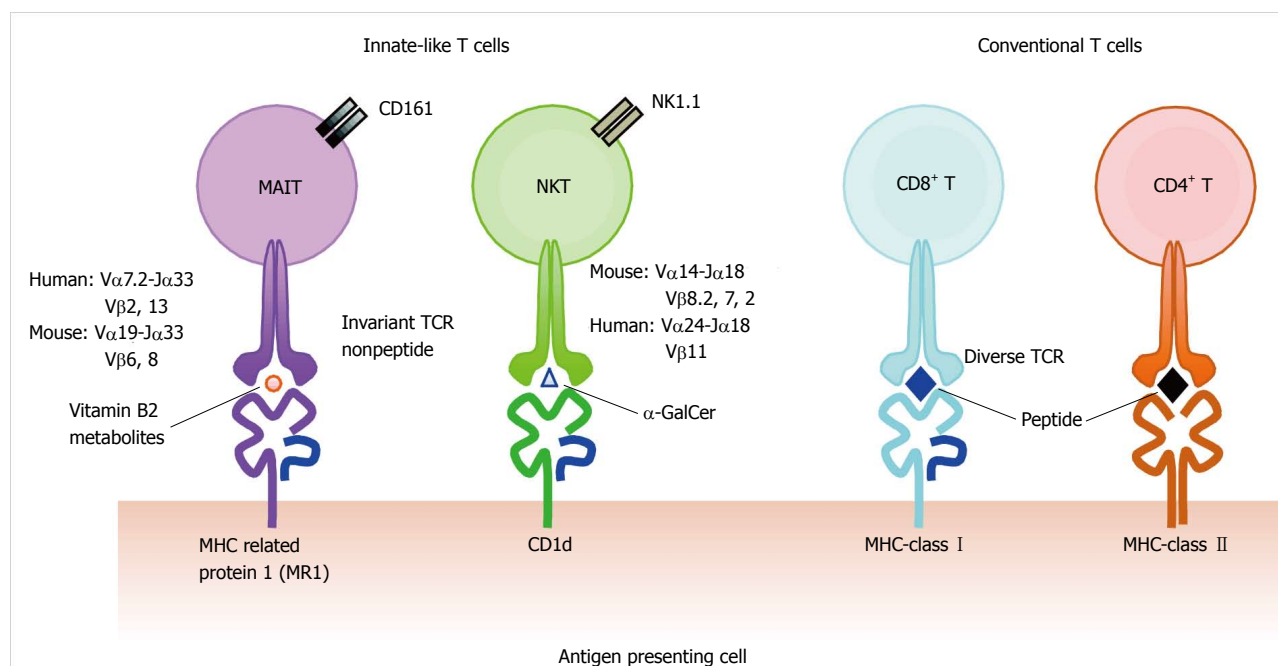


Figure 1 Comparison of the T cell receptors and the antigen presenting molecules among $\alpha\beta$ T cell subsets. Invariant T cell subsets consist of mucosal-associated invariant T (MAIT) cells and natural killer T (NKT) cells expressing invariant TCRs. MAIT cells and NKT cells recognize vitamin B2 metabolites on MR1, and α -galactosylceramide (α -GalCer) on CD1d, respectively. In contrast, conventional CD8⁺ and CD4⁺ T cells possess divergent TCRs and recognize a variety of peptides on major histocompatibility complex-class I and class II, respectively. TCRs: T cell receptors; MHC: Major histocompatibility complex.

others, which anticipates the multifaceted roles in health and diseases^[11,12,22].

MAIT CELLS AND MR1

The TCR of MAIT cells recognizes derivatives of vitamin B2 presented on the monomorphic MHC class-related molecule 1, MR1^[18,23] (Figure 1). MR1 mRNA is expressed ubiquitously in all types of cells, whereas the MR1 protein are not always on the cell surface but mainly in the endoplasmic reticulum^[24,25]. Although vitamin B2 derivatives are exogenous ligands from the biosynthetic pathway that some bacteria and yeasts possess, they are indispensable for the development of MAIT cells, because MAIT cells are absent in germ-free mice^[18]. TCRs for MAIT cells and MR1 are highly conserved during evolution, which suggests the functional and physiological importance of MAIT cells and MR1 in animals^[26]. Indeed, mouse and human MR1 molecules crossover part of the antigen presentation and activation in MAIT cells^[26].

MAIT cell development is dependent on MR1. Lymphoid progenitors derived from CD34⁺ hematopoietic stem cells in the bone marrow migrate to the thymus, wherein they undergo random rearrangement at the TCR loci. MAIT cell progenitors harboring the TCR V α 7.2-J α 33 are selected from CD4/CD8 double positive thymocytes that express MR1 loaded with unknown endogenous ligands^[18,27]. MAIT cells then egress from the thymus as naïve cells and further differentiate into effector/memory cells by recognizing commensal microflora-derived vitamin B2 metabolites bound to MR1 at mucosal sites^[18,19].

MAIT CELLS IN HEALTH AND DISEASES

MAIT cells consist of 1%-10% of T cells in the peripheral blood and of T cells in the intestinal lamina propria and 20%-50% in T cells of the liver, but they are at least 10 times less abundant in laboratory mice^[11,28]. MAIT cells are already present in the tissues of second trimester fetuses. Fetal MAIT cells exhibit a naïve phenotype but have potential functions in the activation and secretion of cytokines upon antigen stimulation^[29]. Although MAIT cells still showing a naïve phenotype and are low in frequency at birth, most of them have acquired a memory phenotype by 3 mo of age, and their frequency increases with age and reaches adult levels within 8-10 years after birth^[11]. This corresponds to the expansion and maturation of MAIT cells by commensal microflora colonizing after birth. The highest number of MAIT cells in PBMC is observed in adults aged 30-50 years, notably in females of reproductive age^[30]. MAIT cells, especially CD8⁺ MAIT cells as the most abundant subset, decrease drastically with age, implying an association with waning immunity in the elderly^[22,30].

The diseases in which a potential implication of MAIT cells has been reported are summarized in Table 1. A well-defined function of MAIT cells in disease settings is the control of infections with bacteria and/or yeasts. MAIT cells are activated by bacteria-infected cells in a MR1-dependent manner, followed by release of proinflammatory cytokines and cytotoxic granules, and eventually killing the infected cells^[16,31-33]. MAIT cells also express multidrug resistance transporter (ABCB1), which implies that MAIT cells are highly resistant to xenobiotics produced by bacteria^[11].

Table 1 Clinical relevance of mucosal-associated invariant T cells

Disease categories	Diseases or status	Features relevant to the diseases	Ref.	
Infectious diseases	Pneumopathy	Decrease in frequency and absolute number of MAIT cells in peripheral blood	[16]	
	Tuberculosis (<i>Mycobacterium tuberculosis</i>)	Decrease in frequency and absolute number of MAIT cells in peripheral blood Enriched in the lung	[16,37,92]	
	HIV/AIDS (opportunistic infection)	Decrease in frequency of MAIT cells in peripheral blood, guts, and lymph nodes Failure of recovery of blood MAIT cells with successful cART Long-term cART restore colonic but not blood MAIT cell levels MAIT cells are depleted but retain functionality	[38-43,93,94]	
	Sepsis (severe bacterial infection)	Decrease in frequency and absolute number of MAIT cells in peripheral blood of patients	[95]	
	<i>P. aeruginosa</i> infection with cystic fibrosis	Decrease in frequency of MAIT cells in peripheral blood of cystic fibrosis patients with <i>P. aeruginosa</i> infection	[96]	
	Cholera (<i>Vibrio cholera</i> O1)	Activation of MAIT cells in the acute phase No change of blood MAIT cell frequency in adult patients, but persistently decreased in child patients	[97]	
	Autoimmune diseases	Multiple sclerosis	Accumulation of MAIT cells in the central nervous system lesions Decrease in frequency of MAIT cells in peripheral blood Increased CD161 ^{high} CD8 ⁺ T cells in peripheral blood Accumulation of MAIT cells in the peripheral nerves	[44-46,48] [98] [44]
Chronic inflammatory demyelinating polyneuropathy				
Psoriatic and rheumatoid arthritis		Enrichment of CD161 ^{high} CD8 ⁺ T cells in the joints and secretion of IL-17 from those cells	[99]	
Rheumatoid arthritis				
Inflammatory bowel disease		Decrease in frequency and absolute number of MAIT cells (in particular, in CD8 ⁺ and DN subsets) in peripheral blood Increased MAIT cell levels in the synovial fluid Decrease in CD8 ⁺ MAIT cells in peripheral blood of CD and UC patients Accumulation of MAIT cells in the inflamed ileon of patients with CD Reduced IFN- γ production in CD patients and increased IL-17 production in CD and UC patients Fewer MAIT cells in the inflamed ileon of patients with CD and UC Increased apoptosis in MAIT cells	[53] [49] [100]	
Psoriasis		MAIT cells reside in not only the dermis of patients but also that of health donors. MAIT cells may contribute IL-17 production in the dermis of patients	[51]	
Celiac disease		Decrease in frequency of MAIT cells in peripheral blood and guts of adult and pediatric patients	[52]	
Systemic lupus erythematosus		Decrease in frequency and absolute number of MAIT cells (in particular, in CD8 ⁺ and DN subsets) in peripheral blood Reduced IFN- γ production Elevated expression of PD-1 in MAIT cells	[53]	
Inflammatory diseases		Asthma	Decrease in frequency of MAIT cells in blood, sputum, and endobronchial biopsy	[101]
		Diabetes type 2/obesity	Decrease in frequency of MAIT cells in peripheral blood Circulating MAIT cells display an activate phenotype MAIT cells are more abundant in adipose tissue	[55,56]
	Acute cholecystitis	Decrease in frequency and absolute number of MAIT cells in peripheral blood	[102]	
	Fibromyalgia syndrome vs Spondyloarthritis vs Rheumatoid arthritis	Defined analysis of MAIT cell phenotype among three diseases that exhibit a similar clinical manifestation Decrease in frequency of MAIT cells in three diseases Three diseases are able to distinguish by surface marker expression	[57]	
	Tissue transplant	Cutaneous acute graft-vs-host disease	Infiltration of CD8 ⁺ T cells, CD161 ⁺ , CCR6 ⁺ , ROR γ t ⁺ in the epidermis and dermis of patients with GVHD	[103]
Hemodialyzed and kidney transplant		Decrease in frequency of MAIT cells in peripheral blood Implication for the susceptibility to infections in the patients	[104]	
Tumors	Kidney and brain tumors	Presence of MAIT cells in tumors	[58]	
Physiological change	Fetus	Rare and immature in the thymus, spleen, mesenteric lymph nodes Mature and enriched in the guts, liver, and lung	[29]	
	Neonate/infant	Naïve phenotype at birth. Acquisition of effector/memory phenotype and increase in frequency and number with age	[11,30]	
	Adult	Maximum levels in the third and fourth decenniums Higher amounts in females with reproductive age than in males	[30]	
	Aging	Decrease in CD8 ⁺ MAIT cells and increase in CD4 ⁺ MAIT cells with age Th2 shift in cytokine profile in elderly	[22,30]	

CD: Crohn's disease; UC: Ulcerative colitis; MAIT: Mucosal-associated invariant T; HIV: Human immunodeficiency virus; AIDS: Acquired immunodeficiency syndrome; *P. aeruginosa*: *Pseudomonas aeruginosa*.

Although MAIT cells are extremely rare in laboratory mice, *Francisella tularensis*-infected mice revealed a massive expansion of MAIT cells in infected tissues earlier than the migration of conventional CD4⁺ and CD8⁺ T cells^[34], which suggests their unique function in host defense against bacterial infection. V α 19 iTCR (invariant TCR) transgenic mice (a MAIT-cell-enriched mouse model) and MR1 knockout mice (a MAIT-cell-deficient model), MAIT cells seemed to prevent the growth of bacterial such as *Mycobacterium abscessus*, *M. bovis* (BCG), *Escherichia coli* and *Klebsiella pneumoniae*^[16,35-37]. Accordingly, patients with bacterial infections such as tuberculosis and pneumopathies showed a decrease in MAIT cells in circulating blood, which might reflect their infiltration into the diseased sites^[16,37]. In HIV-infected patients, MAIT cells were also depleted from the circulating blood irrespective of the disease stage (acute or chronic infection), and even with combinatorial anti-retroviral therapy^[38-43]. Although it is believed that CD4⁺ T cell depletion causes immunodeficiency in HIV-infected patients, innate immune cells such as MAIT cells could play a crucial role in prevention of opportunistic infections with bacteria and/or fungi, which is a manifestation of AIDS.

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system caused by autoreactive T cells. Although it is suggested that myelin-specific CD4⁺ T cells might play a central role in MS pathogenesis, recent studies have indicated that MAIT cells accumulate in brain lesions concomitantly with a decrease in peripheral blood in MS patients^[44-48]. This evidence indicates that MAIT cells may play a pivotal role in MS pathology, but the underlying mechanisms are yet to be elucidated. An increase in IL-18 in the serum of MS patients could signify that MAIT cells tend to migrate into the brain^[46]. In conjunction with the high levels of IL-17 and IFN- γ secretion from MAIT cells in MS patients, one study has demonstrated that MAIT cells in MS exhibited proinflammatory profiles^[45], but another interpreted that these MAIT cells exhibited a regulatory function to suppress the pathogenic Th1 response^[48]. Accordingly, a novel animal model will be required to examine the direct contribution of MAIT cells in MS pathogenesis, as will be described later in this review.

Inflammatory bowel diseases (IBDs), such as Crohn's disease and ulcerative colitis (UC), are autoimmune diseases in which the potential contribution of MAIT cells is suggested owing to their anti-microbial activity, intestinal homing, and capacity to promptly induce both Th1- and Th17-cytokines. Similar to MS patients, a decrease in MAIT cells in the peripheral blood concomitant with an increase in MAIT cells in the injured ileal regions of IBD patients has been reported^[49]. In addition, peripheral blood MAIT cells from IBD patients showed more activated and proliferative state compared with that in healthy controls, suggesting that such alterations impinge on their functions. In fact, MAIT cells from the IBD patients produced significantly more IL-17 than from healthy donors, whereas there was no difference in IL-2 and TNF- α production^[49]. MAIT cells from UC patients produced more IL-22, a Th17-cytokine,

than controls. Upon binding to its cognate receptors on respiratory and gut epithelial cells, IL-22 evoked the expression of mucin and antimicrobial peptides, both of which play a critical role in the protection of epithelial cells from bacteria and/or fungal invasion^[50]. Expression of these proteins may in turns enhance the protection and accelerate healing of cellular damage, implying the tissue protective functions of MAIT cells^[49].

Numerous studies have reported possible implications of MAIT cells in psoriasis^[51], celiac disease^[52], systemic lupus erythematosus^[53], diabetes^[54,55] and obesity^[55,56]. In our recent study, MAIT cells were shown to be useful to distinguish diseases that manifest similar symptoms such as fibromyalgia syndrome, rheumatoid arthritis, and spondyloarthritis by measuring the expression of cell surface antigens, in particular, chemokine receptors associated with homing^[57]. MAIT cells tend to migrate toward peripheral tissues, particularly in inflammatory conditions, because they express a variety of chemokine and cytokine receptors. Most of these studies have implied that immune-mediated tissue damage is induced by the pathogenic proinflammatory features of MAIT cells. In contrast, MAIT cells may protect against the damage caused by inflammation, as described above for UC. Furthermore, a subset of MAIT cells (CD56⁻) accumulated in kidney and brain tumors and may operate in tumor immune responses^[58].

As detailed above, there is no doubt about the importance of understanding the functions of MAIT cells in health and disease. However, the following questions still remain to be answered: What are the underlying mechanisms in immune regulation, particularly in innate immunity? And what are the molecules that control the functions of MAIT cells other than vitamin B2 metabolites? Although laboratory mice are useful to model human diseases, the study of MAIT cells is quite limited owing to their paucity in mice^[18]. Furthermore, MAIT cells hardly propagate *in vitro*^[11]. A recent paper, however, has showed the potential for MAIT cells to proliferate in response to *E. coli* and to anti-CD3/CD28/CD2 antibodies^[33]. The expansion most likely depends on an precise balance between proliferation and activation-induced cell death, because MAIT cells are highly sensitive to activation-induced cell death^[33,38,59]. To overcome these difficulties, we attempted to produce human MAIT cells through iPSC technology.

GENERATION OF MAIT CELLS USING MAIT CELL-DERIVED iPSCS

iPSCs may be established from a variety of somatic cells^[60-62] and be differentiated into T cells, as can embryonic stem cells (ESCs)^[63-65]. Nonetheless, it is near-impossible to obtain a monoclonal T cell with an antigenic specificity. This is primarily due to the fact that iPSCs and ESCs carry the germline configuration of *TCR α* and *TCR β* , which are subject to random gene rearrangement during T cell differentiation, resulting in the generation of polyclonal T cells (Figure 2)^[65]. Although iPSCs have been

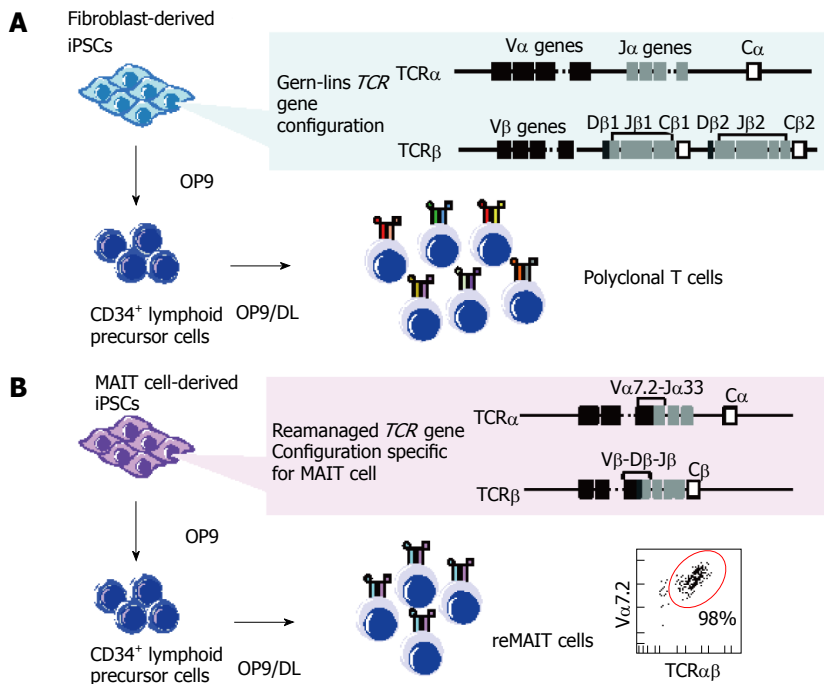


Figure 2 Scheme for T cell differentiation from induced pluripotent stem cells. Induced pluripotent stem cells (iPSCs) derived from normal somatic cells such as fibroblasts possess the germline configuration at T cell receptor (TCR) loci, whereas those from T cells harbor rearranged configurations (A); Upon differentiation in the T-cell-permissive conditions, the resulting T cells possess diverse sets of TCR repertoires; polyclonal T cells. In contrast, mucosal-associated invariant T (MAIT) cells-derived iPSCs exclusively confer MAIT cells in the same differentiation conditions. Note that MAIT cell-derived iPSCs possess a rearranged V α 7.2-J α 33 specific for MAIT cells in the genome (B).

established with terminally differentiated T cells in PBMC, the authors did not address whether or not differentiation of these iPSCs into T cells culminated in regeneration of an antigen-specific T cell clone^[66-68]. Recently, however, iPSCs have been established from tumor antigen-specific or HIV-specific CD8⁺ T cells with intention to rejuvenate T cells harboring the original epitopes, although the efficiency of such redifferentiation into the original clone remains unclear^[69,70]. Well before these reports, we have shown that the progeny of a cloned mouse from NKT cells possessed an in-frame rearranged *TCR α* (V α 14-J α 18) specific for NKT cells in the genome, and an increased number of NKT cells^[71]. This indicated that in-frame rearranged *TCR α* (V α 14-J α 18) had a strong impact on the destiny of T cells in the thymus. Such a notion has been explored further *in vitro*. ESCs prepared through nuclear transfer with hepatic NKT cells (ntESCs), harboring in-frame rearranged *TCR α* (V α 14-J α 18), gave rise to T lymphocytes exclusively comprising NKT cells (> 94%) when ntESCs were subjected to the OP9/OP9-DL system, which is well-known to promote T cell lineage differentiation from pluripotent stem cells^[64,65,72,73]. We have exploited a corollary that iPSCs derived from MAIT cells would efficiently redifferentiate into MAIT cells under the same conditions, because MAIT cells are innate-like T cells, and these iPSCs possess a rearranged *TCR α* (V α 7.2-J α 33), specific for MAIT cells^[21]. This turned out to be the case.

MAIT cells purified from umbilical cord blood (CB-MAIT) as TCR V α 7.2⁺ cells were reprogrammed with Sendai virus (SeV) vector harboring four reprogramming factors (*Oct4*, *Sox2*, *Klf4* and *c-Myc*) (MAIT-iPSCs) without any proliferative stimulation as used in reprogramming of antigen-specific CD8⁺ T cells^[69,70]. SeV is superior to other viruses, such as lentivirus, in that SeV

does not integrate into the host genome, thus leaving the genomic DNA free from interruptions^[21,67,69,74]. As expected, MAIT-iPSCs successfully redifferentiated into MAIT cell-like cells expressing V α 7.2, CD3, CD161, and IL-18R α (reMAIT cells) with high efficiency (> 98%) in T-cell-permissive conditions (Figure 2)^[21]. reMAIT cells generally display a naïve phenotype, but express a high level of CCR6 (a receptor directing mucosal tissue homing and IL-17 expression), recapitulating that CB-MAIT cells that are still in an immature stage prior to exposure to commensal flora^[16,17,21,75,76]. Furthermore, reMAIT cells produce an array of cytokines, chemokines, and cytotoxic granules, such as granulysin, perforin and granzyme A, in an MR1-dependent manner. reMAIT cells also protect mice from Mycobacterial infection upon adoptive transfer, holding a promise to realize cell therapy with these cells^[21]. Taken together, reMAIT cells should function as innate-like T cells, although they are still immature^[16,17,21].

FUTURE PERSPECTIVES – DISEASE MODELING USING MAIT CELLS DIFFERENTIATED FROM iPSCS

reMAIT cells generated from iPSCs will be useful not only for deciphering their immunological functions *in vivo* but also for creating novel disease models in animals. Two types of genetically engineered mice, MR1-knockout mice and TCR transgenic mice, have been widely used to delineate the roles of MAIT cells *in vivo* (Tables 2 and 3). Originally, MR1-knockout mice (MR1^{-/-}) were generated to assess the roles of MR1 in the selection and expansion of MAIT cells *in vivo*^[18]. MR1-knockout mice possessed severely decreased TCR V α 19-J α 33

Table 2 Mice used in study for mucosal-associated invariant T cells

	Genotype	Characteristics	Ref.
Knockout mice	MR1 ^{-/-}	Impaired development of MAIT cells	[79]
Transgenic mice	V α 19 iTCR Tg	Enriched MAIT cells	[17,78-80]
	V β 6 V β 8 Tg	Increase of MAIT cells	[17]

MAIT: Mucosal-associated invariant T; iTCR: Invariant T cell receptor.

Table 3 Mucosal-associated invariant T cells in the diseases

Category	Mouse strains	Disease model	Phenotype	Ref.
Bacterial infection	MR1 ^{-/-}	<i>Escherichia coli</i>	Increase in the bacterial burden	[16]
	V α 19 iTCR Tg	<i>Micobacterium abscessus</i>	Repression of the bacterial burden	
	V β 6 V β 8 Tg			
	MR1 ^{-/-}	<i>Klebsiella pneumoniae</i>	Increased susceptibility to <i>K. pneumoniae</i> infection	[36]
Autoimmune diseases	MR1 ^{-/-}	<i>Mycobacterium bovis</i> BCG	Enhanced bacterial growth at the early stage of infection	[35]
		<i>Francisella tularensis</i>	Delayed adaptive immune reaction	[34]
	V α 19 iTCR Tg	Experimental autoimmune encephalomyelitis (model of MS)	Suppressed disease induction and progression	[78]
	MR1 ^{-/-}	Collagen-induced arthritis (model of rheumatoid arthritis)	Improved CIA score	[86]
	Adoptive transfer J α 33 ⁺ MAIT cells into BALB/c B10.RIII	TNBS induced colitis	Improved disease index	[105]
Others	V α 19 iTCR Tg NOD	Spondyloarthropathy by IL-23	Enthesitis induced by IL-22 produced from IL-23R ⁺ ROR γ ^t CD4 ⁺ CD8 ⁻ T cells (MAIT cells?) in the entheses	[91]
	V α 19 iTCR Tg	Non-obese diabetes	Delayed disease onset	[106]
		Delayed-type hypersensitivity to sheep erythrocytes (type IV allergy)	Suppression of the disease	[106]

MAIT: Mucosal-associated invariant T; IL: Interleukin; CIA: Collagen-induced arthritis; iTCR: Invariant T cell receptor.

expression compared with their littermate controls^[18]. Thus far, MR1-knockout mice have been used as a model devoid of MAIT cells. MR1-knockout mice may have shed light on the roles of MAIT cells *in vivo*. However, the findings from the mice were too complicated to interpret, maybe because in part of the insufficient number of MAIT cells in the control, and the lack of an appropriate reagent to detect mouse MAIT cells. An MR1 tetramer that has been created recently is useful to detect MAIT cells in mice and humans^[77], but tetramer-positive cells may not always be functional cells. Three groups have independently reported V α 19 iTCR transgenic mice as a MAIT cell-enriched model^[17,78-80]. Two reports indicated that MAIT cells in V α 19 iTCR transgenic mice harbored an effector/memory phenotype; CD44^{high}CD69⁺CD25⁺ICOS⁺ and NK1.1^[78-80]. With the ligand-loaded MR1 tetramer, it was found that approximately 40%-50% of MAIT cells were CD4⁺, and the rest being comprised of DN cells and fewer CD8⁺ MAIT cells^[77], whereas in humans few CD4⁺ MAIT cells are present. Such a difference in CD4 or CD8 usage between mouse and human may reflect their physiological roles. In contrast, Martin *et al.*^[17] showed that MAIT cells from their V α 19iTCR transgenic mice were DN and CD8⁺ with few CD4⁺. Furthermore, NK1.1, CD25, CD69, and ICOS were not present in MAIT cells. Such inconsistency demonstrated that MAIT cells

are different in nature from those in transgenic mice. It is plausible that such an alteration stems from the differences in transgenes or commensal flora utilized. Should it be the case, the transgenic mouse may not be adequate to delineate the functions of MAIT cells^[17]. Therefore, it is indispensable to create a novel animal model to address the physiological roles of MAIT cells in health and diseases, and harnessing the results of animals for clinical applications.

In this context, use of humanized mice can be envisaged, because the human cells in question can be engrafted and their functions and development may be examined *in vivo*^[81]. To study the physiological roles *in vivo*, reMAIT cells were adoptively transferred to NOD/SCID or NOG (NOD/Shi-scid IL2R γ ^{null}) mice, both of which are devoid of mature B, T cells, and the later deficient in NK cells, functional macrophages, and dendritic cells^[21]. reMAIT cells migrated and engrafted in tissues such as the intestines, bone marrow, liver, and spleen, which probably mirrors the distribution of MAIT cells in humans^[18,71]. In addition, reMAIT cells dramatically changed the phenotype from naive to mature concomitant with the expression of the chemokine receptors required for the tissue-specific homing. Moreover, reMAIT cells appeared to proliferate in mice, whereas they did not *in vitro*. These results indicated that reMAIT cells from iPSCs responded to external

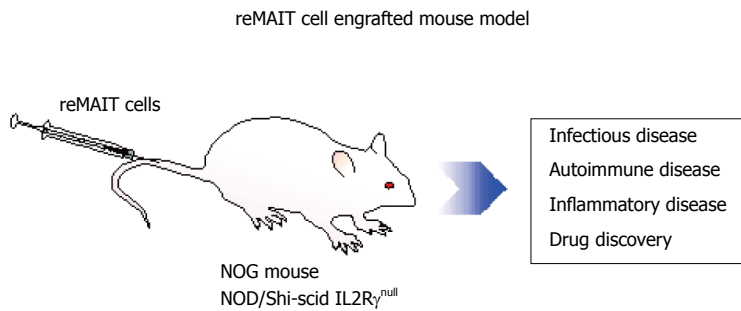


Figure 3 Utility of mucosal-associated invariant T cells from induced pluripotent stem cells (redifferentiation of mucosal-associated invariant T cells) for modeling human diseases. Severely immunocompromised mice received MAIT cells from induced pluripotent stem cells. reMAIT cells are useful for deciphering the physiological functions of MAIT cells in health and disease. MAIT: Mucosal-associated invariant T; reMAIT: Redifferentiation of MAIT.

cues, migrated to different tissues, and proliferated in mice. Such interactions most likely occur *via* chemokine receptors on reMAIT cells and *via* mouse MR1 bound with ligands from commensal flora or with an endogenous one. The data suggest that the function of reMAIT cells could be assessed *in vivo*, which opens up new horizons for modeling human diseases in mice.

Accordingly, the protective mechanisms of MAIT cells against bacterial infection have been examined using reMAIT cells^[71]. Upon adoptive transfer, reMAIT cells protected mice from *M. abscessus*, as demonstrated by a decrease in bacterial burden. Such a protective activity mirrors that observed with MAIT cells from PBMCs^[16]. Granulysin has been identified as an effector molecule in the control of mycobacterial infection. Granulysin is present together with granzymes and perforin in the cytolytic granules of cytotoxic cells such as CD8⁺ T and NK cells as well as MAIT cells^[32,82]. Granulysin plays a crucial role not only in the destruction of infected cells but also in killing pathogens^[83,84]. Given that mice are devoid of granulysin and its homologue^[85], mice harboring reMAIT cells could serve as a novel model to decipher the roles of human-specific factors.

There is accumulating evidence that MAIT cells play a pivotal role in inflammatory and autoimmune diseases. Nonetheless, delineating how MAIT cells are implicated in these diseases has to await the advent of appropriate animal models. Experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA) are animal models for MS and RA, respectively. By using V α 19 iTCR transgenic mice and/or MR1-knockout mice, the implication of MAIT cells in autoimmune diseases has been investigated^[78,86]. In V α 19 iTCR mice, the severity of EAE was ameliorated in both induction and progression of demyelination compared with control littermates^[78,86]. In marked contrast, the severity of CIA was improved in MR1-knockout mice, whereas adoptive transfer of MAIT cells from V α 19 iTCR transgenic mice resulted in aggravation of the disease^[78,86]. EAE and CIA are intended to induce autoreactive T cells, especially focused on Th17 or Th1 responses, through hyperimmunization of putative target antigens (myelin basic proteins or type II collagen) with Freund's adjuvant. Induced T cells could migrate to target tissues and secrete proinflammatory or anti-inflammatory cytokines, which may further worsen tissue damage or help resolve the damage. It has been believed that such mechanisms recapitulate the etiology and pathology

of human diseases. Nonetheless, it is not appropriate to use such mice for disease modeling because MAIT cells do not react with peptide antigens, although they may respond to the components of adjuvant such as those from *M. tuberculosis*. Furthermore, the paucity of murine MAIT cells is another issue. Even though V α 19 iTCR transgenic mice can be used in a disease model, the nature of transgenic MAIT cells may be different from that present in the control. Given that MAIT cells are competent to produce a plethora of cytokines, a nature prerequisite for immunoregulatory functions, the above disease models may not be suitable for deciphering the etiology and pathology, in that such a crucial feature of MAIT cells is largely overlooked or distorted.

Exploring a disease model with reMAIT cells could further our knowledge of the etiology and pathology of MS. It has been reported that inflammatory demyelinating lesions are infiltrated by IL-17-expressing T cells in the mouse brain when they received cerebrospinal fluid from a progressive MS patients^[87]. A longitudinal study in MS patients indicated massive expansion of MAIT cells or MAIT cell-like cells, harboring canonical or atypical TCR V α and β chains but do not react with bacterial antigens, could play an important role in the onset and the formation of early active MS lesions^[47]. The above data implied the presence of yet-to-be-identified ligands responsible for the negative effects of MAIT cells in disease. Use of reMAIT cells could make it possible to examine whether or not sole ligands for MR1 or any epigenetic modifications of MAIT cells are responsible for disease. In either case, mice with reMAIT cells are useful to identify such ligands and to create a novel autoimmune disease model.

Should MAIT cells play a pivotal role in autoimmune diseases, it is tempting to anticipate that granulysin *per se* or in combination with granzymes and perforin exerts a cytolytic activity against the target tissue. In line with this hypothesis, granulysin may play crucial roles in transplant rejection and epidermal necrosis in toxic epidermal necrolysis and Stevens-Johnson syndrome^[85,88,89]. Furthermore, combined with the ectopic expression of human cytokines and/or chemokines, mice with reMAIT cells could be further fine-tuned to mimic human diseases by controlling tissue migration^[90,91]. Provided such an exquisite model is available, we can go to the next step of drug discovery and/or screening. Compounds that interfere either with the development of MAIT cells or the function of MAIT cells can be screened

in such a mouse model (Figure 3).

CONCLUSION

Recent studies have shed light on the unique properties of MAIT cells and on their possible involvement in a variety of human diseases, although MAIT cells have been overlooked behind conventional T cells and other innate immune cells for a long time. The paucity of MAIT cells in laboratory mice and their extremely poor proliferative capacity are the biggest obstacles to fully understand the function of MAIT cells in health and diseases. Reprogramming and redifferentiation of MAIT cells from iPSCs have overcome these difficulties. Furthermore, mice with reMAIT cells will pave the way for unveiling the mechanisms underlying the diseases and open up new horizons in medical research.

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