

# Mucosal-associated invariant T cells in clinical diseases

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## Summary

**Mucosal-associated invariant T (MAIT) cells are innate-like T cells that recognize microbial infection via vitamin metabolites. The discovery of MAIT cells in the past two decades and the recent discovery of MR1 ligands has opened a new field and potential area for cellular immunotherapy using these unique cells. Their evolutionary conservation in mammals underscore their biological role in the host. In the past two years, we have been involved in the generation of MR1 tetramers as a tool for identification of these cells. Many groups have studied the role of these cells in clinical diseases.**

**Objective:** Here, we provide an up-to-date comprehensive review of clinical disease that have been studied with regards to MAIT cells.

**Results:** Original articles and review articles under the topic of MAIT cells and their relation to clinical diseases, both in human and animal models were included in the review.

**Conclusion:** MAIT cells are potential candidates for future cellular immunotherapy. However, more understanding of the biological role of MAIT cells need to be elucidated first. (*Asian Pac J Allergy Immunol 2016;34:3-10*)

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## Introduction

Mucosal-associated invariant T (MAIT) cells are a subset of innate-like T cells defined by their restriction to the non-classical MHC class I-related (MR1) molecule.<sup>1,2</sup> MAIT cells possess a T cell receptor (TCR) with limited diversity that is characterized by a semi-invariant TCR $\alpha$  chain (in humans, invariant Va7.2 pairing to Ja33, Ja12 or Ja20)<sup>3-6</sup> and a predominance of TCR $\beta$  chain from V $\beta$ 13 (TRBV6) and V $\beta$ 2 (TRBV20).<sup>3,4</sup>

MAIT cells preferentially accumulate in the gut lamina propria and thus were given the label “mucosal-associated”. However, these cells are also abundant in the blood circulation,<sup>7</sup> liver,<sup>8</sup> kidney, lymphoid organs (tonsils and lymph nodes), ovaries, prostate,<sup>5</sup> adipose tissue,<sup>9-10</sup> and the skin.<sup>11</sup> In humans, MAIT cells comprise 1-10% of peripheral blood T lymphocytes.<sup>12</sup> Their presence in human peripheral blood peaks at adulthood and declines with age.<sup>13-15</sup>

MAIT cells were originally identified as a CD4-CD8- (double negative; DN) T cell population,<sup>2</sup> but were further characterized showing a predominance of CD8 (in particular CD8 $\alpha\alpha$ > CD8 $\alpha\beta$ )<sup>3,16,17</sup> and DN cells. In a minority of cases, individuals may have MAIT cells expressing a dominant CD4 profile.<sup>3</sup> They are defined by their high expression of CD161 (CD161<sup>++</sup>) and IL-18R and their effector-memory phenotype (CD62L<sup>lo</sup>CD122<sup>int</sup>CD127<sup>hi</sup> CD95<sup>hi</sup>)<sup>7,16,18</sup> and exhibit chemokine receptors reflective of their tissue homing properties, which include CCR6, CXCR6, CCR5, cutaneous leukocyte antigen (CLA) and  $\alpha\beta$ 7 integrin<sup>7,11,18</sup> (Figure 1). Other phenotypic markers that MAIT cells also express include the cytokine receptors IL-12R, IL-23R, IL-2R $\beta$ ; chemokine receptors CCR9<sup>int</sup>, CCR7, CCR5<sup>hi</sup>; transcription factors ROR $\gamma$ t, PLZF and T-bet; the efflux pump ABCB1; and the c-type lectin-like protein NKG2D.<sup>7,17,19</sup> The presence of these surface receptors allow MAIT cells to respond both in an MR1-independent and MR1-dependent fashion;



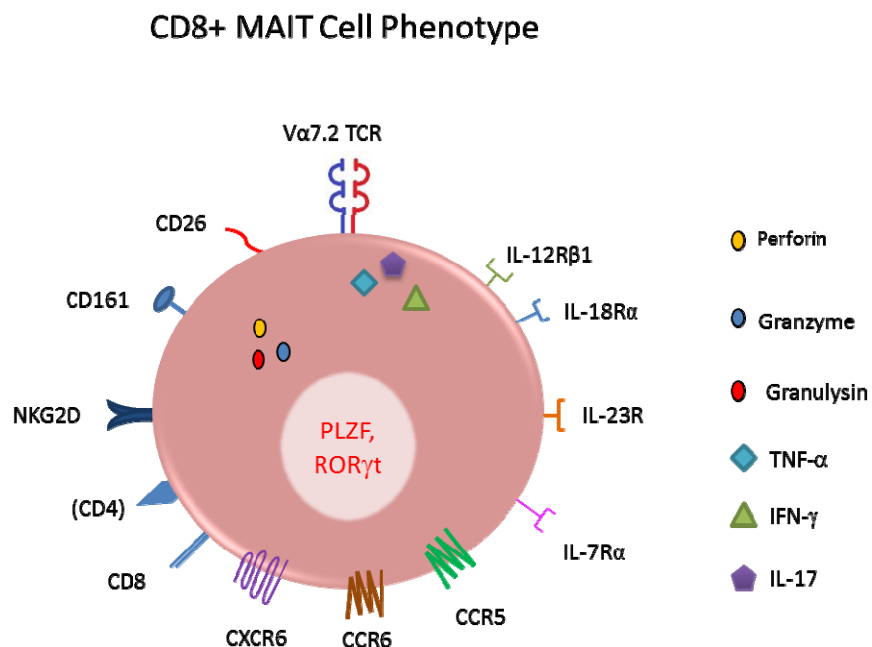
exhibit the ability to secrete a wide spectrum of cytokines and migratory potential to various sites of the host.

Experiments in mice and supported by *ex vivo* experiments of human thymic tissue suggest that MAIT cells are selected on hematopoietic MR1-expressing CD4+CD8+ thymocytes.<sup>20,21</sup> After thymic egress, MAIT cells express a naïve phenotype (CD45RA<sup>hi</sup>, CD27<sup>hi</sup> and CD45RO<sup>lo</sup>) and acquire their memory phenotype (CD45RA<sup>-</sup>, CD45RO<sup>+</sup>, CD62L<sup>lo</sup>, CD122<sup>int</sup>, CD127<sup>hi</sup> and CD95<sup>hi</sup>) prior to birth, as early as the second trimester, even prior to exposure to environmental microbes.<sup>7,19,21.</sup>

The requirements for MAIT cell development include the presence of microflora and B cells within the gut lumen, as MAIT cells are not detected in germ free and B cell deficient mice.<sup>1</sup> MAIT cells are restricted to the non-polymorphic, evolutionarily conserved MHC molecule, MHC class I-related (MR1) molecule.<sup>1,22-24</sup> Their restriction to MR1, which is ubiquitously expressed at low surface levels in cells, and the nature of the MR1 ligands allow potential presentation of MR1 ligands by various cell types and their recognition of microbes in an innate-like fashion.<sup>25,26</sup> MAIT cells have

proliferation capacity as seen with expression of Ki67<sup>19</sup> and proliferate in the presence of interleukin-1 (IL-1) and interleukin-8 (IL-8) cytokines.<sup>20,27</sup> MAIT cells exhibit a Th1 and Th17 cytokine profile and cytotoxic function via degranulation of perforin, granzyme and granulysin.<sup>7,8,28,29</sup>

In 2012, MR1 ligands were discovered by Kjer-Nielsen et al., which laid the foundation for understanding the basis of MAIT-stimulatory microbes as microbes that possess the riboflavin pathway.<sup>25</sup> The following few years, Corbett et al. described the generation of these MR1 ligands as formation of “neo-antigens”, in this case, pyrimidine adducts.<sup>26</sup> Only bacteria and yeasts possessing the riboflavin synthesis pathway were able to stimulate MAIT cells in an MR1-dependent manner; these included *Salmonella enterica* serovar Typhimurium, *Mycobacterium abscessus*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *S. epidermidis*, *Pseudomonas aeruginosa*, *Lactobacillus acidophilus*, *Candida glabrata*, *C. albicans*, and *Saccharomyces cerevisiae*.<sup>30</sup> Bacteria such as *Enterococcus faecalis*, *Listeria monocytogenes*, and group A *Streptococci* do not possess the riboflavin pathway, thus, were unable to stimulate MAIT cells.<sup>30</sup> MAIT cells can also be



**Figure 1.** Human CD8+ MAIT Cell Phenotype. Human MAIT cells are characterized by expression of Vα7.2 and CD161<sup>++</sup> on their surfaces. The majority of MAIT cells are CD8<sup>+</sup> and CD4<sup>-</sup>CD8<sup>-</sup> (DN). A very minimal proportion of MAIT cells are CD4<sup>+</sup>, except in rare cases.

activated via alternative pathways independent of MR1, which allows infectious conditions that may not activate MAIT cells directly through TCR-MR1 interactions, able to indirectly trigger MAIT cell responses eg. viral infections.<sup>1,12,31</sup>

Early studies of MAIT cells in clinical diseases suggest MAIT cell recirculation and enrichment at the site of local infection from peripheral blood in response to infection.<sup>12,28,30</sup> They have been shown to be protective against bacterial infections *in vivo*.<sup>12,28,31,32</sup> In this review, we focus on the clinical aspects of MAIT cells in human (and mouse) models in relation to various diseases. Reviews and key original articles on MR1,<sup>23,24,33-37</sup> MR1 ligands,<sup>38-40</sup> MAIT TCR repertoire<sup>4-6,41</sup>, MAIT TCR-MR1 structural basis of interaction<sup>25,26,42,43</sup> and MAIT cells in the context of unconventional T cells<sup>44,45</sup> have been described elsewhere.

### MAIT cells in infectious conditions

MAIT cells have been known to be involved in anti-bacterial responses from early studies by LeBourhis and Gold.<sup>12,30</sup> Many current studies have only observed correlation of disease with MAIT cell frequency; some have been able to show functional responses of MAIT cells in respond to particular microorganisms; and few have shown a protective role of MAIT cells in mouse models. Here, we review MAIT cell studies in pulmonary bacterial infections, gastrointestinal bacterial infections, sepsis and viral infections.

#### Pulmonary bacterial infections

MAIT cells have been reported to be present in the lungs<sup>46</sup> and early studies demonstrated their bacterial reactivity.<sup>1,12,30</sup> In 2010, Le Bourhis et al. and Gold et al. described a lower MAIT cell frequency in tuberculosis and pulmonary bacterial pathologies than those of healthy individuals and cancer patients.<sup>12,30</sup> Moreover, Le Bourhis demonstrated a higher frequency of MAIT cells from ascites of a patient with tuberculosis when compared to a patient who had ascites from a malignancy, suggesting their accumulation at local sites in response to a bacterial infection.<sup>12</sup> *Mycobacterium tuberculosis*-reactive MAIT cells were also present in the lungs of a healthy individual (lung biopsies obtained for a donor lung that was unsuitable for transplantation).<sup>30</sup> Later on, Jiang et al. also confirmed a similar finding of reduced MAIT cell frequency in active tuberculosis patients.<sup>47</sup> MAIT cells from tuberculosis patients (*M. tuberculosis*-infected) exhibit an increase in programmed death-1 (PD-1) expression, a T cell

exhaustion marker.<sup>47,48</sup> Blocking of PD-1 significantly improved IFN $\gamma$  production by MAIT cells isolated from active tuberculosis patients.<sup>47</sup> Chua et al. was able to depict *in vitro* inhibition of *Mycobacterium bovis* (BCG strain) growth in macrophages and that mice deficient of MAIT cells carried a higher bacterial load than wild-type mice.<sup>31</sup> Sakala et al. used an *in vivo* mouse model of both *M. bovis* (BCG Danish) strain and *M. tuberculosis* strain Erdman (ATCC 35801) and compared responses of MAIT cells by detection with a mouse MR1-5-OP-RU loaded tetramer in WT mice and transgenic mice.<sup>49</sup> Mice with the mycobacterial infection showed recruitment of MAIT cells into the lungs and provided early protection.<sup>49</sup>

Other pulmonary bacterial pathologies that have been studied in humans include cystic fibrosis (CF) with development of *P. aeruginosa* infection.<sup>50</sup> A decrease in MAIT cell frequency was observed in CF patients and even lower in CF patients who developed *P. aeruginosa* infection. This reduction of MAIT cell frequency correlated with the severity of the lung disease.<sup>50</sup> In addition, *in vivo* mouse models demonstrated that mice with MR1 were less susceptible to *K. pneumoniae* infection and had an increased rate of survival, reflecting the role of MAIT cells in bacterial control.<sup>32</sup> The dynamics of MAIT cell recruitment and accumulation within lung tissues in the case of a pulmonary bacterial infection was demonstrated in a mouse model of *Francisella tularensis* live vaccine strain infection.<sup>28</sup> Moreover, it was also shown that MAIT cell effector function was dependent upon the stage of infection.<sup>28</sup>

#### Gastrointestinal bacterial infections

Only a few pathogenic microorganisms of the gastrointestinal tract have been studied in the clinical aspect.<sup>51,52</sup> The gram negative, microaerophilic bacteria *Helicobacter pylori* infects the stomach where it increases the risk of gastritis and peptic ulcer, leading to gastric adenocarcinoma.<sup>53</sup> Booth et al. demonstrated MR1-dependent gastric and peripheral blood MAIT cell activation in response to *H. pylori*-infected macrophages *in vitro*.<sup>51</sup> MAIT cells were capable of secreting Th1 and Th17 cytokines and were able to kill *H. pylori*-infected macrophages. Moreover, they have also shown that MAIT cell frequency in the blood was reduced in *H. pylori*-infected patients when compared to *H. pylori*-non-infected individuals<sup>51</sup> consistent with the *M. tuberculosis* studies suggesting recruitment to sites of infection.

*Vibrio cholerae* O1 infection causes an acute diarrheal disease known as cholera.<sup>54</sup> Leung et al. showed that MAIT cell frequency in adults increased slightly, however this increase was statistically insignificant.<sup>52</sup> In children, *V. cholerae* O1 infection resulted in a decrease in MAIT cell frequency. The frequency of activated MAIT cells peaked at day 7 post infection and gradually declined to levels similar of healthy controls.<sup>52</sup> Moreover, MAIT cell responses also correlated with antibody responses to *V. cholerae* O1 lipopolysaccharide (LPS).<sup>52</sup>

Healthy individuals receiving the attenuated strain of *Shigella dysenteriae*-1 (SC599) showed MAIT cell activation compared to individuals receiving placebo or those who were considered non-responders (from B cell responses).<sup>29</sup> However, data from patients infected with this organism is lacking. Only *in vitro* experiments demonstrate reactivity towards *S. dysenteriae*, but not *S. Typhimurium*.<sup>29</sup>

### Sepsis

The only study to date on MAIT cells and sepsis was done by Grimaldi et al.<sup>55,56</sup> They depicted an early significant reduction in MAIT cell frequency in patients with severe bacterial infections.<sup>55</sup> This reduction was not observed with other innate-like T cells, such as  $\gamma\delta$ T cells or NKT cells. Also, non-streptococcal infection was a determinant of decrease in MAIT cell frequency.<sup>55</sup> This is not surprising as group A *Streptococcus* species do not activate MAIT cells directly.<sup>12</sup> These results suggest that the type of stimulatory or non-stimulatory species of pathogens may dictate MAIT cell responses in the host.<sup>55</sup>

### Viral infections: HIV, HBV, HCV

Despite the inability of viruses to stimulate MAIT cells directly (MR1-dependent manner), MAIT cells are able to sense viral-induced stress conditions and respond to the array of cytokines released from other immune cells when virally-infected. Moreover, chronic viral infection also leads MAIT cells to exhaustion.<sup>57-59</sup> The most widely studied viral infection, to date, in relation to MAIT cells is the human immunodeficiency virus (HIV). Many studies have reported the irreversible reduced frequency of peripheral and lymph nodal MAIT cells in HIV+ patients.<sup>57-64</sup> The earliest observation of MAIT cell frequency reduction in HIV+ patients was done by Walker et al. in 2013, where they described reduction of CD8 $\alpha$ CD161++ T cells, of which MAIT cells are a composition of this

population.<sup>64</sup> Two groups have shown that MAIT cells in HIV+ patients exhibit an increase in their activation status and correlated this activation status with the observed reduction in frequency.<sup>58,60</sup> Correlation between MAIT cell reduction and disease severity (high viral load HIV+, HIV+ on anti-retroviral treatment, HIV+ elite controllers and HIV+ long-term non-progressors) are somewhat still controversial.<sup>58,60</sup> Leeansyah et al. showed that MAIT cell frequency in elite controllers are similar to those of healthy individuals.<sup>58</sup> This is in contrast with Eberhard et al., who showed that the reduction was independent of disease status.<sup>60</sup> Moreover, the etiology for the reduction of MAIT cells observed in HIV+ patients is still in debate. Despite MAIT cells being reported to downregulate CD161 upon activation<sup>58,60,65</sup>, studies by Ussher et al. suggest otherwise. Their results revealed a correlation between V $\alpha$ 7.2J $\alpha$ 33 mRNA transcript levels from HIV+ patients and V $\alpha$ 7.2+CD161++ population frequency when detected with cellular reagents.<sup>66</sup> Thus, the absence of MAIT cells was not due to a shift in the surface expression of MAIT-cell defining markers. However, an earlier study proposed that MAIT cells in HIV+ patients may undergo microbial activation-induced cell death via microbial translocation in the gut after intestinal gut integrity.<sup>57</sup> In addition, the diminished frequency of MAIT cells in HIV+ patients may also attribute to more opportunistic infections as MAIT cells are anti-microbial in nature and that depletion of these anti-microbial cells renders the host more vulnerable to bacterial/yeast infections.<sup>59,67</sup> Saeidi et al. observed a more pronounced reduction in peripheral blood MAIT cell frequency and an increase in programmed death-1 (PD-1) expression, indicating exhaustion, in HIV+ patients co-infected with pulmonary tuberculosis when compared to mono-infected HIV+ patients.<sup>59</sup> However, the alteration of gut mucosal MAIT cell frequency is still inconclusive as one study demonstrated a reduction of colonic MAIT cells from HIV+ patients and frequency was restored with anti-retroviral therapy,<sup>63</sup> whereas another group showed that colonic MAIT cell frequency was preserved in HIV+ patients when compared to healthy individuals.<sup>58</sup> Apart from the reduction in MAIT cell frequency in HIV+ patients, MAIT cell cytokine function was also affected. MAIT cells in HIV+ individuals displayed a lower ability to secrete cytokines, but this defect was partially restored with anti-retroviral therapy.<sup>58</sup> Recently, Leeansyah et al. showed that restoration of MAIT cell cytolytic

effector function can be achieved with interleukin-7 (IL-7),<sup>68</sup> which has been previously reported in its role in licensing resting MAIT cells into an effector status.<sup>8</sup>

MAIT cells were identified as tissue resident immune cells that responded to a pattern-recognition receptor agonist (TLR8 agonist) indirectly via IL-12 and IL-18 activation.<sup>69</sup> This may mimic mechanisms in patients infected with hepatitis C (HCV) and hepatitis B virus (HBV) because MAIT cells do not respond directly to viruses. In HBV+ patients, a more heterogeneity population of CD8 $\alpha\alpha$ /CD8 $\alpha\beta$  expressing T cells were observed, of which MAIT cells make up a component of this population.<sup>64</sup>

### MAIT cells in immune-mediated diseases

MAIT cells have been studied in non-infectious diseases, such as localized inflammatory and systemic immune-mediated diseases, in terms of their frequency and function in relation to disease severity/status. These diseases include both conditions related to the mucosa (gastrointestinal and respiratory disease) and non-mucosal tissue (systemic and cutaneous). Here, we describe MAIT cells in relation to gastrointestinal inflammation conditions, pulmonary diseases and auto-immune diseases.

#### *Gastrointestinal inflammation conditions*

The abundance of MAIT cells in mucosal tissue, especially the lamina propria, suggests their role in gastrointestinal diseases.<sup>1</sup> An early study addressing the role of MAIT cells in bowel inflammation was performed in a mouse model of TNBS-induced colitis. Accumulation of MAIT cells correlated with improvement of colitis.<sup>70</sup> Clinical studies in humans to investigate the role of MAIT cells in bowel inflammation was performed in patients with Crohn's disease and ulcerative colitis, termed inflammatory bowel disease (IBD). IBD patients had a decrease in peripheral blood MAIT cell frequency than healthy individuals. However, recruitment of peripheral blood MAIT cells to the intestinal lumen in IBD patients was reflected in higher frequency of intestinal MAIT cells in inflamed tissue when compared to healthy tissue.<sup>71</sup> In addition, peripheral blood MAIT cells exhibited an altered phenotype and alteration in cytokine response patterns than healthy individuals.<sup>71</sup> However, this finding was challenged by another group who showed similar peripheral blood MAIT cell frequency in IBD patients, but intestinal MAIT cells in inflamed tissue had also a lower frequency than adjacent (10 cm away) healthy tissue.<sup>72</sup> Hiejima

et al. also proposed that the reduction of MAIT cell frequency observed in IBD patients may be due to their pro-apoptotic status, as IBD patients possess higher levels of activated caspase-expressing MAIT cells.<sup>72</sup> In patients with acute cholecystitis (inflammation of the gallbladder), a decrease in circulating MAIT cell frequency was also observed when compared to healthy individuals (age- and sex-matched).<sup>73</sup>

#### *Pulmonary diseases*

Patients with chronic obstructive pulmonary disease (COPD), a disease characterized by inflammatory cellular infiltration and remodeling of the airways, had a reduction in peripheral MAIT cell frequency in both the double negative (DN; CD4-CD8-) and CD8+ population.<sup>48</sup> In severe asthmatic patients, a strikingly reduced number of MAIT cell frequency in peripheral blood of these patients were observed; which was in contrast to the consistent frequency of other T cell subsets (Th2, Th17 and Treg cells) present in severe asthmatic patients compared to healthy individuals. Moreover, this association was related with corticosteroid therapy and serum vitamin D3 levels.<sup>74</sup>

#### *Auto-immune diseases*

Many auto-immune conditions have been studied in the context of MAIT cells. These include multiple sclerosis (MS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), psoriasis and type 1 diabetes mellitus (T1DM).

A few groups have studied the frequency of MAIT cells in MS patients in relation to healthy individuals and other immune-mediated diseases.<sup>75-81</sup> However, studies remain controversial regarding the correlation of frequency of MAIT cells in relation to MS status. Earlier studies detecting MAIT cells using single-strand conformation polymorphism clonotype (SSCP) analysis in peripheral blood of MS patients showed that MAIT cells are not reduced in the peripheral blood when compared to healthy individuals.<sup>81</sup> A second group have shown that in MS patients, peripheral blood MAIT cells are reduced in the circulation, are inversely correlated with MS severity and that these MAIT cells are able to suppress IFN $\gamma$  production from non-MAIT cells.<sup>78</sup> Another group demonstrated an increase of CD161++CD8+ T cells (of which a proportion of cells that express Va7.2 are defined as MAIT cells) in peripheral blood of MS patients when compared to healthy individuals. Lesions of MS lesions in the brain were also observed to bear this CD161++CD8+ T cell

population.<sup>79</sup> It must be taken into consideration the different methods and limited reagents in defining MAIT cells among these studies. The generation of the monoclonal antibodies (mAbs) to V $\alpha$ 7.2 and MR1 tetramers now allow a more accurate definition of MAIT cell identification.<sup>3,16,25,26</sup>

More recently, Willing et al. have narrowed down the investigation to CD8<sup>+</sup> MAIT cells using the V $\alpha$ 7.2 mAb and the frequency of this subset in MS patients as CD8<sup>+</sup> T cells are predominantly infiltrated in MS lesions in the brain<sup>82</sup> and that the majority of MAIT cells possess the CD8 coreceptor.<sup>3</sup> Their finding confirmed findings from Miyazaki et al. that in MS patients, peripheral blood MAIT cells are reduced and proposed an IL-18-dependent recruitment of peripheral blood MAIT cells into MS lesions. Moreover, tracking of MAIT cell clones from brain tissue sections via a combination of immunohistochemistry, laser microdissection and single-cell multiplex PCR in an MS patient demonstrated the presence of identical clones of MAIT cells from brain tissue 18 years apart.<sup>76</sup>

Early *in vivo* experiments for models of MS include experimental autoimmune encephalitis (EAE) in V $\alpha$ 19i transgenic mice, where the researchers induced the progression of EAE by immunization with the myelin oligodendrocyte glycoprotein peptide at amino acids 35-55 (MOG 35-55).<sup>83,84</sup> MAIT cells provided a protective role in the EAE model.<sup>83,84</sup>

An adoptive transfer of MAIT cells to mice with type II collagen-induced arthritis, a mouse model of human RA, exacerbated arthritis by enhancing inflammation.<sup>85</sup> In SLE and RA patients, MAIT cells were shown to be reduced in frequency and dysfunctional (impaired IFN $\gamma$  production) when compared to healthy individuals and patient controls (included patients with ankylosing spondylitis (AS) and Behcet's disease.<sup>86</sup> However, the lower activity of cytokine production is probably due to other factors than direct T cell exhaustion of these cells as they expressed low levels of PD-1.<sup>86</sup>

The only study on psoriasis, by Teunissen et al., demonstrated the presence of MAIT cells in the skin (both dermis and epidermis) and an increase of MAIT cells in psoriatic dermis when compared to those of healthy dermis.<sup>11</sup>

In juvenile type 1 diabetes mellitus (Type 1 DM) patients, MAIT cell frequency observed was at similar levels as those of controls and did not decrease as observed in cases of other diseases.<sup>87</sup> However, long standing (>1 year) T1DM patients

failed to increase as one would expect that the frequency of peripheral blood MAIT cells increase with age.<sup>14</sup> Thus, one possible explanation is that there is actually depletion of peripheral blood MAIT cells in long standing T1DM patients.<sup>87,88</sup> It is worth mentioning type 2 diabetes mellitus (Type 2 DM), in which etiology is not mediated by autoimmunity as such the case in T1DM. Magalhaes et al. performed a study in T2DM and obese patients and showed that peripheral blood MAIT cell frequency was decreased and exhibited an activated phenotype accompanied by an elevated Th1 and Th17 cytokine profile, whilst MAIT cells were more abundant in adipose tissue than in the blood and also exhibited a striking Th17 cytokine profile as well.<sup>10</sup> Obesity was also observed as another factor that related with a lower frequency of peripheral blood MAIT cells.<sup>9,10</sup> Bariatric surgery in obese patients reversibly increased MAIT cell frequency by 3 months post-operative.<sup>10</sup>

### MAIT cells in malignant diseases

The majority of MAIT cells express CD8, along with their ability to degranulate cytotoxic granules and kill target cells.<sup>29</sup> However, MAIT cells have not been studied in the tumor setting widely yet. Up to date, only a few models of human malignancy (both solid tumors and hematologic malignancies) have been investigated.<sup>89-93</sup>

The first study of MAIT cells present in malignant lesions was performed by Peterfalvi et al., where they tracked MAIT cells in kidney and brain tumors via SSCP.<sup>89</sup> Without any cellular MAIT tracking reagent, they have amplified transcripts of the invariant V $\alpha$ 7.2-J $\alpha$ 33 TCR $\alpha$  chain from tumor infiltrating T cells and proposed their role in secretion of pro-inflammatory cytokines.<sup>89</sup>

Two studies with similar results regarding colon malignancy and MAIT cell correlation were reported. The first study performed a retrospective study investigating MAIT cell infiltration in colonic tissue sections within the tumor site compared to adjacent healthy tissue in colorectal cancer.<sup>91</sup> They reported a correlation between a higher recruitment of MAIT cells in the tumor site, when compared to neighboring healthy tissue, with a poor outcome of the disease.<sup>91</sup> The second study similarly examined colonic MAIT cells and compared to adjacent healthy tissues in patients with colon adenocarcinomas.<sup>90</sup> Their results show that there was increased MAIT cell infiltration at the tumor site when compared to unaffected tissue. Investigation into the functional capacity of MAIT

cells demonstrated their defective ability to secrete IFN $\gamma$  and this suppression was due to secreted factors from the tumor microenvironment.

Furthermore, unpublished data from Wallace et al. reports MAIT cell deficiency found in chronic lymphocyte leukemia, a clonal malignant B cell malignancy in the peripheral blood.<sup>92</sup> McGregor et al. also reported peripheral T-cell lymphoma (PTCL) originating from MAIT cells for the first time.<sup>93</sup>

### Future directions

Many studies as reviewed here have tried to correlate MAIT cell frequency with disease, with a few studies demonstrating their phenotypic function in disease. MAIT cells stand as a potential target for MR1 ligands as these cells are present at the highest frequency, when compared to other T cell subset of other specificity.<sup>44</sup> Their abundance in mucosal tissue and ability to recirculate and mobilize within the host to sites of infection, make these cells an even more promising candidate. Moreover, MAIT cells function in an “innate-like” fashion, meaning that their effector functions is always “armed” and respond to antigens very rapidly. However, if MAIT cell agonists are to be used in disease-settings, further studies on the role of MAIT cells in each disease must be elaborated first.

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