

## REVIEW

# MAIT cells: new guardians of the liver

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The liver is an important immunological organ that remains sterile and tolerogenic in homeostasis, despite continual exposure to non-self food and microbial-derived products from the gut. However, where intestinal mucosal defenses are breached or in the presence of a systemic infection, the liver acts as a second 'firewall', because of its enrichment with innate effector cells able to rapidly respond to infections or tissue dysregulation. One of the largest populations of T cells within the human liver are mucosal-associated invariant T (MAIT) cells, a novel innate-like T-cell population that can recognize a highly conserved antigen derived from the microbial riboflavin synthesis pathway. MAIT cells are emerging as significant players in the human immune system, associated with an increasing number of clinical diseases of bacterial, viral, autoimmune and cancerous origin. As reviewed here, we are only beginning to investigate the potential role of this dominant T-cell subset in the liver, but the reactivity of MAIT cells to both inflammatory cytokines and riboflavin derivatives suggests that MAIT cells may have an important role in first line of defense as part of the liver firewall. As such, MAIT cells are promising targets for modulating the host defense and inflammation in both acute and chronic liver diseases.

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## INTRODUCTION

Enteric commensals and pathogens are usually confined to the gut by the intestinal epithelium and mesenteric lymph nodes, but in the presence of intestinal inflammation and increased permeability, the liver is the first organ to receive gut-derived bacteria and their products. Thus, the liver functions as a second 'firewall', clearing commensals from the portal circulation where intestinal defenses are overwhelmed,<sup>1</sup> and is enriched with a number of innate immune cells, including Kupffer cells (liver-resident macrophages), natural killer (NK) cells and innate-like T cells. In the human liver, mucosal-associated invariant T cells (MAIT) cells are the most dominant population of innate-like T cells, comprising up to 50% of all T cells in the liver,<sup>2</sup> which is in contrast to invariant NKT cells (iNKT; ~1%) and  $\gamma\delta$  T cells (~15%).<sup>3,4</sup>

The invariant T-cell receptor (TCR) rearrangement of MAIT cells, V $\alpha$ 7.2-J $\alpha$ 33, was first identified during an extensive analysis of the TCR repertoire of human CD4<sup>-</sup>CD8<sup>-</sup> (double-negative; DN) T cells, Porcelli *et al.*<sup>5</sup> and subsequently shown to be characteristic of a novel population restricted by the non-polymorphic and highly evolutionarily conserved major histocompatibility complex (MHC) class Ib molecule, MHC class I-related protein 1 (MR1).<sup>6,7</sup> The relative abundance of V $\alpha$ 7.2-J $\alpha$ 33 transcripts in human gut biopsies, as well as the enrichment of homologous V $\alpha$ 19-J $\alpha$ 33 transcripts among murine lamina propria lymphocytes compared with intraepithelial lymphocytes or mesenteric lymph nodes,<sup>7</sup> led to this population being called MAIT cells. Importantly, these cells were found to be broadly reactive to bacterial and yeast species,<sup>8,9</sup> because of their ability to

recognize metabolic intermediates of the microbial riboflavin synthesis pathway.<sup>10</sup>

Despite their name, in humans MAIT cells are most enriched in the liver, constituting 20–50% of intrahepatic T cells.<sup>2,11</sup> The dominance of MAIT cells in the liver suggests that they have a major defensive role in maintaining the liver firewall and in driving liver inflammation in disease. In this article, we will discuss what is currently known about MAIT cell biology, and explore what role MAIT cells may have in maintaining liver homeostasis and in liver disease.

## MAIT CELL BIOLOGY

### MR1 and its ligand

MR1 is an antigen-presenting molecule first sequenced in 1995,<sup>12</sup> and in contrast to the highly polymorphic MHC class I molecules, it is highly conserved among mammals,<sup>13,14</sup> with the  $\alpha$ 1– $\alpha$ 2 domains of human and mouse MR1 being 89–90% identical.<sup>13,15</sup> MR1 expression is essential for the development of MAIT cells, which are absent in MR1<sup>-/-</sup> mice.<sup>7</sup>

Two seminal papers in 2010 showed that MR1-restricted MAIT cells could be activated by various species of bacteria and yeast, and were critical for early protection against bacterial infections.<sup>8,9</sup> These reports, together with the observation that MAIT cells are absent in germ-free mice,<sup>7,8</sup> suggested that MR1 presents a microbial ligand. The nature of the MR1 ligand was subsequently discovered by Kjer-Nielsen *et al.*<sup>10</sup> who showed that MR1 can present derivatives of the highly conserved riboflavin and folic acid synthesis pathways. MAIT cells are, therefore, activated by organisms possessing the riboflavin synthesis pathway, including *Mycobacteria*, *Enterobacter*,

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*Pseudomonas*, *Salmonella* and *Candida* species, but not those lacking it (e.g. *Streptococcus pyrogenes* and *Enterococcus faecalis*).<sup>8,9</sup> The most potent MAIT cell activatory ligand found to date is 5-OP-RU (5-(2-oxopropylideneamino)-6-D-ribitylaminouracil), generated from the non-enzymic condensation of an early intermediate of the riboflavin synthesis pathway with glyoxal or methylglyoxal byproducts.<sup>16</sup> Folate-based ligands such as 6-formylpterin and its synthetic analog, acetyl-6-formylpterin, have also been shown to inhibit conventional MAIT cell activity,<sup>17,18</sup> but can activate non-conventional, folate-reactive MAIT cells.<sup>19</sup> MR1-tetramers loaded with riboflavin and folate intermediates have subsequently allowed the specific detection and characterization of human and murine MAIT cells.<sup>16,19–21</sup>

The MR1 transcript is ubiquitously expressed,<sup>12,13</sup> but endogenous surface expression of MR1 has been difficult to detect.<sup>22,23</sup> Recently, however, it was demonstrated that MR1 accumulates in the endoplasmic reticulum in an incompletely folded form, and in the absence of bound ligands only a few MR1 molecules traffic to the surface.<sup>24</sup> Increased ligand availability leads to the association of MR1 with  $\beta$ 2-microglobulin and egress of the MR1- $\beta$ 2-microglobulin-ligand complex,<sup>24</sup> inducing rapid MR1 surface expression.<sup>17,24,25</sup> MR1 surface expression also increases with the nuclear factor- $\kappa$ B-dependent activation of antigen-presenting cells.<sup>26</sup> This contrasts with MHC class II and CD1, which capture their exogenous ligands in endosomal compartments and are highly expressed even in the absence of infection.<sup>24</sup>

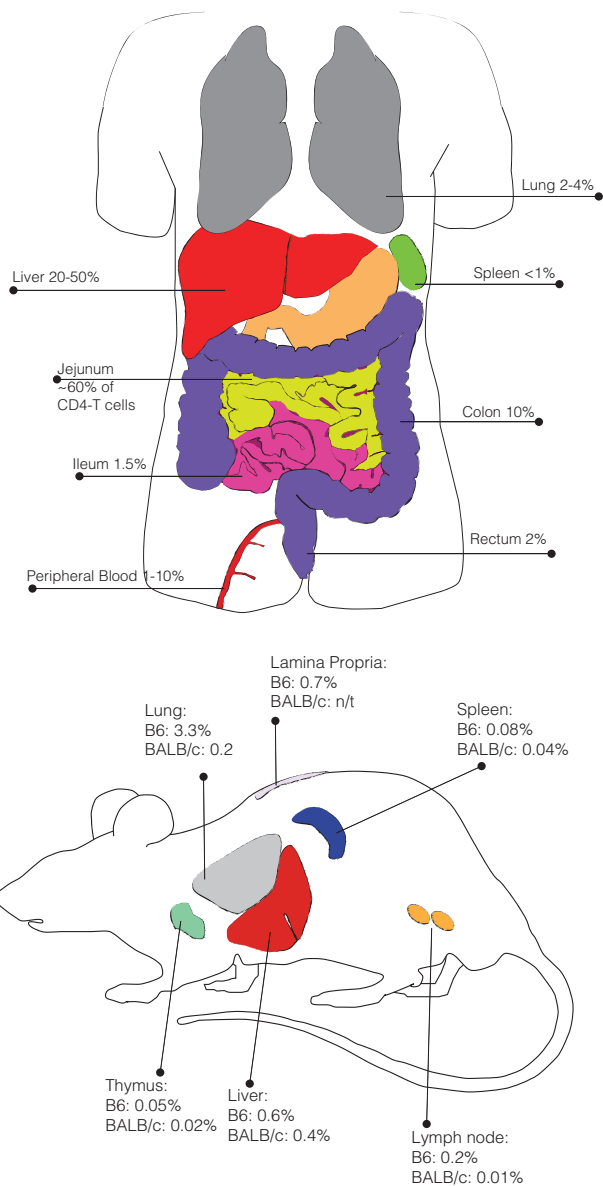
### MAIT cell TCR

The MAIT cell TCR is semi-invariant and relatively evolutionarily conserved within mammals.<sup>6,27</sup> The majority of human MAIT cells express the canonical TCR $\alpha$  chain, V $\alpha$ 7.2-J $\alpha$ 33, although V $\alpha$ 7.2-J $\alpha$ 12 or V $\alpha$ 7.2-J $\alpha$ 20 are also used by a minority of MAIT cells.<sup>20,28</sup> These TCR $\alpha$  chains are preferentially paired with V $\beta$ 2 or V $\beta$ 13.2 in humans.<sup>20,28</sup> In mice, MAIT cells express V $\alpha$ 19-J $\alpha$ 33 that is paired with V $\beta$ 6 or V $\beta$ 8,<sup>6,20,28</sup> although V $\beta$  usage can be variable.<sup>6,20,29</sup> Recently, human nonclassical MR1-restricted T cells that have a diverse TCR repertoire and do not express the V $\alpha$ 7.2 TCR chain have also been identified, which are preferentially activated by folate-based ligands,<sup>19</sup> analogous to type II NKT cells.

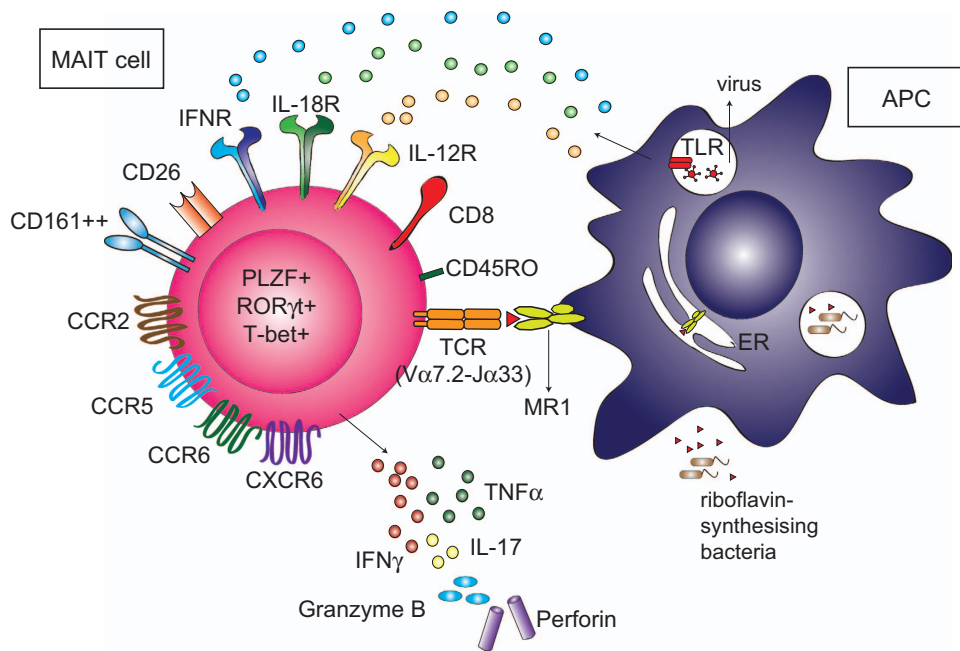
### MAIT cell tissue distribution

MAIT cells are rare in lymphoid tissues,<sup>2,30</sup> because of their lack of CCR7 and CD62L expression, required for lymph node homing.<sup>2,31</sup> Instead, MAIT cells preferentially home to peripheral tissues, mediated by expression of chemokine receptors CCR6 and CXCR6, gut-homing integrin- $\alpha$ 4 $\beta$ 7 and low levels of CCR9.<sup>2,7</sup> Indeed, they are called 'mucosal-associated' because the V $\alpha$ 7.2-J $\alpha$ 33 transcript was enriched in the human gut compared with skin tissues when they were initially characterized.<sup>7</sup> MR1-tetramer studies have since confirmed their enrichment in the gut with different MAIT cell frequencies reported at different anatomical locations within the gastrointestinal tract. A higher frequency of MAIT cells are present in the jejunum (~60% of CD4<sup>+</sup> T cells)<sup>20</sup> compared with reported frequencies in healthy ileum (1.5% of T cells),<sup>32</sup> colon (10% of T cells)<sup>33,34</sup> and rectum (2% of T cells)<sup>35</sup> (Figure 1). Importantly, MAIT cells are further enriched within the liver (20–50% of T cells), as will be discussed later.<sup>2,36,37</sup> MAIT cells are also abundant in human peripheral blood (1–10% of T cells)<sup>2</sup> and the lungs (2–4% of T cells).<sup>38</sup> A lower frequency of MAIT cells is also present in the endometrium and the cervix,<sup>39</sup> and MAIT cell TCR transcripts have been reported in tissues such as kidneys, prostate and ovaries.<sup>28</sup>

In contrast to humans, MAIT cells are rare in commonly used laboratory strains of mice,<sup>6,40</sup> with the exception of the CAST/EiJ strain,<sup>41</sup> and, therefore, the majority of murine studies have used invariant V $\alpha$ 19-J $\alpha$ 33 TCR transgenic (V $\alpha$ 19i-transgenic) mice.<sup>40</sup> MR1 tetramers have allowed characterization of wild-type murine MAIT cells, however, showing that in C57BL/6 mice, for example, there is an enrichment of MAIT cells in the lung (mean 3.3% of T cells), liver (0.6% of T cells) and lamina propria (0.7% of T cells).<sup>21</sup> Interestingly, the frequency of MAIT cells in the tissues of wild-type mice has been shown to markedly increase upon infection with *Francisella tularensis* live-vaccine strain,<sup>42</sup> *Salmonella* Typhimurium or intranasal administration of 5-OP-RU in the presence of a toll-like receptor (TLR) agonist.<sup>43</sup>



**Figure 1** Distribution of human and murine MAIT cells in tissues. The frequency of MAIT cells (defined either by MR1 tetramers or as CD161<sup>+</sup> V $\alpha$ 7.2<sup>+</sup> T cells) within T cells, as has been described in the indicated tissues of mice and humans. MAIT cells are enriched within peripheral organs including the liver and gut, whereas they are less enriched within lymphoid organs. However, MAIT cells are much more abundant in humans compared with common laboratory strains of mice.



**Figure 2** The phenotype of human MAIT cells and their mechanisms of activation. Mature MAIT cells in peripheral blood express the chemokine receptors CCR2, CCR5, CCR6, CXCR6, the C-type lectin-like receptor CD161, the dipeptidase CD26 and a CD45RO<sup>+</sup>CCR7<sup>-</sup> effector memory phenotype, with the majority of human MAIT cells expressing the CD8 coreceptor. MAIT cells also express the transcription factors RAR-related orphan receptor  $\gamma$  (ROR $\gamma$ t), T-bet and promyelocytic leukemia zinc-finger (PLZF) at rest. During bacterial infection, derivatives of the riboflavin biosynthesis pathway are captured by MR1 and presented on the surface of antigen-presenting cells (APCs). Alternatively, viruses can also rapidly activate MAIT cells in an MR1-independent manner owing to the induction of IL-18, IL-12 and IFN $\alpha$ . Activated MAIT cells express IFN $\gamma$ , TNF $\alpha$ , granzyme B, perforin and IL-17.

### MAIT cell phenotype and effector functions

In addition to their distinct chemokine receptor profile, human MAIT cells have a characteristic phenotype that has been described in detail (Figure 2). In adults, MAIT cells express a uniform effector memory phenotype.<sup>2,31</sup> Although cord blood MAIT cells are naïve, they share a preprogrammed transcriptional signature with adult MAIT cells,<sup>44</sup> in line with the acquisition of their innate reactivity and activated phenotype during development.<sup>30</sup> In humans the majority of MAIT cells are CD8<sup>+</sup>, with a small fraction of DN cells, as well as a very minor population that express the CD4 coreceptor.<sup>20</sup> Interestingly, more than half of CD8<sup>+</sup> MAIT cells express the homodimer CD8 $\alpha\alpha$ , with a smaller frequency of cells expressing the CD8 $\alpha\beta$  heterodimer. This is unique to MAIT cells, as conventional CD8<sup>+</sup> T cells express the CD8 $\alpha\beta$  coreceptor,<sup>20,44</sup> and is acquired early in development.<sup>30</sup>

Another key feature of human MAIT cells is the high expression of the C-type lectin-like receptor, CD161, and in the steady state, CD161<sup>++</sup>V $\alpha$ 7.2<sup>+</sup> T cells have been shown to overlap with the cells stained by the MR1 tetramer.<sup>20,45</sup> Furthermore, CD161 is one of the earliest markers to be expressed on MAIT cells, already high in the thymus and fetal organs,<sup>30</sup> as well as in the cord blood.<sup>2,44,46</sup> MAIT cells also express high levels of interleukin-18R (IL-18R), enabling them to rapidly release interferon- $\gamma$  (IFN $\gamma$ )<sup>11,47</sup> and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) (unpublished observations) in response to innate cytokines such as IL-12 and IL-18. This is further confirmed by the activation of MAIT cells by *E. faecalis*, which lacks the riboflavin synthesis pathway, and TLR agonists, in an IL-12- and IL-18-dependent manner.<sup>11,47</sup> In line with this, control of intracellular *M. bovis* bacillus Calmette-Guérin (BCG) growth *in vitro* by murine MAIT cells required IL-12, but was independent of MR1 signaling.<sup>48</sup> This ability to be activated by cytokines alone is shared with other innate T cells,<sup>49</sup> as conventional T cells require TCR signaling before the expression of

cytokine receptors such as IL-18R,<sup>50</sup> and is attributable to the expression of promyelocytic leukemia zinc-finger by these cells.<sup>21,51</sup>

In addition to IFN $\gamma$  and TNF $\alpha$ , which can be induced both in a TCR-dependent and -independent manner,<sup>2,9,47</sup> MAIT cells have a constitutively high expression of RAR-related orphan receptor  $\gamma$  and the associated ability to express IL-17A,<sup>2,31,44</sup> and constitute the main IL-17-producing T-cell population within the human liver.<sup>36</sup> Although rapid IL-4, IL-5 and IL-10 expression has been described in MAIT cells from V $\alpha$ 19i-transgenic mice,<sup>40</sup> the expression of these cytokines from human MAIT cells ranges from none<sup>2,36,52</sup> to low.<sup>28,53</sup> Interestingly, however, IL-10 expression from MAIT cells is particularly high in adipose tissue,<sup>54</sup> suggesting an immunosuppressive function for MAIT cells in certain tissues.

The effector functions of MAIT cells also includes their ability to degranulate and kill bacterially infected or sensitized cells, lysing cells infected with BCG<sup>28</sup> and *Shigella*.<sup>55</sup> *Ex vivo* resting MAIT cells are not efficient killers because of their lack of granzyme B (GrB) and low levels of perforin expression compared with conventional CD8<sup>+</sup> T cells.<sup>56</sup> Upon activation, either in an MR1-dependent manner or longer cultures with inflammatory cytokines, however, they upregulate GrB and perforin, greatly enhancing killing of target cells.<sup>2,56–58</sup> GrB may therefore be a useful activation marker of MAIT cells.

Finally, despite expansion of MAIT cells after birth,<sup>2,46</sup> adult MAIT cells lack expression of Ki67 in the periphery<sup>2</sup> and were initially thought to be poorly proliferative.<sup>2,8,40</sup> However, recent studies have confirmed the ability of murine and human MAIT cells to proliferate in both an MR1-dependent manner and in response to cytokines *in vitro*<sup>21,56,59</sup> and *in vivo*.<sup>42</sup> As MAIT cells are highly sensitive to activation-induced cell death,<sup>60</sup> one possible explanation for the discrepancy between studies may be that overstimulation of MAIT cells in some studies led to the loss of MAIT cells before they were able to proliferate.

## MAIT CELLS AND DISEASE

### MAIT cells in bacterial infections

High evolutionary conservation of MR1 and its recognition of intermediates of the riboflavin pathway, conserved in various species of bacteria and yeast, suggests that MAIT cells have a critical and non-redundant role in microbial protection. Indeed, a number of papers have suggested that MAIT cells have a protective role in bacterial infections. MR1<sup>-/-</sup> mice lacking MAIT cells had a higher bacterial burden in the first few days following intraperitoneal injection of *Escherichia coli* or intravenous injection of *Mycobacterium abscessus*,<sup>8</sup> and were overwhelmed by a fatal burden of intraperitoneally injected *Klebsiella pneumoniae*.<sup>61</sup> Aerosol infection models have demonstrated MAIT cells to be essential for early control of bacterial burden in the lung.<sup>42,48</sup> Interestingly, mice were protected from *F. tularensis* live-vaccine strain even in the absence of conventional  $\alpha\beta$  T cells, but were overcome in MR1<sup>-/-</sup> mice,<sup>42</sup> suggesting that MAIT cells may be important for microbial control in immunocompromised patients.

Various studies of MAIT cell frequencies in patients indicate involvement in bacterial infections. For example, there is a higher frequency of MAIT cells in the lung of patients with *Mycobacterium tuberculosis* infection, with lower frequencies of MAIT cells in the blood.<sup>8,9</sup> Reduced MAIT cell frequencies are, however, only observed in patients with active *M. tuberculosis* infection, but not latent infection,<sup>9</sup> suggesting MAIT cells are recruited to the lung in active disease. Peripheral MAIT cells in these patients also have increased expression of the exhaustion marker, programmed cell death protein 1,<sup>62,63</sup> and their responsiveness to *M. bovis* BCG is increased upon programmed cell death protein 1 blockade<sup>62</sup> (Table 1).

In addition to pulmonary infections, there is evidence of MAIT cell involvement in enteric infections, as MAIT cells are reduced early in the blood of patients that received an attenuated strain of *Shigella dysenteriae* 1,<sup>55</sup> as well as in *Vibrio cholera* O1-infected children.<sup>64</sup> Interestingly, the presence of activated MAIT cells in the periphery was specific to vaccine responders that developed an SD1-lipopolysaccharide-specific immunoglobulin (Ig) A response,<sup>55</sup> and correlated with protective *Vibrio cholera* O1-lipopolysaccharide-specific immunoglobulin A and immunoglobulin G antibody responses.<sup>64</sup> These two studies suggest that MAIT cells have a role in the development of protective antibody responses against polysaccharide antigens.

Last, reduced MAIT cell frequencies have been associated with increased severity of cystic fibrosis, and is particularly enhanced in patients with chronic *Pseudomonas aeruginosa* infections,<sup>65</sup> as well as being a risk factor in critically ill patients with sepsis for subsequent nosocomial infections.<sup>66</sup>

### MAIT cells in viral infections

Although early studies showed MR1<sup>-/-</sup> mice were not susceptible to influenza compared with control mice,<sup>8</sup> MAIT cell frequencies are markedly affected during human viral infections. For example, MAIT cells have been consistently and repeatedly reported to be severely depleted from the periphery of patients infected with human immunodeficiency virus (HIV),<sup>33,35,63,67–69</sup> as well as HIV/*M. tuberculosis*-co-infected patients.<sup>70</sup> MAIT cell loss occurs as early as 2–3 weeks after HIV infection,<sup>70</sup> and does not recover with successful antiretroviral therapy.<sup>33,35</sup> CD8<sup>+</sup> MAIT cells in the rectal mucosa<sup>35</sup> and colon<sup>33</sup> were better preserved, although CD4<sup>+</sup> MAIT cells were specifically lost from the rectal mucosa, in line with the significant loss of all CD4<sup>+</sup> T cells in the rectal mucosa in HIV-infected patients.<sup>35</sup> As peripheral CD8<sup>+</sup> MAIT cells were not specifically infected by HIV,<sup>33</sup> depletion of MAIT cells from the blood of HIV-infected patients is

suggested to be due to either the activation-induced cell death of MAIT cells from HIV-induced microbial translocation into the periphery<sup>33</sup> or exhaustion and downregulation of the MAIT cell marker CD161.<sup>35</sup> Although a recent tetramer study confirmed the loss of MAIT cells from the peripheral blood of HIV-infected patients, with no detectable loss of CD161 expression on MAIT cells,<sup>67</sup> the mechanism behind the severe depletion of MAIT cells in these patients remains to be explained. Nevertheless, the loss of MAIT cells may potentially have a profound effect on microbial protection in HIV-infected patients, as exemplified by the loss of mucosal T-helper type 17 cells in simian immunodeficiency virus-infected rhesus macaques.<sup>71</sup>

In addition to HIV, a loss of MAIT cells from the periphery has also been observed in patients with dengue and severe influenza infection,<sup>72</sup> as well as in chronic hepatitis C virus (HCV) patients,<sup>72,73</sup> as discussed in detail later. *In vivo* MAIT cell activation was demonstrated in these patients, and correlated with disease severity in acute dengue. Activation of MAIT cells by the different viruses was dependent on IL-18 in synergy with IL-12, IL-15 and/or IFN- $\alpha/\beta$ , in line with previous studies showing that IL-12 in combination with IL-18, secreted by monocytes through TLR stimulation, can activate MAIT cells *in vitro*.<sup>11,47</sup> These studies suggest that MAIT cells may have a larger role in the immune system that is not limited to protection against bacterial infection.

### MAIT cells and autoimmunity

There is increasing interest in the involvement of MAIT cells in autoimmune conditions, which has been reviewed in detail elsewhere.<sup>74</sup> In particular relevance to the liver, however, a number of studies have linked MAIT cells with intestinal inflammation. For instance, reduced frequencies of MAIT cells have been consistently demonstrated in the blood of patients with inflammatory bowel disease (both Crohn's disease and ulcerative colitis),<sup>32,75–77</sup> although there are conflicting findings between studies in the frequency of MAIT cells within the inflamed tissues.<sup>32,75,76</sup> MAIT cell frequencies are also altered in coeliac disease, where MAIT cells are depleted from the blood and gut.<sup>78</sup> Although the fate of MAIT cells in the tissue during intestinal inflammation requires further investigation, it is possible that chronic inflammation of the gut leads to both the recruitment and accumulation of MAIT cells, followed by their activation-induced cell death because of bacterial translocation and dysbiosis. In addition to intestinal inflammatory conditions, MAIT cells may also have a role in arthritic diseases, as they have been shown to exacerbate collagen-induced arthritis,<sup>79</sup> whereas depletion of blood MAIT cells has also been reported in patients with systemic lupus erythematosus and rheumatoid arthritis.<sup>31,53</sup> Various reports have also associated MAIT cells with multiple sclerosis, with the presence of MAIT cells in multiple sclerosis lesions confirmed by immunohistochemistry,<sup>77,80,81</sup> although both regulatory and pathogenic roles have been implicated.<sup>80,82</sup>

### MAIT cells and cancer

Little is known about the role of MAIT cells in cancer. An early study reported the increased detection of V $\alpha$ 7.2-J $\alpha$ 33 transcripts in kidney cancer tissue and brain tumors compared with control tissue and peripheral blood samples.<sup>83</sup> Recent studies in colonic adenocarcinoma<sup>84</sup> and colorectal cancer patients<sup>85</sup> have supported these findings, demonstrating highly activated MAIT cell accumulation in tumor tissue, with the degree of MAIT cell infiltration into colorectal tumors negatively correlating with life expectancy.<sup>86</sup> As MAIT cells can secrete both IFN $\gamma$ —which can promote tumor-specific



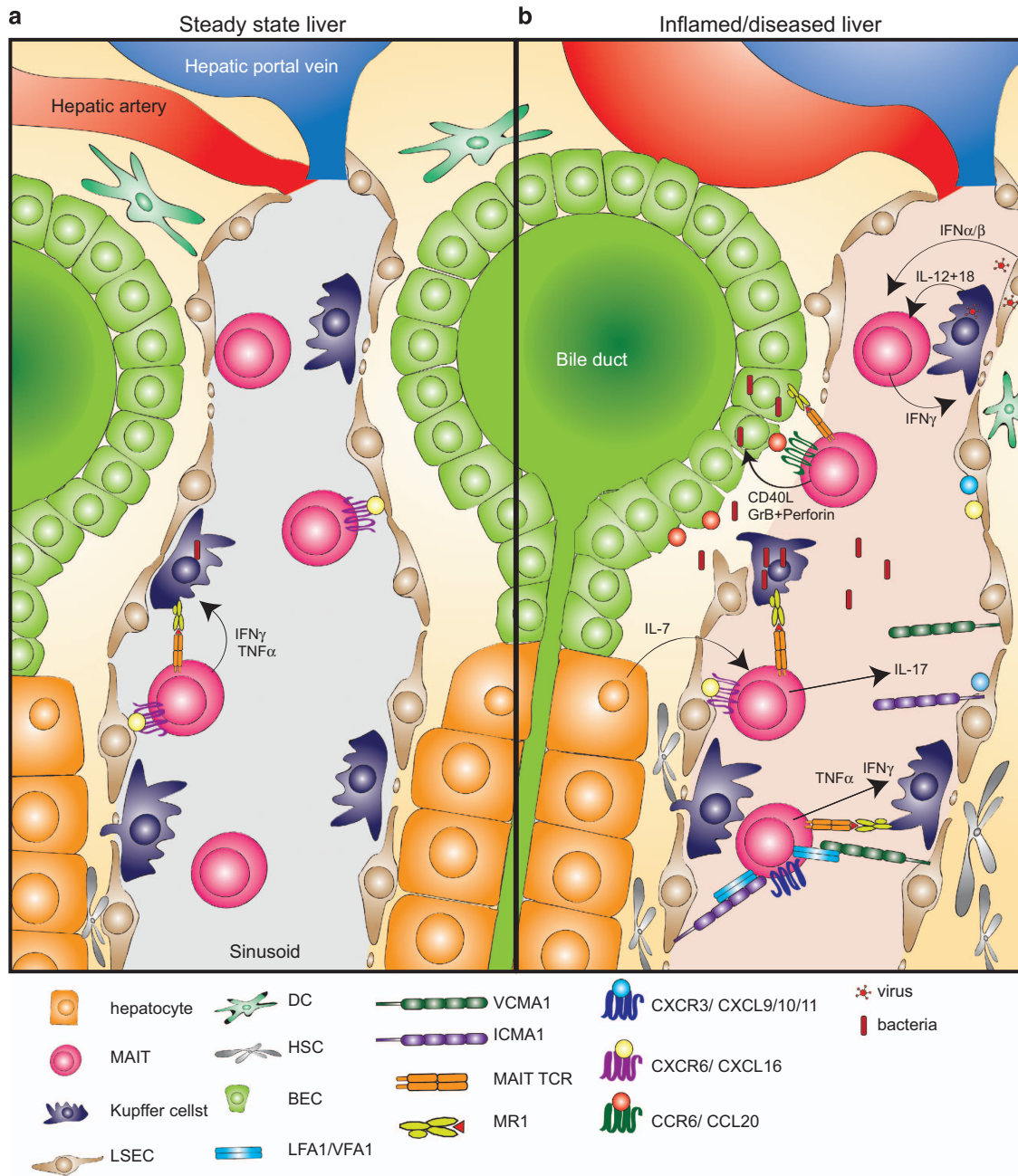
**Table 1 Clinical studies on MAIT cell frequencies, phenotype and function**

Disease/infection	Frequency of MAIT cells		Effect on MAIT cell phenotype		Effect on MAIT cell function		References
	Blood	Tissue	Blood	Tissue	Blood	Tissue	
TB	Loss during active, but not latent, infection	Higher in lung lesions from patients with active infection; loss from tuberculous pleural effusions; no loss in ascitic fluids from patients with tuberculous peritonitis	Increase in PD-1 in active TB		Increased apoptosis and cytokine production in response to BCG; reduced IFN $\gamma$ , TNF $\alpha$ , IL-17F, granulysin, GrB to <i>M. tb</i> lysate+IL-15; PD-1 blockade increases IFN $\gamma$ production to BCG and <i>E. coli</i>		8,9,62
Cholera	Loss (only in children)		Increase in CD38 expression				64
Cystic fibrosis	Loss (associated with <i>P. aeruginosa</i> infection)						65
Sepsis	Loss (associated with riboflavin-synthesizing bacterial infections)						66
HIV	Loss (occurs early, no recovery with ART)	MAIT cells better preserved or unaffected in rectal mucosa and colon; lost from lymph nodes	Increase in CD57, CD38, TIM-3, HLA-DR, PD-1; lower in CD27, IL-7R, CCR6, T-bet, Eomes		Retain ability to produce IFN $\gamma$ , TNF $\alpha$ to riboflavin ligand; reduced cytokines and GrB in response to <i>E. coli</i>		33,35,57,63, 67-69
HIV+TB	Loss (similar to HIV mono-infection, no recovery with ART)		Higher PD-1 and lower CCR6 in HIV/TB treatment-naïve patients				63,70
HCV	Loss (no recovery with treatment)		Increase in GrB with prolonged but not in resolved infection				72,73
Dengue	Loss between acute and convalescent phase of infection		Increase in CD38 and GrB, resolved in convalescent samples				72
Influenza	Loss		Increase in GrB				72
MS	No difference No change	Present in active white matter lesions but not present in non-pathological brain					66 77,107
	Higher	CD161 <sup>+</sup> CD8 <sup>+</sup> IFN $\gamma$ <sup>+</sup> T cells present in MS brain					80
IBD	Loss Loss	Present in MS brain lesions and CSF Higher in injured ileum in CD	Increase in Ki67, NKG2D, BTLA		Reduced IFN $\gamma$ , higher IL-17, higher IL-22 (only in CD) to PMA/iono		81,52 32
	Loss	Higher in colon in UC	Increase in CD69		Increased IL-17 to PMA/iono		75
	Loss	Loss in colon in UC and small intestine in CD	Lower integrin- $\alpha$ 4 $\beta$ 7 in CD		Increased IL-22 (only in UC); increased activated caspase		76
					Annexin V (only in inflamed CD mucosa)		

**Table 1 (Continued)**

Disease/infection	Frequency of MAIT cells		Effect on MAIT cell phenotype		Effect on MAIT cell function		References
	Blood	Tissue	Blood	Tissue	Blood	Tissue	
Coeliac disease	Loss (no recovery with treatment)	Loss from epithelia and lamina propria (prominent in children)					78
Obesity and diabetes	Loss in adults, higher in children (associated with insulin resistance)	Lower frequency in adipose tissue of obese patients compared with non-obese	Increased PD-1		Reduced IFN $\gamma$ to PMA/iono; increased IL-17 to PMA/iono and CD3/GD28	Increased IL-17, and reduced IFN $\gamma$ and IL-10 to PMA/iono	54
	Loss in patients with T2D, T2D+obesity and obesity	Higher frequency in adipose tissue of obese patients compared with blood; no difference in frequency compared with non-obese adipose tissue	Increase in CD25, CD69	Increase in CD25	Increased production of IFN $\gamma$ , IL-2, GrB, IL-17 to PMA/iono in T2D and T2D+obese; reduced activation to riboflavin ligand	Increased IL-17, GrB to PMA/iono, reduced TNF $\alpha$ ; recovers with bariatric surgery	45
	No difference in JT1D		Reduced CD27 expression in JT1D				108
RA	Loss	Higher in synovial fluid compared with blood					53,80
SLE	Loss		Increase in PD-1		Reduced IFN $\gamma$ to <i>E. coli</i> and PMA/iono		53
inflammatory skin conditions (psoriasis, alopecia areata, dermatitis herpetiformis)		Higher in dermatitis herpetiformis; no difference between normal skin and psoriatic, or alopecia areata				Increase in IL-17-producing MAIT cells to PMA/iono in psoriasis	109,110
Asthma	Loss (associated with corticosteroid dose)	Loss in sputum and bronchial biopsies (associated with corticosteroid dose)					111
Chronic liver disease (PSC, PBC, ALD, NASH, NAINB)	Loss, with relative increase in proportion of CD4+ MAIT	Loss, with relative increase in proportion of CD4+ MAIT	increased CXCR3 and CX3CR1				37
COPD	Loss (only in patients with corticosteroid use)	Loss in bronchial biopsies (only in patients with corticosteroid use); no difference in sputum or bronchoalveolar lavage					38
Acute cholecystitis (inflammation of the gall bladder)	Loss						112
Colorectal cancer	No difference	Higher in tumor compared with healthy colon lamina propria			Increased CD8 $\alpha\alpha$ in tumors compared with unaffected colon lamina propria; increased CD69 and PD-1 compared with blood	Lower IFN $\gamma$ and TNF $\alpha$ to PMA/iono	84-86
Kidney and brain cancer		Present in tumor tissues; MAIT clonotypes more dominant than blood					83

All tissue entries show comparison with healthy/non-diseased tissues unless indicated as 'compared with blood'. Alternatively, 'present' means there is no information in the clinical setting. Abbreviations: ALD, alcoholic liver disease; ART, antiretroviral therapy; BCG, Bacillus Calmette-Guérin; CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; CSF, cerebrospinal fluid; GrB, granzyme B; HCV, hepatitis C virus infection; HIV, human immunodeficiency virus infection; IBD, inflammatory bowel disease; JT1D, juvenile type 1 diabetes; MS, multiple sclerosis; PBC, primary biliary cirrhosis; PMA/iono, phorbol 12-myristate 13-acetate+ionomycin stimulation; PSC, primary sclerosing cholangitis; NAINB, non-A, non-B hepatitis; NASH, non-alcoholic steatohepatitis; PD-1, programmed cell death protein 1; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TB, *Mycobacterium tuberculosis* infection; T2D, type 2 diabetes; UC, ulcerative colitis.



**Figure 3** Proposed role of MAIT cells in the liver. (a) In the steady-state liver, MAIT cells home to the bile ducts within the portal tract through their expression of the chemokine receptors CXCR6 and CCR6 where they are located both adjacent to the biliary epithelium and within hepatic sinusoids. This allows them to protect against infection via the biliary tree and from the portal and systemic circulation via the portal vein and hepatic artery. (b) In the event of ascending biliary infection and following bacterial breach of the biliary epithelium, liver MAIT cells are recruited through their upregulation of CXCR3 and increased expression of chemokines (CCL20) and adhesion molecules (intercellular adhesion molecule 1 and vascular cell adhesion molecule 1) in the liver. MAIT cells are activated by riboflavin metabolites presented by MR1 expressed on both professional (Kupffer cells) and non-professional (BECs) antigen-presenting cells. MR1-activated MAIT cells release CD40L, which induces the expression of Fas, as well as cytotoxic molecules Granzyme B and perforin, leading to apoptosis of BECs. MAIT cells also express the proinflammatory cytokines IFN $\gamma$  and TNF $\alpha$ , which activates Kupffer cells, BECs, liver sinusoidal endothelial cells (LSECs) and dendritic cells (DCs), whereas IL-7 produced by inflamed hepatocytes also promote IL-17 production from MAIT cells, leading to further inflammation and activation of Kupffer cells, BECs and hepatic stellate cells (HSCs). MAIT cells also produce IFN $\gamma$  in response to IL-12 and IL-18, secreted by sinusoidal Kupffer cells activated by TLR4 (bacterial LPS) and TLR8 (viral ssRNA) agonists, leading to viral and bacterial control DCs.

T-cell responses, as well as IL-17—which leads to the expansion and accumulation of immunosuppressive neutrophils and myeloid-derived suppressor cells,<sup>87–89</sup> the role of MAIT cells in tumor development may depend on the tumor microenvironment and the ratio between IFN $\gamma$ - and IL-17-secreting cells. Further studies into the role of

MAIT cells in cancer and their immunomodulatory potential, as has been demonstrated with iNKT cells,<sup>90</sup> could have important implications for cancer immunotherapy.

Last, it is important to note that the precise physiological role of MAIT cells in most of these conditions (bacterial, viral, autoimmune

or cancerous) remains to be defined, with the majority of studies focusing on their frequency within the peripheral circulation and tissue, whether they contribute to disease or have a protective role in humans remains unclear.

## MAIT CELLS IN THE LIVER

### Role of MAIT cells in the liver

Mouse models have demonstrated that in the presence of healthy intestinal mucosa, the liver remains a sterile organ,<sup>1</sup> with the mesenteric lymphoid system containing the immune response to commensal gut organisms.<sup>91</sup> Yet, the liver provides an important second 'firewall' where intestinal mucosal defenses are breached or in the presence of systemic infection.<sup>1</sup> The liver hosts not only the large phagocytic Kupffer cell population, dendritic cells, liver sinusoidal epithelial cells and hepatic stellate cells but also rapidly activated innate cells such as NK, iNKT and MAIT populations.<sup>92</sup> The innate reactivity of MAIT cells to both MR1-presented bacterially derived metabolites of riboflavin and proinflammatory cytokines including IL-12, IL-18 and type I IFN indicates that MAIT cells are well placed to have an important role in first line of defense as part of the liver firewall. With little data published to date, we are only just beginning to understand their significance within this complex immunological organ.

MAIT cells are highly enriched in the human liver, representing 20–50% of intrahepatic T cells, compared with the gut.<sup>2,36</sup> This is in keeping with their homing receptor expression profile, and although MAIT cells express the gut-homing integrin- $\alpha 4\beta 7$ ,<sup>7</sup> they express lower levels of the gut-homing chemokine receptor CCR9 compared with other T cells.<sup>2,37</sup> Instead, MAIT cells express receptors that allow them to home to the liver, such as CXCR6 and CCR6, which binds CXCL16 and CCL20, respectively—chemokines constitutively expressed in the liver.<sup>93,94</sup> This liver-homing phenotype is conserved in mice, as murine MAIT cells also express CXCR6,<sup>21</sup> similar to the murine hepatic iNKT cell population.<sup>95</sup> CCL20 is also upregulated in the inflamed liver and drives CCR6<sup>+</sup> T-cell localization to the biliary epithelium.<sup>96</sup> Indeed, recent work by Jeffery *et al.*<sup>37</sup> has described V $\alpha 7.2^+$  and V $\alpha 7.2^+$ CD161<sup>+</sup> cells to predominantly reside around bile ducts within the portal tracts in both healthy and diseased livers. Importantly, bacterially loaded biliary epithelial cells (BECs) were able to activate MAIT cells in an MR1-dependent manner, and suggests a mechanism by which MAIT cells may defend the biliary mucosa against ascending infection from the gut. In the inflamed liver, MAIT cells may be further recruited to the sinusoids through their expression of CXCR3, LFA-1 and VLA-4,<sup>37</sup> as IFN $\gamma$ -inducible CXCR3 ligands, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, have all been shown to mediate recruitment of lymphocytes during inflammation.<sup>97</sup> The distribution of intrahepatic MAIT cells is likely critical to understanding their function within the liver.

Three features of MAIT cells in the context of liver immunosurveillance are important to note. First, although at a transcriptional level, intrahepatic MAIT cells are very similar to their blood counterparts, liver MAIT cells are highly activated and almost all express the activation marker CD69, as well as HLA-DR and CD38.<sup>36,37</sup> This suggests that liver MAIT cells are in a highly activated state, poised to respond to incoming antigen from the gut. Second, intrahepatic MAIT cells, along with CD56<sup>bright</sup> NK cells, are the main source of IFN $\gamma$  after TLR8 stimulation of liver-derived mononuclear cells, mediated by their ability to respond to IL-12 and IL-18 from monocytes.<sup>11</sup> The striking sensitivity of intrasinusoidal cells in this study to the TLR8 agonist ssRNA40, compared with other TLR agonists, suggests that intrahepatic cells are highly reactive to viral and

phagocytosed bacterial RNA,<sup>98</sup> and that MAIT cells are an important effector population in the liver. Third, MAIT cells are the predominant IL-17 producers among intrahepatic T cells (~65% of IL-17<sup>+</sup> T cells) following phorbol 12-myristate 13-acetate/ionomycin stimulation.<sup>36</sup> As IL-17 targets multiple cell types in the liver, including Kupffer cells and BECs, to produce proinflammatory cytokines and chemokines,<sup>99</sup> MAIT cells may be important regulators of hepatic inflammation and fibrosis.

Interestingly, however, liver MAIT cells in the steady state are unable to produce IL-17 upon TCR stimulation.<sup>36</sup> Indeed, MAIT cells from the liver appear less skewed towards type 17 functions (IL-17 and IL-22 production) compared with those of the mucosa. For example, MAIT cells of the fetal liver failed to produce IL-22 on MR1-dependent stimulation, in contrast to those of the small intestine.<sup>30</sup> Similarly, MAIT cells derived from the female genital tract were able to produce IL-17 and IL-22 on bacterial stimulation.<sup>39</sup> The presence of commensal bacteria at mucosal surfaces may drive type 17 skewing of mucosal MAIT cells through IL-1 $\beta$  production by resident macrophages.<sup>100</sup> In the steady state, MAIT cells seem to require IL-7 licensing before acquiring the ability to secrete IL-17 in response to TCR stimulation, potentially by increasing their sensitivity to TCR-mediated signals,<sup>36,57</sup> but liver MAIT cells may become similarly skewed to mucosal MAIT cells during episodes of infection.

Taken together these studies suggest hepatic MAIT cells are highly activated within the liver and likely have a defensive role against a range of extra- and intracellular bacteria, fungi and viruses through their abundant and rapid production of IFN $\gamma$  and IL-17 (Figure 3).

## MAIT CELLS AND LIVER DISEASE

### Inflammatory liver diseases

In the most comprehensive study to date of MAIT cells in liver disease, Jeffery *et al.*<sup>37</sup> describe the distribution, function and phenotype of hepatic MAIT cells from healthy controls and explants from patients with acute non-A, non-B hepatitis, as well as the end-stage chronic liver diseases such as autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, alcoholic liver disease and non-alcoholic steatohepatitis (NASH).<sup>37</sup> Overall, a reduction in MAIT cells was seen in patient blood and livers compared with controls, in agreement with another study of end-stage liver disease.<sup>11</sup> The similar distribution of V $\alpha 7.2^+$  cells and CD161<sup>+V $\alpha 7.2^+$  cells around the bile duct in both controls and the chronic diseases studied would suggest that the presence of these cells is likely more physiological than pathological in this location (or related to end-stage liver disease). Although the specificity of these cells needs to be confirmed, peribiliary MAIT cells may provide defense against ascending infection via the biliary system, as discussed above. However, as ligation of CD40 on BECs leads to their Fas-dependent apoptosis,<sup>101</sup> upregulation of CD40L on MAIT cells in response to bacteria-derived MR1 ligands presented by BECs suggests that MAIT cells could potentially drive bile duct damage, contributing to pathogenesis in biliary disease.</sup>

### Hepatitis C infection

Two recent papers have clearly demonstrated that circulating MAIT cells in chronic HCV patients are reduced in frequency.<sup>72,73</sup> This supports previous observations that blood CD161<sup>++</sup>CD8 T cells, the majority of which are MAIT cells in adults,<sup>2</sup> are significantly reduced in patients with chronic HCV.<sup>44</sup> Whether this represents blood-to-tissue translocation or activation-induced cell death, as has been suggested in HIV infection,<sup>33</sup> has not been addressed. *Ex vivo* analysis of MAIT cells from patients with chronic HCV showed that



activation markers such as GrB, CD38 and CD69 were upregulated,<sup>72,73</sup> and MAIT cells could be activated upon *in vitro* coculture with HCV-exposed antigen-presenting cell.<sup>72</sup> Additionally, type I IFNs, known to have an important role in viral control, were shown to induce MAIT cell production of IFN $\gamma$  in combination with IL-12 or IL-18, and where antigen-presenting cells infected with HCV were cocultured with a vaccine virus-derived soluble type 1 IFN receptor (B18R), MAIT cell activation was inhibited. Interestingly, in an HCV Sofosbuvir treatment trial, those patients in the arm receiving pegylated-IFN, in addition to Sofosbuvir and ribavirin, had a higher sustained virologic response rate, as well as activated circulating MAIT cells compared with the other treatment arms. Whether this indicates a direct role for MAIT cells in HCV control and clearance or whether they are simple bystanders requires further investigation.

### Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease, affecting up to 40% of western adult populations,<sup>102,103</sup> encompasses a spectrum of disorders ranging from isolated, benign hepatic steatosis to progressive NASH. Closely linked to the metabolic syndrome, non-alcoholic fatty liver disease has a prevalence of 70% among type 2 diabetic patients and 90% among the morbidly obese.<sup>104</sup> The pathogenesis of NASH is much debated,<sup>104</sup> and likely the result of a number of complex factors including insulin resistance and disrupted lipid metabolism; lipotoxicity and hepatocyte death; altered intestinal barrier function, gut dysbiosis and bacterial overgrowth; altered systemic adipokines/cytokines and host genetics. A direct role of MAIT cells in NASH has not been studied, but, in the context of altered gut barrier function, dysbiosis of the microbiome and bacterial overgrowth, described as part of the metabolic syndrome, will be an important area to explore. However, a recent study of MAIT cells in obese and type 2 diabetic patients demonstrated a marked reduction in circulating MAIT cells in both patient groups compared with controls.<sup>45</sup> In this study, the residual circulating population expressed the activation markers CD69 and CD25, with enhanced functionality and proinflammatory cytokine production upon mitogen stimulation. Furthermore, MAIT cells were enriched in the adipose tissues compared with the peripheral blood of obese patients, where they were potent and predominant producers of IL-17, with up to 90% of adipose tissue MAIT cells capable of secreting IL-17. Circulating MAIT cell numbers was restored at 3 months following bariatric surgery, whereas they returned to normal function 6 months after surgery. Increased IL-17 from peripheral blood MAIT cells has also been observed in obese children.<sup>54</sup> Changes to the gut microbiome and intestinal permeability that occur in obesity and type 2 diabetic may lead to the accumulation of MAIT-activating microbial products within adipose tissue and account for the activation state and enhanced function of MAIT cells observed. Indeed, IL-7, known to license MAIT cell function,<sup>36,57</sup> is oversecreted by stromal vascular cells from the omental adipose tissue of obese patients.<sup>105</sup> This may explain the enhanced functionality of MAIT cells in this setting where they likely are important drivers of inflammation and thus of the pathogenic chain of insulin resistance, lipolysis, high circulating free fatty acids and hepatic fat accumulation in the development of non-alcoholic fatty liver disease/NASH. However, the onset of diabetes was delayed in non-obese diabetic V $\alpha$ 19i-transgenic mice compared with non-transgenic mice, suggesting that they may also have a suppressive role that is altered in disease.<sup>106</sup>

### CONCLUSION

MAIT cells are emerging as significant players in the human immune system where they represent a major lymphocyte population—this is

most obvious in the liver where their dominance, indeed even their presence, has only been evident in the past few years. Our understanding of the distinct biology of MAIT cells is rapidly increasing as the field widens and appears to include not only responsiveness to bacteria but also to inflammatory and viral signals. Their enrichment within the liver is striking and there is much work to be carried out in understanding the physiologic role of MAIT cells, as guardians of the biliary mucosa, as monitors of sinusoidal hygiene and as part of the liver's defensive firewall. Loss of MAIT cells in fibrotic liver disease, as has been indicated, may lead to weakening of this firewall and increased susceptibility to systemic infections—it may be possible to address this mechanistically in emerging mouse models. Their role in the pathogenesis of liver disease also needs to be defined—clearly they are present at the site of inflammation, but to what extent they are protagonists, protectors or just innocent bystanders again may only be solved by analysis using appropriate mechanistic *in vivo* models. Even with these, given the specific and chronic nature of some of the infectious/inflammatory processes, further clinical correlative and mechanistic studies are needed.

Overall, given their distinctive functions and surface phenotype, MAIT cells represent attractive therapeutic targets to modulate host defense and inflammation in the liver and other organs, and certainly excellent markers of responses to biologic therapies. Both avenues—therapeutic and diagnostic—are ripe for exploitation in the future.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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