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HIGHLIGHTS

REVIEW

Interleukin-17 producing mucosal associated invariant T cells - emerging players in chronic inflammatory diseases?

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Mucosal associated invariant T (MAIT) cells are a population of evolutionarily conserved T cells, which express an invariant T cell receptor (TCR) and represent a significant subset of innate-like T cells in humans, yet their role in immunity is still emerging. Unlike conventional αβ T cells, MAIT cells are not restricted by MHC molecules, but instead uniquely recognize microbially derived vitamin metabolites presented by the MHC-I like molecule MR1. MAIT cells are enriched in mucosal sites and tissues including liver and adipose tissue where they are thought to play an important role in immunosurveillance and immunity against microbial infection. In addition to their putative role in antimicrobial immunity, recent research on MAIT cells, in particular IL-17 producing MAIT cells, has demonstrated their involvement in numerous chronic inflammatory conditions. In this review, we give an overview of the work to date on the function and subsets of MAIT cells. We also examine the role of IL-17 producing MAIT cells in chronic inflammatory diseases ranging from autoimmune conditions, metabolic diseases to cancer. Furthermore, we discuss the most recent findings from the clinic that might help deepen our understanding about the biology of MAIT cells.

Keywords: chronic inflammation · IL-17 · mucosal-associated invariant T cells

Mucosal-associated invariant T cells

Mucosal associated invariant T (MAIT) cells comprise a unique population of evolutionarily conserved T cells, first described in humans by Porcelli and colleagues in the early 1990s, what was further confirmed by another landmark study by Tilloy et al. in 1999 [1, 2]. These cells are characterized by expression of the invariant TCR-α chain, Vα7.2 (TRAV1-2-TRAJ33, TRAJ20, or TRAJ12) in human, or Vα19 (TRAV1-TRAJ33) in mice. This TCR chain is typically associated with a limited array of TCR-β chains, e.g., Vβ2 or Vβ13 in human, or Vβ6 and Vβ8 in mice [3]. This constrained gene usage of the TCR suggests the ability of these cells to target conserved antigens. MAIT cell antigen recognition is not restricted by MHC, instead the MHC class

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I-like molecule (MR1) is recognized by the MAIT TCR [3–5]. The MR1 complex typically presents metabolites derived from the biosynthesis of riboflavin (vitamin B2), a process mediated by many bacterial and yeast species, but not viruses or human cells [6]. This observation is consistent with the finding that MAIT cells are activated by riboflavin synthesizing bacteria, such as *Salmonella* and other *Enterobactericaeae* species [7]. In vitro experiments have identified a number of these riboflavin metabolites as MAIT cell antigens, including stimulatory antigens 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU), 5-(2-oxoethylideneamino)-6-D-ribitylaminouracil (5-OE-RU), 6,7-dimethyl-8-D-ribityllumazine (RL-6,7-diMe), and 7-hydroxy-6-methyl-8-D-ribityllumazine (RL-6-Me-7-OH) [8]. The potency of these antigens varies, with a non-stimulatory MR1 ligand 6-formyl-pterin (6-FP), a natural breakdown by-product of folic acid, also described [6]. The most potent of these stimulating antigens are 5-OP-RU and 5-OE-RU, which are both generated from the riboflavin precursor 5-amino-6-D-ribitylaminouracil (5-A-RU) through non-enzymatic condensation with small ubiquitous metabolites methylglyoxal and glyoxal, respectively [8, 9]. Identification of these potent antigens has allowed for development of highly specific antigen-loaded MR1 tetramers, for improved identification of both human and mouse MAIT cells [10–13].

In humans, MAIT cells are detectable in cord blood and frequencies increase into adulthood before decreasing after the sixth decade of life [14, 15]. MAIT cells are widely distributed throughout the human body, comprising a substantial proportion of T cells in blood (1–10%), intestinal tissues [16, 17], lungs [18], skin [19], adipose tissue [20], and in particular the liver, where MAIT cells can account for up to 50% of all T cells [21]. In a study of human fetal tissues, MAIT cells were found to be rare in fetal thymus, spleen, and mesenteric lymph nodes but enriched in small intestine, liver, and lung [22]. MAIT cell development proceeds in a step-wise process, where thymic selection precedes peripheral expansion and is dependent on commensal microbes and MR1 expressing B cells [23, 24]. Subsequent studies showed that MAIT cell selecting thymocytes express MR1 and both CD4 and CD8, and that MR1 deficient mice lack MAIT cells [25]. Elaborate studies using MR1 loaded tetramers in mice showed that the MAIT cell compartment is composed of three prominent populations, defined by expression of CD24 and CD44 [26]. Of these populations, the $CD24^{-}/CD44^{+}$ subset was the only functionally active population and could be further subdivided into two distinct subsets of $Tbet^{+}$ and $ROR\gamma t^{+}$ MAIT cells. In humans, the stages of thymic maturation of MAIT cells were differentiated by CD27 and CD161 expression. Stage 1 was defined by lack of expression of CD161 and CD27, at stage 2 cells remained $CD161^{-}$ but also gained expression of CD27, whereas at the most mature stage of thymic development MAIT cells were defined as $CD161^{+}$ and $CD27^{pos\text{-}lo}$. In contrast to the stage 3 of murine MAIT cell maturation, human MAIT cells were observed to co-express $Tbet^{+}$ and $ROR\gamma t^{+}$. Upon in vitro stimulation, only a small subset of stage 3 thymic MAIT cells responded by cytokine production in comparison to the stage 3 MAIT cells found in blood, suggesting that further maturation of these cells takes place outside of the thymus [24].

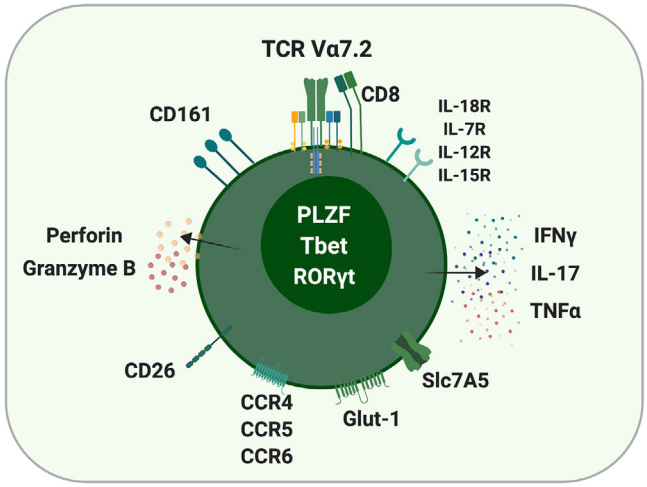

Figure 1. MAIT cell phenotype. In addition to their expression of the invariant TCRVα7.2, MAIT cells can be defined by their expression of several surface molecules including CD161 and CD26. MAIT cells also express several cytokine and chemokine receptors on their surface, including IL-18R and CCR6. Also expressed on the surface of MAIT cells are the nutrient transporters GLUT-1 and SLC7A5, two key transporters in MAIT cell metabolism. MAIT cells can be further characterized by their expression of transcription factors such as PLZF, Tbet, and RORγt, which control the production of cytokines such as IFN-γ and IL-17 during activation. Finally, MAIT cells can also express lytic molecules including perforin and granzyme B.

MAIT cell phenotype and functions

Like other so-called unconventional T cells, such as γδ T cells and invariant NK T (iNKT) cells, MAIT cells possess attributes of both innate and adaptive immunity, e.g., rapid effector function upon activation by conserved ligands and recognized by a classical, albeit semi-invariant, TCR. Human MAIT cells are classically defined by expression of an invariant Vα7.2 TCR chain and high levels of the C-type lectin CD161 [3, 7]. MAIT cells can express CD8, either CD8αα or CD8αβ isoforms, CD4 or can be double negative for both CD4 and CD8, with CD8 expressing MAIT cells representing the majority [27, 28]. The $CD4^{-}/CD8^{-}$ MAIT cell population has recently been described as a functionally distinct MAIT cell subset, producing higher levels of IL-17 and lower levels of IFN-γ [28]. Consistent with their presence in numerous tissue types, MAIT cells express several tissue homing molecules, including CCR5, CCR6, and CXCR6 [29]. MAIT cells also express multiple cytokine receptors, including IL-7R, IL-12R, and IL-18R [7, 30–32]. Several studies have outlined a requirement for cytokine priming or stimulation for full MAIT cell activation, in particular by cytokines IL-7, IL-12, and IL-18 [30, 33] (Fig. 1).

Similar to other unconventional T cell subsets, MAIT cells can be activated independently of their TCR, specifically by cytokines alone [34–36]. This means that MAIT cell activation is not solely reliant on TCR ligation alone, which results in a relatively weak

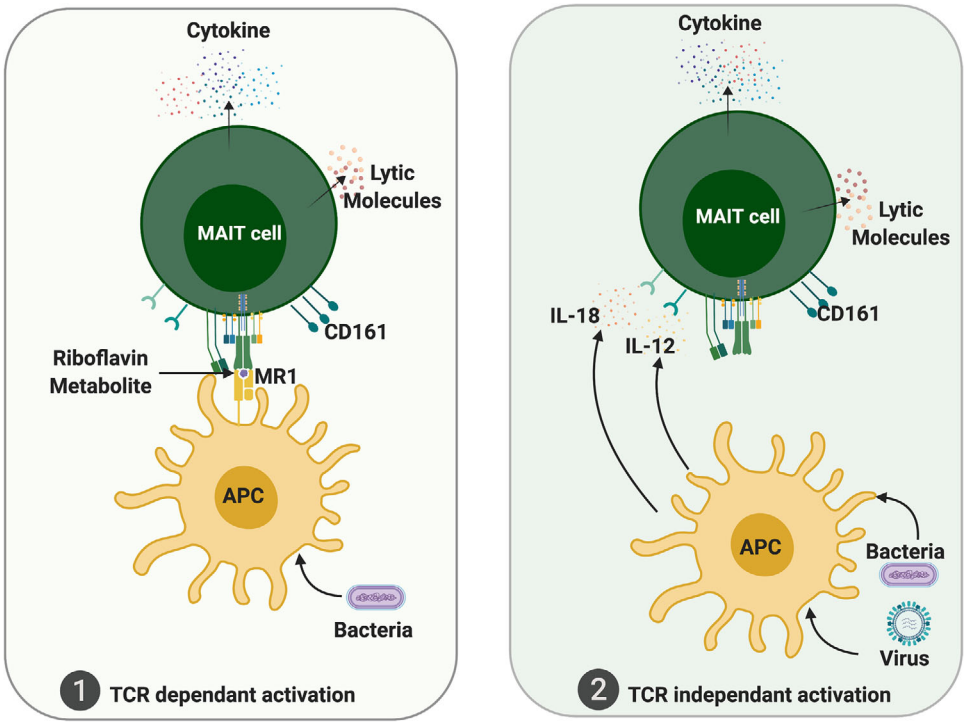

Figure 2. MAIT cell activation. MAIT cells can be activated in a MR1 dependent manner (1) where bacterial ligands are presented by antigen presenting cells (APC) on MR1 and recognized by the invariant Vα7.2 TCR resulting in the production of cytokine and lytic molecules. MAIT cells can also be activated in a MR1 independent manner (2) by inflammatory cytokine such as IL-12 and IL-18 that are produced by innate cells in the presence of viral or bacterial infection, again resulting in the production of effector molecules.

response. Therefore, these cells can respond to a wider set of stimuli than MR1 presented antigens alone, and in a synergistic manner where multiple signals are present [34, 36, 37] (Fig. 2).

Upon activation, MAIT cells can produce multiple cytokines and can be generally divided into MAIT cells that primarily produce Th1 type cytokines including IFN-γ and TNF-α (MAIT1 cells), and MAIT cells that predominantly produce Th17 type cytokines such as IL-17A (MAIT17 cells) [20, 29, 38, 39]. In the human protein atlas, it was noted that MAIT cells expressed among the highest levels of the protein coding gene RORC, which is the transcription factor responsible for IL-17 production [40]. Several other transcription factors have been detailed in MAIT cells including PLZF and Tbet [41]. In addition to rapid cytokine production, MAIT cells possess a full complement of cytolytic effector molecules such as granzymes (granzyme A and B) and perforin, which allow them to lyse bacteria-infected cells [42]. Upon activation, MAIT cells rapidly display this cytotoxic phenotype, which is heightened through TCR interactions and cytokines. The cytotoxic ability of these cells is tightly regulated however, and is ultimately dependent on MR1 ligation, which allows control of bacterial infection while reducing immune-mediated pathology [42]. Numerous recent studies have highlighted the importance of intrinsic metabolic pathways in controlling immune cell functions [43]. We have recently reported on the metabolic pathways controlling MAIT cell cytokine production [38]. Similar to $CD8^+$ T cells and NK cells, MAIT cells increase their rate of glycolysis upon activation, which provides the biological intermediates needed for effector molecule production [38, 44]. MAIT cells express the major glucose transporter GLUT-1 and neutral amino acid transporter SLC7A5 upon stimulation increase their nutrient uptake [38]. Inhibition of glycolysis in MAIT cells reduced the capacity to produce IFN-γ and granzyme B, highlighting the importance of metabolism in MAIT cell effector function [38, 44]. Mammalian target of rapamycin (mTOR) is a well-characterized regulator of glycolysis in effector cells such as NK cells [45]. Upon activation, MAIT cells increase signaling through mTOR and inhibition with rapamycin results in reduced rates of glycolysis and cytokine production, further highlighting the importance of these intrinsic metabolic pathways in MAIT cells [38], (Fig. 3).

MAIT cells in host defense

The ability of MAIT cells to recognize bacterial metabolites via the highly conserved MR1 molecule suggests that these cells play a critical role in immune defense against microbial infections. MR1 KO mice show higher bacterial burden following injection with either *Escherichia coli* or *Mycobacterium abscessus*, thus implicating MAIT cells in immunity against these pathogens [7]. Furthermore, MR1 deficient mice exposed to low dose aerosol infection with *Mycobacterium bovis* demonstrated a higher bacterial burden compared to MR1 sufficient mice. This effect evens out by day 30 post-infection, however, suggesting that MAIT cells drive early containment of mycobacterial infections in the lung [35].

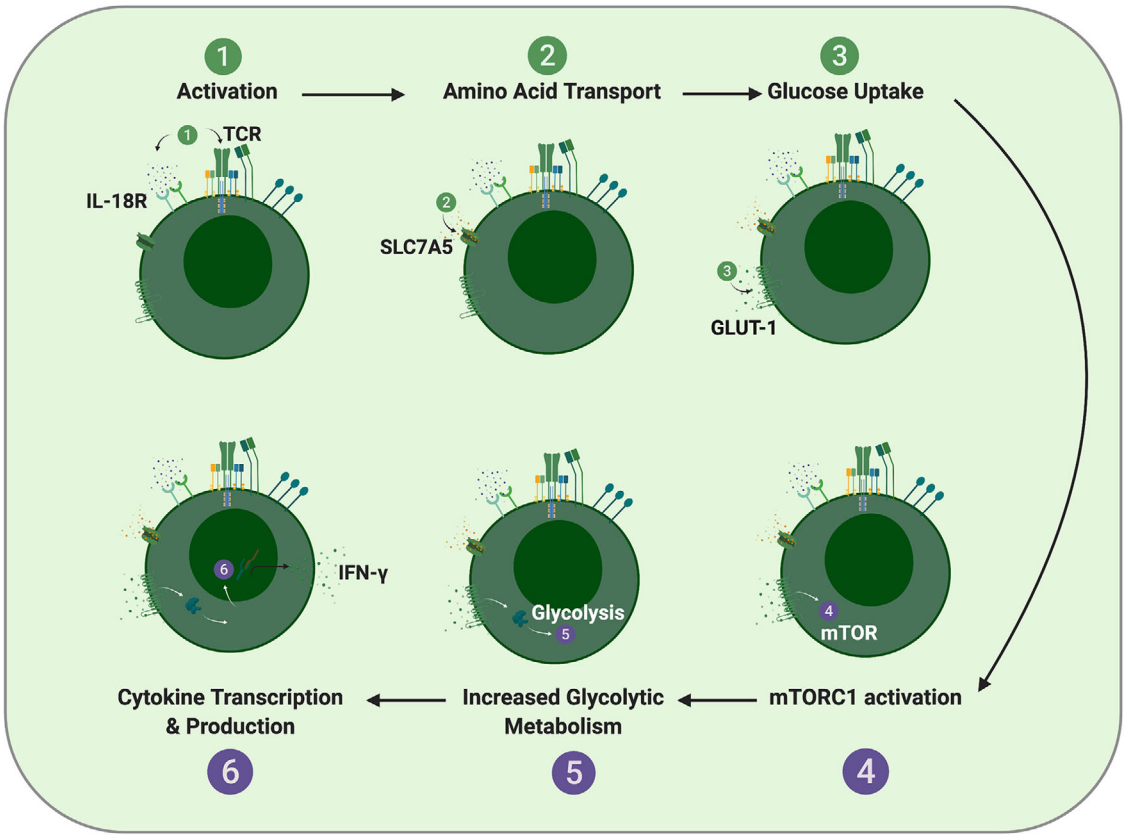

Figure 3. MAIT cell metabolism. Upon activation, MAIT cells increase their consumption of amino acids and glucose (1), which are transported into MAIT cells via SLC7A5 and GLUT-1, respectively (2-3). Upon sensing nutrients mTORC1 activation (4) leads to increased rates of glycolytic metabolism (5) that provides the intermediates for the production of molecules such as IFN-γ and granzyme B (6).

MAIT cells are reduced in the blood but elevated in the lungs of humans with *Mycobacterium tuberculosis* (Mtb), and respond to Mtb-infected MR1 expressing lung epithelial cells [18]. In children with active Mtb infection, MAIT cell frequencies are decreased in the peripheral blood but unlike in Mtb infected adults, they do not accumulate in the lung [46]. MAIT cells have also been shown to respond in a TCR-dependent manner to Gram-negative bacteria such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Salmonella enterica*, as well as Gram-positive bacteria including *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Clostridioides difficile,* but do not respond to *Streptococcus pyogenes* or *Enterococcus faecalis* [7, 47–51]. A decrease in circulating MAIT cells has been reported in a number of bacterial infection settings, with lower MAIT cell presence correlating with severity of infection. This was observed in cystic fibrosis patients during *Pseudomonas aeruginosa*, active Mtb infection, in the mite-borne disease scrub typhus, and in critically ill patients admitted to intensive care units with sepsis, who are also more susceptible to nosocomial infections [48, 52–55].

In addition to their broad antibacterial properties, a role for MAIT cells in viral infection has also emerged, detailing how MAIT cells become activated in a TCR-independent, IL-18-dependent manner in response to human viral infections including influenza, hepatitis C (HCV), and dengue virus [36, 56, 57]. Indeed, MAIT cell activation and IL-18 levels correlated with disease severity in acute dengue infection [56]. It was observed that MAIT cell activation was further enhanced in the presence of other proinflammatory cytokines such as IL-12 and type I IFNs [56]. This cytokine-driven mechanism of MAIT cell activation has also been demonstrated in an in vitro model of Zika virus infection, and resulted predominantly in IFN-γ production [57]. A similar IFN-γ response was observed in HCV infection, which resulted in a reduction of in vitro HCV replication [36]. MAIT cells were also shown to be important in the immune response against severe H1N1 influenza infection in mice, with MAIT cell deficient $MR1^{-/-}$ mice showing higher mortality and greater weight loss than control groups [58].

MAIT cells in chronic inflammatory disease

Acute inflammation is a critical process in the protection and repair process, tightly regulated to resolve after injury or infection. However, numerous studies have provided empirical evidence that many diseases are caused by a systemic and non-resolving inflammation termed chronic inflammation [59]. These diseases are increasing in prevalence and dramatically impacting morbidity and mortality. Chronic inflammatory diseases include rheumatoid

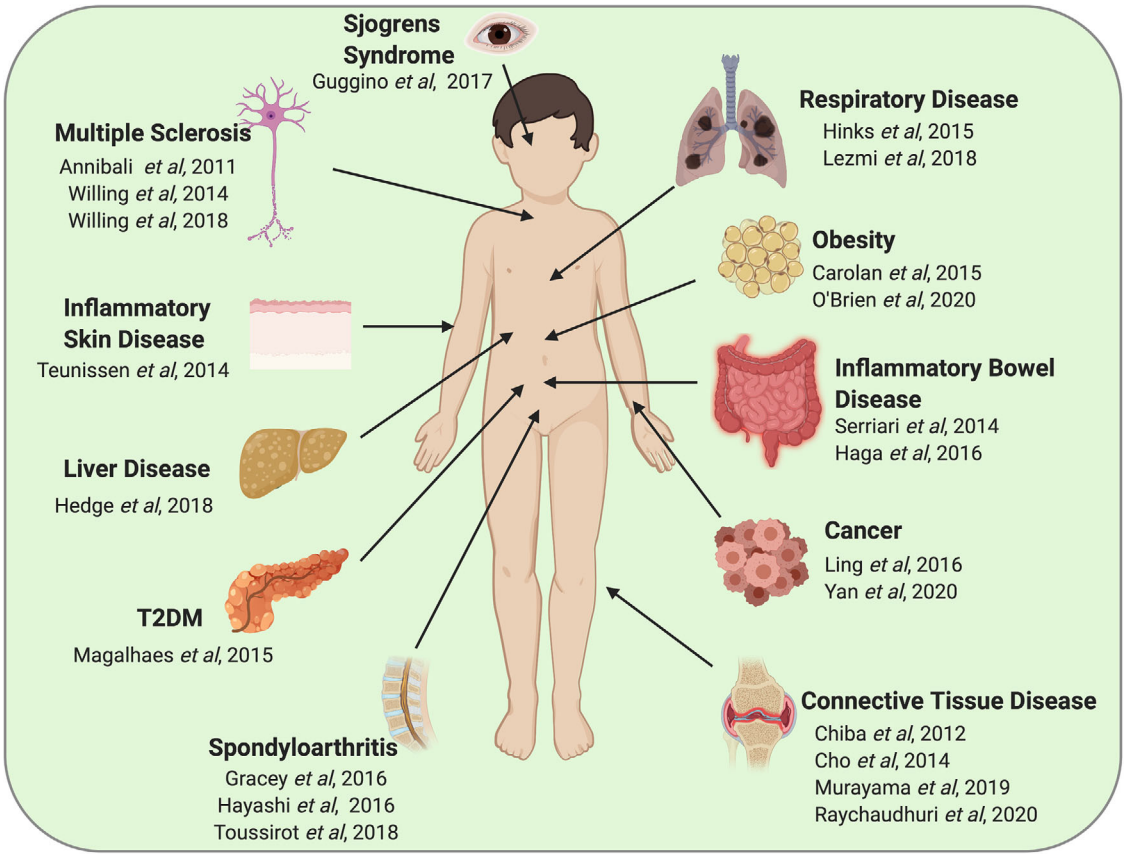

Figure 4. MAIT17 cells in chronic inflammatory disease. Schematic outlining the body of works describing increased MAIT17 cells in chronic inflammatory conditions.

arthritis, non-alcoholic fatty liver, and type II diabetes mellitus. The role of MAIT17 cells in the development and pathogenesis of these conditions is summarized in Figure 4 and discussed herein.

Respiratory disease

Asthma is a respiratory disease characterized by chronic airway inflammation with increased mucus production in the bronchioles, and is associated with activation of an allergen-specific T helper type 2 (T_H2) immune response [60]. Recently, IL-17 has emerged as a pathogenic player in asthma, in particular in severe asthma and immediate responses to bronchodilators [61]. The role of MAIT cells in asthma is unclear with reported reduced frequencies in blood, sputum, and lung biopsies of patients with asthma [62]. In this study, the authors conclude that a loss of MAIT cells in severe asthma might increase susceptibility to bacterial infection, which might impact asthma pathology, suggesting a protective role. However, in a study by Lezmi and colleagues, it was noted that MAIT17 cells were increased in the BALF of asthma patients, and were associated with exacerbations, suggesting a potential pathogenic role [63]. The exact role of MAIT cells in respiratory disease remains to be elucidated, however their relative abundance in humans and association with disease severity, suggests MAIT17 cells may be a major player in asthma pathology either directly or indirectly.

Connective tissue disease

MAIT cells have been implicated in several rheumatoid diseases, including rheumatoid arthritis, systemic lupus erythematosus, and spondyloarthritis [64–68]. Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition which affects the joints. Several immune cell populations have been implicated in the pathogenesis of disease including T cells, B cells, and macrophages [69]. Studies in RA patients revealed significant decreases in peripheral MAIT cells observed in comparison to healthy controls, and these decreases are correlated with disease activity scores [64]. MAIT cells have been shown to migrate into the synovial fluid in RA, mediated by IL-1β and TNF-α driven expression of E-selectin at that site [70]. Chiba and colleagues demonstrated an improvement in disease severity in a murine model of collagen induced arthritis in MAIT cell deficient mice, which was paired with a reduction in IL-17 production [71]. Systemic lupus erythematosus (SLE) is an inflammatory autoimmune condition, which impacts several organs including skin, joints and the CNS [72]. Similar to RA, alterations in MAIT cell frequencies were associated with

disease severity in patients [64]. In a murine model of SLE, IL-17 producing MAIT cells were expanded and their deletion resulted in improved disease severity [73]. Spondyloarthritis is a group of chronic inflammatory conditions, which can affect the joints of the spine and pelvis. Several inflammatory cytokines have been implicated in the pathogenesis of the disease including TNF-α and IL-17 [74]. Three separate studies have investigated MAIT cells in ankylosing spondylitis (AS), with each observing reduced MAIT cell frequencies in the circulation [65, 66, 75]. In one of the studies, Gracey and colleagues reported an increase in MAIT cell numbers in the synovial fluid of patients with AS [65]. All three studies also reported that IL-17 production by MAIT cells was higher, suggesting that MAIT cells play a role in pathogenesis [76]. Sjögren syndrome (SjS) is a systemic autoimmune inflammatory disease that primarily affects the exocrine glands resulting in the severe dryness of mucosal surfaces, principally in the mouth and eyes [77]. MAIT cells were found to infiltrate the salivary glands of patients with SjS, displaying an altered phenotype and IFN-γ production, but no difference in IL-17 was reported [78]. In a subsequent report, Guggino and colleagues showed increased MAIT17 cells in salivary gland tissue of patients with SjS, and provided evidence for activation of the IL-7/IL-23 pathways in polarization of MAIT17 cells in SjS [79]. Based on the studies above, it appears that MAIT cells play an important role in the pathogenesis of connective tissue disease and may represent a novel therapeutic target.

Neurological disease

Multiple sclerosis (MS) is a chronic immune-mediated condition affecting the CNS in which T cells play a central pathogenic role in destruction of the myelin sheath [80]. In humans, CD8 T cells comprise the most abundant cell type in the CNS of MS patients in contrast to animal models [71] and MAIT cells account for approximately 5% of these CNS-infiltrating cells [81]. MAIT17 cells are increased in both the CNS and periphery of MS patients, which indicates that MAIT cells may be driving the inflammation associated with this autoimmune disorder [82]. A recent study by Willing et al. has suggested a role for IL-7 in augmentation of IL-17 production by MAIT cells in MS, where increased surface IL-7R expression on MAIT cells correlated with their IL-17 production [82]. Further evidence for MAIT17 cells in the pathogenesis of MS comes from the identification of an expanded population in MS patients of $CCR6^+$, $CD8^+$, $CD161^{hi}$, $CD3^+$, $IL\text{-}17^+$ cells, which bear all the hallmarks of MAIT cells [83]. The exact role for MAIT cells in the pathogenesis of MS remains to be elucidated but their increased production of IL-17 may highlight them as a potential therapeutic target.

Inflammatory skin disease

Recent studies have begun to elucidate a role for MAIT cells in psoriasis, one of the most common immune-mediated chronic inflammatory skin disorders [84]. Evidence suggests that IL-17A and T_H17-related cytokines are critical in the pathogenesis of this systemic disease [85]. A study by Teunissen et al. shows the presence of $CD8^+$ MAIT cells in the dermis and epidermis of psoriatic plaques as well as healthy skin, with MAIT cells accounting for a proportion of $IL\text{-}17A^+$ $CD8^+$ T cells in plaques [19]. IL-17 producing MAIT cells were predominantly found in the psoriatic lesions and were almost absent in healthy skin. These results identify an additional source of IL-17 in psoriatic skin that may be contributing to the disease [19]. Psoriatic arthritis (PsA) is an inflammatory condition, which affects the joints of up to 25% of psoriasis patients. In the majority of cases, psoriasis precedes the onset of PsA [86]. MAIT cells are found to be enriched in the synovial fluid compared to blood of patients with PsA, and upon stimulation produced more IL-17 than in other rheumatoid conditions [68]. The contribution of MAIT cells to other IL-17-driven inflammatory skin diseases such as atopic dermatitis and hidradenitis suppurativa are unknown to date and require further investigation.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract encompassing two separate diseases: Crohn's disease (CD) and ulcerative colitis (UC) [87]. Both conditions are driven by over production of inflammatory mediators including TNF-α, IL-23, and IL-17 [88]. Serriari and colleagues investigated the frequencies of MAIT cells in cohorts of patients with either UC or CD and reported reduced frequencies in the circulation compared to healthy controls, which was paired with an increase of MAIT cells in the inflamed tissue [89]. In vitro, MAIT cells from both UC and CD produced more IL-17 [89]. These findings were supported by a subsequent study by Haga and colleagues, who reported reduced circulating MAIT cell frequencies and increased IL-17 production in UC patients [90]. Furthermore, increased MAIT cell levels in the inflamed mucosa correlated with disease activity, suggesting a possible pathogenic role for MAIT cells.

Metabolic disease

Obesity is emerging as the number one cause of preventable death in the Western world, underpinning the development of many chronic diseases, such as type 2 diabetes mellitus (T2DM), cardiovascular disease, and many cancers [91]. Obesity has also been identified as a confounding factor in other chronic diseases including psoriasis, arthritis, and cancer [92]. We and others have previously reported reduced MAIT cell frequencies in the periphery of adults living with obesity [20]. MAIT cells isolated from the periphery of these patients displayed a potent IL-17 phenotype, i.e., significantly higher IL-17 production and reduced IFN-γ production following stimulation compared to healthy controls [20, 93]. This predominant IL-17 phenotype may be contributing to the chronic inflammation seen in obesity and insulin resistance

[94]. MAIT cells were found at higher frequencies in adipose tissue compared to blood, in both lean and obese individuals. MAIT cells in healthy adipose tissue produce IL-10, however this production is reduced in MAIT cells from the adipose tissue of obese patients. [20] MAIT cells may therefore play a regulatory role in healthy individuals and initiate a more inflammatory response through their pro-IL-17 phenotype in obese individuals. Following bariatric surgery (1-year post-surgery) MAIT cell levels were increased in blood compared to presurgical levels, however the levels detected were still lower than healthy controls [93]. The data associated with childhood obesity is slightly different. MAIT cell frequencies in the blood of obese children appear to be significantly higher when compared to their lean counterparts. However, as obese children progress into adulthood, their MAIT cell frequency declines [20]. This is not observed in the lean cohort, suggesting that MAIT cell numbers ultimately decline with the progression of obesity. This altered frequency is associated with both increased fasting insulin and insulin resistance, factors driving the development of type 2 diabetes [20]. Similar to adult obesity, increased MAIT cell IL-17 production was also seen in the pediatric obese cohort [20]. Recently, we have demonstrated that alterations in mitochondria ROS are linked to IL-17 production in MAIT cells from patients with obesity. Using several mitochondrial antioxidants, we were able to limit the production of IL-17 by MAIT cells from patients with obesity in vitro [95]. Non-alcoholic fatty liver disease (NAFLD) is characterized by the excess accumulation of fat in hepatocytes, which can drive fibrosis, progressing to cirrhosis [96]. In cohorts of patients with cirrhotic NAFLD, MAIT cell frequencies were reduced in both the periphery and the liver, but displayed elevated MAIT17 cells compared to controls [97]. Using an in vitro system, it was demonstrated that MAIT cells could drive a pro-inflammatory human hepatic myofibroblast phenotype in a IL-17/TNF-a dependent manner, suggesting MAIT cells are a pro-fibrogenic population [97]. The contribution of MAIT cells to the progression of metabolic disease remains to be elucidated but due to their abundance in humans, they may represent a novel therapeutic target.

Cancer

MAIT cells have been detected within many solid tumor types, including breast, lung, liver, thyroid, colorectal, kidney, brain, stomach, and esophagus [98–102] and in multiple myeloma [11]. These emerging studies have demonstrated that MAIT cells are capable of tumor cell lysis in vitro, however, the role of MAIT cells within cancer, and in particular MAIT17 cells, remains unclear. Ling and colleagues report elevated IL-17 production by MAIT cells in colorectal tumors, when compared to a healthy control group [99]. The authors also found increased IL-17 production by MAIT cells co-cultured in vitro with colorectal cancer cell lines, but also observed an MR1 dependent inhibition of the tumor cell cycle in this setting, suggesting a more complex role for MAIT17 cells in cancer [99]. In contrast, a recent study by Yan and colleagues provided evidence for the promotion of tumor metastasis by MAIT cells, in particular MAIT17 cells [103]. Using two murine models, the authors showed increased tumor expression of MR1, which promoted MAIT cell activation and production of IL-17, which subsequently inhibited NK cell antitumor activity [103]. More work is required in order to define the role of MAIT cells in cancer, including in infection driven cancers, and to properly elucidate their immunotherapeutic potential.

Conclusion

MAIT cells represent a significant proportion of the human $CD8^+$ T cell compartment, yet their place in immunity is only beginning to be understood. In recent years, the volume of studies into MAIT cell biology has exponentially increased, largely due to greater availability of antibodies and tetramers. Many of these studies have examined the role of MAIT cells in disease settings, giving new insights into the role played by MAIT cells in disease. The most striking observation common to many different disease states, is the significant alteration in MAIT cell frequency and cytokine profile. In particular, we have discussed the prevalence of MAIT17 cells in chronic inflammatory diseases. Currently, we do not fully understand the environmental signals and molecular pathways driving this expansion of MAIT17 cells. Several studies have implicated IL-7 as a licencing factor for MAIT17 cells [65, 79, 82], however, this was not specific to IL-17 as other studies detailed IL-7 licencing of IFN-γ and Granzyme B [30, 104]. In addition to IL-7 priming of MAIT17 cells, some studies detailed additional cytokines such as IL-12 or IL-23 [79]. Further work will be required to establish the exact cytokine signals driving MAIT cells and if these are common or disease specific. As discussed, our group has highlighted the importance of immunometabolism in controlling MAIT cell cytokine responses, we highlighted altered mitochondria as a potential driver of IL-17 in MAIT cells from patients with obesity [38, 95]. Altered mitochondria haven been linked to IL-17 production in conventional T cells [105–107], however additional work will again be required to determine if this is a major mechanism driving IL-17 production in MAIT cells, and also to elucidate the environmental signals driving mitochondrial dysregulation. It is clear that despite the recent surge in MAIT cell studies, including numerous studies on MAIT17 cells, improved insight into the pathways controlling MAIT17 cells is required.

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Abbreviations: **CD**: Crohn's disease · **IBD**: inflammatory bowel disease · **iNKT**: invariant NK T cells · **MAIT**: mucosal associated invariant T cells · **Mtb**: *Mycobacterium tuberculosis* · **MS**: multiple sclerosis · **mTOR**: mammalian target of rapamycin · **PsA**: psoriatic arthritis · **RA**: rheumatoid arthritis · **SjS**: Sjögren syndrome · **T2DM**: type 2 diabetes mellitus · **TCR**: T cell receptor · **UC**: ulcerative colitis

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