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MAIT Cells in Health and Disease

Nicholas M. Provine[1] and Paul Klenerman[1,2]

[1]Translational Gastroenterology Unit, Nuffield Department of Medicine, University of Oxford, Headington, Oxford OX3 9DU, United Kingdom; email: paul.klenerman@ndm.ox.ac.uk

[2]NIHR Biomedical Research Centre, John Radcliffe Hospital, Headington, Oxford OX3 9DU, United Kingdom

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Abstract

Mucosal-associated invariant T (MAIT) cells have been attracting increasing attention over the last few years as a potent unconventional T cell subset. Three factors largely account for this emerging interest. Firstly, these cells are abundant in humans, both in circulation and especially in some tissues such as the liver. Secondly is the discovery of a ligand that has uncovered their microbial targets, and also allowed for the development of tools to accurately track the cells in both humans and mice. Finally, it appears that the cells not only have a diverse range of functions but also are sensitive to a range of inflammatory triggers that can enhance or even bypass T cell receptor–mediated signals—substantially broadening their likely impact in health and disease. In this review we discuss how MAIT cells display antimicrobial, homeostatic, and amplifier roles in vivo, and how this may lead to protection and potentially pathology.

1. INTRODUCTION—A BRIEF HISTORY OF MAIT CELLS

Mucosal-associated invariant T (MAIT) cells were first identified in humans, mice, and cattle as a population of αβ T cells enriched in the double-negative ($CD4^-CD8^-$) subset expressing an invariant Vα7.2–Jα33 T cell receptor (TCR) (in humans; Vα19–Jα33 in mice and cattle) (1, 2). These cells were found to be restricted by a β_2m-containing molecule, not involving MHC-I, MHC-II, CD1, or TAP. However, it was several years later, in 2003, that Treiner, Duban, and colleagues established the term MAIT cell, due to the relative enrichment of these T cells within mucosal tissues (3). This same seminal study also identified the restricting element of MAIT cells as the MHC-1b molecule MR1 (MHC-related 1), but the nature of the antigen presented by MR1 remained an enigma. It was not until 2012 that Kjer-Nielsen et al. (4) determined that MR1 presented intermediates in the vitamin B [both riboflavin (vitamin B_2) and folic acid (vitamin B_9)] synthesis pathway to MAIT cells. Further work in 2014 clarified that the potent stimulatory ligand in the riboflavin synthesis pathway was a nonenzymatic derivative of 5-A-RU (5-amino-6-D-ribitylaminouracil) (5).

In the years between the identification of MR1 and its ligand, the function and phenotype of MAIT cells began to be characterized. Several studies found that MAIT cells can recognize cells infected by bacteria and produce IFN-γ in response (6, 7). Subsequent work demonstrated that MAIT cells can protect mice from bacterial infection (8). Efforts to phenotype and characterize MAIT cells were dramatically boosted by the development of the 3C10 antibody clone that recognizes Vα7.2 TCR (9). This early phenotypic work established that human MAIT cells are $CD8^+$ or double negative, have a primarily $CCR7^-$ effector memory phenotype, and express high levels of CD161 (9, 10). At this time, it was demonstrated that $CD161^{hi}$ $CD8^+$ T cells are unique among $CD8^+$ T cells in their expression of RORγt and production of IL-17 and IL-22 (11). The synthesis of these findings established that MAIT cells display a mixed type 1 and type 17 phenotype and function (10). Detailed phenotyping of MAIT cells also demonstrated that they share several characteristics with invariant natural killer T (iNKT) cells (reviewed extensively in 12), including, critically, the expression of PLZF, a transcription factor that governs the innate-like functionality of iNKT cells (9). Expression of PLZF similarly imparts MAIT cells with innate-like functionality, as evidenced by the ability of cytokines to induce IFN-γ production in the absence of TCR stimulation (13). This cytokine responsiveness underpins the ability of MAIT cells to respond to disease conditions for which no microbe-derived TCR ligand is available (e.g., viral infections and inflammatory disease).

Finally, the identification of vitamin B_2/B_9 precursors as ligands for MR1 allowed for the subsequent development of MR1 tetramers in mice and humans (14, 15). These reagents have significantly aided our understanding of MAIT cell biology in humans, particularly in tissues and during development. While useful in humans, the MR1 tetramers have fundamentally revolutionized our ability to use mice as a model of MAIT cell biology, as prior to this, reagents were limited. One of the first findings made using the MR1 tetramer in humans was that MAIT cells do not express a single invariant TCR, but restricted TCRs comprising Vα7.2–Jα33, Vα7.2–Jα12, or Vα7.2–Jα20 (14). With these data we have moved to our current understanding of the basic characteristics of MAIT cells as T cells that (*a*) express a semi-invariant Vα7.2–Jα33/12/20 TCR, (*b*) are activated by microbial vitamin B antigens presented by MR1 to execute both type 1 and type 17 effector functions, and (*c*) exhibit innate-like characteristics, governed by expression of PLZF, including the ability to be activated by cytokines independent of their TCR. Although not exhaustive, this summary gives a broad overview of the history of MAIT cell research and provides a solid basis from which to build our understanding of MAIT cell phenotype, development, and function in human health and disease.

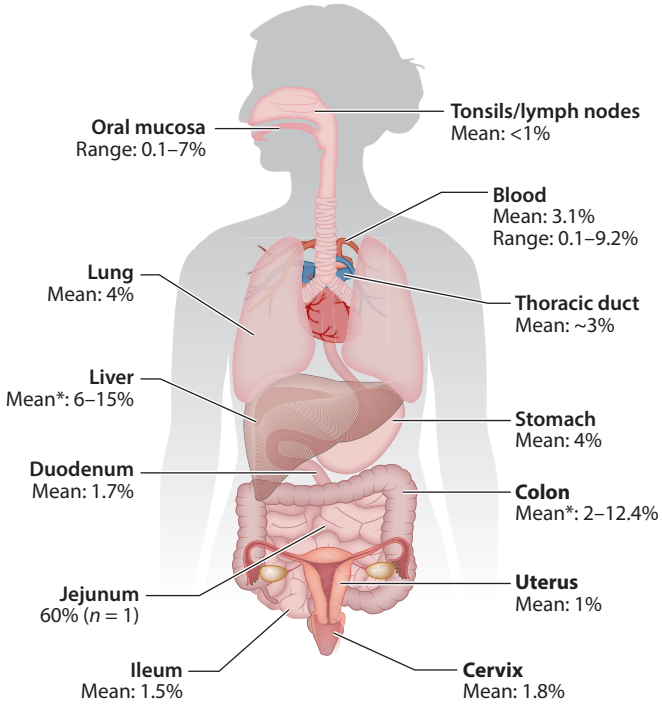

Figure 1

Frequency of MAIT cells in human tissues. The frequency of MAIT cells in the tissues of a healthy adult, as compiled from multiple studies. The frequency is a fraction of all $CD3^+$ T cells, except for in the jejunum, where data are reported as a fraction of $CD4^-CD3^+$ T cells and are reported from one individual. Asterisks (*) indicate ranges of mean values reported from multiple studies. Data are from oral mucosa (45), lymphoid tissue (151, 152), lung (153), blood (20), thoracic duct (63), liver (44, 47, 139), stomach (80, 154), duodenum (47), jejunum ($n = 1$) (14), ileum (155), colon (98, 156, 157), cervix (41), and uterus (41). Note: only data from blood, stomach, and jejunum were generated using MR1 tetramers, while all other data were generated using proxy measures of MAIT cell frequency (i.e., combinatorial staining with Va7.2 TCR, CD161, IL-18Ra, and/or CCR6).

2. BASIC BUILDING BLOCKS OF A MAIT CELL

MAIT cells are a predominantly homogenous population of cells with a very stereotypical phenotype and function. Recent work has tested the limits of this generalization (16), but fundamentally, observed variations in phenotype and function in humans are modest and do not appear to reflect the presence of functionally distinct populations akin to those seen in conventional CD4 T cells [e.g., T helper type 1 (Th1), Th2, and Th17 cells and regulatory T cells (Tregs)] (17). In the periphery, MAIT cells are uniformly $CCR7^-$ effector memory cells (10), which reflects the scarcity of these cells in secondary lymphoid organs and their relative enrichment in blood (average of 3% of $CD3^+$ T cells) and tissues (**Figure 1**). In humans, peripheral MAIT cells are universally $CD161^{hi}$ (*KLRB1*, a C-type lectin-like receptor) and $CD26^{hi}$ (*DPP4*), and both of these markers are routinely used to identify these cells (9–11) (**Figure 2**). The function of these molecules in the context of MAIT cell biology remains unclear (18, 19).

In human blood, MAIT cells are predominantly $CD8^+$ (~80%) or double negative (~20%) with a very minor CD4-expressing population (~1%) (20). Interestingly, $CD8^+$ MAIT cells are enriched for expression of the CD8αα homodimer, as compared to conventional $CD8^+$ T cells,

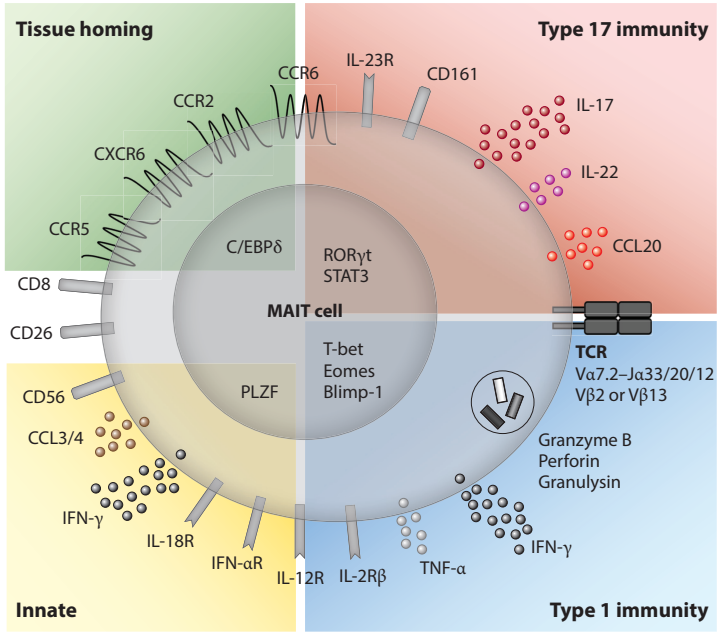

Figure 2

Phenotype and function of MAIT cells defined by the types of transcription factors expressed. Human MAIT cells exhibit multiple functional and phenotypic traits that can be broadly characterized by four types of functions: type 1 immunity (including cytotoxic function); type 17 immunity; tissue homing to the lung, liver, and intestine; and innate-like functionality driven by the expression of PLZF.

which appears to be a differentiation state from CD8αβ-expressing cells (21). Recent work has demonstrated that double-negative MAIT cells are also a differentiation state of $CD8^+$ MAIT cells, which have a more proapoptotic and less functional phenotype (22, 23). Together, these data suggest a differentiation trajectory from $CD8\alpha\beta^+$ to $CD8\alpha\alpha^+$ to double negative and help explain the functional similarities of $CD8^+$ and double-negative MAIT cells.

Many of the fundamental characteristics of MAIT cell biology can be most easily understood by dissecting the unique biology of the MAIT cell TCR, as well as the unconventional combination of transcription factors expressed by these cells.

2.1. The (Semi)invariant T Cell Receptor

As mentioned above, the TCR of MAIT cells recognizes antigen presented by the MHC-like molecule MR1 (3). A number of related stimulatory and inhibitory MR1-binding ligands have been identified, including drug-like molecules, folate derivatives, and riboflavin derivatives (4, 5, 24, 25). However, the most potent activating ligands identified to date are 5-OP-RU [5-(2-oxopropylideneamino)-5-D-ribitylaminouracil] and 5-OE-RU [5-(2-oxoethylideneamino)-5-D-ribitylaminouracil], which are unstable, nonenzymatic intermediates of riboflavin biosynthesis (5). 5-OP-RU and 5-OE-RU are generated by nonenzymatic reactions between 5-A-RU and either glyoxal or methylglyoxal and stabilized within the MR1 cleft through the formation of a Schiff base with lysine 43 (5, 14). Despite evidence for other MR1-binding, MAIT cell–activating ligands, to date the presence or absence of the riboflavin operon in bacterial and yeast species has been the unequivocal identifier of microbes that do or do not activate MAIT cells through the

TCR (26). The choice of riboflavin by the host immune system as a target is intriguing: Not only does this pathway distinguish microbes from host cells but it also reflects the metabolic state of the organisms, with activity responding to changes in nutrient availability, heat shock, and iron requirements (27, 28).

The specificity of the MAIT cell TCR for MR1-loaded antigens is due to its well-defined CDR3 characteristics. Regardless of Vα/Jα pairing, the TCRα chain is the dominant chain involved in recognizing antigen within the MR1 cleft, and productive TCRα chain–mediated antigen recognition requires a tyrosine at residue 95 to facilitate this interaction (5, 29). This TCRα chain pairs primarily with Vβ2 or Vβ13 (*TRBV20* and *TRBV6*, respectively) (**Figure 2**). The CDR3β primarily makes contact directly with the MR1 molecule. In mice, the structure of the TCR follows the same guidelines: Vα19 (*Trav1*) pairs with Jα33 (*Traj33*) to form a ligand-binding TCRα chain, and this pairs preferentially with Vβ6 or Vβ8 (*Trbv19* or *Trbv13*, respectively) (2, 15). Indeed, the architecture of the MAIT cell TCR and its position within the TCRα locus is broadly conserved across mammalian biology (30). The specific construction of the MAIT cell TCR thus allows MAIT cells to recognize and respond to a diverse array of microbial species.

2.2. The Transcription Factors

Upon activation, MAIT cells can execute a diverse array of effector functions that are clearly governed by the unique pattern of transcription factors expressed by these cells (**Figure 2**). Our understanding of MAIT cell function largely derives from the expression of several key transcription factors by these cells: the type 1 transcription factor T-bet (*TBX21*); the CTL-associated transcription factors Eomesodermin (*EOMES*) and Blimp-1 (*PRDM1*); the type 17 transcription factors RORγt (*RORC*) and STAT3 (*STAT3*); and the transcription factor PLZF (*ZBTB16*), which imparts innate-like functionality, akin to iNKT cells (11, 31, 32). In humans, these transcription factors are all coexpressed, and thus, in this regard, MAIT cells appear to be a functionally homogenous population (31, 32). By contrast, in mice, T-bet and RORγt display a mutually exclusive expression pattern, thus giving rise to two populations, of which the type 17 RORγt-expressing population is dominant in C57BL/6 mice (15, 33).

Expression of T-bet, Eomesodermin, and Blimp-1 imparts MAIT cells with properties of conventional CD8 T cells, including production of IFN-γ and the expression of cytotoxic granules (34–37). Interestingly, expression of cytotoxic granule components is tightly regulated in MAIT cells, and only after activation are high levels of perforin and granzyme B observed (31, 32). A portion of MAIT cells have also been shown to express granulysin, an additional cytotoxic granule protein not present in mice (38), but expression does not appear to be regulated by stimulation in the manner seen for perforin and granzyme B (19). This functionality is mirrored phenotypically, where MAIT cells express high levels of the type 1 immunity-associated IL-12Rβ1 (18). Thus, MAIT cells can function as strong type 1 cytotoxic effector cells.

However, MAIT cells also have type 17 functionality driven by RORγt (39) and STAT3 (40), including the expression of IL-17 and IL-22 upon activation (11). Interestingly, in humans, despite universal expression of RORγt, only a small fraction of circulating MAIT cells express IL-17 upon stimulation (10). This modest expression of IL-17 appears to reflect tight regulation, as strong signals such as costimulation with IL-1β or IL-7, prolonged TCR stimulation, or stimulation with *Escherichia coli* can markedly increase IL-17 production (31, 41–44). In addition, the capacity for IL-17 production may reflect the tissue of origin, as MAIT cells from mucosal surfaces, including from the mouth and female genital tract, displayed enhanced IL-17 production as compared to blood-derived MAIT cells (41, 45). Paralleling this type 17 functionality, MAIT cells express high levels of IL-23R (11), the receptor for the canonical type 17 cytokine IL-23 (46).

Finally, MAIT cells express the transcription factor PLZF, which regulates the ability of iNKT cells, Vδ2$^+$ γδ T cells, and natural killer (NK) cells to be activated by cytokines (47–49). This mode of activation is discussed in more detail below in Section 5.2. Fundamentally, expression of this transcription factor is linked with elevated expression of IL-18Rα, IL-18RAP, and IL-12Rβ1 (50), which are all key markers of the MAIT cell phenotype.

Thus, the three major well-studied functional traits of MAIT cells—type 1, type 17, and innate-like functionality—can all be understood by the unique combination of transcription factors expressed by these cells. However, the array of effector molecules that MAIT cells can produce are actually more diverse than this prior work would suggest. Several recent studies have used unbiased RNA sequencing to examine MAIT cell activation following stimulation and have identified production of cytokines, chemokines, and growth factors with diverse functions including the antimicrobial cytokine IL-26 (51); OSM, which is involved in inflammation in inflammatory bowel disease (52); growth factors such as HBEGF (heparin-binding epithelial growth factor); and chemokines such as CCL3, CCL4, and CCL20 (53–55). Exactly how these effector functions are regulated transcriptionally and how key they are to MAIT cell biology remain to be determined.

2.3. Tissue-Homing Properties

MAIT cells are found at relatively high frequency throughout nonlymphoid tissues (**Figure 1**), and the capacity of MAIT cells to home to diverse anatomic sites is reflected in their phenotype (**Figure 2**). MAIT cells express high levels of the liver-homing chemokine receptor CXCR6 (10, 11, 56), thus contributing to the high frequency of MAIT cells within the liver (44, 57). Furthermore, MAIT cells express CCR6 [another RORγt-regulated gene (58)]; CCR2; and CCR5, which allows for trafficking to inflamed tissues, including the intestine (10, 18). Recent work has identified C/EBPδ, a bZIP family transcription factor not expressed on other T cells, as a key regulator of MAIT cell extravasation through the endothelium (59). C/EBPδ expression is necessary for high-level expression of CCR6, but not CCR2, as well as expression of glycosyltransferases involved in the generation of sialyl Lewis^X (sLe^X) motifs on surface proteins, including the ligands for P- and E-selectin (60, 61). Thus, again our understanding of MAIT cell function can be described through the expression of distinct transcription factors.

Our understanding of the ability of MAIT cells to form tissue-resident populations is still evolving. Recently, it was demonstrated by parabiosis experiments, the gold standard technique in mice, that MAIT cells did not recirculate between tissues (62). Splenic and hepatic MAIT cells had less than 10% chimerism after five weeks of parabiosis. Equivalent low levels of recirculation of RORγt$^+$ lung MAIT cells were seen, but interestingly, RORγt$^-$ lung MAIT cells displayed much lower tissue retention, consistent with direct access of this subset to the vasculature. This functionality was reflected by the expression of a tissue-residency gene signature in both murine MAIT cells as well as human MAIT cells from the liver. However, a recent study showed lymph collected from the thoracic duct of human patients has a high frequency of MAIT cells, equivalent to that of the blood (63). TCR clonotype analysis identified a high degree of overlap between blood-derived and lymph-derived MAIT cells within the same individual, suggesting MAIT cells from the lymph are derived from the same pool as MAIT cells found in the blood, which was consistent with the uniformly CCR7$^-$ phenotype. Further work will be required to help clarify these discordant results and thereby enhance our understanding of MAIT cell tissue residency.

3. ESTABLISHING AND TUNING A MAIT CELL POPULATION

Several reviews have recently described the developmental pathways of MAIT cells in detail (12, 64), so we will discuss this topic only briefly (**Figure 3**). Like all T cells, MAIT cells are selected

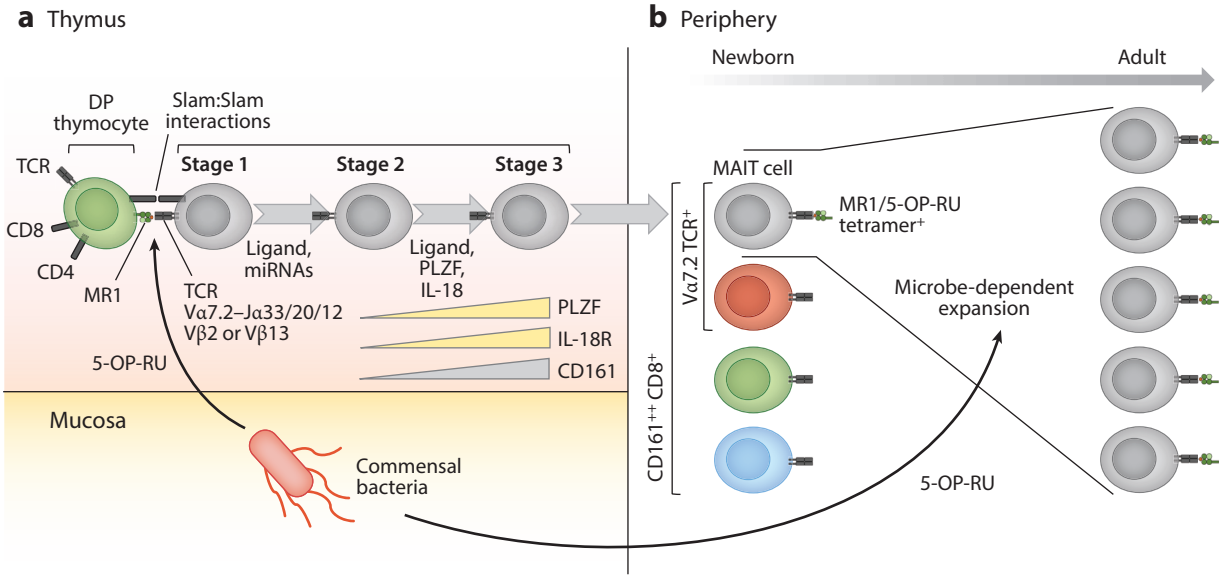

Figure 3

MAIT cell development and expansion is driven by commensal microbiota. (*a*) The MAIT cell–selecting ligand 5-OP-RU [5-(2-oxopropylideneamino)-5-D-ribitylaminouracil] is produced by bacteria at mucosal surfaces and traffics to the thymus, where it is loaded onto MR1 expressed on double-positive (DP) thymocytes. MAIT cells subsequently undergo positive selection on these DP thymocytes, which initiates a multistep intrathymic maturation pathway. In mice, homotypic interactions between Slam family member proteins are required for initiation of the differentiation program. However, in humans the role for Slam family signaling is unclear. The stage 2 to stage 3 transition involves the acquisition of effector functions and a canonical MAIT cell phenotype, driven by PLZF. In mice this occurs intrathymically (pictured), while in humans MAIT cells can transition to stage 3 either in the thymus or in the periphery. (*b*) Thymic output produces few MAIT cells relative to conventional T cells. Thus, in newborns, there are many cells that phenocopy mature MAIT cells ($CD161^{hi}$ $CD8^+$), and even some that coexpress a Vα7.2 T cell receptor (TCR) but are not bona fide MR1-restricted MAIT cells. Expansion of MAIT cells in response to interactions with commensal bacteria leads to their preferential expansion. Thus, by adulthood the entire peripheral blood $CD161^{hi}$ Vα7.2 TCR^+ population is MAIT cells.

in the thymus (9) (**Figure 3*a***). However, unlike conventional T cells, MAIT cells do not undergo positive TCR selection on cortical epithelial cells and instead are selected by double-positive ($CD4^+CD8^+$) thymocytes (65, 66), in a manner analogous to iNKT cells (67). In many regards, the thymic development of MAIT cells mirrors that of iNKT cells, and much can be gleaned by comparing the two cell types (12). However, a recent study has demonstrated that a peripheral microbe-derived ligand (5-OP-RU) can be transported to the thymus and thereby serve as the ligand for positive selection when presented by MR1, in an entirely novel process of thymic selection (68).

Following TCR rearrangement and positive selection, human and mouse MAIT cells undergo a three-stage intrathymic differentiation process (69). Interaction with MR1 is required at each stage, along with distinct cofactors. The stage 1 to 2 transition (in mice $CD24^+CD44^-$ to $CD24^-CD44^-$) requires expression of miRNAs including miR-181a/b (69, 70). SLAM (signaling lymphocytic activation molecule) signaling, via SAP (SLAM-associated protein), also appears critical for development of mouse MAIT cells beyond stage 1 (71), but the role for SAP in human MAIT cell development remains unclear, as SAP-deficient patients have normal numbers of peripheral MAIT cells (9). Transition from stage 2 to 3 reflects a critical developmental step, as MAIT cells acquire effector functionality at stage 3 ($CD24^-CD44^+$ in mice; $CD161^+CD27^+$ in humans) (69). This transition requires expression of PLZF, IL-18, and commensal bacteria, as germ-free mice, or mice deficient in either of these genes, have major reductions in MAIT cell

frequency (3, 15, 69). In mice, this stage 2 to stage 3 transition occurs intrathymically, while in humans, stage 2 and 3 cells can be found in both the thymus and cord blood, suggesting the anatomic location of the transition is more fluid (69).

Following thymic egress, MAIT cells continue to expand and differentiate (**Figure 3*b***). Estimates of thymic output predict constant low frequencies of MAIT cells (9, 69), but peripheral MAIT cell frequency increases dramatically with age over the first ~30 years of life (20, 72, 73). In cord blood, a distinct population of $CD161^{hi}CD8^{+}$ T cells exists, only a small fraction of which are $V\alpha7.2^{+}$ (21). Further, despite nearly all $CD161^{hi}$ $V\alpha7.2^{+}$ T cells in the adult blood being MAIT cells, MR1/5-OP-RU tetramer-binding MAIT cells are only a minority of $V\alpha7.2^{+}$ T cells at birth, and it takes nearly a year for MAIT cells to dominate this population (73). Given this, prior studies examining $CD161^{+}V\alpha7.2^{+}$ T cells in cord blood were likely studying a heterogeneous population of both MAIT and non-MAIT cells (18, 21, 66). Additionally, prior work examining the distribution and function of MAIT cells in fetal tissues may need clarification in light of these new findings (74). The postnatal expansion of MAIT cells coincides with the differentiation into $CD45RO^{+}$ memory cells, consistent with their canonical phenotype (10, 20, 73). As intranasal infection of mice with *Salmonella enterica* serovar Typhimurium induces long-term systemic expansion of the MAIT cell population (75), one can hypothesize that microbial colonization of mucosal surfaces during infancy is a driving factor of this process. Consistent with this hypothesis, bacterial colonization of germ-free mice leads to rapid expansion of thymic and peripheral MAIT cell populations (68). Animal data suggest that B cells are critical for this peripheral expansion, as are commensal bacteria (3, 7, 9). However, of the four BTK-deficient patients analyzed, who have no B cells, one had normal MAIT cell frequencies (3), suggesting that B cells might not be absolutely critical in humans.

4. TECHNICAL CONSIDERATIONS FOR STUDYING MAIT CELLS IN DISEASE

4.1. A Definition

In this review we are functionally defining MAIT cells as (*a*) expressing a semi-invariant Vα7.2–Jα33/12/20 TCR with a tyrosine 95 residue, (*b*) restricted by microbial metabolites presented by MR1, and (*c*) possessing a mixed type 1/type 17/innate-like functional and phenotypic profile (or split type 1 and type 17 functionality in mice). Such a definition is in line with the working definition of a MAIT cell put forward by the vast majority of prior studies (as discussed above) and captures the core traits of a MAIT cell as defined by the last 20 years of research.

Rare, but detectable, T cells that are restricted by MR1/5-OP-RU but do not express a TCR containing Vα7.2 have been reported (76, 77). However, a recent study has demonstrated that on average 80% of the $V\alpha7.2^{-}$ MR1/5-OP-RU tetramer-binding T cells do not share a phenotype with MAIT cells (78), and thus cells that are phenotypically MAIT like but $V\alpha7.2^{-}$ are an exceedingly minor population (~1% of MR1/5-OP-RU tetramer-binding cells in human blood). Furthermore, thymic selection on double-positive thymocytes, discussed above, separates MAIT cells from functionally and developmentally distinct MR1-restricted T cells, which may respond to nonmicrobial ligands (71, 79). Thus, a definition that incorporates not only the specific molecular interactions of the TCR but also the unique functional traits of MAIT cells separates this population from these other recently identified MR1-binding populations.

4.2. Identifying MAIT Cells

On a practical level, MAIT cells can be readily identified by MR1/5-OP-RU tetramers, or in healthy adult human blood using anti-Vα7.2 TCR antibodies combined with a costain for CD161,

CD26, or IL-18Rα (9–11). In mice, the lack of suitable reagents for the Vα19 TCR, combined with a lack of good costaining markers, necessitates the use of murine MR1/5-OP-RU tetramers (15). Even when using MR1 tetramers, it is best to include a costain (e.g., CD161), as tetramer staining can also have some degree of background. When examining MAIT cells in tissues, development, or disease, the use of MR1 tetramers is strongly preferred, as expression of costaining markers can change (69), or discordance between $CD161^{+}V\alpha7.2^{+}$ T cell frequency and MR1/5-OP-RU^{+} T cell frequency can be observed (73, 80).

4.3. Animal Models for Studying MAIT Cells

In conventional BALB/c and C57BL/6 mice, MAIT cells are ~100-fold less abundant than in humans (15). Furthermore, iNKT cells are substantially enriched in laboratory mice compared to humans (81, 82). As these two populations appear to share a largely overlapping homeostatic and functional niche (62, 69), this means that studies assessing the impact of MAIT cells on a disease of interest (i.e., comparing wild-type mice to MAIT cell–deficient *Mr1*$^{-/-}$ mice) likely underestimate the role of MAIT cells. Despite this, several studies have identified nonredundant roles for MAIT cells in a variety of diseases, as discussed in Section 6.

To overcome these limitations, a mouse line with substantially increased frequencies of MAIT cells was generated by crossing C57BL/6 mice with CAST/EiJ mice to generate B6-$MAIT^{CAST}$ animals (33). This genetic difference was mapped to a single locus within the *Trav* gene region. These mice were further crossed to *Rorc-GFP* animals to allow live cell tracking of the two murine MAIT cell subsets ($ROR\gamma t^{+}$T-bet^{-} and $ROR\gamma t^{-}$T-bet^{+}). However, MAIT cells in $B6^{CAST}$ mice do not perfectly phenocopy human MAIT cells in that they produce type 2 cytokines and do not express the full complement of chemokine receptors.

Despite these minor incongruences, this strain of mice is particularly useful for studying the fundamental biology of MAIT cells given the access to ~20-fold-increased cell numbers, especially within tissues. An alternate model to increase murine MAIT cell frequencies is intranasal infection with *Salmonella* Typhimurium or administration of 5-OP-RU with a Toll-like receptor (TLR) ligand (75), but this model has its own limitations, due to the manner of MAIT cell expansion.

Prior to the advent of MR1 tetramers and the B6-$MAIT^{CAST}$ mice, the primary model to study MAIT cells in a mouse was a TCR transgenic strain (83). These Vα19*i*-Tg mice express a recombinant Vα19–Jα33 TCR on a $C\alpha^{-/-}$ background to generate mice where all T cells express the MAIT TCRα chain. However, even in *Mr1-/-* animals there was still development of mature T cells, suggesting that a fraction of Vα19*i*-Tg TCR-containing T cells are restricted by conventional MHC molecules (9). Thus, it is necessary to further compare any results between Vα19*i*-Tg *Mr1*$^{+/+}$ and Vα19*i*-Tg *Mr1*$^{-/-}$ animals to ascertain the MAIT cell–specific effect seen in any phenotype. The development of the MR1 tetramer has subsequently demonstrated that these Vα19*i*-Tg T cells are phenotypically and functionally distinct from the endogenous MAIT cell population (15). For these reasons it remains questionable how accurately data generated in this model reflects the true biology of MAIT cells, and care should be taken when interpreting such data.

5. TRIGGERING A MAIT CELL

MAIT cells can be activated to execute effector functions by two separate pathways: TCR signaling, and cytokine signaling independent of the TCR. Furthermore, these separate pathways can synergize, as is often seen in vivo, to enhance MAIT cell activation (**Figure 4**).

5.1. T Cell Receptor–Dependent Activation

Like all T cells, MAIT cells utilize their TCR to detect antigen presented in the context of an antigen-presenting molecule, in this case MR1 (3). As MAIT cells in the human periphery are

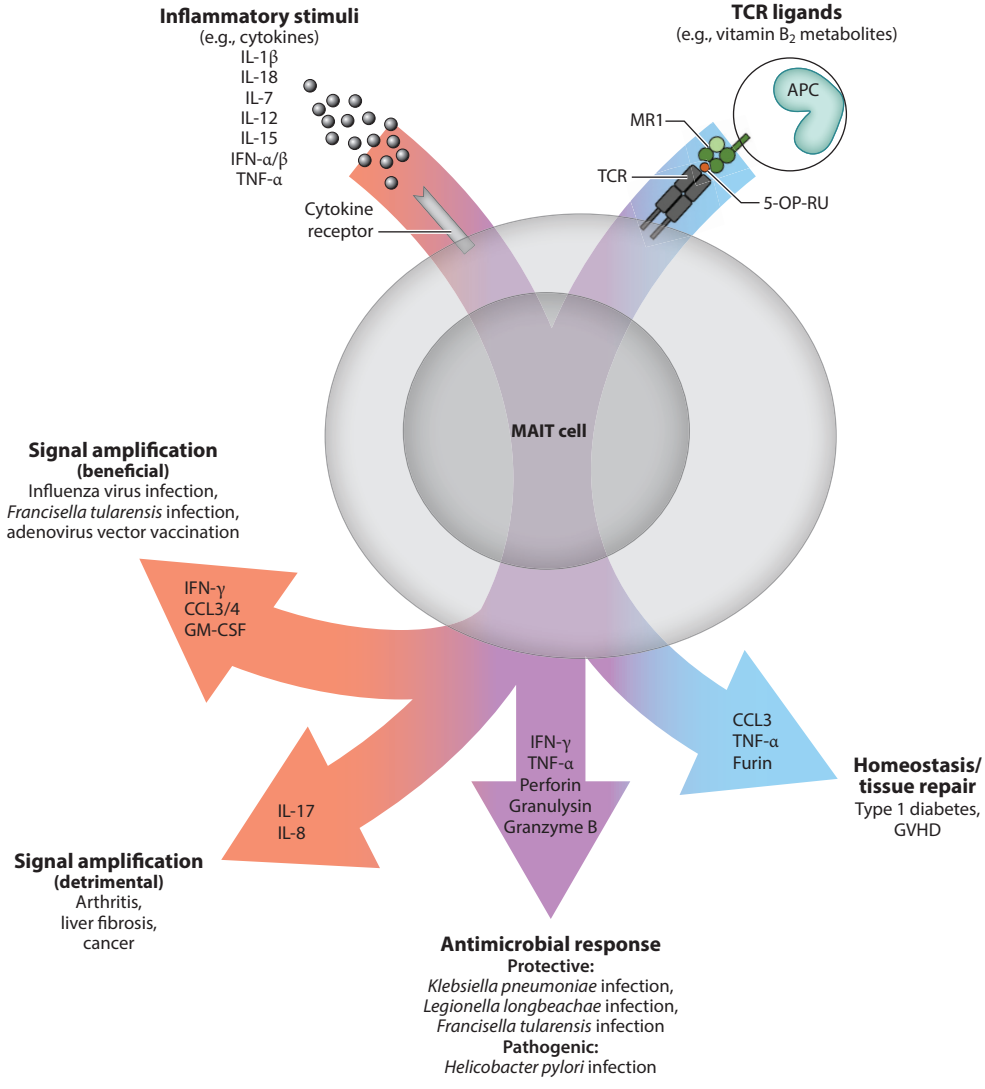

Figure 4

Mechanisms of MAIT cell activation, and how these activation pathways relate to the role of MAIT cells in human disease. MAIT cells can be activated by two mechanisms: (*a*) recognition of inflammatory cytokines (e.g., IL-12 and IL-18) independent of TCR ligands, or (*b*) TCR-dependent recognition of microbial riboflavin metabolites presented by MR1. Cytokine- and TCR-dependent activation can synergize to enhance and modulate activation. The mechanism of activation is strongly linked to the type of effector function executed by the MAIT cell. Combined cytokine and TCR signals drive a potent type 1 antimicrobial response, including cytotoxic function. By contrast, TCR signals without inflammation promote the production of effector molecules associated with tissue repair and homeostasis. Finally, receipt of inflammatory cytokine signals in the absence of exogenous TCR signals drives a signal amplification innate-like response that is either beneficial to the host or pathogenic—presumably depending on the exact nature of the inflammatory stimuli. In the context of bacterial and viral infection, signal amplification is associated with immune cell recruitment, maturation, and host defense. By contrast, in autoimmune diseases, inflammatory diseases, and cancer, signal amplification involves strong type 17 immunity and tissue damage. Abbreviations: 5-OP-RU, 5-(2-oxopropylideneamino)-5-D-ribitylaminouracil; APC, antigen-presenting cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; GVHD, graft-versus-host disease; TCR, T cell receptor.

universally memory cells (10), deliberate priming events are not needed for TCR-mediated activation, allowing for rapid responses upon primary infection (84). However, MAIT cells possess an unusual characteristic in that TCR signaling is tightly regulated and prolonged signaling fails to induce sustained cytokine production or proliferation, unlike with conventional T cells (42, 85). This appears to be in part due to downregulation of a number of components of the TCR signaling pathway in MAIT cells (42). However, costimulation through CD28 can enhance TCR-mediated activation of MAIT cells (19, 42). Given the ubiquitous expression of MR1 across cell types and tissues (86), as well as the expression of MR1 ligands by not only pathogenic but also commensal bacteria (26), this tight regulation might be necessary to prevent inappropriate activation of MAIT cells.

Regardless, TCR signaling is critical for activation of MAIT cells by riboflavin-producing bacteria and yeast (6, 7). MAIT cell–mediated killing of bacterially infected cells also requires signaling through the TCR (19, 32), and MAIT cell–mediated protection of mice from lethal *Legionella longbeachae* infection requires recognition of antigen-loaded MR1 (84). Thus, TCR signaling plays a critical role in the antibacterial responsiveness of MAIT cells.

5.2. T Cell Receptor–Independent Activation

TCR-independent activation of MAIT cells represents an innate-like functionality of these cells, akin to NK cells or other innate lymphoid cells (87). The best-studied mechanism of TCR-independent activation of MAIT cells is through combinatorial signaling by cytokines. IL-12 and IL-18 was the first combination of cytokines identified that induced IFN-γ production by MAIT cells (13, 57). Subsequent work has also identified IL-15, IFN-α/β, and TNF-α as other cytokines capable of synergizing with IL-12 and/or IL-18 to activate MAIT cells (85, 88–90). Although ≥2 cytokines are needed for activation of MAIT cells, cytokines can induce synergistic signaling partners through accessory cells, as has been shown for IL-15-mediated induction of IL-18 by monocytes (88), or IFN-α-mediated induction of TNF-α by monocytes (90). This mechanism of activation allows MAIT cells to respond to microbes that do not produce MR1 ligands, such as viruses or non-riboflavin-producing bacterial species (13, 89, 91). Furthermore, the capacity for TCR-independent activation is likely critical to the involvement of MAIT cells in a number of autoimmune and sterile inflammatory diseases (discussed below in Section 6.3).

Cytokine-mediated activation of MAIT cells appears to induce only a subset of effector functions. IFN-γ and granzyme B are both robustly induced, but TNF-α is induced to much lower levels than is seen following TCR stimulation (13, 57, 89). Despite upregulation of granzyme B, there are no data to suggest that MAIT cells can directly kill target cells in the absence of TCR engagement (19, 32). Furthermore, cytokine stimulation alone fails to strongly induce IL-17 (54), suggesting a type I skewing of effector functions in response to this stimulus.

5.3. Synergy of the Two Activation Modes

Outside of specific circumstances where MAIT cell TCR ligands are absent (e.g., viral infections or sterile inflammation), in vivo activation of MAIT cells likely involves a combination of TCR-derived and cytokine-derived signals. The recent discovery that MR1 ligand can be distributed to distal tissues following surface administration at epithelial surfaces raises the possibility of tonic TCR stimulation (68), which could potentially implicate MAIT cell TCR signaling in situations where no microbes are locally present. In vivo evidence that supports the idea that TCR and cytokine signals synergize includes the finding that administration of synthetic 5-OP-RU to mice only fully activates MAIT cells if TLR agonists are codelivered (75). Consistent with this, in vitro

activation of MAIT cells by multiple ligand-producing bacteria involves both TCR and IL-12/IL-18 signals (13, 28, 57, 92, 93). Beyond IL-12, IL-15, and IL-18, which are capable of activation in a fully TCR-independent manner, additional cytokines have been reported to synergize with TCR signaling, including IL-1β, IL-7, and TNF-α (31, 42, 44, 94). In addition to increasing the magnitude of the MAIT cell effector response, cytokine costimulation can skew effector function, as seen by increased IL-17A production in response to TCR + IL-1β or IL-18 (42).

6. WHAT ARE MAIT CELLS FOR? FUNCTIONS IN HEALTH AND DISEASE

Having discussed the fundamental characteristics of MAIT cell biology, we turn for the remainder of the review to the role MAIT cells play in contributing to or protecting from disease, and how they facilitate these processes. MAIT cells have been implicated in the outcome of a diverse range of diseases, from microbial infection to autoimmune inflammatory diseases to malignancy. Understanding how MAIT cells can contribute to the protection and pathogenesis of such a diverse range of diseases is easiest when viewed through the pathways that activate MAIT cells: TCR stimulation in the context of inflammation (e.g., microbial infection), TCR stimulation without inflammation (e.g., homeostatic conditions), and inflammation without exogenous ligand (e.g., viral or autoimmune inflammatory disease). This review only discusses diseases where the role of MAIT cells is clearly defined through either in vivo animal experiments or human cohort studies. Several published reviews have exhaustive lists of diseases where data on disease pathogenesis is lacking despite alterations in MAIT cell frequency (95, 96).

Regardless of disease and mechanism of activation, a near universal, but poorly understood, response of MAIT cells to disease is a decline in frequency in the blood. This is seen in diseases where MAIT cells play a protective role [such as influenza virus (89, 91)], where MAIT cells are pathogenic [e.g., arthritis (97)], and where no clear association between MAIT cells and disease progression has been established [e.g., HIV infection (98, 99)]. Activation-induced cell death has been implicated as a potential mechanism for the depletion of MAIT cells (98, 100), as has migration to disease-relevant tissues [e.g., in *Mycobacterium tuberculosis* infection and arthritis (97, 101)]. However, accumulation within diseased tissue is not observed in all cases, even when MAIT cells have been linked to disease pathogenesis [e.g., in liver cancer (101–103)]. Intriguingly, elevated glucose concentration induces a MAIT cell–specific increase in apoptosis, suggesting a possible reason for decreased circulating MAIT cell frequency in diabetes and other diseases where metabolic dysregulation is a component (104).

6.1. Antimicrobial Response: T Cell Receptor Stimulation with Inflammation

In many settings of activation in response to pathogenic microbial infection the MAIT cell will receive triggering via both TCR-dependent and -independent pathways, leading to broad and sustained functionality.

6.1.1. Host defense. The earliest studies on MAIT cell function identified them as potent effectors with antibacterial function (**Figure 4**). The significance of this function of MAIT cells is reinforced by data from infection studies where MAIT cell–deficient animals had increased bacterial load and decreased survival following infection with *Klebsiella pneumoniae*, *Francisella tularensis*, or *Legionella longbeachae* (8, 84, 105). Functionally, the response to bacterial stimulation involves robust production of IFN-γ, TNF-α, granzyme B, and perforin by MAIT cells (6, 7, 19, 32). Consistent with a direct antimicrobial function, adoptive transfer of MAIT cells to *Rag2*$^{-/-}\gamma c^{-/-}$ mice

protects from lethal intranasal *L. longbeachae* infection, but not if *Ifng*$^{-/-}$ MAIT cells are transferred (84), indicating that noncytolytic control is critical in this infection model.

While MAIT cells have clear direct antimicrobial capacity in the form of cytotoxicity and IFN-γ secretion, in several microbial infection models it appears the critical function of MAIT cells is in an indirect or helper capacity—one such example is *F. tularensis* infection where MAIT cells are protective (105, 106). Mechanistically, there is impaired recruitment of CD11b^{+} dendritic cells (DCs) into the lungs of *Mr1*$^{-/-}$ mice following intranasal infection, which involves MAIT cell–derived granulocyte-macrophage colony-stimulating factor (GM-CSF) (106). This results in decreased differentiation of monocyte-derived DCs and ultimately impaired accumulation of conventional CD4 and CD8 T cells within the *F. tularensis*–infected lung (105, 106). In vitro, MAIT cells induce DC and monocyte maturation by first sensing cognate TCR ligand (107). Following activation, MAIT cells signal back to the antigen-presenting cell (APC) via the CD40-CD40L axis, which induces upregulation of costimulatory molecules and secretion of IL-12p70 and TNF-α by monocytes and DCs. CD40L-dependent maturation of DCs is one of the canonical functions of CD4 T helper cells and is critical for provision of help to CD8^{+} T cells and B cells (108, 109). Although it remains to be directly demonstrated, these data would suggest that MAIT cells might also be capable of providing help to classical adaptive immune responses.

Intriguingly, MAIT cells can induce activation and proliferation of CD4^{+} and CD8^{+} T cells by triggering the differentiation of neutrophils into an APC (110). Activation of MAIT cells with anti-CD3/anti-CD28 stimulation induced production of GM-CSF, IFN-γ, and TNF-α, which acted synergistically to promote neutrophil survival, activation, and maturation. These conditioned neutrophils displayed enhanced capacity to process and present antigens to CD4^{+} and CD8^{+} T cells. However, follow-up in this area is needed, as a recent study reported 5-A-RU-activated MAIT cells can kill neutrophils in a TNF-dependent manner (111). In the context of CD4^{+} T cell–mediated DC maturation, cognate antigen presentation by the DC to the CD4^{+} T cell is necessary and thereby confers specificity to the process (109). However, in the context of MAIT cells, the activating factors were all secreted and can thus in theory provide nonspecific bystander help within the tissue microenvironment. Intriguingly, neutrophils from patients with bacterial sepsis, but not healthy controls, also displayed these APC-like properties, suggesting a possible role for MAIT cells in modulating neutrophil function in this setting (110).

When considering helper functions of lymphocytes, the other major axis is CD4^{+} T cell help to B cells, through initiation of the germinal center reaction in response to cognate antigen presentation by naive B cells (112). MAIT cells have the capacity to enhance differentiation of memory B cells to plasmablasts and enhance secretion of IgG, IgA, and IgM (113). However, this report did not demonstrate that the B cell help depended on cognate antigen presentation [although B cells can activate MAIT cells (32, 114)], nor did this report demonstrate the capacity for MAIT cells to induce activation of naive B cells and thereby initiate the development of a germinal center. Thus, further work is required to more completely elucidate the extent to which MAIT cells can provide help to B cells. Interestingly in this context, B cells in germinal centers express the highest levels of LLT1 (*CLEC2D*; the ligand for CD161 on MAIT cells) seen in human tissue, and LLT1 triggering on B cells promotes survival in vitro (115).

In sum, in the context of infection with riboflavin-producing bacteria where both cognate antigen and inflammatory signals are abundant, MAIT cells can contribute to host defense both through the direct killing of bacterially infected cells and by promoting the activation and maturation of innate and adaptive immune populations.

6.1.1.1. Case study: a role for MAIT cells in* Mycobacterium tuberculosis *infection? One area of uncertainty with regards to MAIT cells and antimicrobial defense is the exact role of

MAIT cells in control of *M. tuberculosis* infection, which is of substantial interest. Genetic evidence suggests an association between MAIT cells and control of *M. tuberculosis*. The only known polymorphism in *MR1*, which reduces expression, was associated with increased susceptibility to meningeal tuberculosis in a Vietnamese cohort (116). One study identified seven subjects with homozygous deleterious mutations in *RORC* that were clinically identified with disseminated bacillus Calmette-Guérin (BCG) or *Mycobacterium* infection, and these patients completely lacked MAIT cells (117). However, as *RORC* deficiency has more wide-ranging consequences on the immune compartment, including the complete absence of iNKT cells and Th17 cells, these data should not be overinterpreted.

However, experimental work has failed to define a critical role for MAIT cells. MAIT cell–deficient $Mr1^{-/-}$ mice have increased bacterial loads at day 10 postinfection with BCG, but this impaired early control was corrected by day 30 postinfection (118, 119). A recent study suggests that accumulation of MAIT cells within the bronchoalveolar lavage fluid of *M. tuberculosis*–infected rhesus macaques is transient; it peaked at between 7 and 11 weeks postinfection (101), which might explain the transient alterations in bacterial control seen in $Mr1^{-/-}$ mice. Thus, while MAIT cells may sense and be activated by *M. tuberculosis* infection (6, 101, 120, 121), their role in infection needs further investigation. A long-standing hypothesis in the field of *M. tuberculosis* research is that extrapulmonary *M. tuberculosis* infection (e.g., meningitis) is linked to poor early control (122). Thus, the reduced early control of *M. tuberculosis* infection in $Mr1^{-/-}$ mice may explain why genetic associations between MAIT cell defects and *M. tuberculosis* infection are most clearly related to extrapulmonary manifestations.

6.1.2. Pathogenesis in response to microbial infection. While a protective role for MAIT cells has been shown for several models of bacterial infection, the protective nature of MAIT cells is not universal. *Helicobacter pylori* infection, which causes stomach ulcers, resulted in reduced gastritis in $Mr1^{-/-}$ mice as compared to wild-type animals (80) (**Figure 4**). Mice with increased frequencies of MAIT cells due to either prior exposure to *Salmonella* Typhimurium, which expands the endogenous MAIT cell population (75), or expression of the Vα19*i*-Tg TCR, had increased disease severity. Exactly why MAIT cells are pathogenic in this model remains unclear, although the authors speculate that IFN-γ may be involved, as it has previously been associated with *H. pylori*–induced inflammation (123). Thus, care should be taken in attributing MAIT cell activation with a protective role, as this relationship does not always hold. In a similar vein, MAIT cells have also been shown to be one of the dominant T cell populations activated by superantigens (124), with implications for toxic shock syndrome.

6.2. Tissue Repair and Homeostasis: T Cell Receptor Stimulation in the Absence of Inflammation

Several studies have recently defined a novel role for MAIT cells in maintaining the integrity of the gastrointestinal tract, with major consequences for health (**Figure 4**). Strikingly, MAIT cells are protective in the nonobese diabetic (NOD) mouse model of type 1 diabetes (125). $Mr1^{-/-}$ NOD mice had accelerated disease progression compared to their wild-type counterparts. Mechanistically, this was associated with increased intestinal permeability (i.e., impaired integrity); elevated translocation of bacteria, as measured by 16S rRNA levels in lymph nodes; and increased frequencies of islet-specific T cells in the pancreas and lymph nodes. Consistent with a critical role for MAIT cells in maintaining intestinal homeostasis, $Mr1^{-/-}$ mice also had markedly impaired survival following allogeneic bone marrow transplantation, which was associated with increased colonic graft-versus-host disease (GVHD) (126). Again, increased intestinal permeability was

identified in the *Mr1*$^{-/-}$ animals and was associated with increased frequency of donor-derived T cells within the colon. Analysis of a human cohort of bone marrow transplant patients also found that lower circulating MAIT cell frequencies were associated with incidence of acute GVHD (127). Thus, in two very distinct disease models, it appears that MAIT cells play a critical role in reducing pathology, likely through maintaining barrier integrity.

Another recent report has identified a protective role for MAIT cells in a mouse model of non-alcoholic steatohepatitis. *Mr1*$^{-/-}$ mice fed a methionine and choline deficient diet had increased serum alanine aminotransferase (ALT) levels, gross morphologic changes in the liver, and an elevated disease score, as compared to wild-type mice fed the same diet (128). The authors proposed that this was caused by an altered ratio of pro- and anti-inflammatory macrophages within the livers of these MAIT cell–deficient animals, but given the decreased intestinal barrier integrity of *Mr1*$^{-/-}$ mice, further work is required to determine whether this represents a direct role for MAIT cells in modulating macrophage function, or possibly reflects a secondary effect of increased bacterial pathogen-associated molecular patterns and antigens.

Three recent studies examining the functional profiles of MAIT cells following TCR or cytokine stimulation by RNA sequencing have identified a functional gene signature of tissue repair linked to TCR-triggered activation (53–55). This lymphocyte tissue repair signature was first identified in H2-M3-restricted RORγt^{+} CD8^{+} T cells, which are resident in mouse skin, respond to commensal bacteria, and accelerate wound repair (129). This tissue repair signature appears to be functionally active in MAIT cells, as supernatants from activated MAIT cells accelerate cellular monolayer regrowth following physical damage (53). These data suggest a mechanism by which MAIT cells could contribute to the maintenance of intestinal barrier integrity, namely, through promoting healing of microscopic damage that occurs routinely in the intestine—a homeostatic function rather than a classical immune response. This novel function of MAIT cells in turn modulates disease severity for such diverse diseases as type 1 diabetes, acute GVHD, and liver disease, and likely others that are yet to be identified. Exactly which components of the microbiome are responsible for driving such a response and how specific changes in the microbiome composition or metabolism impact MAIT cell functions require further study.

6.3. Amplification of Immune Processes: Stimulation by Inflammatory Cytokines in the Absence of T Cell Receptor Ligands

Triggering of MAIT cells through TCR-independent pathways could be relevant in vivo in a wide range of settings, and such cytokine-driven activation can potentially be protective or pathogenic.

6.3.1. Recruitment of immune cells and signal amplification. MAIT cells can also protect the host from infection even when the pathogen does not express cognate TCR ligands (**Figure 4**), as has recently been shown for influenza A virus infection of mice (130). *Mr1*$^{-/-}$ mice displayed increased mortality following infection with the pathogenic PR8 strain. Mechanistically, MAIT cells were rapidly triggered in the lung by cytokines such as IL-18, IFN-α, and IL-12, and MAIT cell–derived IFN-γ was critical for protection (130). Some antiviral protection may be through direct antiviral action; for example, MAIT cell–derived IFN-γ has been shown to inhibit hepatitis C virus (HCV) replication in vitro (89). However, in the in vivo influenza virus infection studies the major defect in *Mr1*$^{-/-}$ mice was the delayed and impaired accumulation of alveolar macrophages and T cells in the lungs (130), which may have resulted from the lack of early chemokine induction in the MAIT cell–deficient animals. It was also recently demonstrated that MAIT cells play a critical role in promoting adenovirus vector vaccine–induced CD8 T cell responses (90). *Mr1*$^{-/-}$ mice had decreased generation of HCV-specific CD8 T cell responses following immunization with an HCV transgene–expressing chimpanzee-derived adenovirus.

Intriguingly, this impaired recruitment of immune cells following infection of *Mr1*$^{-/-}$ mice is analogous to the impaired recruitment of DCs and T cells seen during *F. tularensis* infection (105, 106). A unified model suggests that TCR signaling is dispensable for MAIT cell–mediated recruitment of innate and adaptive immune populations to the site of infection, and instead a fundamental function of MAIT cells in response to inflammatory cytokines is to act as an intermediary in signaling cascades, which ultimately impacts the development of protective, antimicrobial, adaptive immunity (**Figure 4**).

6.3.2. Pathogenesis in arthritis, fibrosis, and cancer. Since the expansion of interest in MAIT cells in recent years, and the emerging potential of such cells to respond to a range of stimuli, many studies have now been performed to address the role of this cell type in a range of noninfectious conditions.

6.3.2.1. Inflammatory disease. Arthritic diseases [e.g., rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), and psoriatic arthritis] are autoimmune inflammatory diseases where IL-17 is thought to be a major pathogenic factor (131). Thus, given the IL-17-producing potential of MAIT cells (10, 11), there is a clear potential role for MAIT cells in these diseases (**Figure 4**). Indeed, in the collagen injection model of arthritis, MAIT cells show a pathogenic role, as *Mr1*$^{-/-}$ DBA/1j mice [the disease susceptible strain (132)] have reduced clinical scores and joint damage (133). Circulating MAIT cell frequency is reduced in humans with RA, AS, and SLE, as compared to healthy controls (43, 97, 134–137). MAIT cell frequency was higher within the synovial fluid of the inflamed joints of RA and AS patients as compared to matched blood (43, 97, 134). Synovial fluid from the inflamed joint contains TNF-α, which in vitro triggers expression of the adhesion molecules VCAM-1, ICAM-1, and E-selectin on endothelial cells, and production of CCL20, the ligand for CCR6 (134). Together these signals can promote MAIT cell adhesion, suggesting a mechanism by which MAIT cells may be recruited to the inflamed joint. In RA, synovial fluid MAIT cells show higher levels of activation—including IL-17 production—than MAIT cells within patient blood (43, 134), and the level of activation has been positively associated with disease severity (135, 136). However, the role for MAIT cell–derived IL-17 in these diseases remains to be directly tested.

Animal models suggest a direct effector role for MAIT cells in arthritic disease, as *Mr1*$^{-/-}$ DBA/1j mice had unimpaired frequencies of collagen-specific T cells and antibodies, despite reduced disease severity. Furthermore, in the mouse model of arthritis where anti-collagen antibodies are injected, which generates a T cell– and B cell–independent acute disease course (132), *Mr1*$^{-/-}$ mice are again partially protected (133). This argues in this case against a helper role for MAIT cells, a MAIT cell function discussed above (see Section 6.3.1), and instead supports a model for direct pathogenic effector functions.

MAIT cells can also potentially contribute to disease pathogenesis by promoting tissue fibrosis (138, 139). Two studies found that in vitro human MAIT cells could induce proliferation of hepatic stellate cells and myofibroblasts (138, 139) and induce the secretion of a number of proinflammatory cytokines, including IL-6 and IL-8. This activation was dependent on both IL-17 and TNF-α. Furthermore, in a mouse model of chronic liver injury (repeated carbon-tetrachloride administration), the absence of MAIT cells decreased pathology, and the adoptive transfer of Vα19*i*-Tg MAIT cells to wild-type animals enhanced pathology (138). Thus, it appears MAIT cells can directly contribute to liver fibrosis, and possibly fibrosis in other tissues, although the pathways involved require further clarification.

Literature is emerging on MAIT cells in many other inflammatory settings where activation via TCR-independent pathways is likely. In many cases the role of MAIT cells, if any, is not yet clear. For example, in multiple sclerosis, *Mr1*$^{-/-}$ mice show enhanced disease in the experimental

autoimmune encephalomyelitis model, suggesting a protective role (140), while in human studies there is detection of IL-17-producing MAIT cells at the site of disease (141–144), which has been interpreted as indicating a pathogenic role.

6.3.2.2. Cancer. The examination of the role of MAIT cells in cancer has been primarily focused on colorectal cancer (CRC) and hepatocellular carcinoma (HCC). In CRC, MAIT cells are enriched within the tumor as compared to healthy adjacent intestinal tissue (145–148). By contrast, for tumors of the liver, the frequency of intratumor MAIT cells was reduced as compared to that of healthy adjacent tissue, regardless of whether these were primary HCC or CRC metastases (102, 103, 149).

Despite this discordance between the frequency of MAIT cells within the tumor as compared to adjacent healthy tissue, for both of these diseases, patients with the highest frequencies of tumor-infiltrating MAIT cells have the worst clinical course as measured by overall survival and/or disease-free survival (102, 146) (**Figure 4**). Zabijak et al. (146) found significantly worse outcomes for CRC patients with enrichment of MAIT cells in the tumor. A recent larger study (102) demonstrated using three separate cohorts and three independent measures of MAIT cell frequency (flow cytometry, reverse transcriptase PCR for *TRAV1–2/TRAJ33* TCR transcripts, and immunofluorescence histology) a negative association between high frequencies of MAIT cells and positive outcomes in HCC. Mechanistically, it is not clear how MAIT cells are pathogenic in the context of cancer, and other studies have not found such a negative association (103). Substantial further work is required to elucidate this mechanism.

7. CONCLUDING REMARKS

Our understanding of MAIT cell biology has accelerated enormously in recent years, although a definition of their role in the context of human disease is still in its infancy. Through analysis of the rapidly accruing data from humans and animal models, a picture emerges where the underpinning transcriptional building blocks of a MAIT cell are visible as modules of functionality (Th1, Th17, innate, tissue homing), which in turn are expressed as distinctive behaviors such as direct antimicrobial defense, barrier repair, amplifier/helper functions, and proinflammatory roles. Exactly which of these dominate in any given setting is apparently due to the blend of TCR and specific non-TCR signals, but this broad composition—and the associated ability to sense a range of cues—does allow the MAIT cells a wide range of functional options. The final outcomes (a pathogenic, protective, or redundant role) will ultimately depend—like any T cell response—on the site and kinetics of the pathogens involved (150). The twist for MAIT cells and other unconventional lymphocytes is that the ligands involved are common and can be associated with commensals encountered continuously, so a two-step approach to activation that integrates inflammatory cues provides specificity, while maintaining the sensitivity that allows the cells to act as first responders in the context of local tissue damage. Given their extensive immunological toolkit, further understanding of their functional activity in each setting is required to fundamentally advance our knowledge and potentially harness their therapeutic potential.

SUMMARY POINTS

1. MAIT cells are abundant in human blood and nonlymphoid tissues.
2. MAIT cells exhibit a mixed phenotype and function that combines major aspects of cytotoxic type 1 immunity, type 17 immunity, innate lymphocyte functionality, and tissue trafficking.

3. The MAIT cell TCR recognizes microbe-derived metabolic intermediates of the riboflavin and folate biosynthesis pathways presented by the monomorphic MHC-Ib molecule MR1.
4. MAIT cells can also be activated independent of their TCR by inflammatory and antimicrobial cytokines.
5. MAIT cells are activated in a wide array of human diseases—from microbial infection to inflammatory autoimmune disease to malignancy. In all of these diseases their role can be either pathogenic or protective, and the way MAIT cells respond to a given disease depends on the manner in which TCR and non-TCR signals are integrated.

FUTURE ISSUES

1. We need a better definition of a functional role for MAIT cells in the myriad of diseases in which MAIT cells show activation/alteration.
2. We need a better understanding of how MAIT cells are activated in inflammatory diseases. The absence of microbial ligands suggests cytokine-dependent activation, but data are lacking.
3. In inflammatory disease, MAIT cells are often associated with IL-17 production. However, in vitro, IL-17 production is strongly linked to TCR ligation. Thus, there is a gap in knowledge with regard to how type 17 functionality of MAIT cells is regulated in vivo.
4. Given the impaired barrier integrity of *Mr1*$^{-/-}$ mice, how often is the association of MAIT cells with a disease actually attributable to their role in barrier homeostasis?
5. Most, but not all, studies focus on IL-17/IFN-γ/cytotoxic functions of MAIT cells. More research into the alternate functions of MAIT cells is needed: tissue homeostasis, immune cell recruitment, and helper functions.

DISCLOSURE STATEMENT

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