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The MAIT conundrum – how human MAIT cells distinguish bacterial colonization from infection in mucosal barrier tissues

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1. Introduction

Studies focusing on human mucosal-associated invariant T (MAIT) cells have gained considerable momentum in recent years. MAIT cells are found at mucosal barrier sites and their ability to quickly exert effector function indicates a potentially significant role for them in barrier immunity. Changes in MAIT cell frequency and phenotype have been reported in numerous disease settings including acute and chronic infections as well as autoimmune and malignant disorders. Recent reviews provide a comprehensive overview of these clinical studies as well as key aspects of MAIT cell function including antigen recognition, antimicrobial properties and their putative role in the liver[1–11]. Here we provide an overview of the recent human MAIT cell literature to address how a cell that recognizes bacterially-derived antigen and is found in mucosal barrier tissues colonized by commensal bacteria, avoids responding to these commensal-derived antigens while maintaining responsiveness to bacterial infections. We discuss the key role of inflammatory signals in regulating human MAIT cell effector function in this context and review the relationship and the functional properties of human MAIT cells in blood and mucosal tissues. In addition, we highlight gaps in our current knowledge and examine the emerging role of human MAIT cells in controlling barrier immunity tissue homeostasis.

2. Brief Background

MAIT cells are a fairly abundant T-cell subset in humans representing 1–10% of total T-cells in blood and mucosal tissues, and even higher abundance in the liver[12,13]. MAIT cells are characterized by a semi-invariant T cell receptor (TCR) that consists of a conserved TCRα chain[14,15] - TRAV1-2(Vα7.2) and TRAJ33 (Jα33) - paired with a few select Vβ chains[16]. This semi-invariant TCR recognizes antigen in the context of the protein MHC

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class I - related (MR1)[17]. MR1 appears well conserved across species suggesting an essential role for MAIT cells in the immune response[17–20]. Instead of peptides (presented by MHC I and II) or glycolipids/lipids (presented by CD1), MAIT cells recognize metabolites and thus a different type of antigen compared to any other T cell subset[21]. These metabolites are derived from vitamin B synthesis pathways and additional modifications may occur when presented in the context of MR1 and some, but not all of these MR1 binding metabolites can activate MAIT cells[22–27]. Identification of these antigens allowed the development of MR1 tetramers[22,23], which became available to the broader scientific community through the NIH tetramer core in late 2016. In most studies published so far, MAIT cells have been identified via flow cytometry by co-expression of their invariant TCR α-chain, Vα7.2, along with high expression levels of the C-type lectin CD161 (other names include KLRB1, NKR-P1A). MAIT cells in the blood can also be identified by Vα7.2 expression together with expression of the cytokine receptor IL-18Rα[28,29]. Since conventional T cells can also express Vα7.2 and recent reports suggest that CD161 expression can change in certain scenarios[30,31], using MR1 tetramers is likely the most reliable method to identify MAIT cells. However, it is important to consider that staining with anti-Vα7.2, anti-CD161 antibodies versus the MR1 tetramer shows that these populations are nearly, but not fully congruent in the blood[22,23]. This indicates that some $V\alpha7.2^{+}CD161^{hi}$ cells are either not MR1-restricted or do not recognize the specific metabolite used to load MR1, which is plausible given evidence for differential antigen recognition by MAIT cells[32,33]. Importantly, recent studies also provide evidence for the existence of $V\alpha7.2^{-}$ MR1-restricted cells[34,35]. The majority of the currently published literature and literature references in this review are based on the classic definition of MAIT cells ($V\alpha7.2^{+}CD161^{hi}$), but it will be necessary to keep these details in mind as the field moves forward and takes advantage of MR1 tetramers.

3. MAIT cell subsets, phenotypes and function in blood

MAIT cells in the blood are typically $CD45RO^{+}$, $CD62L^{lo}$, $CD122^{int}$, $CCR7^{-}$ and quickly acquire effector function when stimulated[12]. The lack of CD62L and CCR7 expression paired with the ability to quickly respond to stimulation is a hallmark of conventional effector memory T-cells[36] and MAIT cells have thus been referred to as effector memory-like[12]. The reason MAIT cells have these characteristics is presumably due to near uniform expression of the transcription factor PLZF[37]. Expression of PLZF is sufficient to induce acquisition of effector memory-like properties in conventional T-cells[38,39] and is required for the innate-like effector function of NKT cells [40,41] and certain gamma delta T-cells[42]. Once activated, MAIT cells isolated from the blood (or stimulated in the presence of other peripheral blood mononuclear cells, PBMCs) secrete IFNγ, TNFα and express the cytolytic molecule granzyme B[12,28,31,43,44]. Overall, it has become clear that there is more heterogeneity in the MAIT cell population than initially appreciated[45]. A small fraction of MAIT cells isolated from the blood can also secrete IL-17 *ex vivo* following short term stimulation with via CD3/CD28 or PMA and ionomycin[12,46,47]. It is noteworthy that a large fraction of MAIT cells in the blood expresses the transcription factor RORγt[37], which drives T-cells towards IL-17 production[48]. MAIT cells from patients with a loss of function mutation in Stat3 are impaired in their ability to produce IL-17

despite normal RORγt expression indicating a critical role of IL-23R signaling[37]. Additional transcriptions factors expressed in MAIT cells from the blood include Helios, Eomes, and T-bet[49]. How these transcription factors specifically regulate different functional aspects of MAIT cells has yet to be fully elucidated. Finally, MAIT cells in the blood can be divided into different subsets based on CD8 and CD4 co-receptor expression. The relationship of these subsets is unclear, but single cell gene expression analysis from the two major MAIT subsets, $CD8^+$ and $CD8^-$ ($CD4^-$) cells, isolated from the blood demonstrated distinct transcriptional differences[44] and their respective frequencies can change independently following infection[46].

4. MAIT cell activation requirements and implications for their function in mucosal tissues

MAIT cells have been identified in human mucosal tissues that are colonized by commensal bacteria including intestines, rectal mucosa and vaginal tissue[12,17,44,50]. Importantly, both commensal and pathogenic species of bacteria have intact riboflavin synthesis pathways and generate metabolites with agonist properties for MAIT cells [51]. Thus, in contrast to conventional T cells[52], MAIT cells cannot use antigen specificity to distinguish commensal from pathogenic bacteria. How can MAIT cells be in close proximity to commensals in tissues without becoming activated given that MR1 is also readily available on antigen-presenting cells[26]? A recent study from our lab demonstrated that once purified, MAIT cells needed more than a TCR signal to acquire sustained effector function and that inflammatory cytokine signals (IL-12/15/18) synergized with the TCR signal to induce potent effector function[44]. In this revised model of MAIT cell activation, encounter with commensal-derived antigen (i.e. a TCR signal only) is not sufficient to activate MAIT cells unless inflammatory cytokines are present (Figure 1), which are typically elicited in the context of a pathogenic infection. The synergistic interaction of cytokine and TCR signal has also been reported in the context of IL-15. IL-15 is a pleiotropic cytokine often produced early during infection by a wide range of cells with potent survival and immunomodulatory effects on T-cells[53]. IL-15 expression within inflamed tissues can provide a co-stimulatory signal to drive memory T-cell effector function[54]. Similar to what has been reported for conventional T cells, *Sattler et al* showed that addition of IL-15 in the context of suboptimal TCR activation increased MAIT effector function *in vitro*[55]. While limited antigen availability resulted in minimal IFNγ production by MAIT cells, addition of IL-15 resulted in a synergistic effector response. A comparable effect has been reported for IL-7, which also increases MAIT cell responsiveness[13]. Additional studies are needed to interrogate how MAIT cell function is modulated in various inflammatory environments.

How MAIT effector function is eventually turned-off in mucosal tissues, despite the potential continuous antigen exposure from commensals, is unknown. It is important to keep in mind that even healthy mucosal barrier tissues have basal levels of inflammation and additional (MAIT cell intrinsic and extrinsic) control mechanisms are likely in place to help regulate MAIT cell functional properties. Finally, inflammatory cues such as IL-12, IL-15 and IL-18 can be sufficient to activate MAIT cells[56] and do this by directly acting on MAIT cells[44,57] similar to what has been reported for conventional memory T cells[58].

Both conventional memory T cells and MAIT cells can be bystander-activated during viral infections[59–61], but the exact role of MAIT cells during the course of a viral infection is still unclear.

5. MAIT cell subsets, phenotypes and function in mucosal tissues

The tissue microenvironment varies in different anatomical locations and may influence MAIT phenotype and function. Single cell gene expression analysis comparing MAIT cells isolated from blood and rectal mucosa of healthy donors revealed that MAIT cells located in the tissue have increased expression of pro-inflammatory transcripts (but not necessarily protein) such as TNFα and this was more pronounced in the $CD8^+$ MAIT cell subset compared to the $CD8^-$ subset[44]. This increase in pro-inflammatory transcripts could allow MAIT cells to respond rapidly in the tissue. Interestingly, expression of these transcripts was not uniformly high all MAIT cells, which displayed a bimodal expression pattern for many of these genes [44] as previously reported in other single cell gene expression analysis datasets[62]. The extent of functional heterogeneity within the MAIT cell population in tissues is still unclear. However, MAIT cells identified in fetal mucosal tissue and the female genital tract (FGT) were shown to have a bias towards IL-17 and IL-22 function compared to MAIT cells in the blood[50,63]. Both of these cytokines have pivotal roles in regulating barrier immunity and tissue homeostasis [64,65] indicating that MAIT cells have a more complex role than just being a guardian against bacterial infections.

6. MAIT cell trafficking patterns and potential

Most MAIT cells in the blood express CCR6[12,44,46,66], which is implicated in trafficking to mucosal tissues and liver, since its ligand CCL20 is expressed in steady state conditions in organs like gut, lung and liver. Interestingly, CCL20 is typically considered to be the sole ligand for CCR6, but some evidence suggests that beta-defensins may bind to CCR6 as well[67]. In general, T-cell trafficking is guided by tissue-selective adhesion and chemokine receptors that allow cells access to specific tissues including mucosal barrier surfaces[68]. The chemokine receptor expression profile of MAIT cells has not been thoroughly characterized yet though has important implications for homing potential. Reported expression patterns are summarized in Table 1. While expression of CCR6 indicates that MAIT cells can access a wide range of tissues, the lack of CCR7 and CD62L expression suggests that they lack the ability to migrate from blood to lymph nodes via high endothelial venules (HEVs)[69]. Data from lymph node (LN) biopsies of cancer patients and characterization of MAIT cells in fetal tissues suggest that MAIT cells are rare in lymph nodes (LN) [12,63]. The origin of the few MAIT cells found in the lymph node is unclear, since MAIT cells can theoretically also access LNs by leaving tissue and entering LNs via the afferent lymphatics. The signals that control these steps are not nearly as well defined as the steps required for LN entry from blood via HEVs, but two reports provided compelling evidence that CCR7 expression on conventional T-cells greatly enhances their ability to exit peripheral tissues and enter the afferent lymphatics[70,71]. There is currently no direct evidence indicating if MAIT cells leave tissue or if they become tissue-resident akin to conventional tissue-resident memory T-cells[72]. Expression of cytotoxic and regulatory T-cell molecule (CRTAM), which controls residency of T-cells in the gut[73], is also enhanced

in MAIT cells isolated from tissues[44], supporting the notion that a resident population is plausible. In addition, MAIT cell frequencies in the blood are diminished in context of various infections and autoimmune diseases, sometimes irreversibly, which could be explained if cells are retained within tissues [1–11].

Conclusion

MAIT cells are located in barrier tissues to perform front-line host defense and have increased pro-inflammatory transcripts within these tissues compared to their blood counterparts highlighting that they are poised to respond rapidly at these sites. We discussed a model (Fig. 1) for MAIT cell activation to explain how these cells control their potent effector function at barrier surfaces. Sustained TCR-mediated responses only occur in the presence of inflammatory signals that are typically indicative of an infection. The need for inflammatory signals to elicit cytotoxic effector function may serve to prevent unwanted responses at these sites to commensal-derived antigen in steady state conditions. Recent studies also suggest a role for MAIT cells in maintaining epithelial integrity and tissue homeostasis via IL-17 and IL-22 production. Additional studies are needed to better understand the full functional potential, the migratory properties and the longevity of MAIT cells in steady state and in disease settings to ultimately facilitate therapeutic targeting.

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Highlights

- MAIT cells are located in barrier tissues to perform front---line host defense
- MAIT cells in these tissues have increased pro---inflammatory transcripts compared to their blood counterparts and are poised to respond rapidly
- A TCR signal is not sufficient to induce sustained MAIT cell effector function, which may prevent MAIT cell responses to commensal antigen in mucosal barrier tissues
- Inflammatory cytokine signals synergize with the TCR signal to induce potent effector function

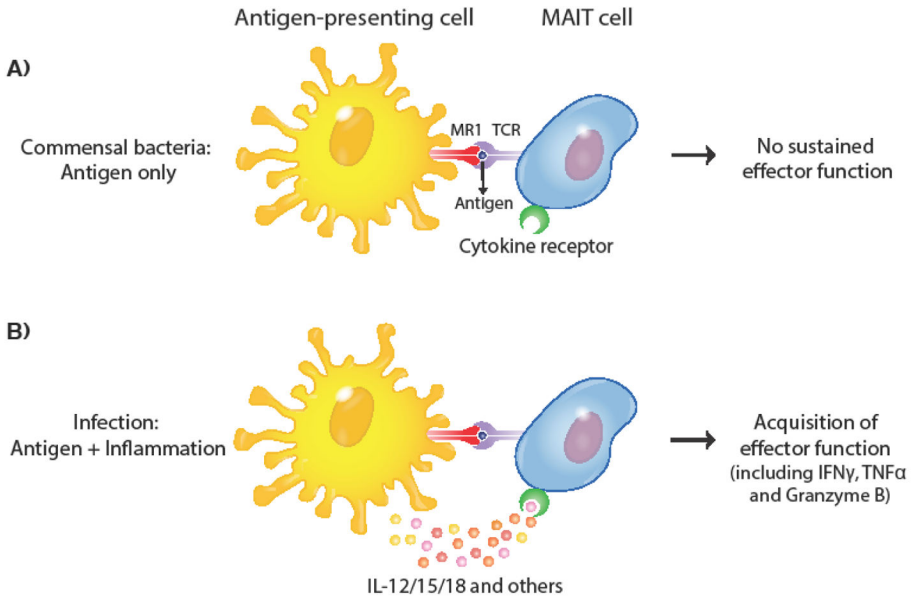

Figure 1. Model of MAIT cell activation

A functional riboflavin synthesis pathway is found in commensal and pathogenic species, which can lead to MR1-dependent presentation of metabolites to MAIT cells. **(A)** A TCR signal alone is not sufficient to elicit robust effector function, thus commensal-derived antigen in the absence of additional inflammatory cues is not sufficient to elicit MAIT cell effector function **(B)** Proinflammatory cytokines including IL-12/15/18 are elicited following infection and synergize with the TCR signal to elicit robust effector function.

Table 1

Chemokine receptor profile for MAIT cells in human blood

Chemokine Receptor	Fraction of MAIT population*	References
CCR2	>80%	[66]
CCR5	>80%	[12,66]
CCR6	>80%	[12,46,66]
CCR7	−	[12]
CCR9	+	[12,63]
CXCR3	<5%	[12,46]
CXCR4	60–80%	[12,66]
CXCR6	>80%	[12,46,66]

*When frequencies are not reported, + and − simply indicate the overall trend of expression