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The emerging role of MAIT cell responses in viral infections

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Abstract

Mucosa-associated invariant T (MAIT) cells are unconventional T cells with innate-like antimicrobial responsiveness. MAIT cells are known for MR1-restricted recognition of microbial riboflavin metabolites giving them the capacity to respond to a broad range of microbes. However, recent progress has shown that MAIT cells can also respond to several viral infections in humans and mouse models, ranging from HIV-1 and hepatitis viruses to influenza virus and SARS-CoV-2, in a primarily cognate antigen-independent manner. Depending on the disease context MAIT cells can provide direct or indirect antiviral protection for the host, may help recruit other immune cells, but may also in some circumstances amplify inflammation and aggravate immunopathology. Furthermore, chronic viral infections are associated with varying degrees of functional and numerical MAIT cell impairment, suggesting secondary consequences for host defense. In this review, we summarize recent progress and highlight outstanding questions regarding the emerging role of MAIT cells in antiviral immunity.

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Introduction

Conventional αβ T cells recognizing peptides presented by MHC molecules represent the main part of the T cell compartment. However, there are several exceptions to this paradigm with substantial T cell populations recognizing non-peptide antigens presented by mechanisms distinct from the standard MHC class I and II antigen presentation pathways (1). In humans, the largest such unconventional αβ T cell population are the mucosa-associated invariant T (MAIT) cells, normally found at levels of 1–10% of T cells in peripheral blood (2, 3). These unconventional T cells express a semi-invariant TCR repertoire and recognize small non-peptide antigens presented by the non-polymorphic and evolutionarily conserved MHC class I-related protein 1 (MR1) (4–6). MAIT cells primarily recognize microbial vitamin B2 metabolites, including the strong agonist 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) (7), although a range of other MR1-presented antigens have also been characterized (8).

MR1-restricted responses of MAIT cells are rapid and innate-like with production of diverse cytokines such as IFNγ, TNF, IL-17 and IL-22 (2, 9), as well as potent cytolytic effector function against infected cells and bacteria mediated by perforin, granzymes and granulysin (10–14). Notable features of these cells include expression of a broad set of tissue homing chemokine receptors (2), as well as a tissue residency transcriptional program (15). Tissue localization influences the functional profile of MAIT cells, with stronger propensity to express IL-17 in oral mucosa (16), female genital mucosa (17), and lung (18), as compared blood where expression of IFNγ and TNF dominates.

Consistent with their ability to take up residency in tissues, MAIT cells play important roles in different aspects of barrier immunity (19–21). Findings in murine models support their significant role in the control of bacterial infections in the lung, including *Francisella tularensis* (22, 23), *Legionella longbeacheae* (24), and *Klebsiella pneumoniae* (25). Recent evidence indicates that activation of MAIT cells in tissues has consequences outside their direct antimicrobial function, as they can contribute to tissue maintenance and repair in an MR1-dependent manner (26–28). MAIT cells are recruited to wounds via the CXCR6/CXCL16 axis and contribute to wound closure via the production of amphiregulin (29). It is thus becoming clear that MAIT cells have broad functions in protecting and maintaining barrier tissues.

MAIT cells in viral diseases

Beyond their role in MR1-restricted antimicrobial immunity, it is now known that MAIT cells respond strongly to many viral infections (30–32) (Table I). Here, we will briefly review some key discoveries and patterns, as well as highlight some outstanding questions for future research. Most data in the field comes from studies in human infectious diseases. However, we also discuss work from mouse models of viral and bacterial infections where relevant to the human disease context.

HIV-1

The first observation of MAIT cell involvement in human viral disease was the finding that they were numerically and functionally impaired in peripheral blood in patients with chronic HIV-1 infection (33, 34). Loss of MAIT cells was found to be irreversible by antiretroviral therapy (ART) (33–35), although the functional responses of residual MAIT cells to *E. coli* stimulation tended to recover at least partially (12, 33, 34). This pattern was initially unexpected as MAIT cells are mostly CD8+, and very few express CD4 and appear resistant to infection (34), despite high levels of CCR5 expression (36). Furthermore, the depletion of MAIT cells was less pronounced in gut mucosal tissues (33), giving rise to the hypothesis that loss from blood may at least partly be a consequence of recruitment to tissues where they may respond to microbial translocation (37, 38). In this context it is interesting to note that mice deficient in MR1 have been reported to exhibit impaired gut barrier integrity and increased microbial translocation (39). MAIT cell depletion in HIV-1 infected individuals was associated with activation levels (33), and a role for activation-induced pyroptosis in MAIT cell loss has been suggested (40).

The level of depletion at different tissue sites varies as MAIT cells in lung (41) and lymph nodes (42) are lost, whereas they are relatively preserved in female genital mucosa (43), as well as in gut mucosa (33). Chronic HIV-1 infection is thus not only associated with loss of peripheral blood MAIT cells, but perhaps rather with a level of redistribution to some mucosal sites. The numerical loss of MAIT cells in blood is also paired with functional impairment, although some recovery of responsiveness occurs as patients initiate ART (12, 33). IL-10 production by monocytes in response to HIV-induced chronic IFNα stimulation may at least partially explain the impaired MAIT cell responses to bacteria in this context (44). Notably, the small subset of CD4+ MAIT cells contributes to the HIV reservoir in persons on long-term effective ART (45).

In contrast to the loss of MAIT cells in chronic HIV-1 infection, recent studies demonstrated that acute HIV-1 infection is associated with MAIT cell expansion (46). Activated MAIT cells expand during the first weeks of HIV-1 infection both in blood and in gut mucosa (46), and a similar pattern was seen in pigtail macaques acutely infected with SIV (47). MAIT cell activation during acute HIV-1 infection correlated with markers of microbial translocation, and MAIT cells acquired increasing expression of CD56 as infection progressed (46). This is significant as CD56 expression is associated with an enhanced level of innate cytokine responsiveness in MAIT cells (9). Interestingly, recent findings *in vitro* suggest that MAIT cells are activated by HIV-1 in a cytokine-dependent and MR1-independent manner, and mediate antiviral effects via chemokines CCL3, 4 and 5 (48).

Human T-Lymphotropic Virus type 1 (HTLV-1) is another retrovirus that infects CD4 T cells and interrupts immune system function (49). Similar to HIV-1 infection, persons infected with HTLV-1 have a reduced frequency of MAIT cells in circulation, and residual MAIT cells are highly activated and display lower responses to bacterial stimulation (50). It is interesting to speculate that impaired MAIT cell frequency and function could contribute to the increased susceptibility to *Mycobacterium tuberculosis* reported for HTLV-1 carriers (51).

Viral hepatitis

Among all human organs investigated so far, the liver has the highest concentration of MAIT cells representing often 10–30% of the hepatic T cell pool (2, 52). This enrichment together with the role of the liver as site of filtration of blood coming from the gut, has prompted an interest in how MAIT cells respond to hepatitis virus infections. In this regard patients with chronic hepatitis C virus (HCV) infection resemble HIV-1 infected individuals in that MAIT cell levels are low in circulation and residual cells are functionally impaired (53–55), and do not readily recover after direct-acting antiviral treatment-induced clearance of HCV (53, 55). In contrast to HIV-1 infection, these numerical and functional impairments are observed already in acute stages of HCV infection (56), and loss of MAIT cells is evident both in blood and in the liver (54). Interestingly, the frequency of intrahepatic MAIT cells was observed to be inversely correlated with fibrosis, and intrahepatic MAIT cells were activated and maintained cytotoxic potential (54).

Hepatitis B virus (HBV) infection is associated with a similar pattern of MAIT cell loss, albeit probably a bit slower and less severe (57, 58). This pattern changes in HBV infected people who become co-infected with Hepatitis delta (HDV) and develop a severe form of viral hepatitis, which is associated with drastic loss of MAIT cells (59). Available data from these different studies suggest that IL-18 produced in response to hepatitis virus infection may drive the activation and exhaustion of MAIT cells in this context (54, 59).

Viral infections of the respiratory tract

The human lung contains relatively lower levels of MAIT cells than the liver, more in line with the percentages seen in peripheral blood (41, 60). Nevertheless, recent results indicate that MAIT cells can play both protective and pathogenic roles during pulmonary viral infections. In mice, MAIT cells provide a protective effect against influenza virus infection, and this effect seems to be mediated by IFNγ (61). In humans, activation of MAIT cells in response to influenza virus infected lung epithelial cells *in vitro* depends on IL-18, which triggers IFNγ and granzyme B expression (62). In both mice and humans, higher levels of MAIT cells in the host were associated with better outcome (61, 62).

Compared to influenza, a different picture has emerged from studies of patients with severe COVID-19. In such patients SARS-CoV-2 infection provokes strong activation of MAIT cells and leads to a rapid and sharp decline in circulating MAIT cell numbers in peripheral blood, with an apparent enrichment in the airways (63–65). The loss of MAIT cells is much more pronounced than for other T cell subsets in terms of percentage and absolute counts (63). Strikingly, in severe COVID-19 higher MAIT cell activation levels are associated with and predictive of mortality (63, 64, 66). This does not exclude the possibility that MAIT cells may afford some protection in most non-severe cases of COVID-19. It is currently unclear if the MAIT cell compartment rebounds in individuals who recover from severe COVID-19. The work by Flament et al. indicated that the severe COVID-19 MAIT cell phenotype was associated with a progressive shift from a type I IFN immune profile towards an IL-18 immune environment via a transcriptional switch in monocytes and macrophages

(64). Thus, IL-18 may drive both protective and pathogenic MAIT cell responses depending on the disease context.

Measles virus (MV) is a highly contagious pathogen causing acute respiratory viral illness in unvaccinated individuals. Recent findings indicate that MAIT cells are directly targeted by MV via their high expression of the MV receptor CD150, and infected cells die by apoptosis (67). Taken together, considerable emerging evidence now points to MAIT cells playing diverse important roles in respiratory viral infections.

Zoonotic and vector borne RNA viruses

Hantaviruses are single-stranded negative-sense RNA viruses belonging to the Bunyavirales order that infect humans upon inhalation of dust containing rodent excrement. Two recent studies have investigated the response of MAIT cells in patients infected with hemorrhagic fever with renal syndrome (HFRS) caused by Puumala orthohantavirus (PUUV) (68), or in patients with HFRS caused by Hantaan virus (HTNV) (69). Both studies see similar patterns of MAIT cell activation, decline in circulation, functional impairment, and eventually partial recovery in convalescent patients. However, the two studies differ regarding findings on the main drivers of MAIT cell activation, where activation by PUUV appears to be dependent on IFNα (68), while activation by HTNV appears dependent on IL-18 (69).

Dengue virus (DENV) and Zika virus (ZIKV) are flaviviruses transmitted mostly via mosquito bites. DENV infection in humans was found to be associated with increased MAIT cell activation as assessed by CD38 and granzyme B expression, with just slight reduction in cellular frequency in blood (70, 71). MAIT cell activation in response to DENV *in vitro* was dependent on antigen presenting cell expression of IL-12 and IL-18, in an MR1-independent manner (70). Furthermore, IL-18 levels and MAIT cell activation correlated with disease severity in patients with acute dengue infection (70). Similar IL-18-mediated activation was observed in response to ZIKV infection *in vitro* (71).

Mechanisms of MAIT cell activation in response to virus

The data available so far indicate that MAIT cell responses to viral infections are driven primarily by innate cytokines produced by other cells in response to virus, with little or no direct contribution of MR1 (Fig. 1). Cytokines that have been shown to stimulate MAIT cell responses include IL-12, IL-15, IL-18, IL-7 and IFNα/β (12, 68, 70, 72–74). It is important to note that the effector functions elicited by cytokines are relatively limited to activation with upregulation of CD69, cytolytic arming with upregulation of granzyme B, and expression of IFNγ. This effector profile is relatively limited, but on the other hand these responses happen with rapid “innate-like” kinetics. Another important aspect is that most of the activating cytokines are not very efficient activators alone, and combinations are much more potent such as the combination of IL-12 and IL-18. In an infected host these cytokines may also act in sequence and involve different cells, as some cytokines such as IL-12 have more restricted expression patterns than for example IL-18, and others such as IFNα may have faster kinetics. Interestingly, this was nicely illustrated by the response to chimpanzee adenovirus Ox1 (ChAdOx1) vaccine vector, where robust MAIT cell activation

required both IFNα produced by plasmacytoid dendritic cells and monocyte-derived IL-18 (75). In this setting, robust activation also needed secondary TNF production by monocytes in response to IFNα. Altogether, current understanding of factors involved in MAIT cell activation suggests that modes of activation will depend on the type of virus, and which cells and organs this virus infects. It is important to note that the cytokine-mediated activation discussed above does not exclude involvement of MR1-presented antigens derived from cellular metabolomes, microbiota and co-infecting bacteria. This will be important to study in particular in situations of barrier breach and microbial translocation.

Downstream consequences of MAIT cell activation for adaptive immune responses

It is likely that the most significant immediate anti-viral effect of MAIT cell activation occurs via the production of IFNγ, such as with the example of influenza virus infection in mice (61). Thus, MAIT cell responses may be similar to NK cells in the viral infection context. However, MAIT cells may be more efficient in infiltrating tissues and responding to inflammatory cues via their expression of for example CCR5, CXCR3, CCR2, CCR6 and CXCR6, which will allow homing to sites such as liver and lung (2, 76). However, the work with ChAdOx1 has indicated that the rapid activation of MAIT cells also provides an adjuvant-like effect, allowing stronger generation of antiviral CD8 T cell responses in mice (75). In line with this, MAIT cell activation in mice infected with the bacterial pathogen *F. tularensis* promoted monocyte differentiation *in vivo* via GM-CSF production and subsequent recruitment of CD4 T cells (77). Yet another example of MAIT cell promotion of effective adaptive immunity comes from work with *Vibrio cholerae* where MAIT cells promoted B cell differentiation and *V. cholerae* specific IgA responses (78). Infections with *F. tularensis* and *V. cholerae* give rise to riboflavin metabolite antigens and are in this way clearly distinct from the viral infection situation where direct MR1-dependent activation of MAIT cells is unlikely to occur. However, recent findings in mouse models indicate that MAIT cell activation by MR1-presented agonist can induce adaptive humoral viral immunity via dendritic cell activation and priming of follicular T helper cell responses (79). Thus, the adjuvant effect of MAIT cells could be influenced by interferons and cytokines triggered by the virus. Additionally it is tempting to speculate that MR1-presented antigen derived from unrelated microbes in the virus-infected host may also provide such stimulus in situations where gut, skin or lung barrier integrity is compromised. In this context it is interesting to note that in the human viral COVID-19 mRNA vaccine setting, it was recently observed that MAIT cells correlated positively with the magnitude of SARS-CoV-2 spike protein-specific CD4 T cell and antibody responses (80). In summary, emerging evidence suggests that MAIT cells may influence the magnitude and quality of downstream adaptive immune responses.

Emerging evidence of viral immune evasion

Viruses have evolved numerous ways of targeting components of immune pathways to avoid or delay recognition by host immunity (81). This includes active targeting and downregulation of MHC class I molecules (82), as well as non-classical CD1d molecules

(83), by viral mechanisms to prevent antigen presentation to T cells. Emerging evidence now indicates that the MR1 antigen presentation pathway is also inhibited by several viruses (Fig. 1). McSharry et al. found that several herpesviruses, including herpes simplex virus type 1 (HSV-1), suppress MR1 cell surface expression and target intracellular MR1 for proteasomal degradation, whereas MR1 at the cell surface escapes HSV-1-dependent targeting (84). The HSV-1 downregulation of MR1 is dependent on the viral protein US3 and inhibits MAIT cell activation (84). Another herpesvirus, the cytomegalovirus (CMV), was also recently reported to inhibit MR1 surface expression via the action of the US9 glycoprotein (85). Viral targeting of intracellular MR1 stores for degradation was recently found for Varicella Zoster virus (VZV), and this was partially mediated by the VZV ORF66 gene product (86). Together, these virus-mediated mechanisms for targeting MR1 define an emerging immune-evasive strategy that disrupts the MR1 antigen presentation pathway. More studies are needed to understand the importance of these mechanisms for the host-pathogen relationship during viral infection.

Future perspectives

We now know that many viral infections are associated with numerical and functional changes in the MAIT cell compartment. However, more studies are needed to understand the downstream consequences of these changes for the host. Considering recent advances, one could expect consequences for control of microbial infections and for the relationship with microbiota at mucosal surfaces, as well as for the ability of MAIT cells to contribute to wound healing. A better understanding of the underlying mechanisms of MAIT cell impairment during and after viral infections would help efforts to restore them. Here, there is evidence that the IL-7Rα/IL-7 axis plays a role, as IL7RA polymorphisms influence MAIT cell resilience during chronic HIV-1 infection (87), and IL-7 treatment of humans can boost MAIT cell numbers *in vivo* (88, 89) The supportive effects of IL-7 on MAIT cells extends boosting their function *in vitro* in different disease contexts (12, 90, 91), but more research is needed in this area. Furthermore, we know too little about the actual roles, both protective and potentially immunopathogenic, that MAIT cells play during serious viral diseases. For example, what differs in the MAIT cell response between their apparently protective role during influenza virus infection and their seemingly detrimental role during severe COVID-19? Are antiviral MAIT cell responses always MR1-independent, or are there instances where MR1 presents altered cellular metabolome products or microbiota-derived antigens to trigger MR1-restricted antiviral MAIT cell responses as recently suggested by findings from *in vitro* assays with HBV (58)? Finally, the potential of MAIT cells as a biomarker of disease risk should be further explored, as supported by the recent observation that MAIT cell levels are associated with CMV reactivation in allogeneic hematopoietic stem cell transplantation recipients (92).

Conclusions

Our understanding of how MAIT cells respond and are impacted during the acute and chronic stages of viral infection has improved considerably over the last decade. However, in many ways we have thus far only scratched the surface and, as outlined above, many key questions remain. Given the unique immunobiology of MAIT cells and MR1, including

a high level of evolutionary conservation, the relative lack of MR1 polymorphisms, high numbers of MAIT cells in healthy individuals, and rapid innate-like responsiveness, it is likely that MAIT cell responses play a role in many acute conditions including viral infections.

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Abbreviations used in this article:

ART	antiretroviral treatment
CMV	cytomegalovirus
DENV	Dengue virus
ChAdOx1	chimpanzee adenovirus Ox1
HTNV	Hantaan virus
HFRS	hemorrhagic fever with renal syndrome
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis delta virus
HSV-1	herpes simplex virus 1
HTLV-1	Human T-Lymphotropic Virus type 1
MAIT	mucosa-associated invariant T
MR1	MHC class Ib-related
MV	Measles virus
PUUV	Puumala orthohantavirus
VZV	Varicella Zoster virus
ZIKV	Zika virus

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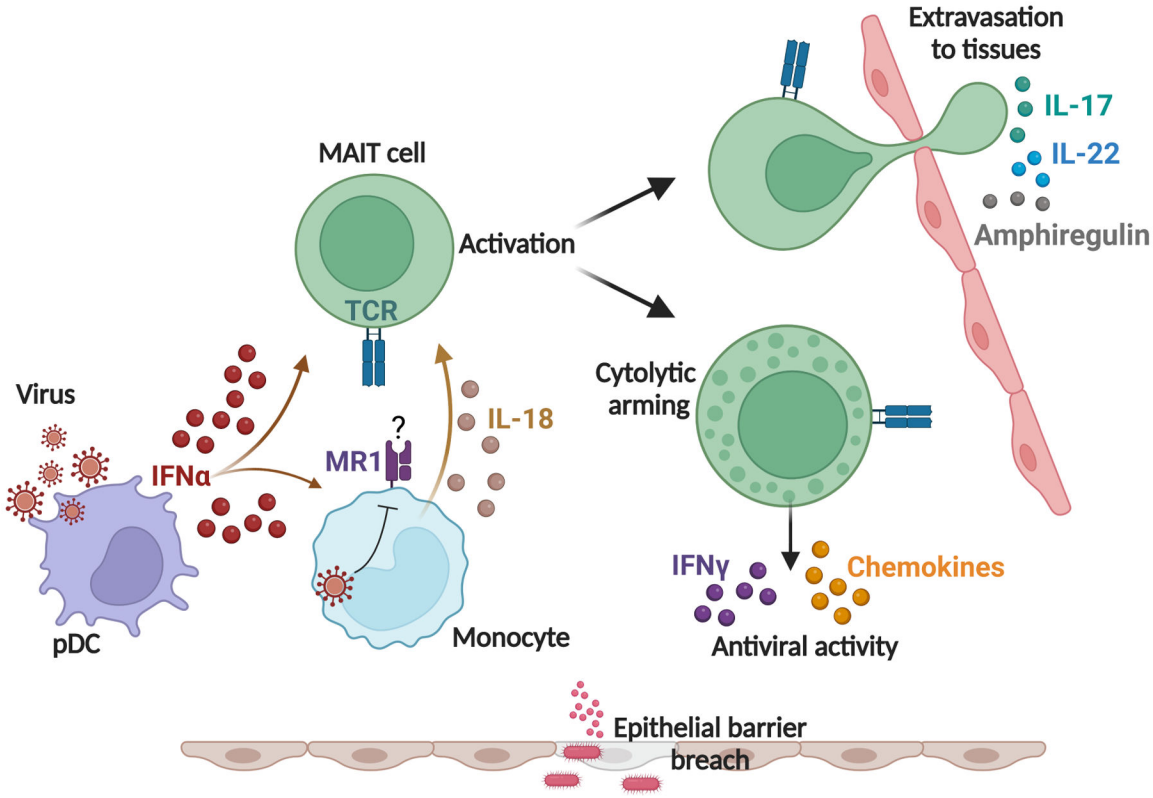

FIGURE 1.

Model of MAIT cell activation in response to viruses. MAIT cell activation in the virus infection context is primarily driven by cytokines including IFNα and IL-18, and it is unclear if TCR-mediated activation is involved. The description of subsequent responses is mostly based on *in vitro* studies with some support also from *in vivo* studies in humans and mouse models. The involvement of MR1-restricted responses to virus antigen or microbial translocation antigens is currently unclear or hypothetical, as indicated by the question mark. Created with BioRender.com.

Table I.

Summary of MAIT cell responses to diverse viral infections

Virus	Host species	Acute infection	Chronic infection	Convalescent/ Treated	Immune evasion	Consequence for host	Key references
HIV-1	Human	Activation/ expansion	Loss/ exhaustion	No/limited recovery	N.D.[a]	Antiviral via chemokines	33, 34, 35, 46, 48
HTLV-1	Human	N.D.	Loss/ exhaustion	N.D.	N.D.	N.D.	50
HCV	Human	Activation	Loss/ exhaustion	Limited recovery	N.D.	N.D.	53, 54, 56
HBV	Human	N.D.	Weak loss	N.D.	N.D.	Antiviral activity	57, 58,
HDV	Human	N.D.	Severe loss/ exhaust	N.D.	N.D.	N.D.	59
SARS-CoV-2	Human	Strong activation & loss	N.A.[b]	Partial recovery	N.D.	May be pathogenic in severe cases	63, 64, 65, 66
DENV	Human	Activation	N.A.	N.D.	N.D.	N.D.	71
ZIKV	Human	Activation	N.A.	N.D.	N.D.	N.D.	71
PUUV	Human	Activation/ loss	N.A.	Partial recovery	N.D.	N.D.	68
HTNV	Human	Activation/ loss	N.A.	Partial recovery	N.D.	N.D.	69
FLU	Human	Activation	N.A.	N.D.	N.D.	Probably protective	61, 62
FLU	Mouse	Activation	N.A.	N.D.	N.D.	Antiviral via interferon	61, 62
MV	Human	N.D.	N.A.	N.D.	Direct infection	Probably loss of MAIT cells	67
HSV-1	Human	N.D.	N.D.	N.D.	Downreg. MR1	N.D.	84
VZV	Human	N.D.	N.D.	N.D.	Downreg. MR1	N.D.	86
CMV	Human	N.D.	N.D.	N.D.	Downreg. MR1	Role in CMV reactivation in HSCT	85

[a] N.D., Not determined.

[b] N.A., Not applicable.