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Perturbation of MAIT and iNKT cells in HIV infection

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Abstract

Purpose of review: To analyze the possible role that the “unconventional” T cell populations MAIT cells and iNKT cells play during HIV infection and following ART treatment.

Recent findings: A substantial body of evidence now demonstrates that both MAIT and iNKT cells are depleted in blood during HIV infection. The depletion and dysfunction of MAIT and iNKT cells are only partially restored by suppressive ART, potentially contributing to HIV related comorbidities.

Summary: The deficiency and dysfunction of MAIT and iNKT T cell subsets likely impacts on immunity to important co-infections including *Mycobacterium tuberculosis*. This underscores the importance of research on restoring these unconventional T cells during HIV infection. Future studies in this field should address the challenge of studying tissue-resident cells, particularly in the gut, and better defining the determinants of MAIT/iNKT cell dysfunction. Such studies could have a significant impact on improving the immune function of HIV-infected individuals.

Keywords: iNKT, MAIT, unconventional T cell, ART, mucosa

Introduction:

Unconventional T cells, restricted by non-MHC proteins, exhibit both the antigen specificity of classic adaptive immunity and the rapid responsiveness of the innate immune system, giving them a unique role in the immune response to viral and microbial pathogens(1). In humans, unconventional T cells tend to share expression of CD161 (NKR-P1A)(2), and of the CD161-expressing lymphocytes, iNKT cells and MAIT cells have a clearly restricted TCR repertoire. iNKT cells are more abundant than MAIT cells in mice, whereas MAIT cells are more numerous in humans, comprising up to 15% of circulating CD8+ T cells. iNKT cells are selected and develop their innate-like phenotype and function in the thymus prior to egress. They also express the transcription factor ZBTB16 (PLZF), which is crucial for their innate/effector functions(3, 4). In contrast, MAIT cells are naïve and low in frequency in the thymus, and only low amounts of the TCR Vα7.2-J33 transcripts are found in cord blood(5-7), although phenotypically cord blood MAIT cells share many transcriptional features with their adult counterparts(8). The biology of these two cell types has been recently compared in detail elsewhere(9). .

In the context of infection, both MAIT and iNKT cells respond via rapid expression of effector cytokines e.g. TNF, IFN-γ, IL-17 and GM-CSF(10-14). They also both produce the cytotoxic molecules granzyme B and perforin(15, 16), which causes a sequence of events that lead to target cell death via the caspase pathway(17). In addition to TCR-mediated activation, both MAIT and iNKT cells can be activated in a TCR-independent manner relying on cytokine stimulation (typically IL-12, IL-18 and/or IL-15)(18-21). Modulation of MAIT or iNKT cells during HIV infection could potentially have impacts on host defence against bacteria, yeasts and viruses(20, 21). In this review we summarize the current understanding of the impact of

HIV infection on MAIT and iNKT T cell subsets and highlight the translational potential of these cells in HIV treatment, prevention and cure approaches.

MAIT Cells:

Mucosal-associated invariant T-cells (MAIT cells) are innate-like T cells that express a semi-invariant T-cell antigen receptor (TCR) and rapidly produce cytokines upon activation(22). Expression of the Vα7.2 TCR (rearranged typically with Jα33), restriction by the evolutionary conserved non-polymorphic MHC-related protein MR1, as well as expression of the C-type lectin CD161++ and IL18R, help define human MAIT cells. MR1 presents vitamin B metabolites produced by some but not all bacteria and fungi. The most potent riboflavin (vitamin B2) antigen for MAIT cell activation and development are 5-OP-RU and 5-OE-RU(23-25). Human MAIT cells typically express either CD8αβ or CD8αα dimers, but can occasionally exhibit a CD4/CD8 double negative (DN) phenotype and, rarely, CD4. MAIT cells share key differentiation factors with Th17 cells, which include: transcription factors (RORγt and RUNX2), cytokine expression (IL17A and IL22) chemokine receptors (CCR6 and CCR2), and cytokine receptors (IL23R and IL18R).

MAIT cells in untreated HIV infection

While MAIT cells are widely known for their anti-microbial role, their role in viral infections has also recently been investigated(12, 26). Depletion of MAIT cells in blood of patients with chronic viral infections, such as HBV, HCV and HIV, is common. Dramatic early and non-reversible loss of CD161++/MAIT cell numbers has been particularly observed in HIV infection(27, 28). This loss is further confirmed in SIV infection in rhesus macaques(29). Low frequencies of MAIT cells were observed in peripheral blood, mesenteric lymph nodes, and broncho-alveolar lavage fluid of SIV-infected macaques. Decreases of MAIT cells were

coupled with increased proliferation and a highly public TCR repertoire, although without redistribution to other anatomical sites. Systemic decrease of MAIT cells may be attributed to enhanced turnover in SIV infection that may cause impairment of protection against certain opportunistic infections.

There are several possible explanations as to why MAIT cells are depleted during HIV infection. The loss of MAIT cells in blood could potentially be due to down regulation of CD161 expression leading to an underestimation of $CD161^{hi}V\alpha7.2+$ MAIT cells. However, use of MR1/5-OP-RU tetramers has confirmed previous findings of MAIT cell depletion(30). Decreases in blood together with up regulation of tissue homing markers (CCR2+, CCR5+, CCR6+, CCR9+, CXCR6+) and the detection of MAIT cells in affected tissues indicate that they may migrate into tissues during infection(18). This may be relevant to bacterial translocation from the gut during HIV infection and subsequent immune activation, leading to MAIT cell migration into the gut, where they are then subjected bacteria-induced apoptosis(28).

The loss of MAIT cells is also evident in HIV/TB co-infection(31), and may contribute to increased susceptibility to *M. tuberculosis* infection, or to other bacterial and fungal infections(28). Patients with HIV and concomitant HCV co-infection have even lower peripheral MAIT cell frequencies with high levels of immune activation (CD38+HLA-DR+). Higher frequencies of intra-hepatic MAIT cells compared to peripheral blood was observed regardless of infection status, but these frequencies were still lower than that found in uninfected controls(32, 33). This suggests that the low frequency of MAIT cells observed in HIV/HCV co-infection is not solely due to migration to inflamed sites, but also depletion at the site of infection(34). Deletion of MAIT cells during infection may result in impairment of mucosal immunity and may contribute to the well-described reduction of barrier function in

HIV disease(35).

MAIT cells in the age of ART

Impairment of MAIT cell function in ART-naïve individuals chronically infected with HIV (~6-8years) has been observed(35, 36). Impairment of IFN-γ and IL-17A cytokine secretion by MAIT cells upon *E.coli* stimulation is partially restored with ART, although TNF production and CD69 expression was not restored with therapy. In untreated acute infection (median, 4 months) residual MAIT cells were found to be functionally active and may be able to assist in controlling bacterial infection during HIV infection(30). IL-17A production was partially restored after 5 years of ART, whereas treatment for 2 years was not able to restore IL-17A production(28), indicative of a very slow recovery of MAIT cell function following therapy. Taken together, while depletion of MAIT cells occurs early, functional impairment may develop later during established HIV infection: treatment may partially and slowly restore MAIT cell function in chronic patients(37). Early diagnosis and early treatment may be vital to improve functionality during HIV infection.

Expression of immune checkpoint receptors (ICRs) has been implicated in many disease settings to confer immune activation/inhibition that leads to exhaustion. PD-1 has been shown to be highly expressed on MAIT cells in peripheral blood of HIV-infected and HIV/TB co-infected individuals). TIM-3 expression was also elevated on MAIT cells in chronic HIV infection compared to uninfected controls. Treatment with ART was able to significantly lower TIM-3 levels but not PD-1 levels on MAIT cells(35). Expression of other ICRs, such as LAG-3, CD244, CTLA-4 and TIGIT are yet to be investigated on MAIT cells in different stages of HIV infection. Whether the high expression of ICRs correlate with impaired function of MAIT cells is to be determined.

IL-7 is a pleiotropic cytokine that has many functions(38) which include acting as a growth factor for gut mucosal lymphocytes, conferring strong survival signals for homeostatic proliferation of memory T cells, and enhancing Th1 and Th17 cytokine production. IL-7 has been shown to activate resting MAIT cells from healthy donors to become cytotoxic granzyme B expressing effector cells(39). IL-7 plasma levels positively correlate with higher MAIT cell frequencies and improve function in HIV-infected patients. IL-7 treatment significantly restored MAIT cell effector function in vitro, even when ART was not administered(40). Thus, the immunotherapeutic properties of IL-7 together with ART should further be explored to harness the protective function of MAIT cells in HIV disease.

Future directions: MAIT cells and HIV prevention

It is now clear that MAIT cells have the ability to sense viral infections through specific cytokine-driven mechanisms. There is a general decrease in MAIT cell frequencies during several chronic viral infections, although these observations were mostly made on peripheral blood. Much work remains to be done to understand the role of MAIT cells during HIV infection. There is a strong need to characterize the MAIT cells from different mucosal tissue compartments, particularly the GALT of HIV-infected individuals. Additional cohorts of elite controllers, viremic controllers, TB-HIV co-infection and HCV-HIV co-infection should be carefully studied. Gastric MAIT cells have to been shown to express tissue resident markers CD69 and CD103, and can rapidly respond to *H. pylori* infection(41). It remains to be seen if MAIT cells in tissue compartments of HIV-infected subjects are able to respond to HIV and play a role in preventing acute infection of CD4 T cells. Assessment of immune-senescence and cell exhaustion needs to be studied in more detail in both blood and tissue compartments, with particular emphasis on inhibitory receptors that may affect MAIT cell function. The

interaction of MAIT cells and other innate and adaptive cells within tissue compartments should be investigated as they serve as sources of cytokines during viral infections leading to MAIT activation. Finally, to what extent MAIT cell frequencies and functions can be restored in HIV and what approaches beyond extended ART could impact on this is an important translational question. If the tissue-homing and cytotoxic potential of MAIT cells could contribute to the control of latent reservoir (as well as promoting overall host immunity) this would be a novel approach to HIV cure strategies.

iNKT Cells:

iNKT cells (also known as Type I NKT cells) are a CD1d-restricted T cell subset characterized by the expression of a semi-invariant TCR (Vα24-Jα18 most commonly paired with Vβ11)(1). Other NKT cell subsets, such as the more diverse group of Type II NKT cells(42), will not be considered in this review. Human iNKT cells represent approximately 0.1% of peripheral blood T cells and exhibit functional heterogeneity based on the expression of the CD4 and CD8 co-receptors(43). iNKT cell phenotype, function and antigen specificity have recently been comprehensively reviewed(1, 44).

iNKT cells in untreated HIV infection

It has been 16 years since van der Vliet *et al*(45), Sandberg *et al*(46) and Motsinger *et al*(47) reported the depletion of iNKT cells in the peripheral blood of HIV-infected individuals. Since then, numerous cohort studies have confirmed their observations(48-54), and suggested that iNKT depletion occurs rapidly after acute infection(30, 45, 54). Depletion is observed in both HIV-1 and HIV-2 infection(55), occurs independently of the clade of HIV-1 infecting virus(49, 50), and correlates with markers of HIV disease progression in the vast majority of cohorts(46, 54, 55). Although the mechanisms of iNKT loss may be multifactorial(45), the

major contributing factor is the selective depletion of the $CD4^+$ iNKT subset(46, 49, 51, 52, 54, 55). A subset of $CD4^+$ iNKT cells express CCR5(47), and *in vitro* studies have confirmed that both resting and antigen-activated $CD4^+$ iNKT cells are highly susceptible to HIV infection(46, 47, 56). Similar results have been reported during SIV infection of non-human primates(57, 58) with the exception of sooty mangebeys, which naturally lack $CD4^+$ iNKT cells and exhibit no iNKT depletion during non-pathogenic SIV infection(59).

Despite the importance of the gut-associated lymphoid tissue (GALT) as a site of HIV replication and associated microbial translocation, data on mucosal iNKT cell populations during HIV infection is scarce. To date, only two studies have assessed GALT iNKT cells in infected individuals, with divergent results. Ibarrondo *et al(60)* reported that $CD4^+$ iNKT cells, which were enriched in the GALT relative to PBMC, were substantially depleted in HIV-infected subjects. This depletion correlated with viral load and systemic T cell activation, while peripheral $CD4^+$ iNKT depletion did not. In contrast, Paquin-Proulx *et al*(61) observed a non-significant increase in the proportion of gut iNKTs that were $CD4^+$ in HIV-infected subjects, with no changes in total iNKT frequency compared to controls. In this cohort, GALT iNKT IL-10 and IL-4 production were associated with lower levels of immune activation and microbial translocation. Despite the challenging nature of identifying and collecting sufficient iNKT cells from GALT samples for analysis, more studies are needed to conclusively determine the relationship between gut dysbiosis, immune activation and iNKT responses during HIV infection.

Phenotypic and functional characterization of the residual peripheral iNKT population suggests that chronic HIV infection also leads to iNKT cell anergy or exhaustion. Multiple studies have confirmed the activated phenotype of iNKT cells during infection (as measured

by CD69, CD38 and HLA-DR expression)(48, 49, 52, 55) and identified defects in αGalCer- or PMA-induced cytokine production and proliferation(54, 62-64). These functional deficiencies are typically attributed to the elevated expression of ICRs or differentiation markers such as PD-1(48, 62), LAG-3(65), CD57(48, 49)and, most recently, 2B4(51). Despite correlations between surface phenotype and function, however, only a single study has directly demonstrated a relationship between exhaustion marker expression and lack of cytokine production on an individual cell level(65). Furthermore, the only study to attempt to restore iNKT function in vitro by blocking PD-1 signalling was unsuccessful(62), leaving substantial gaps in our understanding of the mechanisms regulating iNKT exhaustion and functional capacity during HIV infection.

iNKT cells and control of HIV disease progression

The multifunctional nature of iNKT cells has led to speculation that the depletion of the $CD4^+$ subset and compromised function of the remaining iNKT population could contribute to HIV disease progression. Data surrounding this question, however, remains speculative and circumstantial. *In vitro*, αGalCer stimulation of PBMCs can inhibit HIV replication via an IFNγ-dependent mechanism(66). Long-term non-progressors (LTNP), who naturally control HIV infection, exhibit significantly higher iNKT frequencies and improved iNKT cell function compared to normal progressors(48, 64), but studies of LTNP are hampered by the difficulty of determining causality between a given immune phenotype and HIV control. Perhaps the most intriguing results in this area come from Rout *et al(67),* who reported that in macaques, baseline iNKT cell frequencies correlated with the preservation of post-infection $CD4^+$ T cell counts, suggesting a potential impact of iNKT cells on early disease progression. Unfortunately, no additional data is available to confirm this observation, and in an

interventional study of two pigtail macaques, Fernandez et al(68) found no clear impact of αGalCer administration and iNKT activation on the progression of subsequent SIV infection.

iNKT cells in the age of ART

The majority of data support only a partial restoration of both iNKT cell frequency and cytokine production during combination antiretroviral therapy (ART)(48, 52, 53, 65, 66, 69), although some cohorts have reported either full reconstitution of the iNKT compartment(70), or no restoration at all(62, 64, 71). In some cases, ART restored only the $CD4^-$ iNKT subset(69), while in other cases, results varied depending on the time of ART initiation(66) or the discrimination of individuals who did or did not achieve suppression of viremia(72). Residual depletion and exhaustion of the iNKT compartment even during suppressive ART and conventional $CD4^+$ T cell reconstitution is consistent with data for other unconventional T cell subsets(28, 73), and suggests the potential clinical utility of immunotherapies designed to boost unconventional T cell immunity. ART-treated individuals remain at elevated risk of co-infections, most notably *Mycobacterium tuberculosis* (Mtb)(74). Mtb infection activates iNKT cells(75), and patients with active TB exhibit iNKT cell defects similar to those observed in HIV-infected patients(52, 76). Clinical interventions designed to reverse iNKT exhaustion or increase iNKT frequency might therefore improve TB-related immunity in HIV-infected ART-experienced populations. Immune checkpoint inhibitors have shown promise in cancer immunotherapies designed to restore anti-tumor T cell responses(77), and might be similarly useful in restoring iNKT function during ART. Further work in this area, however, will require a more incisive effort to determine the most important determinants of iNKT dysfunction in HIV and generate proof-of-concept studies.

Future directions: iNKT cells and HIV prevention or cure

Despite the presence of both iNKT cells(78) and substantial CD1d expression in the female reproductive tract (FRT)(79), the capacity of iNKT cells to limit or prevent HIV transmission is hampered by viral immune evasion strategies. Both Nef(80, 81) and Vpu(78, 82) interfere with the surface expression of CD1d in dendritic cells, limiting iNKT effector functions against infected cells. Alternately, iNKT cells may prove useful to HIV vaccine design. iNKT cells can provide B cell help both in vitro(83) and in vivo(84), making αGalCer a potent adjuvant. Preliminary studies of two mucosal HIV vaccines, administered either sublingually, orally or intranasally, found that αGalCer boosted cellular immune responses(85, 86) and resulted in neutralizing antibody responses at the genital mucosa(86). αGalCer also boosted the both the cellular and humoral immunogenicity of an HIV DNA vaccine(87). All of these studies, however, were limited to mouse models, with human or non-human primate data lacking. Finally, iNKT cells are emerging as candidates for immunotherapy-based HIV cure strategies. As second-generation chimeric antigen receptor T (CAR-T) cells show clinical promise against multiple forms of cancer, there is a similar potential for engineered T cells to be used as anti-HIV effectors(88, 89). iNKT cells may provide several benefits over traditional T cells in immunotherapy, given their potent cytotoxic function and an improved safety profile due to a lack of MHC restriction(90). Adoptive transfer of *in vitro* expanded iNKT cells has already been tested in a human clinical trial(91), and CAR-iNKT cells have shown potent anti-tumor activity in animal models(92). A phase 1 trial to assess the safety of CAR-iNKT cells in neuroblastoma is currently underway (NCT03294954).

Conclusions:

A substantial body of evidence now demonstrates that both MAIT and iNKT cells are depleted during HIV infection and only partially restored by suppressive ART. It is very

likely that the combined deficiency of these unconventional T cell subsets impacts on immunity to a variety of co-infections including *Mycobacterium tuberculosis*, underscoring the value of restoring unconventional T cell subsets in persons living with HIV (Fig 1). Future studies in this field should address the challenge of studying tissue-resident cells, particularly in the gut, and better defining the determinants of MAIT/iNKT cell dysfunction. Such studies could have a significant impact on improving the immune function of HIV-infected individuals.

Key Points:

- Both MAIT and iNKT cells are depleted from peripheral blood during untreated HIV infection
- ART does not fully reconstitute the frequency or function of residual iNKT/MAIT cells
- Determinants of residual iNKT/MAIT cell dysfunction, i.e. immune checkpoint receptors, are poorly defined
- Restoration of iNKT/MAIT cells in HIV-infected individuals may have important benefits for antiviral and antimicrobial immunity

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Figure Legends:

Figure 1. *iNKT and MAITs cells in HIV infection*. Virally driven cytokines produced by antigen presenting cells in blood and tissue lead to cellular activation and increase apoptosis. Overall, these events causes loss of function in iNKT and MAIT cells and reduce anti-microbial/anti-viral function from these cells.