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MAIT Cells in COVID-19: Heroes, Villains, or Both?

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ABSTRACT: Mucosa-associated invariant T cells (MAIT cells) are unconventional, innate-like T lymphocytes with remarkable effector and immunoregulatory functions. They are abundant in the human peripheral blood and also enriched in mucosal layers and in the lungs, SARS-CoV-2's main ports of entry. Once activated, MAIT cells produce inflammatory cytokines and cytolytic effector molecules quickly and copiously. MAIT cells are best known for their antibacterial and antifungal properties. However, they are also activated during viral infections, typically in a cytokine-dependent manner, which may promote antiviral immunity. On the other hand, it is plausible to assume active roles for MAIT cells in infection-provoked cytokine storms and tissue damage. SARS-CoV-2 infection may be asymptomatic, mild, severe, or even fatal, depending on sex, age, the presence of preexisting morbidities, and the individual's immunological competence, or lack thereof, among other factors. Based on the available literature, I propose that MAIT cells regulate the host response to SARS-CoV-2 and constitute attractive targets in the prevention or clinical management of coronavirus disease 19 (COVID-19) and some of its complications. Unlike mainstream T cells, MAIT cells are restricted by a monomorphic antigen-presenting molecule called MHC-related protein 1 (MR1). Therefore, MR1 ligands should modify MAIT cell functions relatively uniformly in genetically diverse subjects and may be tested as immunotherapeutic agents or vaccine adjuvants in future studies.

KEY WORDS: SARS-CoV-2, coronaviruses, pandemic, innate-like T cells, antiviral immunity, cytokine, inflammation, toxic shock, immunotherapy, vaccination

I. INTRODUCTION

In December 2019, a pneumonia associated with a novel and highly contagious coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hereafter referred to as CoV2, emerged in Wuhan, China. CoV2 is an enveloped, positive-sense, single-stranded RNA virus, to which there is no preexisting immunity, except perhaps in the case of cross-reactivity or prior exposures to similar viruses (e.g., common human coronaviruses).[1] CoV2 hijacks human angiotensin-converting enzyme 2 (hACE2) in order to enter host cells.[2] To date, the ongoing coronavirus disease 19 (COVID-19) pandemic has resulted in more than 5.5 million infections, claimed nearly 350,000 lives, and crippled the global economy. There is currently no vaccine or cure for COVID-19, and the management of severe cases relies on supportive measures such as mechanical ventilation in the intensive care unit (ICU).[3]

An effective vaccine should elicit highly specific adaptive immunity to CoV2 and immunological memory for future encounters with the same or antigenically similar invaders. Equally important, vaccines save lives by helping achieve herd immunity at the population level.[4] However, adaptive responses are never perfect and have their own limitations. For instance, they do not work equally in genetically diverse humans, due in large part to the polymorphic nature of human leukocyte antigen (HLA) class I and II molecules, which present antigenic peptides to conventional $CD8^+$ and $CD4^+$ T cells, respectively. Activated $CD8^+$ T cells primarily serve in the capacity of cytotoxic T lymphocytes (CTLs), and effector $CD4^+$ T cells "assist" B cells in antibody (Ab) production. Also of note, adaptive responses decline in the old age,[5] which is a risk factor for the severity of COVID-19 illness.[6] Moreover, COVID-19 results in lymphopenia and T cell exhaustion, especially in older patients and in those requiring ICU care.[7] Finally, CoV2-specific Abs may not be protective or

may even enhance the infection.[8,9] Such hurdles are often inevitable and obviously should not dissuade the scientific community from pursuing optimal vaccines against COVID-19. In the meantime, while the entire world is still reeling from the pandemic's dire consequences and vying for a vaccine, there has been increasing interest in targeting innate immune cells in search of a rapid remedy.

In this article, I will briefly introduce a subset of innate-like T cells, called mucosa-associated invariant T (MAIT) cells, which I propose may constitute an attractive prophylactic or therapeutic target in COVID-19. I will highlight some of MAIT cells' most remarkable antiviral, immunomodulatory, and inflammatory characteristics in support of this theory and lay out some of the work that lies ahead for making MAIT cell–based interventions a reality of the future.

II. MAIT CELLS IN BRIEF

MAIT cells are unconventional T lymphocytes that circulate with high frequencies, comprising up to 10% of all T cells, in the human peripheral blood. They are also enriched in the gut, in the lungs, and in the liver.[10–13]

MAIT cells express a canonical T cell receptor (TCR) α chain (Vα7.2-Jα33 in humans and Vα19-Jα33 in mice),[14–16] which is paired with one of only a selected few TCR β chains to form a semi-invariant TCR (*i*TCR).[17,18] The MAIT *i*TCR recognizes a unique array of compounds, including neoantigens containing vitamin B derivatives of microbial origin [e.g., 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU)][19–21] and certain drugs, drug metabolites, and drug-like molecules,[22] in the context of a monomorphic protein called MHC-related protein 1 (MR1).[23] Most MAIT cells express CD8 as their co-receptor for antigen (Ag) and display a $CD45RO^{+}CD62L^{low}$ effector memory-like phenotype.[10] They are the predominant population among $CD3^{+}V\alpha7.2^{+}CD161^{hi}$ cells and can be accurately identified using 5-OP-RU-loaded MR1 tetramers that bind specifically to MAIT cell *i*TCRs.[18,24]

Once activated, MAIT cells produce a variety of inflammatory mediators, including T helper (T_H)-1-type, T_H2-type, or T_H17-type cytokines (e.g., IL-2, IFN-γ, TNF-α, IL-4, IL-5, IL-13, IL-17A, IL-22) and cytolytic molecules.[25,26] These mediators enable MAIT cell participation in host defense and in immunoregulatory feedback and feedforward loops either to the benefit or to the detriment of the host. It is thus not surprising that protective or pathogenic roles for MAIT cells have been demonstrated or suggested in various diseases and conditions, including infectious diseases,[27–29] sepsis,[30] toxic shock,[31] allergy,[32] autoimmunity,[33] and malignancy.[34,35] Recent evidence suggests that MAIT cells can also operate in an MR1-dependent fashion to promote tissue repair.[36–40]

III. MAIT CELL RESPONSES TO VIRAL PATHOGENS

Viruses lack the vitamin B biosynthesis machinery.[27] However, they can activate MAIT cells in an MR1/*i*TCR-independent, cytokine-driven manner. *In vitro* co-culture systems have revealed that MAIT cell activation by viruses typically requires IL-18 production by myeloid cells, often in synergy with IL-12 and/or other cytokines (e.g., IL-15 and type I IFNs).[41–43] Importantly, von Wilgenburg et al. demonstrated that MAIT cells primed by IL-12 and IL-18 can suppress hepatitis C viral (HCV) replication in hepatocytes via an IFN-γ-dependent mechanism.[41]

MAIT cell activation has been reported in human infections with hepatitis A virus,[44] hepatitis B virus,[44] HCV,[41,45,46] dengue virus,[41,43] influenza A virus (IAV),[41] human T-lymphotropic virus type 1 (HTLV-1),[47] and more recently CoV2,[48] sometimes accompanied by signs of cellular exhaustion. In addition, several groups have suggested that MAIT cell depletion during chronic infections with human immunodeficiency virus (HIV), HCV, or HTLV-1 may be due to activation-induced cell death.[47,49,50] Residual MAIT cells may or may not retain their full capacity to respond to cognate bacterial ligands.[51–53] Regardless, a numerical shortage in the MAIT cell compartments of patients with chronic viral infections is likely to render them prone to opportunistic bacterial and fungal infections.

Loh et al. found peripheral blood MAIT cell frequencies to be higher in hospitalized patients who

recovered from avian H7N9 IAV pneumonia than in those who succumbed to the infection,[42] suggesting a beneficial role for MAIT cells during acute IAV infection. More recently, MAIT cells were shown to accumulate in the lungs of IAV-infected mice, where they expressed elevated levels of CD69, CD25, and granzyme B.[54] Importantly, adoptive transfer experiments documented a protective role for MAIT cells during *in vivo* IAV infection.

MAIT cells in patients with viral infections may exhibit increased expression of cytolytic molecules. However, whether such "armed" effectors are capable of detecting and destroying virus-infected cells has yet to be experimentally demonstrated.[25]

Collectively, MAIT cell behaviors during viral infections vary considerably, depending on the type of viral pathogens encountered, the acuteness or the chronicity of infection, and the tissue environment in which MAIT cells reside or amass.

IV. MAIT CELLS AS HEROES IN COVID-19?

MAIT cells are strategically located in mucosal layers and in the lungs, CoV2's main ports of entry, where they comprise up to 20% of all T cells in humans.[13] Several facts and observations suggest potentially protective roles for MAIT cells during CoV2 infection (Fig. 1). First, MAIT cells appear to participate in host defense against certain other respiratory viruses, including IAVs.[42,54] Second, they are considered "emergency responders" to infection by virtue of their effector memory-like characteristics.[10] Third, unlike conventional naïve T cells, MAIT cells express high levels of receptors for IL-12 and IL-18,[31,55] cytokines that are produced during infection with viral invaders, including CoV2 and other coronaviruses.[48,56,57] In fact, IL-18 may predict and promote recovery from COVID-19.[58] Fourth, once activated, MAIT cells upregulate IFN-γ and TNF-α among other cytokines and cytolytic effector molecules (e.g., granzymes),[25] which should help eliminate CoV2 and accompanying pathogens. Fifth, MAIT cells recognize MR1 ligands harbored by a relatively wide spectrum of bacteria and fungi,[27,28] some of which are known causes of respiratory infections. This function may serve to protect against superinfections, which may manifest as potentially deadly complications of COVID-19.[59,60] Sixth, crosstalk between MAIT cells and other effector cell types with antiviral functions may be established, and MAIT cell stimulation may result in transactivation of downstream NK cells, invariant natural killer T (*i*NKT) cells, and CTLs,[35,61] thus adding another layer to anti-CoV2 immunity. Seventh, MAIT cells participate in tissue repair mechanisms[39] and may, as such, help expedite the recovery process in the aftermath of CoV2 infection.

According to a recent report by Jouan et al.,[48] MAIT cell frequencies drop in the peripheral blood but rise in the airways of critically ill COVID-19 patients. Importantly, higher $CD69^+$ peripheral blood MAIT cell frequencies on day 1 post-admission were associated with reduced hypoxia on day 7. Although more controlled studies on this subject are needed, this observation supports a beneficial, if not protective, role for MAIT cells in COVID-19.

V. MAIT CELLS AS VILLAINS IN COVID-19?

Dysregulated MAIT cell responses to pathogens or their products can have inflammatory repercussions for the host. We previously implicated MAIT cells as a major culprit in the immunopathogenesis of toxic shock syndrome (TSS) and its associated cytokine storm.[31] We found that MAIT cells can launch a heavy-handed response to bacterial superantigens by producing very large quantities of proinflammatory cytokines, such as IFN-γ and TNF-α. Importantly, this response was predominantly mediated by IL-12 and IL-18, cytokines that are also abundantly produced during viral infections.[48,56,57] COVID-19 should no longer be viewed as a merely geriatric problem linked with immunosenescence or preexisting morbidities. It can also be catastrophic in otherwise healthy adults and in a small number of children who present with serious inflammatory symptoms reminiscent of TSS and incomplete Kawasaki disease.[62] The emerging syndrome of the afflicted children is now called the "pediatric multi-system inflammatory syndrome [potentially] associated with COVID-19". Whether MAIT cells contribute to such and similar manifestations should be considered in future investigations.

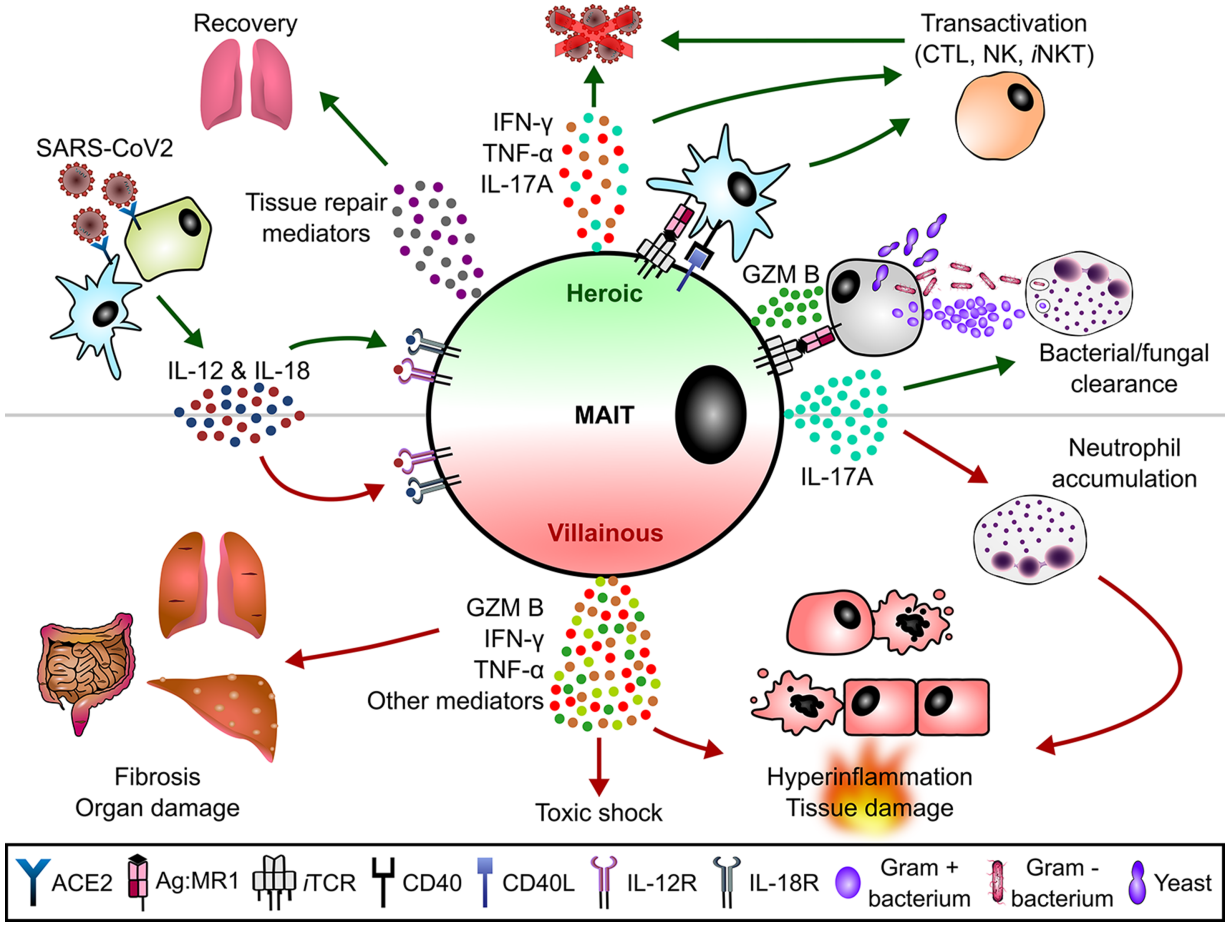

FIG. 1: Mucosa-associated invariant T cells (MAIT cells) can play protective (heroic) roles, pathogenic (villainous) roles, or both in COVID-19. Infection of angiotensin-converting enzyme (ACE)2^{+} host cells by SARS-CoV-2 results in production of a number of cytokines, which likely include IL-12 and IL-18. MAIT cells respond to these cytokines by releasing inflammatory mediators of their own, such as IFN-γ and TNF-α. Some of these mediators should help clear SARS-CoV-2 infection, for instance through transactivation of natural killer (NK) cells, invariant natural killer T (*i*NKT) cells, and cytotoxic T lymphocytes (CTLs), among other mechanisms. Under certain circumstances and in certain tissue contexts, MAIT cells produce IL-17A, which facilitates the recruitment of neutrophils to the site of infection. Several other substances secreted by MAIT cells promote tissue repair and recovery. Once activated, MAIT cells also upregulate cytolytic effector molecules [e.g., granzyme (GZM) B], which destroy host cells infected by bacterial and fungal pathogens responsible for secondary infections. MAIT cells can engage and mature dendritic cells (DCs) through CD40L-CD40 and invariant T cell receptor (*i*TCR)-MHC-related protein 1 (MR1) interactions, thus promoting classic antigen presentation to mainstream T cells and antipathogen immunity. On the flip side, excessive, untimely, or dysregulated MAIT cell activation and effector functions may lead to toxic shock syndrome–like manifestations, endothelial, stromal and parenchymal cell injury, direct or collateral organ damage, scarring and tissue fibrosis.

It is becoming increasingly clear that COVID-19 affects multiple organ systems with a possibility of immune-mediated collateral tissue damage. Excessive or prolonged cytokine production and cytotoxicity by MAIT cells may be particularly deleterious in tissues where MAIT cells are frequent and co-present with ACE2-expressing parenchymal, stromal, and/or endothelial cells. These include

the lungs, the intestines, and the liver.[63,64] ACE2 is widely expressed in respiratory and gastrointestinal tracts. In the human liver, ACE2 expression is pronounced in cholangiocytes.[65] Therefore, CoV2 may directly attack cholangiocytes, thus reducing bile acid excretion and causing liver injury.[66] On the other hand, NK cell-mediated, NKG2D-dependent destruction of cholangiocytes in rotavirus-induced biliary atresia has been previously described in a mouse model.[67] Interestingly, Rha et al. recently found that circulating MAIT cells in patients with acute hepatitis A exhibited increased "innate" cytotoxicity, which was also mediated by NKG2D engagement and positively correlated with serum alanine aminotransferase levels, indicative of liver damage.[44] Therefore, a hypothetical scenario can be envisaged in which CoV2 infection of $ACE2^{+}$ cholangiocytes renders them susceptible to hepatic MAIT cell-mediated lysis, culminating in cholangiopathy and secondary hepatocyte injury.

Finally, uncontrolled production of some of the mediators secreted by MAIT cells to fight infection may backfire and cause serious long-term morbidities. For instance, IL-17A, a potent cytokine that mobilizes neutrophils to combat extracellular bacteria at mucosal sites, may exacerbate tissue inflammation and also has potential pro-tumorigenic properties.[35,68] Moreover, the tissue repair and wound healing activities of MAIT cells,[36–38,40] if sustained, may promote fibrosis and tumor growth.[39] MAIT cells are potentially profibrogenic entities,[69,70] and lung tissue scarring leading to pulmonary fibrosis has been suggested as a potential immune-mediated outcome of COVID-19.[71,72] Firmly validating such theories will require the interrogation of the MAIT-lung interface in long-term COVID-19 survivors.

VI. MAIT CELL–BASED INTERVENTIONS

Before MAIT cells can be hailed as heroes or denounced as villains in COVID-19, much remains to be learned about their behavior. Regardless of the nature of their roles across different age groups in the presence or absence of comorbidities, MAIT cell–based interventions may be fruitful. At this point, one cannot also rule out the possibility that MAIT cells play both beneficial and detrimental roles even within a patient, in which case exploring phase-tailored interventions may be warranted, in conjunction with our modalities.

MAIT cells are reactive to a number of cytokines, including but not limited to IL-18 and IL-12.[31,55] Therefore, temporary, dose-optimized, local administration of the right cytokine pairs or cocktails may be helpful in boosting antiviral immunity through MAIT cell activation. On the contrary, when MAIT cells are suspected of triggering or perpetuating hyperinflammatory syndromes and cytokine storms, one may attempt to block the functions of cytokines that activate or are secreted by MAIT cells.

The speed and the robustness with which innate and innate-like cells respond to pathogen-associated molecular patterns, microbial products, and various stimuli make them perfect targets when fast-acting therapies are urgently needed. It is thus not surprising that bacille Calmette-Guérin (BCG) administration has been attempted in frontline healthcare workers, with outcomes that have yet to be determined.[73,74] It is noteworthy that BCG activates MAIT cells[28,75] among other effects in potentiating "trained immunity". I propose that some of the beneficial effects of BCG in COVID-19, if confirmed, stem from their MAIT cell-stimulating activity.

MR1-binding, vitamin B-based MAIT cell agonists (e.g., 5-OP-RU)[19–21] and nonstimulatory ligands (e.g., acetyl-6-formylpterin [Ac-6-FP])[21,76,77] do exist. Nonmicrobial small molecules that bind to and downregulate MR1 have also been described.[78] Importantly, a number of available drugs and drug-like molecules, metabolites, and fragments, such as salicylates and diclofenac metabolites, may be loaded onto MR1 and presented to MAIT cells.[22] Notably, diclofenac metabolites were demonstrated to activate MAIT cells. It is tempting to speculate a scenario in which such and similar drugs and compounds can be expeditiously repurposed for COVID-19, a possibility that can be readily tested in preclinical models.

MAIT cell-based therapies may offer two additional advantages. First, given the monomorphic nature of MR1, its ligands may be used invariably in diverse human populations.[79] Therefore, HLA restriction is not an obstacle to the feasibility of testing MR1 ligands as potential therapeutics. Moreover,

although circulating at lower frequencies, MAIT cells maintain their functional competence in the vulnerable elderly.[80] Therefore, their optimal expansion may boost anti-CoV2 immunity.

As immunologists, we often rely on mouse models. Unlike in humans, MAIT cells are scarce in conventional strains of laboratory mice.[81] However, mouse MAIT cell populations can be expanded, for instance for adoptive transfer experiments.[54] Mouse and human MAIT cells are more phenotypically and functionally similar than previously thought.[18] In addition, MR1 and the MAIT *i*TCRα are evolutionarily conserved,[23,82,83] and 5-OP-RU can be used to activate both mouse and human MAIT cells.[19–21] Therefore, at least some of the results to be obtained in mouse studies of MAIT cells may be translatable to the clinic.

Human ACE2-transgenic mice and wild-type BALB/c mice have been employed in COVID-19 investigations.[84] A hamster model of CoV2 infection may also be informative in protection studies,[85] despite the fact that experimental tools for hamster studies are not plentiful. Nevertheless, these relatively simple animal models, along with the more complex and more appropriate nonhuman primate models of CoV2 infection, will be invaluable in drug safety and efficacy testing. The adjuvanticity and therapeutic effects of MAIT cell agonists need to be explored after their physicochemical attributes, such as their stability and aqueous solubility, are improved for *in vivo* applications. Furthermore, whether and to what extent MR1 ligands may cause *i*TCR internalization could help determine the frequency of their administration in multidose treatment protocols.

VII. FUTURE DIRECTIONS AND CONCLUDING REMARKS

Recent years have witnessed intensifying inquiries into the significance of invariant T lymphocytes in health and disease. Much work still lies ahead to fully characterize the roles played by these cells in infectious diseases, including COVID-19, and their complications.

It will be pertinent to determine MAIT cell frequencies and functions in longitudinal studies monitoring the immune status of CoV2-infected subjects as they progress from an asymptomatic state to mild disease to either recovery or critical illness. Possible changes in MAIT cell frequencies or activation profiles may be potentially useful as prognostic biomarkers. As indicated in previous sections, elevated percentages of circulating MAIT cells were associated with recovery from avian influenza,[42] and their high expression levels of CD69, an activation and tissue retention marker, appeared to predict milder hypoxia in the course of COVID-19.[48] Comprehensive clinical investigations using large cohorts and mechanistic studies in relevant animal models will be required to address a presumptive link between MAIT cell functions and COVID-19 manifestations or outcomes.

Severe morbidity and mortality in COVID-19 have been attributed to certain preexisting conditions, such as obesity, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, cardiovascular disease, and malignancy.[6,86–89] Numerical or functional abnormalities in the MAIT cell compartment have also been reported in these conditions.[90–94] Although the immunopathogenesis of both COVID-19 and indicated predisposing conditions are multifactorial, understanding how MAIT cells fit into this large and complex picture warrants further investigation.

Different clinical manifestations of COVID-19 at the two ends of the life spectrum are notable and need to be thoroughly investigated in both sexes. Epidemiological data point to the sexual dimorphism of COVID-19, with the male sex being a risk factor for increased disease severity.[95] According to a meta-analysis of more than 200,000 patients, although the prevalence of confirmed COVID-19 cases remained similar among men and women, male patients were at least twice more likely to require intensive care and also exhibited higher odds of death.[96] A recent report has even suggested a link between the high androgen levels manifested by male androgenetic alopecia and the severity of COVID-19.[97] Antipathogen immune responses differ quantitatively and qualitatively between the sexes, which is largely dictated by the differential regulation of defense mechanisms by male and female sex hormones. In general, while androgens suppress cell-mediated immunity, estrogens can

provide protection in severe infections and sepsis.[98] A previous study found comparable MAIT cell levels among male and female healthy subjects.[99] However, an annual decline in circulating MAIT cell frequencies was more pronounced in men. Hormonal regulation of blood and tissue-resident MAIT cell homeostasis and functions will be an exciting line of inquiry.

It is important to discern how the physiological or pathological behaviors of MAIT cells can be altered by their sequential stimulation with cytokines and MR1 ligands, and vice versa. A viral infection will expose MAIT cells to inflammatory cues and mediators, which may be followed by secondary infections with bacterial or fungal opportunists harboring MR1 ligands. On the other hand, researchers may choose to explore the possibility of expanding MAIT cells by MR1 ligands before or during an antiviral cytokine response. The potential adjuvanticity of MR1 ligands in the general context of prophylactic vaccination is another subject of interest. They may indirectly activate secondary antiviral effectors, such as NK cells, *i*NKT cells, and CTLs.[35,61] MAIT cell stimulation can also lead to dendritic cell maturation in an MR1- and CD40L-dependent fashion,[100] which should assist adaptive pathogen-specific $CD4^+$ and $CD8^+$ T cell responses. The hypotheses provided herein should be tested in future studies.

COVID-19 is a rapidly evolving situation. As we learn more about the protective or pathogenic roles of various immune cell types in the course of the ongoing pandemic, our questions will also grow in number. MAIT cells possess powerful effector and regulatory functions and should be considered in prophylactic and therapeutic approaches.

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