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INSIGHTS

An unconventional view of COVID-19 T cell immunity

Hui-Fern Koay[1,2], Thomas S. Fulford[1], and Dale I. Godfrey[1,2]

In this issue of *JEM*, Jouan et al. (https://doi.org/10.1084/jem.20200872) report the activation and skewed function of unconventional T cells in severe COVID-19 patients. This may reflect a role in COVID-19 immunity or pathogenesis and potentially identifies new therapeutic targets for this disease.

The ability to decipher features that discriminate mild and severe disease is critical to combat the pathophysiology of COVID-19, which is imparted not only by the SARS-CoV-2 viral infection, but also by the host immune response that contributes to acute respiratory distress syndrome in severe cases. Early studies identified an immune signature associated with severe COVID-19 disease, including lymphopenia (Tan et al., 2020); excessive production of pro-inflammatory cytokines, including IL-1β, IL-6, IL-10, and TNF (Chen et al., 2020a; Giamarellos-Bourboulis et al., 2020); and extensive activation of both innate and adaptive immune cells, which include B and T cells, natural killer cells, innate lymphoid cells, and myeloid cells such as neutrophils and monocytes (Kuri-Cervantes et al., 2020). While conventional MHC-restricted CD4 and CD8 T cells are clearly involved in COVID-19 disease, the role of MHC-unrestricted T cells has been less clear.

In this issue of *JEM*, Jouan et al. (2020) specifically investigated the dynamics of unconventional T cells in severe COVID-19. Three populations of unconventional (also known as innate-like) T cells were examined: CD1d-restricted natural killer T (NKT) cells, MR1-restricted mucosal-associated invariant T (MAIT) cells, and gamma-delta T (γδT) cells. Collectively, these cells represent ∼10% of peripheral T cells that, upon activation, can rapidly respond with diverse cytokine production and potent cytolytic activity without the need to undergo clonal expansion and differentiate into effector cells (Godfrey et al., 2015). Of relevance to COVID-19, unconventional T cells exhibit tissue-homing properties, are abundant in lungs, and are key players in the frontline responses against pathogens and inflammatory diseases (Godfrey et al., 2019; Godfrey et al., 2015).

The authors examined the frequency and phenotype of NKT, MAIT, and γδT cells in a cohort of intensive care unit (ICU)–admitted COVID-19 patients (Jouan et al., 2020) and compared them to samples obtained from non–COVID-19 ICU patients as well as healthy donors. As previously reported, COVID-19 patients had decreased circulating T cells; furthermore, they showed an even greater reduction of MAIT cells, NKT cells, and the Vδ2⁺ subset of γδT cells. All three cell types exhibited a heightened activation state with a functional bias toward IL-17A and away from IFN-γ production. These findings are in line with other recent studies that have reported altered frequencies and function of MAIT (Kuri-Cervantes et al., 2020; Parrot et al., 2020), NKT, and γδT cells (Odak et al., 2020; Rijkers et al., 2020) in severe COVID-19 patients. The authors also showed a marked increase in the levels of inflammatory cytokines including IL-1β, IL-6, and IFN-α in endotracheal aspirates compared with matched blood and, moreover, the presence of MAIT cells and γδT cells with heightened levels of activation in COVID-19 endotracheal aspirates (Jouan et al., 2020). Notably, over-representation of T and MAIT cells was not observed in the aspirates from non–COVID-19 ICU patients, suggesting trafficking of these cells to the lungs is specific to severe COVID-19.

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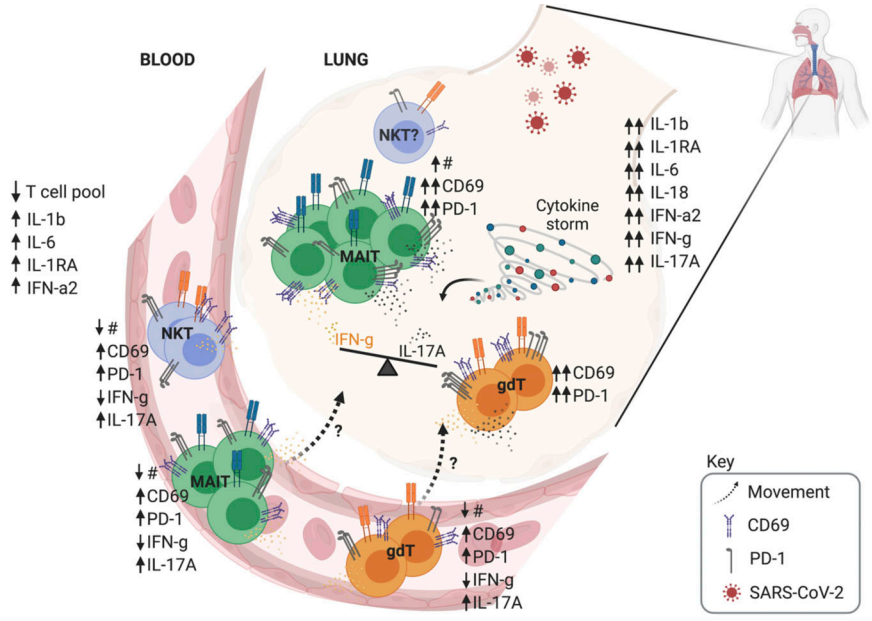
Further stratification of COVID-19 patients into those who were discharged and those who remained in critical care revealed that MAIT and NKT cells in the former group expressed higher levels of CD69. Additionally, a clinical correlation was found between CD69 expression by MAIT and NKT cells at time of admission and reduced hypoxemia after 7 d. Of relevance, a separate study has reported high levels of CD69 on MAIT cells in deceased patients, whereas CD69 expression levels normalized in convalescent patients (Parrot et al., 2020). Hence, whether the early activation of these cells contributes to disease resolution or is a bystander effect in severe COVID-19 disease remains undetermined. In favor of a protective role, unconventional T cells can rapidly secrete antiviral cytokines such as IFN-γ and TNF and are known to play beneficial roles in the context of viral clearance (Loh et al., 2016). However, in severe COVID-19 subjects, activated

[1]Department of Microbiology and Immunology, University of Melbourne, The Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia; [2]Australian Research Council Centre of Excellence in Advanced Molecular Imaging, University of Melbourne, Melbourne, Victoria, Australia.

Dale I. Godfrey: godfrey@unimelb.edu.au; Hui-Fern Koay: hf.koay@unimelb.edu.au.



Presence and activation of unconventional T cells during severe COVID-19. Numbers of NKT, MAIT, and γδT cells decreased in peripheral blood and are found in lung aspirates with heightened levels of activation as measured by CD69 and PD-1 during severe COVID-19. These unconventional T cells may be activated by the cytokine storm as a result of severe viral infection in the lung, and may also secrete multiple factors such as IL-17A and IFN-γ and contribute to this cytokine milieu and/or disease pathology.

MAIT cells were skewed toward IL-17 production (Jouan et al., 2020; Parrot et al., 2020), which could suggest a deleterious, pro-inflammatory role rather than a protective antiviral contribution.

The stimuli that lead to the activation of unconventional T cells in COVID-19 is unclear. Viruses do not directly encode for antigens such as vitamin B metabolites for MAIT cells, lipid antigens for NKT cells, or phosphoantigens for Vδ2 γδT cells. It is possible that unconventional cells are activated in a TCR-independent manner as a result of the hyper-inflammatory cytokine milieu during disease, as suggested by unchanged TCR levels on MAIT and NKT cells (Jouan et al., 2020). These cells are known to respond to inflammatory cytokines, such as IL-12, IL-18, and TL1A (Leng et al., 2019; Ussher et al., 2014). Indeed, in previous studies, MAIT cell frequencies have been associated with recovery from influenza infection (Loh et al., 2016; van Wilgenburg et al., 2018) and reduced replication of hepatitis C virus (van Wilgenburg et al., 2016) in a TCR-independent manner. However, the activation of these unconventional T cell populations may also be instigated by up-regulation of undefined endogenous antigens, potentially acting as danger signals emanating from virally infected host cells or other cells in the environment. Moreover, with perturbations within the lung microbiome during severe COVID-19 (Fan et al., 2020), including secondary bacterial infections (Chen et al., 2020b; Zhou et al., 2020), it is entirely possible that unconventional T cells are responding to an increase in bacterial antigens associated with severe COVID-19 infection.

Though their precise roles remain unclear, this report nonetheless suggests that unconventional T cells are involved in severe COVID-19 pathology and/or recovery, warranting further investigation into their precise contribution and immunotherapeutic potential in this disease. More nuanced studies are necessary to directly explore the exact contribution of unconventional T cells, which may include COVID-19 animal models (such as humanized ACE2 mice or studies with mouse-adapted SARS-CoV-2 virus) coupled with the ability to manipulate unconventional T cell numbers and activity (e.g., CD1d KO, MR1 KO, and TCRδ KO mice). Given the wide variability in unconventional T cell numbers in humans, in which they range from undetectable to >10% of T lymphocytes (Godfrey et al., 2015), it will be critical to determine whether deficiencies or excesses of unconventional T cell populations contribute to COVID-19 disease severity and/or resolution. In particular, the numbers of NKT, MAIT, and γδT cells diminish with age and are almost absent in elderly humans (Gherardin et al., 2018). Might this be related to the fact that elderly humans are far more vulnerable to this disease? A mouse model–based approach could also shed light on the precise mechanisms of action of unconventional T cells, such as the contribution of cytokines (e.g., IL-12/IL-18 KO mice) versus TCR-mediated activation (e.g., antibody-blocking of CD1d- or MR1-mediated TCR signaling) and the possible role of secondary bacterial infection (e.g., antibiotic-treated animals). Conversely, such models will enable studies to explore whether unconventional T cell activation can be harnessed to enhance protection against COVID-19; for example, treatment of infected mice with NKT cell or MAIT cell antigens α-galactosylceramide or 5-OP-RU, respectively. While it is more difficult to assess the role of γδT cells in mice because their targets vary widely to those of human γδT cells, particularly for Vδ2 γδT cells that are not present in mice (Pang et al., 2012), it can be achieved by adoptive transfer of human PBMC, with or without γδT or Vδ2 T cell depletion, into immunodeficient mice (Wang et al., 2001).

As COVID-19 continues its global devastation, the world watches and waits, hoping that "conventional" immunotherapy approaches such as vaccines, antibodies, and cytokine therapies will bring this disease under control. Considering that COVID-19 inexplicably ranges from asymptomatic and mild to severe and fatal symptoms, we need studies like this from Jouan et al. (2020) to form a comprehensive understanding of immunological correlates to these diverse outcomes. Such studies may also provide valuable predictive markers for disease severity and offer more tailored treatment options. Now, more than ever before, immunologists have many more tools in the toolbox to bring to this problem, and unconventional T cell–based immunotherapy represents an important avenue for further exploration.

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