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Natural killer cells and unconventional T cells in COVID-19

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NK cells and diverse populations of unconventional T cells, such as MAIT cells, γδ T cells, invariant NKT cells, and $DNT_{αβ}$ cells are important early effector lymphocytes. While some of these cells, such as NK cell and MAIT cells, have well-established roles in antiviral defense, the function of other populations remains more elusive. Here, we summarize and discuss current knowledge on NK cell and unconventional T cell responses to SARS-CoV-2 infection. Also covered is the role of these cells in the pathogenesis of severe COVID-19. Understanding the early, both systemic and local (lung), effector lymphocyte response in this novel disease will likely aid ongoing efforts to combat the pandemic.

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Introduction

Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 and spread throughout the world [1,2], we have in a short time gained in-depth understanding of both the virus, the host immune response against it, and factors contributing to coronavirus disease 2019 (COVID-19) [3]. In this Review, current knowledge of antiviral responses of natural killer (NK) cells and unconventional T cells in SARS-CoV-2 infection will be summarized followed by a discussion on the role of these cells in the aberrant immune response characteristic of severe COVID-19 (Figure 1). NK cells are innate lymphocytes abundant in peripheral blood but also found in many peripheral tissues including liver, lung, and uterus [4]. They respond without prior sensitization and are important in tumor surveillance, pregnancy, immune homeostasis, and as early (cytotoxic) effector cells during viral infections [5]. Indeed, the most compelling evidence for the importance of NK cells in antiviral immunity comes from patients with selective NK cell deficiencies who often suffer from life-threatening viral infections [6]. Unconventional T cells constitute an ever-expanding family of distinct T cell subpopulations that, instead of showing reactivity against conventional peptide — major histocompatibility complex (MHC) proteins, recognize a diverse set of ligands presented on MHC or MHC class I like molecules [7] (Box 1). Although perhaps less studied in the context of viral infections as compared to NK cells, unconventional T cells such as mucosal-associated invariant T cells (MAIT cells), CD1d-reactive natural killer T (NKT) cells, CD4 and CD8 double-negative αβ T cells ($DNT_{αβ}$ cells), and γδ T cells have also been reported to respond in SARS-CoV-2 infection [8••,9••,10••].

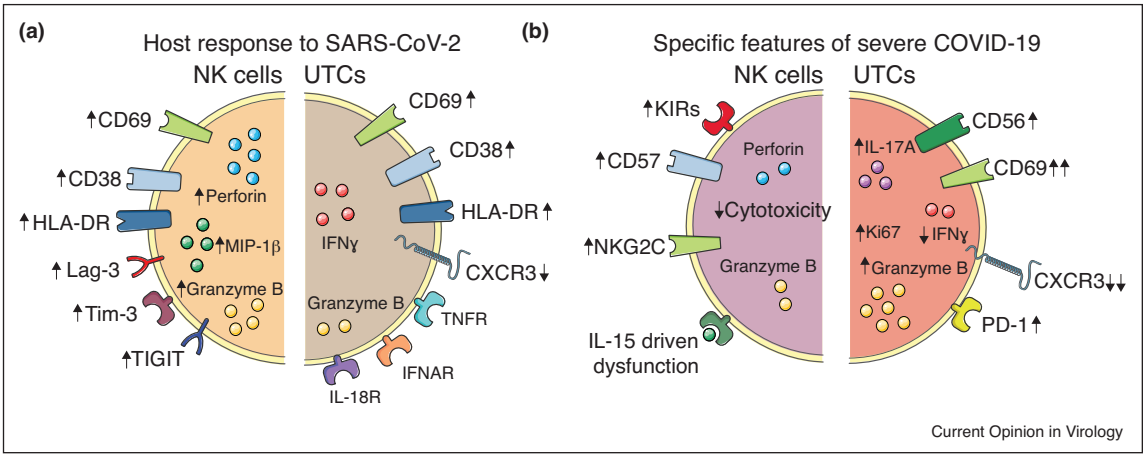
NK cell and unconventional T cell responses against SARS-CoV-2

Since only a fraction of individuals infected with SARS-CoV-2 develop severe COVID-19 and aberrant immune responses have been associated with COVID-19 pathogenesis it is of importance to delineate beneficial and/or appropriate antiviral responses from other responses rather contributing to disease. Thus, in the upcoming paragraphs, beneficial responses from NK cells and unconventional T cells will first be discussed.

The early NK cell response to SARS-CoV-2 infection

NK cells are classically divided into cytokine producing $CD56^{bright}$ NK cells and cytotoxic $CD56^{dim}$ NK cells [4] and $CD56^{dim}$ NK cells can be further stratified in less or more differentiated subsets based on surface expression of receptors such as NKG2A, CD57, CD62L, and KIRs [11,12]. In acute SARS-CoV-2 infection, both the $CD56^{bright}$ and $CD56^{dim}$ NK cell subset drop in cell numbers in circulation [13••,14••,15] and this occurs even in mild infection [16]. This drop in numbers likely reflects active homing of NK cells from circulation to the lung since increased presence of NK cells in bronchioalveolar lavage (BAL) has been reported [17,18]. This homing is likely mediated by CXCR3, CXCR6, CCR5 on NK cells [19] and respective chemokines are increased in BAL of COVID-19 patients [17,20]. In this regard, it is interesting to note that CXCR6 is part of the major genetic risk loci for development of severe COVID-19 [21]. A role for CXCR3 and CCR5 for NK cell homing to lung is in line with what has been reported in acute influenza A virus (IAV) infection in mice [22]. However, similar chemokine

Figure 1



Phenotypic and function alterations in NK cells and UTCs in SARS-CoV-2 infection.
(a) The host response of NK cells and UTCs to SARS-CoV-2 infection is illustrated with modulation of surface receptors (arrows indicate change in expression) as well as intracellular effector molecules. **(b)** Specific features of NK cells and UTCs that have been associated with severe COVID-19.

receptor — chemokine combinations have also been suggested to direct NK cell homing to skin during acute dengue virus infection [23] suggesting them to not be specific for lung homing in acute SARS-CoV-2 infection.

Box 1 Unconventional T cell populations

The unconventional T cell populations covered in the current review are briefly introduced below. Except for these, other populations exist (reviewed in Ref. [7]) but have until now not been studied in COVID-19.

MAIT cells: Defined by co-expression of TCR-Vα7.2 and CD161 (or using a 5-OP-RU tetramer), predominantly CD4/CD8 double negative or CD8+, and recognizes riboflavin metabolites presented on MR1. Enriched at mucosal barriers and in the liver and have primarily been studied in the context of bacterial infections.

CD1d-restricted NKT cells: Displaying an invariant TCR composed of Vα24 typically paired with Vβ11 recognizing, among other things, endogenous glycolipids presented in CD1d. These cells have the capacity to produce a broad range of Th1, Th2, and Th17 cytokines as well as exhibiting cellular cytotoxicity.

γδ T cells: First T cells to appear in the thymus during its ontogeny, human γδ T cells mainly express the Vδ2 (coupled with Vγ9) and, to a lesser extent, the Vδ1 TCR chains. Their TCR can recognize exogenous and endogenous molecules, including bacterial toxoids, viral proteins, microbial lipids (presented by CD1d), and phosphoantigens (through the expression of butyrophilins).

$DNT_{\alpha\beta}$ cells: Mainly studied in the context of autoimmunity, they are also involved in anti-tumor immunity. In mice, $DNT_{\alpha\beta}$ originate from the thymus and possess a polyclonal TCR repertoire, although distinct from other UTC subsets and conventional T cells. Their antigen specificity and TCR restriction is still unknown.

Beyond reduced numbers of NK cells in peripheral blood and subsequent homing to lung tissue, NK cells also display a highly activated phenotype in acute SARS-CoV-2 infection, are actively proliferating, and have retained functional capacity [13••,14••,24]. NK cell activation was reported to be in particular pronounced among $CD56^{bright}$ NK cells and within $CD56^{dim}$ NK cell subsets displaying a less differentiated phenotype [13••]. It also occurred independently of NK cell education status [13••], a functional maturation process NK cells undergo regulated by inhibitory receptors recognizing cognate HLA molecules [25]. Such a response-profile is similar to what has previously been reported in several other acute viral infections, including those by dengue virus, tick-born encephalitis, West Nile virus, and attenuated yellow fever virus [23,26–28]. Altogether, this would suggest the NK cell response to be cytokine-driven in acute SARS-CoV-2 infection since $CD56^{bright}$ NK cells and less differentiated $CD56^{dim}$ NK cells are superior in responding to cytokines as compared to more differentiated $CD56^{dim}$ NK cells [11,12]. However, the exact signals driving NK cell activation in acute SARS-CoV-2 infection remains to be elucidated.

Beyond peripheral blood NK cells, lung also contains tissue-resident NK cells [4] and these have been shown to respond to IAV [29]. However, despite several studies utilizing single-cell RNA sequencing (scRNA-seq) on BAL of COVID-19 patients, through which it is possible to assess the local NK cell response [13••,17,18], a detailed mapping of the lung-resident NK cell compartment still remains to be performed. Additionally, if, and through which receptor ligand interactions, NK cells

possibly recognize SARS-CoV-2 infected target cells should be studied in the future.

MAIT cells in SARS-CoV-2 infection

A wide range of viruses, including influenza A (IAV), hepatitis C (HCV), dengue and human immunodeficiency virus (HIV) have been reported to induce MAIT cell activation in humans (reviewed in detail in Refs. [30] and [31]). As viruses do not synthesize riboflavin (see Box 1), the functional regulation of MAIT cells in viral infections is believed to occur through TCR-independent mechanisms, particularly through interleukin (IL)-12, IL-18 and type I interferons (IFNα) [31].

In SARS-CoV-2 infection, several groups have reported a substantial quantitative reduction of the circulating MAIT cell pool, in keeping with previous observations in other viral infections [30]. On the other hand, residual circulating MAIT cells showed a significant increase in expression of several activation markers (e.g. CD69 and granzyme B) [8••,9••,10••,32–35]. Functionally, circulating MAIT cells are skewed towards a type 3 inflammatory state, and display impaired IFN-γ production potential and increased IL-17A release [9••,10••], similar to the Th17 skewing described for CD4+ T cells in severe COVID-19 [36]. Intriguingly, a recent study proposed that gender might have an impact on MAIT activation and lung infiltration [37], but further work is needed to further investigate such findings. MAIT cell depletion in peripheral blood is likely secondary to their migration to the inflamed lung, as supported by the increased MAIT cell frequencies in bronchoalveolar fluid (BALF), pleural fluid (PF), and endotracheal aspirates (ETA) of COVID-19 patients [9••,10••,32]. Chemokines such as CCL20, CXCL10/11 and CXCL16, have been proposed to drive MAIT cell recruitment, and scRNAseq data on putative ligand-receptor interactions indicate myeloid cells (i.e. neutrophils and macrophages) as a primary source of chemotactic signals in the lung [32]. In light of the occurrence of secondary bacterial infections in severe COVID-19 [38], a TCR-dependent MAIT cell activation mechanism is possible, through the MR1-dependent recognition of riboflavin derivatives of microbial origin [8••,39]. Moreover, work from Flament *et al.* showed an MR1-dependent MAIT cell activation after co-incubation with SARS-CoV-2 infected macrophages [8••], although the antigenic determinants of this activation remain unclear. On the other hand, TCR expression levels, usually decreased in case of TCR engagement, have been found unaltered in MAIT cells and other unconventional T cells from COVID-19 patients, suggesting a preferential cytokine-driven activation [10••].

Finally, in relation to vaccines against SARS-CoV-2, a seminal study investigating the mechanisms of immune response upon vaccination using adenoviral-based platforms (such as ChAdOx1) dissected a cytokine network where pDC and monocyte-derived factors (i.e. IFNα and TNF/IL-18) promote MAIT cell activation and subsequent release of anti-viral cytokines such as granzyme B and IFN-γ [40]. Importantly, genetic evidence from *Mr1*$^{-/-}$ mice support the view of MAIT cells as crucial determinants of adenoviral-based vaccination efficacy, and future studies should determine whether this importance is conserved also in case of mRNA-based vaccination.

Responses from other unconventional T cell populations

The peripheral lymphodepletion coupled with an activated and proliferative state of residual circulating cells induced by acute SARS-CoV-2 infection applies also to other UTC subsets, in addition to MAIT cells. In γδ T cells, a specific reduction of the Vδ2 subset associated with COVID-19 severity has been confirmed in many studies, while the abundance of the Vδ1 subset was mainly unaffected by SARS-CoV-2 infection [10••,32,33,41–43]. Both Vδ1 and Vδ2 subsets are known to mediate wide anti-viral effects [44], but interestingly a selective expansion of the Vδ2 fraction was reported after SARS-CoV-1 infection during the 2003 outbreak [45]. In addition, Odlak *et al.* observed that naïve γδ T cells were selectively maintained in circulation, suggesting a specific recruitment of the mature/effector fraction to the lung [43]. However, γδ T cell frequency in ETA, BAL and PF was not different from that observed in blood [10••,32]. In line with the general immune recovery following virus clearance, γδ T cell abundance is normalized in convalescent patients [46], although follow-up studies would be important to assess eventual long-term effects of acute SARS-COV-2-infection.

Work specifically focused on iNKT cells is still largely lacking, and available evidence so far described conflicting results, likely due to different subset identification strategies. As an example, Jouan *et al.* observed a ≈10-fold reduction of iNKT cell frequency in severe COVID-19 patients, while we and others did not detect significant quantitative alterations in either mild or severe COVID-19 [9••,42]. Surprisingly, Stephenson *et al.* reported that the enrichment of iNKT cell abundance was positively associated with COVID-19 severity [34]. Thus, further work is needed to explain such discrepancies and investigate the functional alterations within the iNKT pool in SARS-CoV-2 infection.

While DNT$_{αβ}$ have been mainly overlooked in the context of COVID-19, we reported a striking proliferative capacity in this subset, coupled with substantial induction of conventional activation markers such as CD38, but not CD69 [9••]. As for other UTC subsets, DNT$_{αβ}$ down-regulate CXCR3 in severe COVID-19 patients, suggesting a potential lung recruitment mediated by CXCL9/10/11 [9••]. Finally, a CyTOF-based longitudinal immunomonitoring highlighted the tight co-regulation of DNT$_{αβ}$

and neutrophil frequencies during COVID-19 recovery [46], presenting unexpected analogies with our previous observations in mice [47].

Taken together, while compelling evidence have so far highlighted the deep alterations occurring within several members of the UTC family, many aspects of the cytokine-driven and, potentially, TCR-dependent UTC response to SARS-COV-2 infection and recovery remain elusive and require further investigation.

COVID-19 pathogenesis, NK cells, and unconventional T cells

Whilst most individuals infected with SARS-CoV-2 develop mild symptoms, a subgroup instead enters a severe (and sometimes fatal) disease course where inappropriate immune responses are thought to be major contributors. Below, current knowledge on the possible contribution of NK cells and UTCs to such outcomes are discussed.

NK cell dysfunction in severe COVID-19

NK cell hyperactivation, likely driven by IL-6, IL-6R, and IL-18, is a feature of severe COVID-19 as compared to mild or moderate disease [13••,48]. However, with prolonged hyperactivation comes dysfunction by which prolonged IL-15 stimulation has been suggested to contribute [49••,50]. In line with this, through scRNA-seq, genes involved in cytotoxic activity are suppressed in NK cells in severe COVID-19 [51]. Indeed, chronic stimulation with IL-15 has been shown to drive NK cell dysfunction, partly via epigenetic reprogramming [52]. Another feature of severe COVID-19, first reported by Maucourant *et al.* and later confirmed in two other independent studies, is the expansion of adaptive-like NK cells [13••,24,53]. Adaptive-like NK cell expansions were originally described in response to cytomegalovirus (CMV) infection [54], are characterized by high expression of NKG2C, CD57, and inhibitory self-KIR receptors [55] and undergo epigenetic reprogramming during their differentiation [56]. Except for in CMV infection, such expansions have previously also been reported in hantavirus [57], chikungunya virus [58], and HIV-1 infections [59], but always on a CMV-background similar to now in COVID-19 [13••]. However, whether adaptive-like NK cell expansions contribute to COVID-19 pathogenesis, instead target possible reactivation of CMV [60], or are part of an appropriate antiviral host-response needs to be determined in future studies. In this regard it is interesting to note that HLA-E, the ligand to the activating receptor NKG2C found on adaptive-like NK cells, is increased on lung parenchymal cells and immune cells from COVID-19 patients [13••] and that SARS-CoV-2, by itself, might induce this upregulation [61]. Finally, compared to in moderate COVID-19, NK cell numbers, as well as numbers of T cells, are reduced at the site of infection at the expense of granulocytic and myeloid-derived suppressor cells [17,18,62]. The interplay between NK cells and such cells in relation to COVID-19 pathogenesis should be assessed in future work.

MAIT cell activation associate with COVID-19 outcome

MAIT are by far the UTC subset showing the most prominent phenotypic alterations during acute SARS-CoV-2 infection, in terms of extent of their depletion and of induction of classical early activation markers, such as CD69 [9••,10••]. Up to 100% of MAIT cells can express CD69 in severe COVID-19 [9••,10••], and cytokines crucial for direct MAIT activation, such as IL-18, correlate to some extent with CD69 levels [8••,10••]. This correlation is likely to have functional relevance *in vivo*, given the high IL-18 receptor expression on MAIT cells [30] and the fact that IL-18 is part of the molecular signature of the inflammatory 'misfiring' observed in severe COVID-19 [63]. Along these lines, CD69 levels on MAIT cells (but not in other UTC subsets) were even further elevated in non-surviving COVID-19 patients, and positively correlated with several clinical parameters such as granulocyte numbers, PaO2/FiO2 ratio and CRP [8••,10••]. Indeed, models exclusively based on MAIT cell activation markers (i.e. expression of CD69, granzyme B, and IFN-γ) efficiently predicted the final outcome of SARS-CoV-2 infection [8••]. Hence, an exacerbated MAIT cell activation could contribute to severe COVID-19 symptomatology, especially considering that MAIT cells (together with γδ T cells) are amongst the immune subsets that mostly shape the overall cytokine milieu in blood and tissues in COVID-19 patients [32]. On the other hand, an adequate MAIT cell response to danger signals such as IFNα and IL-18 is essential for the optimal triggering of the adaptive immune response, as shown by vaccination studies [40]. Collectively, the delicate balance of a finely regulated activation of UTC, and particularly of MAIT cells, emerges as a crucial determinant of both efficient viral clearance and occurrence of SARS-CoV-2-derived immunopathological events.

Conclusions

As apparent from studies reviewed above, it is clear that both NK cells and UTCs robustly contribute to the early antiviral immune response against SARS-CoV-2. They further have the capacity to relocate to the site of infection through distinct chemokine — chemokine receptor pathways where they can likely target infected cells but also interact with other recruited immune cells. In parallel, both NK cells and MAIT cells might also contribute to pathogenesis in severe COVID-19. However, although we in record time have learnt immensely about these cells in COVID-19, as outlined above throughout the text, many important outstanding questions remain to be answered.

Conflict of interest statement

Nothing declared.

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