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T Cell Subsets and COVID-19: Function and Dysregulation Effect

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Abstract T-cell responses are an important component of the human immune response to viral infections and specifically for viral clearance, establishing memory recall and inducing antibody responses. In SARS-CoV-2 infected individuals, lymphopenia and/or T-cell exhaustion somehow contributes towards the development of severe diseases. In contrast, long-lived memory T cells play a key role in preventing severe cases of COVID-19 disease. Exposure to SARS-CoV-2 either through infection or vaccination generates immune cells that provide long-term immunity to SARS-CoV-2 which is crucial for the development of herd immunity. In this review, we summarize what is currently known about various T cell subsets such as CD4+ and CD8+ T cells in response to SARS-CoV-2 and the specific T cell responses linked to natural, vaccine-induced and hybrid immunity highlighting the need to look beyond blood to fully understand how T cells function in the tissue. Understanding the T cell-specific immune responses in various body tissues could facilitate the formulation of better therapeutic strategies for COVID-19 patients.

Keywords: *Cell-mediated immunity; SARS-CoV-2; Immune responses, T helper cells; Cytotoxic T cells; Adaptive immunity*

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain (Wu et al., 2020; P. Zhou et al., 2020). This pandemic first surfaced in December 2019 in Wuhan, China and spread worldwide (Wu et al., 2020; P. Zhou et al., 2020). SARS-CoV-2 contains four structural proteins:

spike (S) protein, envelope (E) protein, membrane (M) protein, and Nucleocapsid (N) protein and sixteen non-structural proteins (NSP1 to 16) (Naqvi et al., 2020; M. Y. Wang et al., 2020). Coronaviruses' entry into host cells is mediated by the S protein (M. Y. Wang et al., 2020). SARS-CoV-2 enters human cells via receptor angiotensin-converting-enzyme 2 (ACE2) and the co-receptor transmembrane serine protease 2 (TMPRSS2) (Scudellari, Megan, 2021; Walls et al., 2020; Wrapp et al., 2020). SARS-CoV-2 initiates both innate and adaptive immune responses (García, 2020). Early immune responses primarily have a protective role, however, dysregulated and exacerbated inflammatory responses can fail in viral clearance and lead to worse disease outcomes (García, 2020; Toor et al., 2021). T cells form a key component of the adaptive immune response to viral infection (Toor et al., 2021). SARS-CoV-2 elicits antiviral immune responses by helper T cells (Th) and cytotoxic T cells (CTLs) (Toor et al., 2021). Antiviral immunity is mediated by the generation of neutralizing antibodies generated by B cells and CTL-mediated immunity (García, 2020; Toor et al., 2021). Cytokines produced by Th cells help immune cell recruitment and activate both CTLs and B cells. CTLs are important because of their specific cytotoxicity for infected cells.

SARS-CoV-2 can infect T cells via S protein-mediated endocytosis and internalization although the virus is not able to replicate in these cells (W. Wang et al., 2020). A decline in peripheral T cell subsets is a unique characteristic in patients presenting with acute SARS-CoV-2 infection and this is followed by a rapid normalization of the cell counts during the convalescence (T. Li et al., 2004). As demonstrated for the Middle East Respiratory Syndrome (MERS) coronavirus, the translation of viral RNA proteins induces apoptosis in T cells, leading to the lymphocytopenia observed in COVID-19 patients (Chu et al., 2016). Lymphopenia and/or T-cell exhaustion can worsen clinical outcomes in COVID-19 patients, whereas T-cell-mediated inflammation can contribute towards lung pathology and secondary complications seen in severe disease cases (García, 2020).

2. Materials and Methods

2.1 Literature Search Strategy

This study is a scoping review. We searched on Pubmed for literature on:

1. What are the types of T cells that are associated with COVID-19 disease caused by SARS-CoV-2?
2. What are the phenotypes of the SARS-CoV-2 specific T cells during and following COVID-19 disease?
3. What are the dysregulation effects of the T cells induced following COVID-19 disease caused by SARS-CoV-2?

We used a search strategy composed of a combination of the following search terms: "T cells and COVID-19", "T cell immune response and COVID-19" "T cell function in COVID-19 disease", "CD4+/CD8+ in SARS-CoV-2 infection", "SARS-CoV-2 specific T cells", "SARS-CoV-2 specific T cells and diabetes", "SARS-CoV-2 specific T cells and Tuberculosis".

2.2 Inclusion and Exclusion

The study included articles that targeted both animal and human participants. These would be articles which contained information answering our research questions. The most important is that it should be clear and sufficient information, including positive or negative, to answer the questions. We excluded mostly the unrelated, duplicated, unavailable full texts, or abstract-only papers. These exclusions were stated in advance to refrain the researchers from bias.

3. Results and Discussion

3.1 T helper (Th) cells

T helper (CD4+) cells have been associated with the control of primary SARS-CoV-2 with the SARS-CoV-2-specific CD4+ T cells thought to differentiate into T follicular helper (Tfh) and Th1 cells (Or Caspi, Michael J. Smart, 2020). SARS-CoV-2-specific CD4+ T cells predominantly have

a central memory (CD45RA-, CCR7+) phenotype (Spoerl et al., 2021) and central memory cells have the potential to home secondary lymphoid tissue (Martin et al., 2015). Tfh cells provide help to B cells for affinity maturation, antibody production and long-term humoral immunity and or memory B cells.

SARS-CoV-2-specific circulating Tfh (cTfh) frequencies have been associated with disease severity and a substantial fraction of SARS-CoV-2 cTfh are CCR6+ (Juno et al., 2020). CCR6 is a chemokine receptor associated with migration to mucosal tissues (Weiskopf et al., 2020a). Potentially cTfh that are CCR6+ would be indicative of mucosal airway homing as observed in common cold coronavirus HKU1 (Weiskopf et al., 2020a). Expression of CCR6 may also indicate the existence of Th17 cells however the expression of interleukin-17α (IL-17α) protein, the marker for Th17 cells on these cells has been reported to be low or undetectable (Or Caspi, Michael J. Smart, 2020; Rydyznski Moderbacher et al., 2020). SARS-CoV-2-specific CD4+T cells produce IL-22 robustly which is associated with tissue repair in the lung (Dudakov et al., 2015; Rydyznski Moderbacher et al., 2020) and gut suggesting that SARS-CoV-2 specific CD4+ T cells may actively participate in lung tissue repair during COVID-19 (Dudakov et al., 2015; Rydyznski Moderbacher et al., 2020).

The cells have antiviral activities which are elicited through the production of interferon-gamma (IFN-γ) (Or Caspi, Michael J. Smart, 2020; Rydyznski Moderbacher et al., 2020; Weiskopf et al., 2020a) and other pro-inflammatory cytokines. The dominant cytokine produced by SARS-CoV-2-specific CD4+ T cells from COVID-19 patients is IFN-γ (Or Caspi, Michael J. Smart, 2020; Rydyznski Moderbacher et al., 2020; Weiskopf et al., 2020a). SARS-CoV-2-specific CD4+ T cells from patients with COVID-19 consistently do not have Th2 characteristics (Grifoni et al., 2020) but in other few COVID-19 patients, Th2 responses were prevalent (Grifoni et al., 2020). CD4+ T cells, assist cytotoxic (CD8+) T cells to proliferate and differentiate. CD4+ CTL can have direct cytotoxic activity against virally infected cells in a class II antigen presentation-restricted manner although the cytotoxicity degranulation marker CD107a has been minimally observed on SARS-CoV-2-specific CD4+ T cells (Or Caspi, Michael J. Smart, 2020; Weiskopf et al., 2020a). The degranulation process is when the granule membrane is fused with the plasma membrane of the activated CD8+ T-cell, and the content of the granule is released into the immunological synapse between the CD8+ T-cell and the target cell (Or Caspi, Michael J. Smart, 2020; Weiskopf et al., 2020a).

Some studies have reported that COVID-19 patients have cytokine profiles of IL-2, IFN-γ, and IL-4 (Akbari et al., 2020; Gadotti et al., 2020). T cell response revealed SARS-COV-2 specific CD4+ IL-2-producing CD4+ in COVID-19 patients, in up to 75% of the patients displaying bi- or trifunctional INF-γ/IL-2/TNF-α profile (Tincati et al., 2020). Similar SARS-COV-2 specific CD8+ functionality was determined despite lower frequency and magnitude. The polyfunctional T-cell responses have been associated with better immunity in several infections (Harari et al., 2006; Oh et al., 2012, 2019; Shin et al., 2019).

Regulatory T (Treg) cells are a subset of CD4+ T cells involved in maintaining immune homeostasis and self-tolerance by inhibiting the pro-inflammatory activities of CD4+ and CD8+ effector T cells, natural killer cells, and antigen-presenting cells (M. O. Li & Rudensky, 2016; Newton et al., 2016; van der Veeken et al., 2016). Naturally occurring Treg cells are CD4+, CD25+, and Forkhead box P3 (FoxP3)+ cells that develop in the thymus (Schmetterer et al., 2012). The role of Treg cells during viral infection is for the maintenance of immune homeostasis, specifically, in controlling the severity of viral immunoinflammatory lesions (Suvas et al., 2004). Pattern changes in the frequency of Treg cells in

COVID-19 patients have been observed and this could be one of the reasons for the hyperactivated immune responses and damaged lungs in severe COVID-19 patients. Tregs may play an important role in the regulation of immune responses to COVID-19 (H. Wang et al., 2021). Treg cells can prevent cytokine storms, accelerate the resolution of acute respiratory distress syndrome (ARDS), and suppress the development of lung inflammatory disorders during the COVID-19 disease (Lee et al., 2010; Loebbermann et al., 2012; Rahimzadeh & Naderi, 2021).

3.2 Cytolytic (CTL) cells

CTLs mostly CD8+ T cells are very important in clearing the virus-infected cells. The presence of virus-specific CD8+T cells has been associated with better COVID-19 infection outcomes (Jordan, 2021). SARS-CoV-2 CD8+ T cells are specific for a range of SARS-CoV-2 antigens, with S, N, M, and open reading frames (ORF3a) proteins well represented. (Jordan, 2021). In acute COVID-19, SARS-CoV-2-specific CD8+ T cells exhibit high levels of molecules associated with potent cytotoxic effector functions, such as IFN-γ, granzyme B, perforin, and CD107 (Rydyznski Moderbacher et al., 2020). Activated CD8+ T cells kill virus-infected cells using TNF-related apoptosis-inducing ligand, secretion of cytolytic molecules (perforin and granzymes) and the binding of CD8+ T FasL to Fas expressed on the surface of virus-infected cells thereby initiating death-receptor pathway (Jiang et al., 2020).

CD8+ T cells in COVID-19 patients highly express CD38, human leukocyte antigen-DR isotype (HLA-DR), CD69, CD25, CD44 and Ki67 confirming that CD8+ T cells during the SARS-CoV-2 infection are highly activated and are capable of proliferation (Jiang et al., 2020). SARS-CoV-2–specific CD8+ T cells include large proportions of both central memory (CD45RA-, CCR7+) and terminally differentiated cells (CD45RA+, CCR7-) (Spoerl et al., 2021). Central memory T cells have greater recall potential, enhanced IL2 production, proliferation, and survival capacity (Martin et al., 2015). Central memory T cells can differentiate into either Th1 or Th2 in the absence of polarizing cytokines (Martin et al., 2015). Terminally differentiated T cells re-express CD45RA and display a loss in multipotency. Multipotency is the ability of the cells to become another cell type and to proliferate (Weissman, 2000).

3.3 Evidence for a protective role of T-cell immunity in the control of COVID-19 infection

There is increasing evidence that cellular immunity supports have a potential role in both preventing initial SARS-CoV-2 infection and limiting the magnitude of disease following infection (Moss, 2022; Sette & Crotty, 2021). The adaptive immune response is required for viral clearance during COVID-19 infection. Antibodies play an important role in viral neutralisation, however, there is evidence that the virus can spread through cell-to-cell contact, which is immune to antibody neutralisation (Zeng et al., 2022). Several other viruses have demonstrated this mechanism (Skelly et al., 2021) suggesting that T-cell-mediated immunity may be important for viral clearance. Some reports have suggested that SARS-CoV-2 infection may induce T cells without seroconversion (Sekine et al., 2020a). Virus-specific memory T cells have been shown to persist for many years after infection with SARS-CoV-1 (Skelly et al., 2021). Memory CD4+ T cells and CD8+ T cells were detected in 100% and 70% of patients who recovered, respectively. These memory T cell responses were detected for multiple SARS-CoV-2 proteins, including spike protein as well as nucleoprotein and membrane protein.

SARS-CoV-2-specific T cells in the convalescent COVID-19 infection phase were required to acquire an early differentiated memory phenotype (CCR7+ CD127+ CD45RA−/+ T cell factor 1 (TCF1+)). This phenotype has been associated with stem-like properties and was previously reported in

the context of other viral infections and successful vaccines (Neidleman et al., 2020). In the convalescent phase, SARS-CoV-2-specific T cells showed anamnestic responses to cognate antigens, marked by substantial proliferation and polyfunctionality (Sekine et al., 2020b). These identified memory T cell responses were directed against both the internal (nucleocapsid) and surface proteins (membrane and/or spike) in some individuals lacking detectable circulating antibodies specific for SARS-CoV-2. Further, almost twice as many healthy individuals who donated blood during the pandemic had memory SARS-CoV-2 specific T cell responses versus antibody responses (Sekine et al., 2020b). In another study, they found that SARS-CoV-2-reactive T cells in convalescent patients acquired a multifunctional (triple positive for INF-γ, IL-2 and TNFα) phenotype, which may be considered a correlate of protective immunity (Seder et al., 2008; Steiner et al., 2020).

The current COVID-19 vaccines elicit robust T-cell responses that likely contribute to protection against hospitalization or severe disease leading to death. A robust, stable, and fully functional spike protein-specific CD8+ T cell responses were elicited after prime mRNA vaccination in individuals who had low levels of neutralizing antibodies. (Oberhardt et al., 2021). In the same study following vaccination, the proportion of naive spike protein-specific CD4+ T cells decreased, suggesting a vaccine-induced activation (Oberhardt et al., 2021). T-cell responses are also important for generating and maintaining high-affinity antibodies. Dual vaccination with BNT162b2 led to reliable induction of virus-specific CD4+ T cell responses (Papadatou et al., 2023). These CD4+ responses detected by day 8 after priming expressed high levels of IFN-γ and IL-2, and low levels of IL-4, indicating a Th1 cell profile (Skelly et al., 2021). T-cell responses after dual vaccination are of similar magnitude to those seen after natural infection, although they seem to be somewhat more differentiated (Sahin et al., 2021).

T cell cross-reactivity is a phenomenon of the immune system defined as the recognition of two or more peptide-MHC complexes (pMHCs) by the T cell receptor (TCR) (Petrova et al., 2012). Cross-reactivities of T cells against SARS-CoV-2 have been proposed and identified in patients with COVID-19 infections (Weiskopf et al., 2020b) by the presence of SARS-CoV-2 cross-reactive CD4+ T cells specific to the spike protein in donors who were not exposed to SARS-CoV-2 (Braun et al., 2020; Petrova et al., 2012). However, the biological role of the pre-existing cross-reactive CD4+ T cell remains unclear. Nevertheless, cellular responses induced by vaccines have shown strong cross-protection against variant concerns and support the concept that cellular responses contribute substantially to disease control (Skelly et al., 2021).

Hybrid immunity applies to individuals with a prior SARS-CoV-2 infection who were then vaccinated against SARS-CoV-2 or vice versa (Abu-Raddad et al., 2021; Bates et al., 2022; Goldberg et al., 2021; Kojima et al., 2021). It has been demonstrated that there is relatively higher protection for previously infected individuals with or without an additional vaccination dose compared to previously uninfected vaccinated individuals (Abu-Raddad et al., 2021). After several months persons with hybrid immunity are better protected against further infection compared to uninfected persons who have received two vaccine doses (Abu-Raddad et al., 2021). Data on the efficacy of hybrid immunity are inconsistent but point in the direction of hybrid immunity being superior as compared to either vaccine-induced (without a booster) or natural immunity alone (Abu-Raddad et al., 2021; Y. Wang et al., 2021). The protective importance of hybrid immunity is the combination of higher numbers of SARS-CoV-2-specific memory B cells, higher neutralizing antibody titers and the infection imprinted IFN-γ and IL-10 cytokine profile in CD4+ T cells (Y. Wang et al., 2021).

3.4 Dysregulation of T cells in COVID-19 patients

Although T cells help to coordinate antiviral immune responses, support humoral immune responses, limit viral replication, and remove infected cells, some studies have reported an exhausted or senescent T cell phenotype with decreased polyfunctionality and cytotoxicity during acute and convalescent SARS-CoV-2 infection (Diao et al., 2020; Mazzoni et al., 2020; H. Y. Zheng et al., 2020a; M. Zheng et al., 2020). Programmed cell death 1 (PD1), T cell immunoglobulin (TIM-3), and mucin-containing protein 3 are exhaustion markers that T cells also exhibit (Shiri et al., 2020). T cell subsets co-expressing Tim-3 and PD1 were identified in patients with severe COVID-19 infections (H. Y. Zheng et al., 2020b). Exhausted CD8+ T cells mainly express PD1, cytotoxic T lymphocyte-associated antigen-4 (CTLA4), T cell immunoglobulin and ITIM domain (TIGIT), and Tim-3. TIGIT expression in CD8+ T cells was shown to correlate with COVID-19 disease progression (H. Y. Zheng et al., 2020b).

However, T cells struggle in clearing SARS-CoV-2 in patients with type 2 diabetes mellitus (T2DM). Hyperglycaemia during T2DM may impair T cell function via the induction of oxidative stress which increases intracellular glucose concentration and mitochondrial proton gradient releasing reactive oxidative species (ROS) (Tong et al., 2021; Xia et al., 2017). Oxidative stress has a clear, detrimental effect on CD8+ T cell responses as it reduces the production of key effector cytokines (Kesarwani et al., 2013). ROS causes structural modifications of the cell receptor signalling proteins (Kesarwani et al., 2013). Another factor that impairs T cell function is glycaemia variability, just like hyperglycaemic, obesity due to adipose and medication such as metformin inhibits the expression of IFN-α in humans via mammalian target of rapamycin (mTOR) complex 1 pathway (Tong et al., 2021; Zatterale et al., 2020). Metformin also impairs CD4+ cells resulting in a hyperinflammatory response in COVID-19 patients with T2DM (Shoshan-Barmatz et al., 2021).

Co-infection with other diseases such as Tuberculosis (TB) significantly reduces the SARS-CoV-2 -specific immune responses (Petrone et al., 2021; Riou, du Bruyn, et al., 2021). T cells, particularly CD4+ T cells, are part of the immunological response to tuberculosis (Petrone et al., 2021). COVID-19 disease is characterized by lymphopenia but patients with active or latent TB infection can respond to the TB-specific antigens (Tan et al., 2020). In contrast, these patients have a poor immune response to the SARS-CoV-2 infection (Petrone et al., 2021). This observation may be the result of the massive compartmentalization of T cells in infectious foci or by elimination of effector T cells when threatened with high doses of the antigens (Petrone et al., 2021). TB infection impairs the functional capacity and premature functional exhaustion of SARS-CoV-2-specific CD4+ T TB-COVID-19 co-infected patients (Ong et al., 2020; Riou, Du Bruyn, et al., 2021).

Overreaction of the T cell-mediated immune response may lead to complications in severe COVID-19 patients such as pulmonary complications. Pulmonary complications are due to the high expression of CCR4 on the surface of both CD4+ and CD8+ T cells. CCR4 is the lung homing receptor and increased CCR4 expression on T cells promotes a stronger immune response directly in the lungs but this can also result in stronger attraction and activation of T cells in the lungs that may lead to damage to the lungs if not well-regulated (Spoerl et al., 2021). Both CD4+ and CD8+ T cells express significant levels of CD69, CD38 and CD44, in COVID-19 patients with CD4+ T cells also expressing OX40. This is an indication of T cell over activation or overreaction. Furthermore, some investigators have reported a significant increase in the expression of OX40 and

4–1BB in COVID-19 patients who required intensive care unit (ICU) treatment (Y. Zhou et al., 2020) suggesting T cell activation in such patients.

T cell overactivations in COVID-19 patients is characterized by, among other factors, higher level of inflammatory cytokines, other than IFN-γ and the inflammatory cytokine level is related to disease severity. The levels of interleukin (IL) 2R, IL6, IL8, IL10, and TNF-α were significantly higher in severe compared with non-severe patients (Qin et al., 2020). In another study, they reported a lower level of IFN-γ produced by CD4+, CD8+, and natural killer T cells in moderate and severe cases (Chen et al., 2020). Overactivated T cells and increased inflammatory cytokines may enhance the lung's immunopathological damage. (Liu et al., 2020).

4. Conclusion

T cell responses are very critical for immune protection against SARS-CoV-2; however, exacerbated T cell activation may cause T cell exhaustion. There is evidence suggesting that SARS-CoV-2-specific T-cell responses are essential for viral clearance, may prevent infection without seroconversion, provide robust memory, and mediate recognition of two or more viral variants. These T-cell responses are elicited both following natural infection and vaccination. There is some evidence of cross-reactivity with seasonal and or endemic coronaviruses. Despite remarkable progress, there remain many critical questions that need to be resolved about T cell immunity to SARS-CoV-2. Understanding the roles of different subsets of T cells in protection or pathogenesis is crucial for preventing and treating COVID-19. T-cell responses in severely ill patients may be impaired, overactivated, or inappropriate, and further research is required to elucidate this to inform treatment strategies. However, it is unclear whether the strength of the T cell response in the peripheral blood reflects the T cell response intensity in the respiratory tract and other SARS-CoV-2-infected organs. Further studies should characterize the T cell memory's differentiation state and durability in the tissues or SARS-CoV-2-infected organs. An important application of T cell responses in tissue and SARS-CoV-2-infected organs will be towards the evaluation of the SARS-CoV-2 vaccine and other immunotherapeutic strategies.

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Author contributions

C.M.B: Design, Conceptualisation; Writing, Review. **W.L.M:** Design, conceptualisation, Review. **CK, TN, AK., D.T.M, G.P.B.:** Review.

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Conflict of interest

The authors declare no conflict of interest.

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