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MINIREVIEW

Relational interaction between T-lymphocytes and SARS-CoV-2: A review

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Summary. – Coronavirus disease 2019 (COVID-19) has turned out as one of the worst medical and economic misfortunes across the globe. The etiological agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of the *Coronaviridae* family and represents a disease manifestation from asymptomatic to severe respiratory damage. High transmissibility and contagious nature of the virus helps it to flourish in a large population. The immune system aids to retain the virus, but with accelerated cytokine secretion, it could transform into double edge sword resulting in unrestrained systemic inflammation which might become life-threatening. SARS-CoV-2 sets substantial impact on T-lymphocytes during its course of infection. The number of CD4+ T, CD8+ T, and T_{reg} cells tend to decrease profoundly in case of severe illness. Besides, the virus modulates the CD4+ T/ CD8+ T and Treg/Th17 cells ratio and induces the functional exhaustion of T cells to make them inefficient. T cells define the pathogenesis of severe cases and provide major contributions in antiviral defense. Therefore, the apprehension of T-lymphocytes in SARS-CoV-2 infection would implicate in developing antivirals, disease control, and would broaden the way for vaccine formulation. Thus, the review depicts the significance of T-lymphocytes interaction with SARS-CoV-2.

Keywords: SARS-CoV-2; COVID-19; T-lymphocytes; cytokine; inflammation; immune response

1. Introduction

A very recent and ongoing pandemic emergency arises from a zoonotic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has thrown the entire world into a strenuous situation. Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 brought forth the global health crisis since the report of its first case in Wuhan, China in December 2019. Soon, COVID-19 affected several countries and was declared as pandemic by the World Health Organization (WHO). Prior to this, world has witnessed the outbreaks of SARS-CoV and MERS-CoV (Middle east respiratory syndrome coronavirus) in China and Saudi Arabia, respectively. Except for Antarctica, every continent is in the hold of COVID-19 (WHO, 2020).

SARS-CoV-2 is a single-stranded, enveloped, positive-sense RNA (+ssRNA) virus belonging to the family *Coronaviridae*. Among the four genera of coronaviruses i.e. α, β, γ, and δ; β coronavirus group comprises of most important human coronaviruses including CoV-OC43,

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Abbreviations: ACE-2 = angiotensin-converting enzyme 2; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; IFN = interferon; MERS-CoV = Middle east respiratory syndrome coronavirus; NKT = natural killer T cells; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNF = tumor necrosis factor

SARS-CoV, MERS-CoV and SARS-CoV-2 (King *et al.*, 2011; Pal *et al.*, 2020). The sequence analysis of SARS-CoV-2 shows 89% identity with bat SARS-like-CoVZXC21 and CoVZC45; 82% with human SARS-CoV and only 50% with MERS-CoV (Chan *et al.*, 2020; Lu *et al.*, 2020). SARS-CoV-2 also shares a wide similarity with pangolin CoV (Liu *et al.*, 2020b; Zhang *et al.*, 2020). Thus, bat and pangolins are viewed as a natural reservoir for the virus (Han, 2020; Liu *et al.*, 2020b; Zheng, 2020).

The virion of SARS-CoV-2 is spherical or pleomorphic in shape and has a diameter of around 60–140 nm. The genome of SARS-CoV-2 is ~ 30 kb with 5' cap and 3'-poly-A tail. It encodes four structural proteins namely, nucleoprotein (N), membrane (M), envelope (E), and spike (S) and 16 non-structural proteins (Davies *et al.*, 2020; Jiang *et al.*, 2020a; Li *et al.*, 2020a). The infection caused by SARS-CoV-2 may occur as asymptomatic, mild, or severe form. Approximately 80% of patients suffer from mild cough and fever while 20% need hospitalization. Among the hospitalized cases, 50% can experience severe respiratory failure, a type of acute respiratory distress syndrome (ARDS) (Huang *et al.*, 2020). However, it has been reported that an asymptomatic individual with low viral loads can disseminate the virus and affect the susceptible population (Gao *et al.*, 2020). COVID-19 has been reported to have a case fatality rate of ~ 6.6% which may vary from country to country (Toyoshima *et al.* 2020).

After entering into the human body, virus stimulates the innate immune response through pattern recognition receptors (PRR) (Fung and Liu, 2019) which further lead to the secretion of several multifunctional chemokines and cytokines which trigger the inflammation resulting in injury to lung epithelium and microvasculature (Chu *et al.*, 2020; Rokni *et al.*, 2020). Consequently, cells of the adaptive immune system are recruited to fight the virus. However, during an interplay between SARS-CoV-2 and the immune system, dysregulation in the T cell subset alters the CD4+ and CD8+ T lymphocyte population. This immune imbalance leads to aberrant cytokine response which worsens the condition of COVID-19 causing ARDS, and even multi-organ failure, in some cases. The immune system plays a pivotal role in deciding the fate of infection. With the increment of new studies, knowledge regarding immune cells involved in COVID-19 infection is continuously evolving. Thus, in the current review, we aim to comprehensively describe the importance of T-lymphocytes interaction with the virus during SARS-CoV-2 infection.

2. Virus entry

The S protein of SARS-CoV-2 contains receptor binding domain (RBD) which binds the angiotensin-converting enzyme 2 (ACE2) receptor, a metallopeptidase expressed

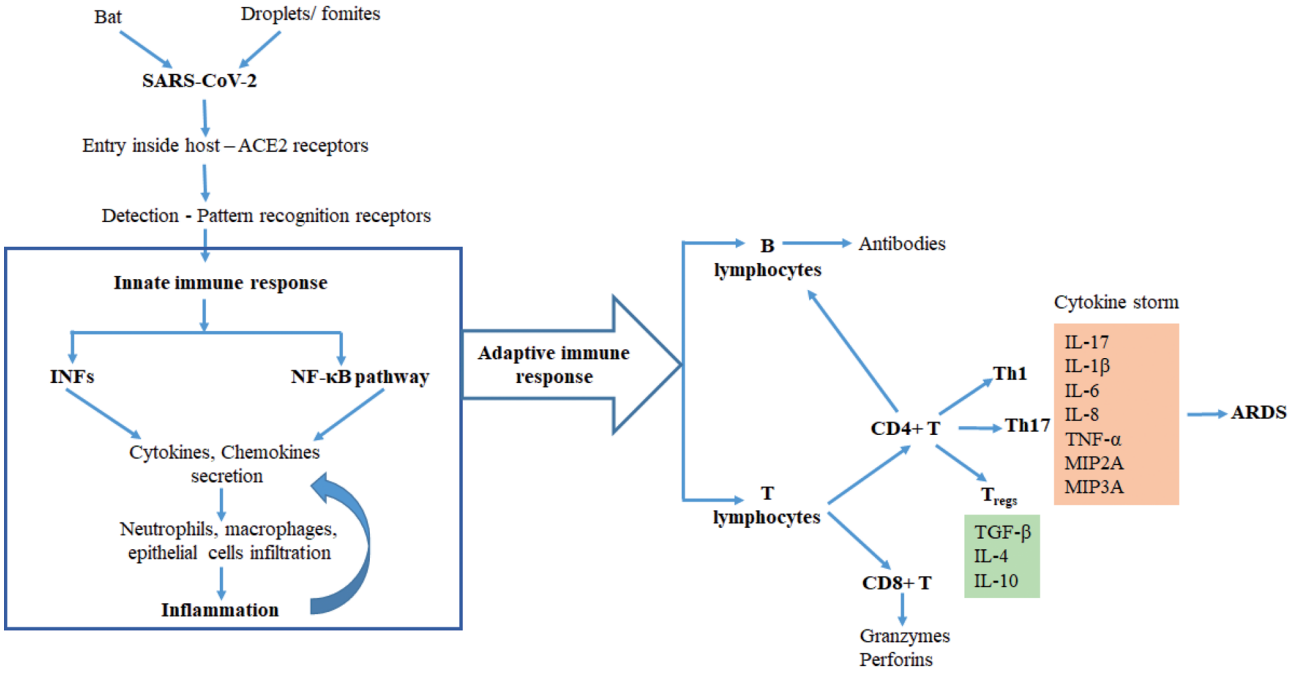

Fig. 1

Host immune response upon SARS-CoV-2 infection

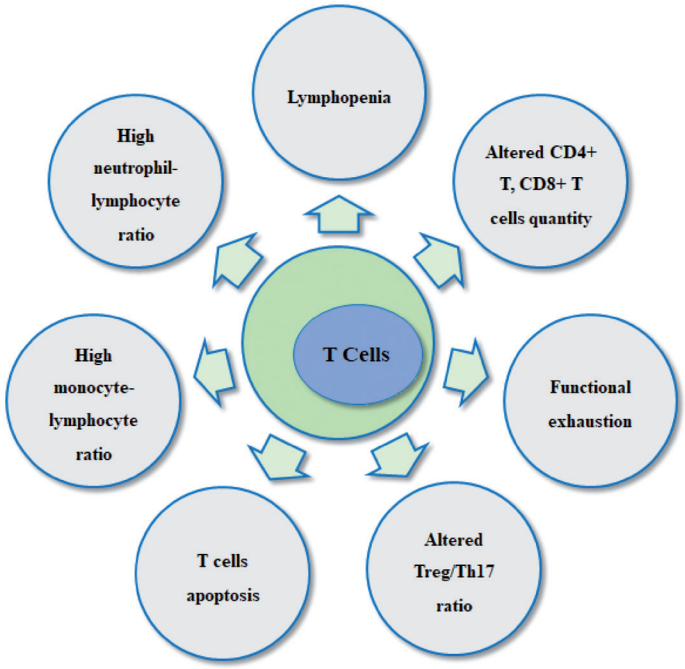

Fig. 2

Impact of SARS-CoV-2 on T cells during the course of infection

on cells of several tissues that include lungs, especially type-I and -II pneumocytes, small intestine, kidney, liver, heart, arterial and vein endothelium (Hamming *et al.*, 2004; Walls *et al.*, 2020; Zou *et al.*, 2020). It has been shown that S protein of SARS-CoV-2 has 10–20-fold stronger affinity for ACE2 receptors than that of SARS-CoV (Shang *et al.*, 2020; Wrapp *et al.*, 2020). The cleavage of S protein between S1/S2 mediated through the host transmembrane protease-serine protease 2 (TMPRSS2) facilitates the fusion of S2 subunit with the cell membrane allowing the entry of viral RNA into the cytoplasm (Hoffmann *et al.*, 2020; Letko *et al.*, 2020). This viral RNA then serves as a template for viral replication and transcription followed by the assembly of virus particles in the ER-Golgi intermediate compartment (ERGIC) and release from cells by budding (Hogue and Machamer, 2007).

The entry of virus is recognized by PRRs, such as Toll-like receptors (TLR) and RIG-I-like receptors (RLRs) causing arousal of the innate immune response (Arpaia and Barton, 2011; Kell and Gale 2015). The innate immune system leads to the production of interferon (IFN), and activation of nuclear factor-κB (NF-κB) pathway which stimulates release of inflammatory mediator cytokines mainly IL-6 and IL-8 (Dosch *et al.*, 2009; Velazquez-Salinas *et al.*, 2019; Costela-Ruiz *et al.*, 2020). These pro-inflammatory cytokines stimulate additional chemokines and cytokines causing inflammation. Activated with chemokines, neutrophils, and other innate immune cells infiltrate the affected area. SARS-CoV-2 is sensitive to early defense mechanism but the release of a large quantity of virions could succeed in inhibiting antiviral effect (Rose and Weiss, 2009; Konno *et al.*, 2020). A surge in serum cytokine level has been reported from several patients in the course of SARS-CoV-2 infection (Costela-Ruiz *et al.*, 2020; Huang *et al.*, 2020; Tang *et al.*, 2020). Further, increased production of cytokines leads to the recruitment of the adaptive immune response (Fig. 1).

3. Lymphocytes: an adaptive immune response

Lymphocytes are one of the eminent subtypes of white blood cells performing a fundamental role in the adaptive immune response. Two broad branches of lymphocytes are B- and T-lymphocytes, majorly contributing to cellular events in viral infection. It is well understood that B-lymphocytes produce a humoral response by producing antibodies against the pathogen, whereas, T-lymphocytes provide a cell-mediated response. SARS-CoV-2 evokes antibody response against N and S protein (Amanat *et al.*, 2020; Cong *et al.*, 2020). Antibodies developed against S protein correspond to neutralizing antibodies, which can potentially block the virus engagement with host receptors (Amanat *et al.*, 2020). IgM antibodies first develop

after three to six days after infection, while IgG antibodies after around a week (Li *et al*., 2020b).

4. T-lymphocytes and SARS-CoV-2 interaction

T-lymphocytes originate from the thymus and mature under the influence of various cytokines. During maturation, they are subjected to antigen receptor gene rearrangement to achieve T cell receptors which are unique to each T cell (Omman and Kini, 2019). T cells play a decisive role in viral clearance by selectively eliminating virus-infected host cells. CD4+ T, CD8+ T, Th, Treg, and NKT cells are the major subtypes of T cells executing immune defense during the SARS-CoV-2 infection (Fig. 2).

4.1 CD4+ T and CD8+ T cells

CD4+ T cells are helper cells that assist the B-lymphocytes in antibody production after antigen recognition, whereas CD8+ T cells as cytotoxic cells serve for eliminating infected cells. CD4+ T and CD8+ T cells recognize the antigen presented by major histocompatibility class II (MHC II) and I (MHC I), respectively. Lymphopenia is the characteristic feature exhibited by SARS-CoV-2 infection in more than 80% of infected patients (Diao *et al*., 2020; He *et al*., 2020; Jiang *et al*., 2020b; Qin *et al*., 2020; Wan *et al*., 2020; Zhou *et al*., 2020). A study conducted on 123 COVID-19 patients has reported a reduction of both CD4+ T and CD8+ T cells in severe patients compared to mild ones (Wan *et al*., 2020). Another study with 452 patients which showed a decrease in all subsets of T-lymphocytes along with B-lymphocytes in severe cases also shows that the quantity of memory helper T cells gets affected more than the naïve helper T cells (Qin *et al*., 2020). An analysis from China has demonstrated that CD4+ cells level is decreased in patients admitted to the intensive care unit (ICU) as well as in non-ICU patients. However, CD8+ T cells are markedly decreased in ICU patients (Zhou *et al*., 2020). Lower lymphocyte count is coupled with the disease progression (Wan *et al*., 2020). The study aimed for understanding the endowment of CD39 and CD73 in immune regulation pinpointed that both CD8+ T and NKT cells with low CD73 expression, possess higher cytotoxic activity than their CD73+ homologs. In COVID-19 patients, CD73- CD8+ T cells, and CD73- NKT cells are more proficient in granzyme B (GrB), perforin, tumor necrosis factor (TNF-α), or IFN-γ secretion irrespective of the disease status. Likewise, lower levels of CD73 on CD8+ T cells and NKT cells corresponded with serum ferritin levels. The study revealed that the CD8+ T and NKT cells with CD73- CD39+ are not so efficient in cytokine secretion as the CD73-CD39- cells. CD8+ T and NKT cells with CD73- subset has a higher count in COVID-19 patients with regard to the healthy donors, whilst CD39+ and CD39- did not show much variation among COVID-19 patients and healthy donors (Ahmadi *et al*., 2020).

Apart from quantitative reduction, T cells undergo functional exhaustion in SARS-CoV-2 infection. In previous reports, flow cytometry analysis revealed the presence of PD-1+ and Tim-3+ exhaustion markers on CD8+ and CD4+ T cells, and their number was higher in more severe cases (De Biasi *et al*., 2020; Diao *et al*., 2020). Increment of an inhibitory receptor, NKG2A manifestation on CD8+ T and NK cells renders functional exhaustion, hampering CD107a, IFN-γ, IL-2, GrB, and TNF-α production (Zheng *et al*., 2020). T cells express a very low extent of ACE2 receptors implying that virus may be using some alternative receptor like CD147, CD26, or enhancing its affinity towards existing receptors (Wang *et al*., 2020a). It is pondered that, the activation molecules like CD147 and CD26 may assist in virus entry inside the T cells, resulting in activation-induced cell death (AICD) (Vankadari and Wilce, 2020; Wang *et al*., 2020b). SARS-CoV-2 does not cause productive T cell infection, on the contrary escalates the T cells apoptosis through up-regulated TNF-α and IFN-γ (Diao *et al*., 2020; Refaeli *et al*., 2002). The elevated levels of TNF-α, IL-6, and IL-10 cytokines are inversely related to the T cell population pointing towards the involvement of these cytokines in downregulating the T cell population. Some researchers have noted T cells, macrophages, and monocytes as a source of these secreted cytokines (Kany *et al*., 2019; Minciullo *et al*., 2016), albeit, some authors disagree with this theory (Diao *et al*., 2020). In an autopsy investigation of lung tissue from patients that died of COVID-19, inflammatory cell conglomeration has been observed with major quantity being governed by lymphocytes especially CD4+ T cells (Xu *et al*., 2020; Yao *et al*., 2020). Single-cell RNA sequencing (scRNA-seq) report of bronchoalveolar lavage fluid of COVID-19 patients highlighted the increased CD8+ T cell infiltrate with clonal expansion (Merad and Martin, 2020). Histopathology of hilar lymph nodes and spleen from patients that died from COVID-19, revealed lymphocyte necrosis mediated by Fas-FasL interactions (Feng *et al*., 2020). The above studies can be correlated with the cause of lymphopenia as well as with the diminished peripheral blood CD4+ T and CD8+ T cell counts. High neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) in COVID-19 patients are linked with severance of infection and used as indicators for diagnostic efficacy (Kong *et al*., 2020; Kuri-Cervantes *et al*., 2020; Sun *et al*., 2020). NLR ≥ 3.13 signifies an increased risk of severe COVID-19, thereby determines deviation in inflammatory and immune response balance (Kong *et al*., 2020).

The marked immunogenic response of memory T cells has been correlated with S, M, N, and ORF3a proteins.

Increased frequency of CD8+ T cells specific for M and N protein along with high CD8+ T to CD4+ T cells ratio has also been observed (Dong *et al*., 2020). A phenotypic study of SARS-CoV-2 specific T cells by applying a mass spectrometry-based single-cell cytometry (CyTOF) from convalescent patients showed that approximately 67.3% +/- 12.6% of SARS-CoV-2-specific CD4+ T cells express CD127. The magnitude of CD127+ SARS-CoV-2-specific CD4+ T cells remain stable over a period of time. CD127 is a part of the IL-7 receptor and promotes T cell proliferation in coordination with CD132. On the other hand, CD8+ T cells show an eminent number of CD45RA rather than CD127. Even though CD45RA+ T cells bear mixed population of naïve (Tn) cells, terminally-differentiated effector cells (Temra) and stem cell memory cells (Tscm); Temra cells were the biggest subsets of the SARS-CoV-2-specific CD8+ T cells. In the absence of CCR7 expression, CD8+ Temra cells are unable to return back to lymph nodes hence remain in blood, lungs, and spleen. Additionally, authors have confirmed the presence of SARS-CoV-2-specific CD4+ Th1 cells in convalescent cases (Neidleman *et al*., 2020). Weiskopf *et al*. (2020) has documented the change of CD8+ T cells towards Temra cells in patient with ARDS. Also, the memory phenotype of CD4+ T cells that are located in T cell receptor (TCR) at pre-infection point indicate the contribution of cross-reactive memory T cells in SARS-CoV-2 recovery (Minervina *et al*., 2020). Alongside, high clonal expansion of TCR in mild cases compared to a severe one, shed the light on T cell-specific response in symptoms abatement (Huang *et al*., 2020).

4. 2 Th follicular cells

Th follicular cells (Tfh), a peculiar subgroup of CD4+ T cells co-operate with B cells and dendritic cells (DCs) to intensify humoral response. Increased Tfh count has been reported in mild and recovering COVID-19 patients (Thevarajan *et al*., 2020; Yang *et al*., 2020). Exalted Tfh cells in circulation have corelated concurrently with decreasing viral load in non-severe cases (Thevarajan *et al*., 2020). Nonetheless, Tfh cells deficiency could be seen in secondary lymphoid organs of decedent COVID-19 cases suggesting that impaired antibody maturation may be instrumental in death (Duan *et al*., 2020). Adult *Rhesus macaque* after being infected with SARS-CoV-2 has shown the aggregation of proliferating, and activated Tfh cells in peripheral blood. Germinal center Tfh cells specific for SARS-CoV-2 S and N protein propose them as a target for vaccine development (Kuri-Cervantes *et al*., 2020). Immune response inclination in favor of Th17 cells stimulates IL-17 and GM-CSF levels. IL-17 has a great part in neutrophil activation and induction of IL-6, IL-1β, and TNF-α leading to neutrophils recruitment to the lungs and evoking cytokine storm in COVID-19 pathogenesis (Wu and Yang, 2020). Intensified Th17 response has been recorded in SARS-CoV and MERS-CoV as well (Josset *et al*., 2013; Mahallawi *et al*., 2018).

4. 3 Regulatory T cells

A no less important subset of T-lymphocytes known as regulatory T cells (Tregs) applies essential checks on proliferating immune cells. Tregs divulge the fork-head box transcription factor-Foxp3 marker and also contain higher IL-2 receptor α-chain (CD25) and low/null IL-7 receptor α-chain (CD127) in combination with some additional molecules like CD39 and CD73 (Borsellino *et al*., 2007; Kim *et al*., 2007; Kobie *et al*., 2006). Significant mitigation in naïve (CD45RA+CD3+CD4+CD25+ CD127low+) and induced (CD45RO+CD3+CD4+CD25+CD127low+) Tregs cells were restricted in critical COVID-19 cases (Allegra *et al*., 2020; Chen *et al*., 2020; Liu *et al*., 2020a; Stephen-Victor *et al*., 2020). Transcriptomic data of bronchoalveolar lavage explored the exaggerated level of IL-2R (CD25) in severe cases which intervene in IL-2 bioavailability urging for Tregs cells apoptosis which can be asserted with the alleviated level of FoxP3 (Stephen-Victor *et al*., 2020). In a mouse model, Treg cells prove out amiable to clear ARDS inflammation (Walter *et al*., 2018). Thereupon, defeated Treg cells may pave the way for pneumonia and lung injury in COVID-19.

5. T-lymphocytes intermeshing with hyper inflammation

Overwhelming cytokine response in SARS-CoV-2 is the central component in hyper inflammation (Mangalmurti and Hunter, 2020; Mahmudpour *et al*., 2020; Ragab *et al*., 2020; Ye *et al*., 2020). IL-6, pluripotent cytokines perform a formidable job in the shaping of the Tfh cells, differentiation of Th17 cell subsets, and development of plasma cells (Velazquez-Salinas *et al*., 2020). Accentuated IL-6 instigate Th17 cells by deterring Treg cells, thereby altering Treg/Th17 ratio, which predominates systemic inflammation and lung injury too (De Biasi *et al*., 2020; Muyayalo *et al*., 2020). Thus, it is anticipated that the changed Treg/Th17 ratio in COVID-19 affected pregnant women may be attributed to detrimental pregnancy outcomes (Muyayalo *et al*., 2020). Th17 fosters IL-17 that ultimately advocates IL-1β, IL-6, TNF-α, G-CSF, as well as chemokines like IL-8, IP10, MIP2A, MIP3A activating more immune cells, and metalloproteinases that ameliorate tissue injury. Secondly, IL-17 foments chemokine (C–X–C motif) ligands (CXCLs) that engage neutrophils into the infected tissue (Capone and Volpe, 2020; Stoppelenburg *et al*., 2013). In-

flated cytokine response can be pertaining to septic shock, myocardial damage, circulatory failure, and even death by multi-organ failure in some cases (Robba *et al*., 2020; Sánchez-Recalde *et al*., 2020; Zaim *et al*., 2020). Alongside, Treg cells nourish the anti-inflammatory cytokines such as TGF-β, IL-4, and IL-10 to monitor exuberant immune responses (Kleinewietfeld and Hafler, 2014). The above credentials point out the Th17 and Treg cells interconnection in disease advancement and control.

6. Conclusion

T-lymphocytes execute a remarkable role to combat SARS-CoV-2 infection. Yet dysregulation of host immune system makes good environment for the virus to sustain inside the host. The virus modulates T cell subsets differentiation and upswing plasma cytokines level yielding severe inflammatory response by localizing immune cells in different target organs. Furthermore, it leads to exhaustion and senescence of T cells to worsen the patient's condition. Therefore, efforts towards the maintenance of immune system equilibrium could help to speed up the recovery rate. Despite tremendous studies in a short time span, dynamics of progression of SARS-CoV-2 infection and host response against it stands challenging for researchers. Assorted grey areas are there to study particularly with regard to the immune system interaction in pursuance of disease control, which would be crucial in the advancement of the existing knowledge of the disease and to frame effective prevention and control strategies.

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