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Review Article

Functional Status of different subsets of Dendritic cell and T cell in COVID-19: an immunological perspective

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ABSTRACT

COVID-19. demands a world-wide emergency in this century is caused by. the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Scientists throughout the world are looking for a remedy to cure human beings from this, pandemic. To understand how our immune system responds to this dreadful virus, we need to investigate very precisely the immunopathology of COVID-19. Dendritic cell (DC) is a component of our innate immune system and makes a bridge between our innate and adaptive immunity and it also presents antigen to T cell. DCs and T cells both play a crucial role in several viral diseases. In this review, we summarize the dynamic changes of different subsets of dendritic cell like conventional dendritic cells (cDCs), plasmacytoid dendritic cell (pDCs), monocyte-derived dendritic cell (moDCs), and different types of T cells like CD8+T cytotoxic cell and CD4+T helper cell subsets (T helper1, Th2, Th17, Treg, Tfh) in mild and severe COVID-19 patients as compared to healthy donors. This review may help to better understand the maturational and functional status of DCs and T cells response in COVID-19 patients and provide immunotherapeutic strategies for patients.

Introduction:

Undoubtedly COVID-19 is the most significant and challenging subject for the entire world in this century so far. Several countries throughout the world are affected by this pandemic disease. It is a severe upper respiratory disease caused by the virus SARS-CoV-2. It is very much similar to SARS-CoV which was the then pandemic in China in the year of 2003-2004. COVID-19 was first detected in Wuhan, China in December 2019.World Health Organization (WHO) declared COVID-19 as a pandemic on 11 March, 2020 [1]. Total 3,38,42,281 confirmed cases have been detected and 10,10,634 death have occurred. world-wild. In India, 63,12,584 confirmed cases have been detected and 98,678 death have occurred as on 1st October, 2020 (WHO) [2].

SARS-CoV-2 is a positive-sense single stranded RNA (+ssRNA) virus [3]. It has many types of structural proteins such as S (Spike), M (Membrane), E (Envelop) protein which help in the formation and stability of viral envelope. The Nucleocapsid Protein (NP) and E protein play a crucial role in viral infection and replication [4]. It has been reported that E protein is identical to the counterparts ofspecific Bat and Pangolin coronavirus isolates E protein [5]. The M protein is important for budding process of Corona viruses [6]. Interaction between the virus and host cell is mediated by the S protein of the virus and host's angiotensin converting enzyme 2 (ACE2) receptor which has to be processed by protease TIMPRESS-2 (transmembrane protease, serine 2) [7]. After viral fusion with the host cell then SARS-CoV-2 enters to the cytoplasm and releases their viral genome. After that translation of viral polymerase protein and proteolysis RNA replication follows. Then sub-genomic transcription and translation of genomic protein in the endoplasmic reticulum take place. Now the formation of NP takes place by the help of S, M, E structural proteins, and is followed by the release of the viruses through exocytosis [8]. Expression of ACE2 receptor is very low in monocytes, macrophages, and T cells of the lung, so the mechanism through which SARS-CoV2 directly infects immune cells needs further investigation. There may be possibility that the virus is able to bind other specific receptors and/or any other mechanism of viral entry mode which can be exploited by the virus [9].

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Dendritic cell is a potent antigen presenting cell in our body, acting as a bridge between innate and adaptive immune system and plays an important role in the activation of naïve T cell[10]. There are mainly two types of dendritic cell subsets in human body: (1) Conventional dendritic cell (cDCs): they have the ability to promote adaptive immune system during infection. There are some specific cDCs specific markers e.g. CD11 and CD141.They mature and become DC1 and they secrete (IL-12), (IL-6), TNF-α and direct Th1 polarization of naïve T cells. (2) Plasmacytoid dendritic cells (pDCs): they have the ability to produce antiviral type I interferon (IFN-I) against viruses [11]. Some specific markers of pDCs are CD123, TLR7, and TLR9 which mature to become DC2 and direct Th2 polarized immune response [12]. Apart from these two, there is another subset of DC: Monocyte-derived dendritic cells (moDCs), which are associated with infections and inflammations. They secrete IFN-γ and IL-17A and induce Th17 and Th1 differentiation [13].

In case of viral infection dendritic cell presents the antigen for CD4+T cell through MHC class II molecule. CD4+T cell recognizes the antigen through their TCR and differentiates into specific subset as per the signal it receives. CD4+T cells have many subsets such as Th1 (T helper), Th2, Th17, Treg, TFH etc., that are characterized by their different cytokines production. CD4+T cell can activate Th17 and Treg by the production of IL-6 or IL-21 and TGF-β. CD4+T cell also produce IL-6 and IL-21 and activate T follicular helper cell (TFH) and along with B cell TFH helps antibody production. CD4+T cell also activate Th1 by the production of IL12 and IFNγ [14]. It is well-known that the developmental programs of Th17 and Tregs are reciprocally interconnected [15]. In this review, we summarize the dynamic changes of different subsets of dendritic cell like conventional dendritic cells (cDCs), plasmacytoid dendritic cell (pDCs), monocyte-derived dendritic cell (moDCs), and different types of T cells like CD8+T cytotoxic cell and CD4+T helper cell subsets (T helper1, Th2, Th17, Treg, Tfh) in mild and severe COVID-19 patients as compared to healthy donors for better understanding of the COVID-19 immunopathogenesis.

Different subsets of Dendritic cell and COVID-19: cDC in COVID-19:

According to Zhou et al.(2020), they classified three patient groups for their study.(i) Acute patients (APs), they are in severe condition and admitted to hospital, they need oxygen supplementation. (ii) Convalescent patients (CPs) group, they are partially recovered from the disease, they don't need oxygen support and hospitalization, and the thirdgroup (iii) Healthy donors (HDs), they don't have symptoms. It has been reported that the frequencies of CD11c+ cDCs in total DC was increased in convalescent patients (CPs) group [16]. Expression of the co-stimuatory marker CD86 was decreased in APs as compared to CPs and HDs. Maturation and functionof cDCs was greatly cell responses against SARS-CoV-2.They also found by the analysis of mixed lymphocyte reaction assay that CPs and HDs dendritic cells were capable to induce CD4+ and CD8+ T cells proliferation but DCs in APs were incapable to induce CD4+ and CD8+ T cells [16]. Cerrillo *et al*. (2020) reported that the population of CD141+cDC is compromised in case of mild and severe symptom COVID-19 patients [17]. CD1c+ cDCs population is also decreased in the blood during severe disease progression [17].

pDC in COVID-19:

pDCs express FcεRIα (receptor for IgG), TLR-7, TLR-9 which help to recognize single stranded RNA [18]. In pDC, FcεRIα and TLR-9 oppose one another expression by downregulate each other's function [18].CD40 is a maturation marker present in pDC. With the help of TLR-9 it induces the production of type I antiviral IFN. A mild downregulation of CD40 was observed on pDCs in COVID-19 patients [17]. Consequently, the production of type I IFN was also decreased and the rapid loss of pDCs means that, it helps the virus to escape from the innate immune system [19]. It has been also reported that the number of CD123hi pDCs was significantly decreased in COVID-19 patients [17].

moDC in COVID-19:

According to Yang et al. (2020), it has been hypothesized that moDC couldn't support viral replication but permissive to SARS- CoV-2 infection and protein expression. In moDCs, SARS-CoV-2 cannot activate any kinds of pro- inflammatory cytokines or chemokines [20]. Signal transduction and activation of transcription 1 (STAT1) is a transcription factor located in chromosome no. 2 in humans. In case of viral infection, anti-viral interferons induce STAT1 pathway which activates genes that are required for immune system to combat the pathogen. STAT1 phosphorylation is required in maturation of moDC. But STAT1 expression was decreased in case of severe COVID-19 patients. Therefore, the maturation of moDC was also hampered [20]. SARS- CoV-2 reduces IFN-γ signaling in moDCs through antagonizing STAT1 phosphorylation [20]. It was evidenced that the frequency of monocytic myeloid-derived suppressive cells (M-MDSCs) was significantly higher in APs as compared to HDs [16].

T cell response in COVID-19:

T cell response in COVID-19 is still not clearly understood, it may have good or bad role in this disease. Here we review some most recent studies on various subsets of T cell in COVID-19.

Lymphocytopenia in COVID-19:

Lymphocytopenia means abnormally very low level of lymphocyte in blood. It is a common symptom of any kinds of respiratory disease. So, it is also an important hallmark of COVID-19 patient. But in case of recovered patients, the lymphocytopenia is resolved [21]. According to Liao *et al*.(2020), autopsy study of COVID-19 patient's lung and bronchoalveolar lavage fluid showed the presence of lymphocytes in lungs but the lymphocytic infection is very less in lung [22]. On the other hand, another report of Chua *et al*. (2020) showed that the amount of cytotoxic T Lymphocyte (CTL) is low in severe COVID-19 patients compared to mild COVID-19 patients and healthy donors [23]. Lymphocytopenia might be a result of high-level of IL-6, IL-10, TNF-α production, potentially through a direct effect of these cytokines on T-cell populations and/or indirect effect on other immune cell types [24]. Lymphocytopenia also affects CD4+T cells, but how it affects the mechanism is still unknown [25]. It has been suggested that the T lymphocytopenia was likely associated with the significant reduction of CD4 T cell proliferation [16]. However, the frequency of total percentage of T cells was positively correlated with only Ki67+ CD4+T cells among APs but not with activated CD38+HLA-DR+ CD8+T cells. Interestingly, most AP and CPpatients'

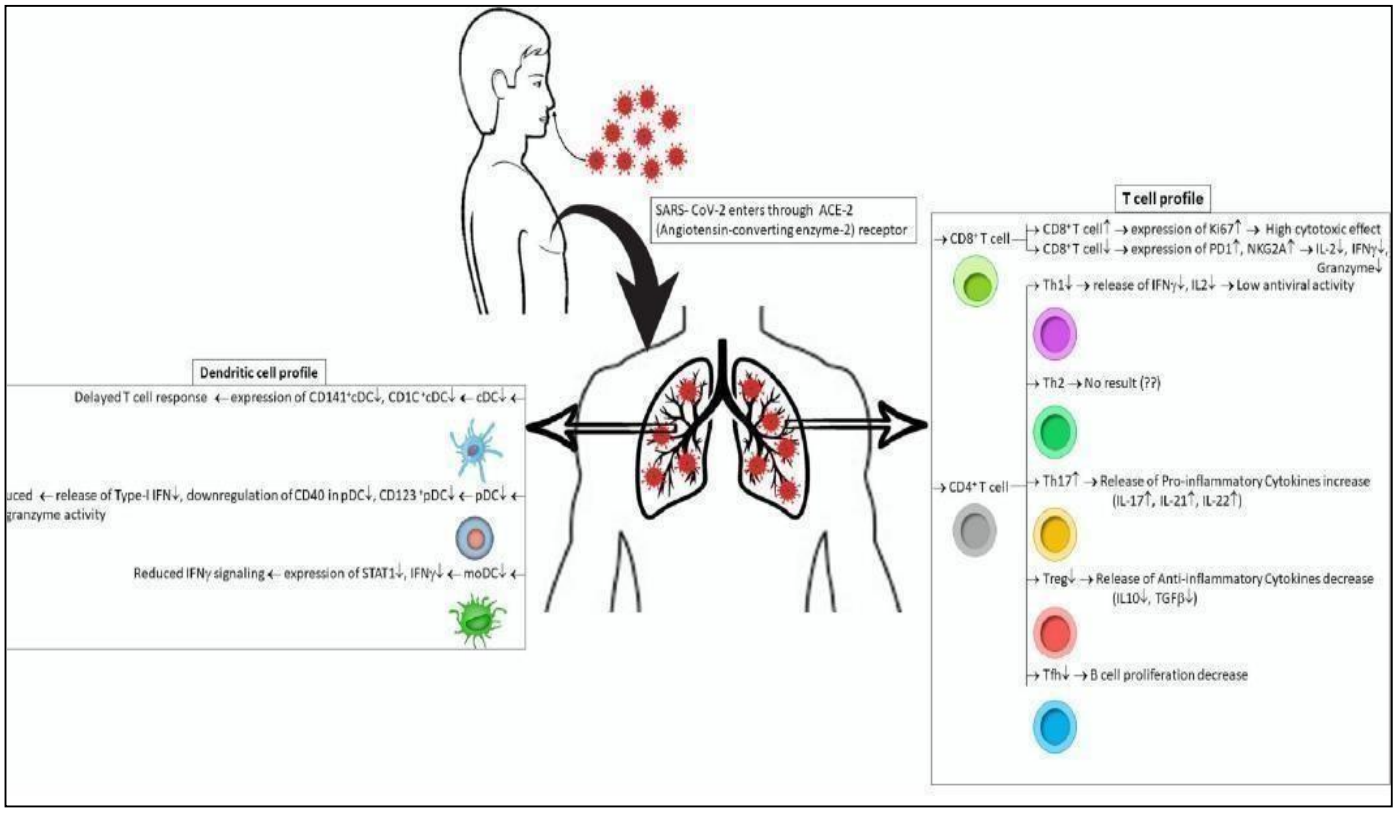

Figure 1: Brief outline for functional status of dendritic cells (DCs), T cells and their different subsets in COVID-19.

CD4+T but not CD8+T cells expressed higher amount of PD-1 than those of HDs, indicating a state of CD4 activation or possible exhaustion [16].

CD8+T cell on COVID-19:

CD8+T cell response varies patient to patient in COVID-19, in some cases CD8+T cells are hyperactivated and some other cases CD8+T cells are exhausted [26]. According to Jan Paces *et al*. (2020), the higher expression of PD1, TIM3, LAG3, CTLA4, NKG2A, CD39 inhibitory receptors results in decreasedCD8+T cell's functions. Consequently, the production of antiviral cytokines likeIL-2, IFN-γ and granzyme were also decreased in severe cases [24, 7]. However, in recovered patients, the production of NKG2A was decreased that means CD8+T cell restored their function [7]. ACE2 receptor is very low in CD8+T cell so the virus can not directly infect in CD8+T. It has been reported by Jan Paces *et al*. (2020) that the very high-level production of IL-6, IL-2 and TNF-α by macrophages stimulated CD8+Tcells functionality[7].Increased numbers ofCD38+HLA- DR+ activated CD8+ T cells orKi67+ proliferating CD8+ T cells were also observed in many, but not all, patients [24]. According to Wen *et al*. (2020) the higher clonal expression of CD8+T cell in peripheral blood and bronchoalveolar lavage (BAL) might be the result of recovery or mild disease [27]. It has been observed that in case of CPs not only viral specific CD8+T cell response but memory CD8+T cell response was also observed [28].

CD4+T cell and its different subsets in COVID-19:

Th1 cells are associated with antiviral infection and characterized by the production of IFN-γ, IL-2, TNF, IL-3, CSF2, IL-23A
and CCL20 [29]. It has been identified that the frequency of Th1 cell was lower among other SARS-CoV-2-reactive CD4+T cells in COVID-19 patients along with lower secretion of IFN-γ, IL-2 [29]. On the other hand, another report by Chen *et al*. (2020) showed that the production of IFN-γ by Th1 cell is higher in patients with moderate disease than in patients with severe disease [30]. The roll of Th2 on COVID-19 remains unclear for severe COVID-19 patients, but the patients with mild disease have normal level of Th2 expression [31].

Another important subset of T lymphocyte, Th17 cells which produce IL-17 A (also termed IL-17) play crucial roles by recruiting neutrophils and other cytokines in lung inflammatory diseases [32, 15]. According to Muyayalo *et al*. (2020) it has been shown that the proinflammatory cytokines like Th17A, IL-17, GM-CSF, IL-21, IL-22 are highly increased in severe patients in comparison to mild patients and healthy donors; it indicates that Th17 cell's expression is increased in severe patients [33]. High level of Th17 recruits more monocyte and neutrophil and activates other downstream cytokine (G-CSF, IL-1β, IL-6, TNF-α) and chemokine (CXCL1, CXCL-2, CXCL10, CXCL10, and CCL20) cascade [33]. However, there was contrasting view too. Meckiff *et al*. (2020) reported lower frequencies of TH17 cells among SARS- CoV-2-reactive CD4+ T cells [29].

On the other hand, Treg cells are characterized by the expression of CD3, CD4, CD25, CD127 markers. Treg cells can produce anti- inflammatory cytokines like IL-4, IL-10, TGF-β and control excessive immune expression [34]. According to Neurath *et al*. (2020) it has been reported that in severe COVID-19 patients the expression of Treg cells is decreased and it indicates dysregulation of pro-inflammatory immune response that may result in hyperinflammation and tissue injury [35]. Along with this several studies have reported a highly increase in IL-6 level and other some inflammatory cytokines in severe COVID-19 patients than found in the mild and healthy donors [36,37]. IL-6 with TGF-β promotes the differentiation of naïve CD4+T cells to Th17, and inhibits TGFβ1, that induced Treg differentiation [38]. In this way the elevated circulating IL-6 levels contribute to dysregulation of the Treg/Th17 cell ratio [39].

Tfh is an important subset of CD4+T cell which stimulates B cell proliferation via the activation of co-stimulatory signal CD40. Tfh cells are characterized by the expression of some markers like CXCR-5, PD-1, ICOS, Bcl-6 etc.Tfh cells resides in germinal center and produced CXCR13, IL-21, CD200, BTLA and POU2AF1 cytokines and helps to B cell proliferation. There was the increased frequency of SARS- CoV-2-reactive Tfh cells with dysfunctional and cytotoxicity features in severe COVID-19 patients [29]. According to Varajan *et al*. (2020), it has been reported that in case of mild COVID-19 patients Tfh level was high but in severe patients Tfh level was decreased [40]. But during recovery the level of Tfh cells gradually increased. Thus, it indicated that Tfh cells may have very important role in COVID-19 [41].

T cell memory in COVID-19:

An important question is whether the protective T cell memory is generated or not in case of SARS-CoV-2 infection or vaccination, although vaccination will await trial result. According to Grifoni *et al*. (2020) it has been reported that, in case of recovered COVID-19 patients 'memory CD4+T cell and CD8+T cell were detected in 100% and 70% respectively [28]. Another report from Dong *et al*. (2020) showed that memory T cell were detected not only for spike protein but also for nucleoprotein and membrane protein [42]. Although, it remains unclear that whether memory T cells give protective immunity or not. According to Cañete *et.al* (2020), it has been reported that potent memory CD8+T and CD4+T cell response are found in asymptomatic patients also, that increase our hope of protective immunity in post SARS-CoV-2 infection [43]. Further study will tell us how T cells can build memory in COVID-19 patients. T cell memory study is also important for examining vaccine induced T cell response.

Discussion:

COVID-19 pandemic demands an emergency situation through the globe. The rate of SARS-CoV-2 infection gradually increases day by day. It is now a life- threatening disease to all of us. Now not only the symptomatic patients but also the asymptomatic patients can also spread the disease [44]. It has been observed from several studies that the occurrence of this disease is predominated in old age (>65) humans [45]. Now it is an urgent need of in- depth investigation of COVID-19 immunopathogenesis and especially the role and status of two key players of our immune system, DC and T cells. It has been observed that the number of conventional dendritic cells was decreased in severe COVID-19 patients. However, there were significant increases of the cDC: pDC ratios in the AP group than that in HD and CP groups. High cDC: pDC ratios of about 50-fold might perhaps serve as a potential biomarker of severe sickness [16]. It was also observed that the maturation of pDCs is decreased in severe cases, it could lead todecreased

IFN-γ production, and SARS-CoV-2 easily escaped innate immune system [18,19]. In case of moDCs, STAT1 expression is very much decreased, so moDCs maturation is also decreased in severe and mild patients [20].

T cell associated lymphocytopenia is also an important sign of COVID-19 patients. It might be a result of high level of IL-6 production by macrophages [22,23,21]. CD8+T cell response is varying from patients to patients [26]. In some cases, it was observed in severe patients that, high production of PD1, NKG2A, TIM3, LAG3 (inhibitory receptors) leads to decrease in CD8+T cell functions [24,27].In another case, it was observed that Ki67, the maturation marker for CD8+T cell was increased in severe COVID-19 patients. So, it indicates that CD8+T cell is hyperactivated [24]. Different subsets of CD4+T cell are also associated with COVID-19 disease. Th1 cells number and function are reduced in case of severe patient (IFN-γ production is low) but in mild patients Th1 cell count is normal [29,30]. But therole of Th2 remains unclear in COVID-19 disease [31]. Th17is increased in severe COVID-19 patients and produces proinflammatory cytokines, on the other hand Treg is decreased in severe case and the imbalance of Th17 and Treg were found in COVID- 19 patients that lead to higher inflammation on lung tissue [32,34].

Another subset Tfh is also decreased in severe patients but after recovery the Tfh count is also normal [29,40]. Apart from these, an interesting finding was that the significantly higher frequencies of CD4+T cell responses were found than CD8+T cell against both NP (Nucleocapsid Protein) and RBD (Receptor Binding Domain) of SARS- CoV-2 [16].

Combining all these data together we can conclude that DCs are decreased in number and exhausted in COVID-19 patients. In addition to it, there is delayed T cell response along with huge pro-inflammatory cytokines production such as IL-6, IL-10, TNF-α etc. However, we need further study on the exact role and status of Tfh, Th17, Treg which may provide us a new therapeutic strategy to recover and to save millions of lives from COVID-19.

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Abbreviations:

COVID-19: Coronavirus Disease 2019; SARS-CoV- 2: Severe Acute Respiratory Syndrome coronavirus 2; DC: Dendritic Cell; mDC: Myeloid Dendritic Cells; pDC: Plasmacytoid Dendritic Cell; CDC: Conventional Dendritic Cell; moDC: Monocyte- derived Dendritic Cell; NP: Nucleocapsid Protein; ACE2: Angiotensin converting enzyme 2; TIMPRESS-2: Transmembrane protease serin 2; TFH: T Follicular Helper; STAT1: Single transduction and activation of transcription 1

References:

1. https://www.who.int/dg/speeches/detai l/who-director-general-s-opening- remarks-at-the-media-briefing-on- covid-19 11-march-2020
2. https://covid19.who.int/
3. Walls C, Park Y, Tortorici M, et al. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020; 180: 281– 292.
4. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J. 2019; 16:69.
5. Bianchi M, Benvenuto D, Giovanetti M,et al. Sars-CoV-2 Envelope and Membrane Proteins: Structural Differences Linked to Virus Characteristics. Hindawi BioMed Res Int. 2020; Article ID 4389089, 6 pages.
6. Alsaadi J, Jones I. Membrane binding proteins of coronaviruses. Future Virology, 2019; 14(4): 275– 286.
7. Paces J, Strizova Z, SmrzDet al. Covid-19 and the immune system. Physiol Res. 2020; 69:379-388.
8. Hoffmann M, Weber H, Schroeder S, et al. SARS-CoV- 2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell, e8, 2020; 181, 271–280.
9. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382:727–733.
10. Chakraborty K, Chatterjee S, Bhattacharyya A. Modulation of CD11c+ lung dendritic cells in respect to TGF-β in experimental pulmonary fibrosis. Cell Bio Int. 2017; 41(9):991- 1000.
11. Zhou Z, Ren L, Zhang L. Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients. Cell Host & Microbe, 2020; 27: 883–890.
12. Chakraborty K, Chakraborty P. Role and Status of Dendritic Cells in Pulmonary Arterial Hypertension: A Literature Review. EC Pulmonol Resp Med. 2020; 29-35.
13. Chow K, Lew A, Zhan Y, et. al. Monocyte derived dendritic cell promote Th polarization, whereas conventional dendritic cell promotes Th polarization. J Immunol. 2016; 196 (2): 624-636.
14. Azkur A, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020; 75:1564–1581.

15. Chakraborty K, Chatterjee S, Bhattacharyya A. Impact of Treg on other T cell subsets in progression of fibrosis in experimental lung fibrosis. Tissue and Cell. 2018; 53:87-92.

16. Zhou R, Wong Y, Liu L, et al. Acute SARS-CoV-2 Infection Impairs Dendritic Cell and T Cell Response. Immunity. 2020; 07:026.

17. Cerrillo I, Landete P, Aldave B, et al. Differential Redistribution of Activated Monocyte and Dendritic Cell Subsets to the Lung Associates with Severity of COVID-19. medRxiv, 2020. https://doi.org/10.1101/2020.05.13.20 100925.

18. Kerkmann M, Rothenfusser S, Hornung V, et al. Activation with CpG-A and CpG-B oligonucleotides reveals two distinct regulatory pathways of type I IFN synthesis in human plasmacytoid dendritic cells. J Immunol. 2003; 170:4465–74.

19. Catanzaro M, Fagiani F, Racchi M, et al. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS- CoV-2. Springer Nature, Signal Transduction and Targeted Therapy, 2020; 5:84.

20. Yang D, Chu H, Hou Y, et al. Attenuated interferon and pro- inflammatory response in SARS-CoV- 2- infected human dendritic cells is associated with viral antagonism of STAT1 phosphorylation. J Infect Dis. 2020; 222(5):734–745.

21. Cervantes L, Pampena M, Meng W, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. Sci Immunol. 2020; (5) 49:eabd7114.

22. Liao M, Liu Y, Yuan J, et al. Single- cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat Med. 2020; 8:842–844.

23. Chua R, Lukassen S. COVID-19 severity correlates with airway epithelium–immune cell interactions identified by single-cell analysis. Nat Biotech. 2020; 38:970–979.

24. Chen Z, Wherry E. T cell responses in patients with COVID-19. Nat Rev Immunol. 2020; 20:529–536.

25. Herati R, Silva L, Vella L, et al. Vaccine-induced ICOS+CD38+ cTfh are sensitive biosensors of age-related changes in inflammatory pathways. bioRxiv, 2019; 711911 [Preprint].

26. Wilk A, Rustagi A, Zhao N,et al. A single-cell atlas of the peripheral immune response in patients with severe COVID-19. Nat Med. 2020; 26: 1070–1076.

27. Wen W, Su W, Tang H, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. Cell Discov. 2020; 6:31.

28. Grifoni, A, Weiskopf D, Ramirez S, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell, e15, 2020; 181:1489–1501.

29. Meckiff B, Suastegui C, Fajardo V, et al. Single-cell transcriptomic analysis of SARS-CoV-2 reactive CD4+ T cells.Biorxiv,2020;doi:https://doi.org/10.11 01/2020.06.12.148916

30. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020; 130:2620–2629.

31. Laing A, Lorenc A, Barrio I, et al. A consensus Covid-19 immune signature combines immuno-protection with discrete sepsis-like traits associated with poor prognosis. Preprint at medRxiv,2020; https://doi.org/10.1101/ 2020.06.08.20125112 (2020).

32. Capone A, Volpe E. Transcriptional regulators of T helper 17 cell differentiation in health and autoimmune diseases. Front Immunol. 2020; 11:348.

33. Muyayalo K, Huang D, Zhao S, et al. COVID-19 and Treg/Th17 imbalance: Potential relationship to pregnancy outcomes. Am J Reprod Immunol. 2020; 00: e13304.

34. LaMarca B, Cornelius D, Harmon A, et al. Identifying immune mechanisms mediating the hypertension during preeclampsia. Am J Physiol Regul Integr Comp Physiol, 2016; 311(1): R1-R9.

35. Neurath M. Covid-19 and immunomodulation in IBD. Gut, 2020; 69(7):1335-1342.

36. Tufan A, Guler A, Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk. J Med Sci. 2020; 50(SI-1):620- 632.

37. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARSCoV-2 infected patients. EBio Med, 2020; 55:102763.

38. Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006; 441(7090):235-238.

39. Zhang C, Wu Z, Li JW, et al. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents, 2020; 55(5):105954.

40. Thevarajan I, Nguyen T, Druce J, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med. 2020; 26: 453–455.

41. Mathew D, Giles J, Baxter A, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science. 2020; (369) 6508: eabc8511,1210.

42. Peng Y, Mentzer A, Liu G,et al. Broad and strong memory CD4 and CD8 T cells induced by SARS-CoV-2 in UK convalescent COVID-19 patients. Preprint at bioRxiv, 2020; https://doi.org/10.1101/2020.06.05.13 4551 (2020).

43. Cañete P, Vinuesa C. COVID-19 makes B cells forget, but T cells remember. Cell (2020), doi: https://doi.org/10.1016/j.cell.2020.09. 013.

44. Tan J, Liu S, Zhuang L,et al. Transmission and clinical characteristic of asymptomatic patients with SARS-CoV-2 infection. Future Virol. 2020; (15) 6.

45. Moderbacher C, Ramirez S, Dan J, et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity, Cell (2020), journal pre proof doi: https://doi.org/10.1016/j.cell.2020.09. 038