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Review Article

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The Immune Cells and Its Link to COVID-19

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Abstract

World health organization has declared SARS-CoV-2 infection as a worldwide pandemic on March 11, 2020 and it is continuously affecting public health throughout the globe. The disease progresses from mild symptoms to a pneumonia like condition with severe inflammation of the respiratory tract due to cytokine release or cytokine storm that is the major characteristic of this disease. T cells numbers decrease and become exhausted in COVID positive patients this might be due to excessive amount of IL 10, IL 6, and TNFα. CD8+T cells and NK cells have showed functional impairment on differentiation, maturation and adequate amount cytokine production which lead to compromise the host immune response against SARS-CoV-2 infection. IFNY behaves as a protective cytokine at early or recovery stages and at severe stage, it acts as more pathogenic by inducing anti-viral responses. This review has summarized the current states of immune responses regarding SARS-CoV-2 infection. It might be helpful on offering new understandings and therapeutic approaches for COVID-19.

Keywords: SARS-CoV-2, T Cells, NK Cells, B Cells, IFNY

Introduction

The onset of the new decade has been with the spreading of a novel corona virus disease COVID-19 from the Chinese province of Wuhan to more than 200 countries across the world. This worldwide spread has led the World Health Organization to declare COVID-19 a pandemic on 11 March 2020. Clinical symptoms of COVID-19 are mild fever, cough, dyspnea and in few severe cases it leads to respiratory failure or death [1, 2]. SARS-CoV-2 is closely connected with MERS (Middle Eastern Respiratory Syndrome) and SARS-CoV-1 coronaviruses, prevailing local outbreaks in 2012 and 2003 respectively [3]. The entry of corona virus into the host cells happens by attachment of viral spike (S) protein to host ACE2 (angiotensin-converting enzyme 2) receptor and resulting increase serum Angiotensin II level [4].

Respiratory viruses have induced excessive inflammatory responses, which might result in robust cytokine production [5, 6]. The reason of dysregulation of immune system due to corona virus till remains elusive. Scientific community still investigates how SARS-CoV-2 infections disturb the immune homeostasis and activate inflammatory responses in host. A study suggested, corona virus might effectively mislead the innate immunity causing a delayed or inadequate response in patient [7]. As SARS-CoV-2 is a RNA virus, the genomic content can bind to the pattern recognition receptors (PRR) like cytosolic RLRs (RIG1 like receptor) and extra or intra cellular TLRs (Toll like receptor). The downstream pathways followed by COVID infection via PRRs start triggering the secretion of certain cytokines. IFNY is the prominent cytokine that plays a vital role in inducing antiviral responses by transmitting signal via JAK/STAT pathway for the activation of interferon-stimulated genes [8]. It was also found, IFNY is protective in early stage of disease and during severity, it becomes pathogenic [9]. HLA (Human leukocyte antigen) alleles are complex polymorphic components of the viral peptide presentation process that initiate adaptive immune response to eliminate the infection. Recently an in silico analysis has identified certain HLA alleles having more predicted SARS-CoV-2 peptide that might provide evidence of genetic susceptibility or resistance to SARS-CoV-2 infection [10]. Several studies have explained about the status of Natural killer (NK) cells during infection, they found reduction in the number of NK cells, diminishing surface receptors and impairment in the production of cytokines [11-14]. However, CD8+T cells number is reduced in COVID-19 patients, their cytotoxic activity maintained by producing proinflammatory molecules [15]. At the same time, severe patient showed a decrease in number of CD4+T cells and helper CD4+T cells number was enhanced in recovering patients along with elevated levels of Granzyme A, Granzyme B and Peforin [16-18].

This review focuses on the response of innate and adaptive immune cells in the context of SARS-CoV-2 infection that might be helpful for understanding the overall scenario of host defense mechanism against COVID-19.

Innate immune cell response to SARS-CoV-2

Innate immunity is non-specific to any particular pathogen; by screening the conserve characteristics or features of pathogen, it is quickly activated to destroy invaders. Innate immunity comprises of wide range of lymphoid and myeloid cell types. Natural killer cells were found significantly higher in blood of COVID-19 patients compared to healthy and its count reduced gradually during severity of the disease [19]. Initial contact of SARS-CoV-2 with host cells via ACE-2 (angiotensin-converting enzyme 2) receptor expressed on cells in blood vessels, gastrointestinal tract, heart, kidney and specifically epithelial cells of alveoli [3, 20, 21]. SARS-CoV-2 infection has down regulated ACE2 expression, which might compromise the innate response of COVID-19 patients [4]. NKG2A (NK group 2 member A) is a heterodimeric inhibitory receptor prominently expressed in NK (Natural killer) cell and activation of NKG2A transmits the inhibitory response by suppressing cytotoxicity and cytokine secretion of these cells [22]. NKG2A over expression has been recently demonstrated in NK cells and CD8+T cells of SARS-CoV-2 infected patients which might be another reason for suppression of immune response against COVID-19 [19]. In COVID-19 patients GM-CSF (Granulocyte-macrophage colony-stimulating factor) producing CD14+HLA-DR inflammatory monocytes (IM) have been found higher in number by flow cytometric analysis [23]. Single cell transcriptomic data also revealed the cellular expansion of CD14+IL 1β+ monocyte and detected low IL 1β level in severe COVID-19 patients [24]. Data suggested elevated pro inflammatory cytokine like IL 6, IL 7, IL 2, IFNY, Interferon gamma-induced protein 10 (IP 10), Monocyte chemo attractant protein-1 (MCP-1), Macrophage Inflammatory Proteins (MIP), Granulocyte-colony stimulating factor (GCSF) and GM-CSF have been found in COVID-19 patient, in addition, IL 6 was shown to be correlated with disease severity [1, 25, 26]. In vitro study has indicated SARS-CoV infection could induce macrophage pyroptosis and inflammasome activation via NLRP3 dependent pathway [27, 28]. Due to increased level of IFNY and GM-CSF in the blood plasma of a COVID-19 patient, signal transmitted via JAK/STAT pathway for the activation of interferon-stimulated genes which can enhance the amount of other cytokines. During MERS-CoV and SARS-CoV infections, the signals are transmitted via MAPK pathways by phosphorylating the intermediate protein sub-units [15, 28, 29].

Several studies have mentioned about NK cells association with COVID-19 severity and its number being less in blood in these patients [11-14]. Single cell transcriptomic study revealed equal presentation of these cells on the basis of some signature genes in lungs of both patient as well as healthy controls [30]. Number of CXCR3 ligand-producing monocytes was found higher and CXCR3 ligand was increased in lung tissue of SARS-CoV-2 infected patients which might help in migration of other immune cells to target. In other respiratory viral infection like influenza, majority of lung NK cells were nonresident and they were infiltrated from peripheral blood [30-32]. This might suggest the recruitment of NK cells in lungs of COVID-19 patient facilitated by CXCR3 pathway.

Percentage of CD16 expressing NK cells were decreased in peripheral blood upon SARS-CoV-2 infection [33]. In SARS-CoV-1 infection, Killer-Immunoglobulin Receptors (KIR) positive NK cells frequency was less compared to healthy individuals [34]. Collectively, data suggested in COVID-19 patient there was impairment in maturation or infiltration of NK cells as CD16 and KIR were essential for development as well as recruitment of these cells to lungs. Peripheral blood NK cells of COVID-19 patients have showed decreased expression of Granulysin, Granzyme B, IFNY, TNFα, CD107a and Ksp37 which suggests an impaired cytotoxic nature [14, 35]. Non-cytotoxic innate lymphoid cells (ILCs) have not been studied well in the context of COVID-19. ILC 2 produces IL 13 which helps in recruitment of macrophages and induced hyperactivity in influenza infection [36].

Golonka et al. has emphasized the positive impact of TLR5 on SARS-CoV-2 infection [37]. They proposed TLR5 can induce cytokines which might restore the impaired response of innate cell. Data shows SARS-CoV infection induces up regulation of TLR7 in monocytes but it is not clear whether it can possibly trigger innate immune response against COVID-19 [38].

HLA alleles code for cell surface protein displayed on antigen presenting cells like dendritic cells and macrophages of innate immune system. Those are critical components of the viral antigen presentation process that confer severity of disease as well as differential viral susceptibility [10]. Individuals with the HLA-B*46:01 genotype show high risk of SARS-CoV infection [39]. Several other HLA alleles including HLA-B*54:01, HLA-B*39:01 and HLAB*13:01 were identified in severe acute respiratory syndrome and their association with disease has been well-explained [40]. Recently, in silico analysis revealed that HLA-B*15:03 has highest predicted binding peptide and HLA-B*46:01 has least possible conserve peptide for SARS-CoV-2 [10].

T cell response to SARS-CoV-2

T lymphocytes play major role in viral infection, where CD8+T cells clear out the infected cells and CD4+T cells convey the signal to B cells for antibody formation, which together minimize viral burden. Overall reduction in number of CD4 and CD8+T cells was observed in SARS-CoV-1 infection; several current studies emphasize the occurrence of T cells lymphopenia in moderate and severe COVID-19 cases [41-43]. The percentage of CD8+T memory cells was higher than that of CD4+T memory cells in SARS-CoV survivors and it suggested virus specific T cells could confer long-term immunity [44]. Patients recovered from COVID-19 showed robust T cells response against viral N (nucleocapsid), M (membrane) and S (spike) proteins and one third cases of total recovery have expressed N specific T cell response [45]. Flow cytometric analysis revealed that 1.3% and 1.4% cells were COVID-19 specific CD8T and CD4+ T cells in patient respectively. Limited data available on phenotyping of CD4 and CD8+T cells by considering various surface markers. According to the percentage of CCR7 and CD45RA expressing T cells, CD4 central memory or CD8 effector memory and effector memory with RA positive cells were predominant in SARS-CoV-2 infected patients [46]. Spike protein specific response induced the expression of CD154 and CD137 on T cells and this T cells population was found in 83% of SARS-CoV-2 infected cases with increased expression of HLA-DR, CD38, and Ki-67 [47]. Certain functional and phenotypical modifications of T cells due to SARS-CoV-2 infection are analyzing continuously and some reports have suggested enhanced frequencies of activated T cells with expression of CD25, CD38, CD44, CD69, HLA-DR and Ki-67 in patient with COVID-19 [16-18, 24, 30, 45, 47]. CD8+T cells response seems to be stronger than CD4+T cells in SARS-CoV-2 infection on the basis of cytotoxic activity and effector like function [16, 17]. Follicular helper CD4+T cells number was enhanced in

recovering patients along with elevated levels of Granzyme A, Granzyme B and Perforin [16, 18]. Xu etal. found a significant decrease in the number of both CD8 and CD4+T cells in SARS-CoV-2 infected patients and also confirmed the cells were highly activated by expressing HLA-DR (CD4 3.47%) as well as CD38 (CD8 39.4%) [15]. In addition, high proportions of CCR6+Th17 cells were also identified in COVID-19 positive cases [15].

CD8+T cells found were rich in cytotoxic granules releasing Granulysin (64•2%), Perforin (31.6%) and both Granulysin and Perforin (30.5%) in COVID-19 positive patients [15]. As shown by recent study, increased level of pro inflammatory molecule reported due to COVID-19 infection and enhanced level of IFNY, IL 1β, CCL2 and CXCL10 strongly induced activation of Th1 cell function [1]. Another study highlighted that SARS-CoV-2 infection has also increased Th2 response by secreting IL 10 and IL 4, which are anti-inflammatory in nature [48]. TNFα, CXCL10 and CCL2 concentration was seen higher in infected patients requiring ICU admission compared to less severe patients [48]. COVID-19 infected patient showed increased Th17 response due to the excessive presence of IL 6 driven by viral infection. So increased IL 6 level in blood plasma plays an indicator for disease severity and might be used as a prognostic indicator for COVID-19 [49-51]. Chen et al recently reported that IFNY expressing CD4+T cells were markedly lower in severe case than moderately infected patients [42].

B cells and COVID- 19

B cells show humoral immune response by producing antibody to clear the pathogen and memory cells to prevent reinfection. SARS-CoV-2 infection induces B cell response by generating virus specific IgG, IgM and IgA along with neutralizing IgG antibodies after certain days of infection [52]. Huang et al. well described the kinetics of antibody reaction against SARS-CoV-2 [52]. Study declares, within 7 to 14 days after the onset of COVID-19 symptoms, virus specific antibody is produced in a detectable range in the blood plasma of patient [53-55]. Common antibody detected are against internal nucleocapsid protein and the external spike glycoprotein of SARS-CoV-2 [56-58]. Binding domain of spike glycoprotein is more immunogenic and antigen binding site of antibody binds to it leads to neutralize and also blocks ACE2 to avoid viral entry to host cells [57, 59]. Receptor binding domain specific CD19 positive B cells were sorted from COVID-19 patients after 9-28 days of infection and carried for gene sequencing. From the sequencing data, it was demonstrated that the monoclonal antibodies had relatively no or less somatic mutations with diverse repertoire and variable binding reactivity [57].

Conclusion

COVID-19 pandemic brings a high degree of severity in individuals with compromised immune system. Immune cells with limited function represent the major barrier for COVID-19 recovery. During prolonged infection of SARS-CoV-2, cytotoxic T cells and NK cells start losing their cytotoxic properties that are required for eradicating viruses.

Cytokine storm is an unfavorable circumstance that occurs due to robust inflammatory
reactions in case of SARS-CoV-2 infection [60, 61]. This condition could be considered as major contributor to inflammation and excessive swelling in respiratory tract. Several reports have validated, cytokine storm is mostly obtained from monocytes, macrophages and T cells by secreting excess amount of cytokines like TNFα, IL 6 and IL 10 [60, 61]. Based on Diao et al. investigation, secretion of cytokine has not been originated from T cells and cytokine storm might promote necrosis or apoptosis of T cells that consequently lead to a decrease in number of cells [62]. Therefore, it needs further investigation to know the sources of cytokine release and its mechanism of production in COVID-19 patients.

In vitro study demonstrated that virus specific antibody inversely correlates with viral load and positively correlates with rate of neutralization. It indicates a successful neutralization process in majority of individuals with COVID-19 and explains the greater association of higher antibody titers with more severe cases [55, 63, 64]. This study also suggests robust antibody alone is not sufficient to neutralize the viral peptide in severe cases. So further studies are needed to determine the extent of antibody response towards disease pathophysiology.

Based on availability of data, T cell exhaustion happens in COVID-19, which affects adaptive immunity by losing the effector function like differentiation, maturation and cytokine production. Over expression of NKG2A receptor induces inhibitory response in NK cells as well as CD8+T cells of COVID-19 positive patients resulting impairment in cytotoxic properties which over all compromises the anti-viral immune responses.

Questions regarding the contribution of antibody, restoration of impaired immunity and mechanism of cytokine production during COVID-19 infection are urgently required to address. Accordingly, more in vitro, ex vivo and in silico experiments with animal study by considering broad range of participants are important for the new findings regarding COVID-19 infection.

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