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Review Article

SARS-Cov-2 STRATEGIES TO AVOID INNATE IMMUNE CELLS

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Abstract

The pandemic of serious acute respiratory disorder of corona virus 2 had also led to millions of infections, as well as the function of immune responses in initial COVID-19 remains unknown. SARS-Corona virus-2 infection reduced the number of immune cells, including natural killer T lymphocytes, monocytes/macrophage, and dendritic cell. The need to further understand the virus-host interaction that controls the severity of the disease and the outcome of infection has been further emphasized by RNA viruses. The innate immunity moderates the detection of pathogens and the activation of effective antiviral programs that limit virus replication, reduce virus distribution and activate adaptive immunity as part of the early antiviral protection. Numerous strategies to neutralize pathogen identification and antiviral responses throughout the cell have been indefinitely developed by viral pathogens. The main mechanisms that used SARS-CoV-2 to interfere with and impair genetic immune cells because then that they can conquer the immune system are illustrated in this analysis

Key words: SARA-COV-2, COVID-19, Innate immune cells, Pathogenesis, Evasion mechanisms and Modulation

1. Introduction

Infection with viruses poses a unique challenge to a host's livelihood. The virus' capacity to reproduce and remain throughout the host depends on the position of the antiviral protective factors throughout the host. The antiviral immunity study showed successful immune responses to accommodate antivirals and improved understanding of the variety of viral immunomodulatory methods that weaken these defensive lines (Mahalingam *et al.*, 2002). Viruses have the ability to evade immune response by sequestration, cytokine escape, block of antigen presentation, natural killer cell activities evasion, antigenic change and escape from apoptosis (Hilleman, 2004). In Wuhan, China, the Covid-19 is pandemic triggered by SARS-Coronavirus-2 was first reported in December 2019.It has spread internationally since then, already infecting millions of people around the world. Averagely, 4.9 percent is the worldwide case fatality rate for all populations (Florindo *et al.*, 2020).

RNA viruses of Corona virus (CoVs) may circumvent host antiviral responses and inflict pain mostly on cell types they invade. Others appear to resist antiviral protections of host, while many others elicit an aberrant or excessive immune response. The SARS-Coronavirus-2 is member of Coronaviridae and cause Covid-19 pandemic outbreak disease resulted extreme pulmonary disease. SARS-CoV-22 permits several strategies (Katze *et al.*,

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2008). There are three main proteins in the envelope: the S glycoprotein, which is suitable for detection and receptors fusion, small protein envelope (E) and glycoprotein M, which are involve in the viral budding plus release (Rota *et al.*, 2003). Binding between spike (S) protein of the coronavirus with 1 or 2 receptors of body cell are mediated by infection of human cell; angiotensin converting enzyme-2 (ACE2) or CD147 (Perlman and Netland, 2009) through envelope, there are 3 major proteins: S glycoprotein, which is suitable for detection and receptors fusion, envelope protein (E) and M glycoprotein, that are involve in viral budding plus release (Rota *et al.*, 2003). Human cell infection is occurred by CoV spike (S) protein binding with 1 or 2 host cells. There are two subunits of the S-protein: S1 glycoprotein that acts as receptor-binding domain and S2 glycoprotein, that influence viral membrane's fusion with membrane of host cell membrane (Bonavia *et al.*, 2003). The activation and viral entry of the spike glycoprotein is regulated by lysis of (S) protein by host transmembrane proteases, Serine 2 (TMPRSS2) (Hoffmann *et al.*, 2020). S-glycoprotein has 2 sub-units: S1-glycoprotein that serves as Receptor-Binding Domain (RBD) and S2 -glycoprotein that move the viral membrane fusion and host cell membrane (Bonavia *et al.*, 2003). The activity and viral entrance are investigated by S-glycoprotein break host protease, serine 2 (TMPRSS2) (Hoffmann *et al.*, 2020).

Several sophisticated studies have shown that SARS-Coronavirus-2 and SARS-Coronavirus which uses like ACE2 cellular entry receptor for trigger infections, even though 40 % of the amino acids were similar in external subdomain (RBD) (Zhou *et al.*, 2020). Since many Coronaviruses often uses ACE2 as just a cellular receptors but still haven't triggered any main outbreaks, it has been believed which some other factors in host can lead to the highly effective dissemination of individual SARS-CoV-22 dissemination in relation to ACE2 (Hung *et al.*, 2020).

Activities that inhibit innate immune responses are produced by invading viruses to establish a space of opportunity for successful virus replication, frequently causing illness. In the end, the balance between both the efficacy of the host's innate and adaptive responses as well as the virulence and also its capacity to escape the host's inflammatory cells on the part of a virus combined determines the illness (Kikkert, 2020). In this review, highlight will be on SARS-CoV-2 strategies that inhibit Innate immunity and interfere with innate immune cells function, these strategies including: Viral actions which cause host shut-off and modulation of the formation of stress granules, downregulation on molecules expressed by innate immune cells and viral ability to infect antigen presenting cells (APCs).

2. Identification of Innate Immunity

The arrangement of inducible cell lines, includes; macrophages, epithelial cells, and DCs, provides an innate immunity. They use different systems of sensing pattern recognition receptors (PRR) (Iwasaki, 2012) to identify pathogen-associated molecular patterns (PAMP) in different cell sites, including ssRNA and dsRNA domains (Kikkert, 2020) *via* intracellular signal transduction pathways, several forms of triggering PRRs cause IFN-I induction and inflammatory agents. In identifying viral RNA, RIG-I-like receptors (RLR), Toll-like receptors (TLR) and cytosolic protein kinase R (PKR) are essential for PRR (Wu and Chen, 2014). Epithelial cell SARS-CoV-2 infection starts when the S protein of virus attaches to ACE2 (Hoffmann *et al.*, 2020). Innate immunity signaling can trigger membrane-bound TLR2 identification of S glycoprotein by activation of the nuclear factor k-B (NFk-B) cascade in epithelial and macrophages (Dosch *et al.*, 2009). Viral ssRNA can also be reached *via* the endosome lumen at viral entry and activate intracellular TLRs, primarily TLR7/8 (Kumar *et al.*, 2009). Covid-19 current and future outlook (Li *et al.*, 2020) and structural properties comprising dsRNA domains were recognized by another form of cytosolic PRR, especially MDA-5 or PKR, which in turns increases antiviral display levels (Thiel and Weber, 2008). The transcription factors required for development of IFN-I and inflammatory markers are therefore

stimulated by TLR and RLR via the 3/7 IRF and NF k-B pathways (Dosch*et al*., 2009).

The liberation of IFN-I from hosts endothelial cells is elicited after invasion of the lung cells and viral identification by immune system. IFN-I is secreted by DCS and macrophages inside the lung upon virus identification by their PRRs. Communally, by suppressing virus replication, maintaining antigen presentation to CD+4 and CD+8 T lymphocytes, improving unique T lymphocytes responses and cytotoxicity to CD+8 T lymphocytes and NK cells, potent antiviral reaction (Sallard *et al*., 2020). Clearance of COVID-19 infection was documented in mild - severe cases, like breathing difficulties, nausea, dry cough and dyspnea, during ten days of the initial of effects (Lauer *et al*., 2020). After this brief inflammation reaction, the alveolar macrophages remove all contaminants from apoptotic virus-infected cells, restrict surfactant accumulation, and resolve inflammation through the lung microenvironment by cytokines secretions such as interleukin1-10, (TGF-β) and raised display of control point inhibitors like CD200 which aim to back niche to its co-niche (Hussell and Bell, 2014). Around each other, this enables optimal tissue renovation, lung wall recovery, and airway clearing where, after the brief inflammatory process within the air sacs, efficient gasses transfer is cultivated (Gwyer Findlay and Hussell, 2012) (Figure - 1).

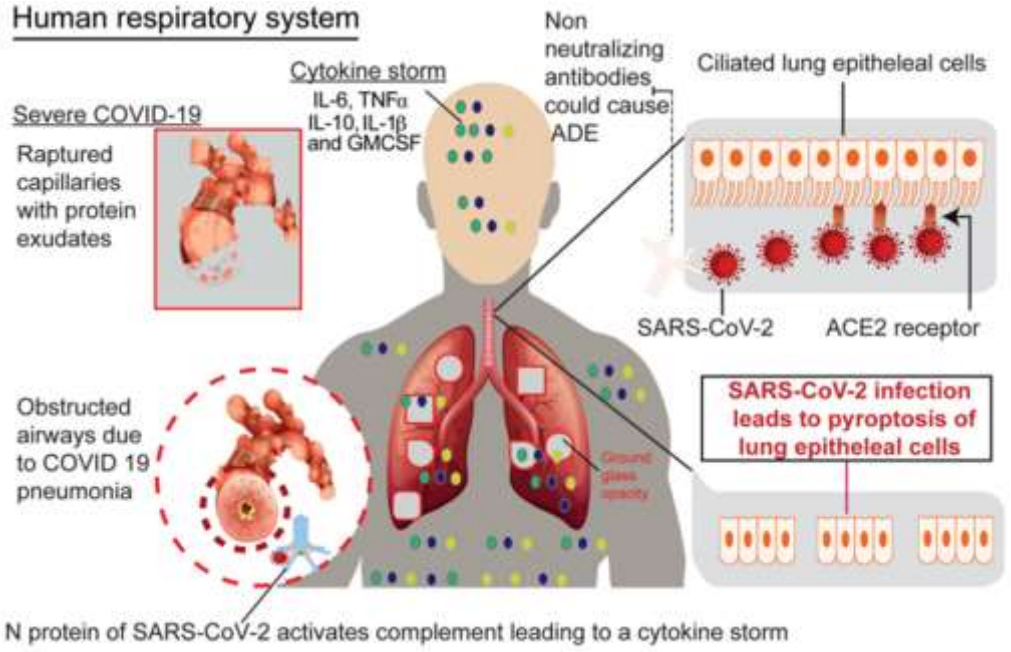

Figure - 1: Innate Immune Identification of SARS CoV- 2

3. Immunological events which drive to severe COVID-19.

Alternatively, all barricades formed by the host immune system can be overcome by the virus and successfully infected within the lung microenvironment afterwards (Tay *et al.,* 2020). This is followed by the transmission of pathogens to many other tissues and cells, where a tragic track of gross structural pathology is left by the virus in its wake. (Huang *et al.,* 2020). SARS-CoV-2 avoids identification of any neutralization antibodies generated by previous SARS CoV infection. SARS CoV cross-neutralizing antibodies may contribute to Antibody-Dependent Enhancement (ADE) in the worse scenarios (Hotez *et al.,* 2020). ADE responses from SARS CoV-2 (Iwasaki and Yang, 2020) are much more likely to arise from unneutralizing antibody which attach to areas of S-protein outside of RDB domain. Through ADE, the antibodies connected to the unneutralized virus force access via macrophages thru the Fc receptor (FcR) and reprogram them to release proinflammatory cytokines which help the pathogenesis of virus

(Peiris *et al.*,1981). The signaling of IFN I also is impaired by SARS-CoV-2, which leads to the delayed secretion of interferon type I. The enormous reproduction of a virus through epithelial cells and also the activated entrance of the virus through alveolar macrophages lead to higher mortality of pyroptosis cells as amounts of cytokines like interleukin-1 beta and interleukin-6, which stimulate the inflammasome production are improved (Conti *et al.,* 2020). There is a huge loss of alveolar macrophage frequency (Liao *et al.,* 2020). These inflammatory macrophages instead pass processed proteins to the acquired immunity in a misguided way, along with other disordered Antigen-presenting cells (APCs), due to poor virus-specific T cell responses. Multiple T lymphocytes secrete high cytokines level that are important for viral elimination in the TH1/IL-17 family (Pacha *et al*., 2020). As a consequence, this hyper-activated condition depending on host-specific T lymphocytes responses and another influences T cell functioning. In relation, CD+4 T cells have also been reported to have faulty IFNγ production from individuals with extreme COVID-19 symptoms and, as such, wrongly orchestrated cell subsets support other cell subgroups (Zheng *et al.*, 2020a). Lastly, the proteins of SARS-N CoV-2 attaches to Mannose Binding Lectin (MBL), progressing to an activation of the alternative pathway. This drive to production of different inflammatory cytokines and anaphylatoxin chemokines, like C5a, which act as chemoattractants for several inflammatory cells, like neutrophils, monocytes and eosinophils, during deposition (Gao *et al*., 2020). This in portion leads to the emerging cytokine storm as cytokines like interleukin-6 and 10, GMCSF, IL1β, and TNF-alpha are produced excessively uncontrolled (Jose and Manuel, 2020). With both, this accidental release of inflammatory cytokines occurred in local or systemic pathology. Inner lungs, pulmonary endothelium, endothelial cells and bronchoalveolar blood vessels are damaged, resulting in increased capillary permeability, disseminated intravascular coagulation, delineation of focal haemorrhagic and alveolar area protein vasculature (Tian *et al*., 2020). Difficulty breathing results from insufficient oxygen demand and low gas exchange effectiveness, during the Computed Tomography(CT) scans provides the lungs a bi-lateral ground-glass opacity (Xu *et al.,* 2020). As a consequence of cytokine storm, numerous organs failure which is distinguished by clot formation and increased D-dimer rates inside the cardiovascular device arises. Sever kidney damage so induces necrotic disruption of spleen and lymph nodes (Wadman *et al.,* 2020) (Figure - 2).

4. Viral escape mechanisms from Innate immunity

Coronavirus use techniques of immune weakening or latency for overcome body antiviral protection, enable either speed replication (Finlay and McFadden, 2006) or inflammatory reaction exacerbation (Merad and Martin, 2020). Virulence factors may mediate virus adherence through S protein to epithelial cells, promote invasion enzymes or provide resistance to pathways of innate immunity, like interferons response, natural killer cytotoxicity, and immunological responses, to spread through intercellular spaces. It has been recently mentioned that many structural and NS proteins are shared by SARS-CoV-2 as well as other coronaviruses, specially SARS (Lu *et al.,* 2020). Such findings indicate that pathogenesis and virulence factors between the two viruses are putatively identical. At various stages of infection, airway innate immune cells function and usually involve epithelial cells, NK, DCs and pulmonary macrophages (Yoshikawa *et al.,* 2009).

Interference with DCs function

A significant link between the innate and adaptive immunity is given by dendritic cells (Borges *et al.,* 2020). Dendritic cells were important players in the presentation of antigen, production of cytokine, priming specific T lymphocytes responses, and lost function of DC in Covid-19 patients could drive to has been postponed immune responses (Rao *et al*., 2020).

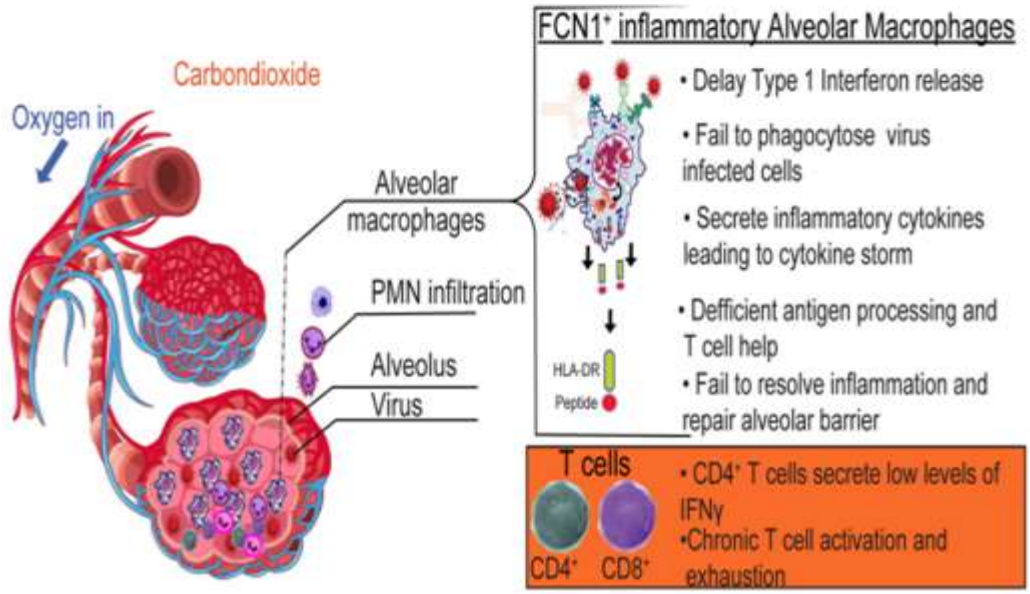

Figure - 2: Immunological happens which drive to severe COVID-19

Viruses have established an array of immune evasion strategies to prevent destroying by the human immune system. Provided the significance of DCs throughout the immune response toward viruses (Cervantes-Barragán *et al.,* 2009), viruses would have developed ways to interfere with their function (Mesel-Lemoine *et al.,* 2012). DCs are primarily available in two kinds: young DCs and matured DCs (Zhao *et al.,* 2010). Infantile DCs, like bronchioles and alveoli in the lungs, are present throughout the skin and mucosal tissue (Peebles and Graham, 2001). In the existence of any intruder, they present antigens to naive T lymphocytes and modify their responses mostly through cytokine production (Steinman and Pope, 2002). SARS-CoV employs the following techniques to mess with DC processes:

- Initiating ineffective adaptive immunity: SARS-CoV down - regulated the expression on adolescent DCs of co - stimulatory cell - surface receptors (CD80/86) and class II MHC molecules and interacts with the introduction of viral antigen (Law *et al*., 2005). Low production of antibody and increase SARSCoV-2 viral load are one outcome of this loss of maturation in DCs (Peiris *et al.,* 2003).
- Huge upregulation of cytokines and chemokines, such as IL-6, IL1β, induced protein 10 (IP10), ligand 2 (C-C motif) chemokines (CCL2), and IL-8 neutrophil-attractants in the lungs (Mesel-Lemoine *et al.,* 2012).

Conserved virus stimulatory structures are essential for the entry, invasion and replication of cells (Pollara *et al.,* 2005). The primary determinant of tropism for coronaviruses like SARS-CoV and SARS-CoV2 is S glycoprotein, which attached to receptors presented on body cells (Li, 2016). Because of the evidence referred to angiotensin converted enzyme-2 expression by DCs, specially interstitial dendritic lung cell, DC can be infected with SARS CoV2, indicates that DCs can be interfere with SARS-CoV-2 (Kovacs *et al.,* 2013). More lately, through CD147-spike binding proteins, a new station of infection was established (Wang *et al.*, 2020). Additionally to T cell B cells and macrophages, dendritic cells display CD1477 (Woodhead *et al*., 1998), substantiating the possibility of infected dendritic cell by SARS-CoV-2. Whereas, coronavirus

receptor analysis is essential for viral entry (Li, 2016), connection factors can greatly improve infection (Marzi *et al*., 2004). A C-type lectin distributed on macrophages and dendritic cells, Dendritic cell-specific nonintegrin catching intracellular adhesion molecule (DCSIGN) (Marzi *et al*., 2004).

It also seems that DC-SIGN and L-SIGN have same roles in the SARS-CoV infection. DCSIGN or L-SIGN activation alone will not affect the invasion of SARS-CoV, while Improves the degradation of the already restricted cells (Marzi *et al*., 2004). It has huge consequences for SARS-CoV infection pathogenesis to realize which DC-SIGN displaying dendritic cells will absorb and transport SARS-CoV to sensitive cells (Yang *et al.*, 2004). In a recent review, bulk RNA sequence examination of the whole lung cells in older adult specimens displayed greater DC-SIGN gene expression (CD209), i.e. >60 years of age. (Cai *et al.*, 2020). Enhanced DC-SIGN description can therefore as well result to a pathogenesis of much more significant SARSCoV-2 pathogens reported in elderly people. In relation to DC-SIGN, many dominant share are being implicated throughout the active entrance and reproduction of SARS-CoV-2 in cells, like furin enzymes (Walls *et al.*, 2020). Furin has been a proprotein convertase essential for the treatment of residual protein active forms (Lin *et al*., 2008). Contribution to degrade of viral protein and bacterial exotoxins. A study indicated that DCs and monocyte originating from monocytes are strict from healthy volunteers for SARSCoV-2 disease and viral protein levels, but didn't assistance successful replication of SARS-CoV-2 (Yang *et al*., 2020). Funnily, SARS-CoV-2 invade dendritic monocyte-derived cells showed a robust raise in furin and DC-SIGN activation that wasn't detected to like extent following SARS-CoV infection. This indicates which SARS-CoV-2 could modify dendritic monocyte-derived cells to promote infection (Siegal *et al.*, 1999). This information raise concerns about the function of dendritic cells throughout the immune pathogenesis of COVID-19. Given the expected sensitivity of DCs to SARS-CoV-2 mediated avoidance pathways, mostly normal immune competent peoples infected with SARS-CoV-2 develop non-severe COVID-19 and start to recovery. There really is compelling research which SARS-CoV-2 adversely impacts DCs portions and activities. Post 24 - 72 hours immunization of SARS-CoV-2 DCs from healthy subjects, cell viability reduced (Zhou *et al*., 2020). In the periphery blood of patients both with severe and geriatric SARS-CoV-2 infections, there's also a decline in the proportion of dendritic cells, more probably plasmocytic phenotypes in serious situations (mean of 13 and 30 days following appearance of illness, respectively) (Cervantes Barragán *et al.*, 2009). These results show SARS-CoV-2 could has cytopathic effects on DCs, resulting in a decrease in their numbers. Fresh researches have proven that the both monocyte-derived DCs from healthy persons poisoned with SARS-CoV2 and conventional DCs of severe SARS-CoV-2 infected clinicians with SARS-CoV-2 have been published by CD11 with respectfulness to SARS-CoV-2 attenuation of dendritic cellular activity. Activation of costimulatory molecules CD80 and CD86 also was impeded in conventional dendritic cells, and so was development of allogeneic CD+4 and CD+8 T lymphocytes and the acquired T lymphocytes response to SARS-CoV-2 (Zhou *et al*., 2020). Furthermore, a pro-inflammatory phenotype is assumed by monocyte-derived dendritic cells following SARS-CoV-2 infection. The altered phenotype gained by DCs was attributable to SARS-CoV-2 message transmitter antagonism and transcription 1 activator (STAT1) phosphorylation (Yang *et al.*, 2020).

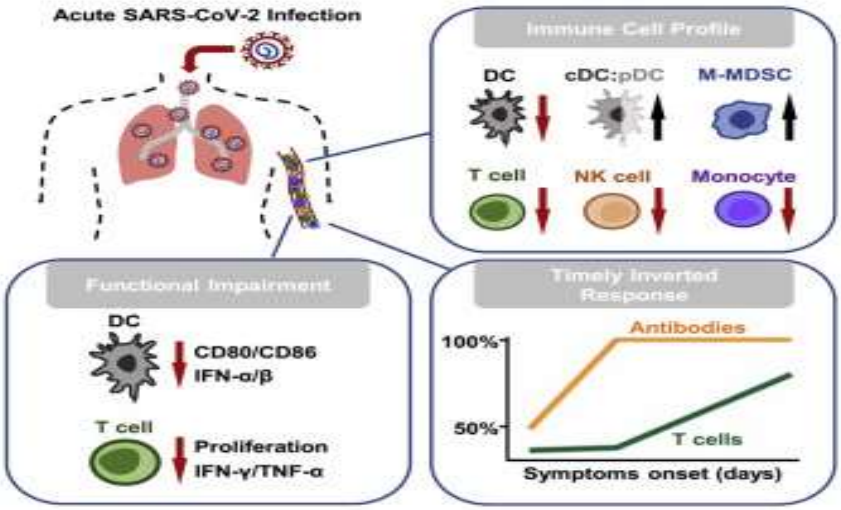

Figure - 3: Profile of immune cells throughout SARS-CoV-2-infection

DC Impairment

SARS-CoV2 infection appears to directly target dendritic cells, with a new review of COVID-19 clinicians reducing the intensity and role of DC and concordant decrease in corresponding T cell activation. In regard to pushing cytokine storm forward, SARSCoV2 can be infect dendritic cells DCs to less DC maturation hence depressing T cell-mediated response (Zhou *et al*., 2020). Through SARS-CoV-2 infection, severe DCs with functional impairment were reduced significantly and proportions of typical DCs to plasmacytoid DCs are improved among severe clinicians. In regard to lymphocytopenia, late Receptor Binding Domain (RBD) and nucleocapside protein (NP)-specific T lymphocytes results were found in the first three weeks following onset of symptoms, when neutralizing antibodies are developed rapidly and efficiently in clinicians. Furthermore, relative to CD8 T cells, relatively further CD4 T cells were included in severe RBD- and NP-specific T cell response. Our research indicates that defective DCs could lead to severe pathogenesis of COVID-19 and also have consequences for the development of vaccines, together with timely reversed strong antibodies but weak responds of C+D8 T cells (Zhou *et al*., 2020) (Figure - 3).

Interference with Macrophage function

In any infection, macrophages are primary innate immune cell (Mogensen, 1988). These are extremely maneuverable innate cell which can be divided into pro-inflammatory "M1" macrophages (capable sources of inflammatory cytokines and intermediaries that kill infectious species, virus-infected cells or tumor cells) and simply and phenotypically (essential for tissue repair and parasitic infections) more controlled "M2" macrophages (Ley, 2017). Both stimulation states are important for a "balanced" immune reaction, although the M1/M2 model of macrophage activation is also an excessive notion of the these diverse and complex innate cells (Orecchioni *et al*., 2019). Through ageing and persistent inflammatory diseases, macrophages may change towards a more M2-like morphology. (Costantini *et al*., 2018). Classical stimulation of M1 macrophages is triggered by sensitivity to LPS/IFNγ whereas conversely stimulated M2 macrophages induce interleukin-4, 10, 13 and glucocorticoids. (Arora *et al*., 2018). The stimulation of immune cells, like macrophages, can be significantly influenced by the nature of T cell response and, in general, by the cytokines produced by T cells throughout infection (Heusinkveld *et al*., 2011).

SARS-CoV-2 could invade macrophages, indicating that even in order to avoid immunity, SARS-CoV-2 specifically deceives macrophages. The impact of SARS-CoV2 infection upon macrophage function is uncertain, but it is understood that macrophage infection induces changed functional states

through other CoVs. Afflicted macrophages with MERS-CoV display high levels of (MHC I), CD80 as well as CD86 (Channappanavar *et al.*, 2019). MHC II down - regulation have lately been consistently reported in clinicians with COVID-19 in monocytes and B lymphocytes (Wilk *et al.*, 2020). The newly released interactome SARS-CoV-2 offers some possible better understanding of the mechanisms for which this virus may interference with macrophage study (Gordon *et al.*, 2020). Blocking interferon signalling in macrophages can limit ISG expression, like cytokine-induced MHC II expression (Keskinen *et al.*, 1997). The SARS-CoV-2 protein Nsp5 associates with histone deacetylase 2 (HDAC2) epigenetic regulator (Keskinen *et al.*, 1997), which controls the expression of MHC II and cytokine secretion (Gordon *et al.*, 2020). Even though it is uncertain if SARS-CoV-2 prevents or stimulate HDAC2 activity, this association indicates a potential direct modification of the cytokine storm and antigen presentation. SARS-CoV-2 Nsp13 and ORF8 interact with multiple components of the Golgi trafficking mechanism and can use this as a method to restrict MHC exports to the cell surface (Zhang *et al.*, 2020). While these immunoevasory processes largely remain theoretical, SARS CoV-2 ability toward invade and associate with several proteins which are important for macrophage function shows a strong potential to affect on activity of macrophage, and during universal immune response (Taefehshokr *et al.*, 2020).

Interference with NK cell function

Natural killer cells are important for the management of viral infection and dysfunction of Natural killer cells (NK) cells associates with the persistence of SARS-CoV-2. In severe patients with COVID19, decreased levels of peripheral blood NK cells are usually found (Zheng *et al.*, 2020b). In the license of NK cells and their corresponding cytotoxic activities, killer-immunoglobulin like receptors (KIRs) that displayed alongside CD16 upon this cellular membranes of NK cells play an important role (Sivori *et al.*, 2019). In peripheral blood in SARS-CoV and SARS-CoV-2 infections, natural killer cells display KIRs and CD16 are importantly reduced, suggesting either decreased progression of NK cells or movement of circulating natural killer cells towards peripheral tissues of SARS-CoV-2 clinicians. Furthermore, in SARS-CoV-2 infection, reduced NK cell numbers lead to higher IL-6plasma levels (Wang *et al.*, 2020a). *In vitro*, interleukin-6 and soluble interleukin-6 receptors prevent healthy donor NK cells from producing perforin and granzyme B, which can be recovered by therapy with tocilizumabab blocker IL-6R (Cifaldi *et al.*, 2015).

One more technique is the up-regulation of human inhibitory receptors used by SARS-CoV-2 to modify NK cell-mediated cytotoxicity. The NKG2A receptor (Zheng *et al.*, 2020b) is unique to the HLA-E/HLA-I complex peptide (Lauterbach *et al.*, 2015). Development communication include all up - regulated appearance on NK cells of Covid-19 infected clinicians by certain HLA-I complexes and HLA-I based signaling peptides (Nguyen *et al.*, 2020) or overexpression of NKG2A on NK cells (Yaqinuddin and Kashir, 2020).

In persistent viral infection and tumor, NKG2A inhibitory receptor expression onto NK cells resulted throughout the functional depletion of NK cells (André *et al.*, 2018). NK cells were observed to be functionally deficient in SARS-CoV-2 clinicians, as demonstrated by enhanced NKG2A expression and reduced levels of CD107a, IFN-γ, IL-2 and granzyme B in NK cells. (Zheng *et al.*, 2020b).

Additionally, previous studies have suggested up - regulated expression of genes involved inhibitory receptors including TIM3 and LAG3 in NK cells in COVID-19 clinicians. (Hadjadj *et al.*, 2020). The effects of this high prevalence of stressed NK cells remain unclear for SARS-CoV-2 patients. While NK cell numbers and activity appear to be decreased in COVID19 clinicians, anti-S protein antibody are capable of inducing NK-cell-mediated antibody-dependent cell cytotoxicity during an invitro model of SARS-CoV-2 infections, indicating that healthy NK functional cells must contribute to the protection of SARS-CoV-2 infection (Pinto *et al.*, 2020).

Possible approaches that can cause exhaustion of natural killer cells through SARS-CoV-2 are

- NKG2A inhibitory receptors.
- Low display of granzymes and perforin by SARS-Cov2 S protein and amplification of interleukin-6.
- Raise display of HLA-E, is ligand for NKG2A receptor by certain HLA-I molecules. Upon detection of HLA-I on the infected cell, NK cell activation is abrogated.
- Programmed cell death (Apoptosis) by indirect pathways (Bouayad, 2020)

Interference with Neutrophil function

Neutrophilia is also early parameter of SARS-CoV-2 infection, although this is un-clear if this improve is responsible for release of suppressed neutrophil community vs. activation cells of bone marrow (Rodriguez *et al*., 2020). Although it is uncertain to what degree neutrophils are important for COVID-19 pathophysiology, substantial neuronal loss in autopsied COVID-19 patients has been reported. (Yao *et al*., 2020). For COVID-19 patients, infiltration was not the only route through which neutrophils could cause pathology. In a number of inflammatory conditions, like blood clots, sepsis, and respiratory failure, the pathological effects of neutrophil extracellular catches (NETs) have been reported (Ali *et al.,* 2019). Extracellular binding of neutrophils consists of DNA extracellular fiber, histones, proteases such as neutrophil elastase, microbicidal proteins, and oxidizing enzymes such as myeloperoxidase, generated in response to many pathogens by neutrophils. NETs cause and spread inflammation and thrombosis if not properly treated (Twaddell *et al*., 2019).

5. Conclusion

Innate and acquired immune responses can be triggered by SARS- CoV-2 infection. Nevertheless, both locally and systemically, unregulated inflammatory innate responses and weakened adaptive immune responses can lead to detrimental tissue damage. SARS- CoV-2 has various pathways of immune escape that target DCs, macrophages, NK and neutrophils to modify and inhibit innate immune response. In this case, the specialized immune response will be misled and the virus will be able to replication and dissemination in other organs then pathogenicity occurs and overcomes host immunity, this level of COVID-19 could cause death.

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