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Immunology and Pathophysiology of Covid-19 disease-A Review

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ABSTRACT

Novel coronavirus (severe acute respiratory syndrome coronavirus-2 or SARS-CoV-2) is the causative agent of COVID-19. SARS-CoV-2 belongs to the β-coronavirus family and shares extensive genomic identity with bat coronavirus suggesting that bats are the natural host. SARS-CoV-2 uses the same receptor, angiotensin-converting enzyme 2 (ACE2), as that for SARS-CoV, the coronavirus associated with the SARS outbreak in 2003.Other receptors used by SARS-CoV-2 are CD147 and CD26. It mainly spreads through the respiratory tract with lymphopenia and cytokine storms occuring in the blood of subjects with severe disease. In severe cases this viral infection cause damage in the lungs, heart and kidney which ultimately leads to multiorgan failure and finally death. This suggests the existence of immunological dysregulation as an accompanying event during severe illness caused by this virus. The early recognition of this immunological phenotype could assist prompt recognition of patients who will progress to severe disease. This review summarizes the understanding of how immune dysregulation and altered cytokine networks contribute to the patho-physiology of COVID-19 patients. As pathological examination has confirmed the involvement of immune hyperactivation, cytokine storm and acute respiratory distress syndrome in fatal cases of COVID-19, several disease-modifying anti-rheumatic drugs (DMARDS), such as hydroxychloroquine and tocilizumab, have been proposed as potential therapies for the treatment of COVID-19. Further research on the immunological mechanisms associated with COVID-19 can lead to the development of newer drug targets and therapies against this deadly virus.

Keywords: COVID-19, Coronavirus, Innate immunity, Adaptive Immunity, Cytokine Storm, Biomarkers.

INTRODUCTION

The novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2), causing COVID-19 disease, is the most dangerous corona-virus ever identified, capable of infecting animals as well as humans across

the globe. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects pulmonary epithelial cells. In severe cases, COVID-19 is accompanied by excessive activation of the innate immune system with progressive inflammation and a cytokine storm from activated cells, particularly in the airways, leading to the acute respiratory distress syndrome (ARDS). WHO has declared COVID-19 as a global pandemic. Though very little information about the potential protective factors of this infection is known. There is an urgent need for public health measures, not only to limit the spread of the virus, but also to implement preventive approaches to control severe COVID-19, e.g., by reduction of the excessive inflammation. Aged people are very much prone to severe respiratory infection than young people, probably due to the relation between old age and deficient nutrition and immunity.

CoV belong to the genus Coronavirus in the *Corona-viridae* family. CoVs are pleomorphic RNA viruses with special crown-shape peplomers between 80 and 160 nM in size and a genome of 27–32 kb (Wit *et al.,* 2016). Four coronavirus genera (α, β, γ, and δ) have been characterized so far, with human coronaviruses (HCoVs) detected as being in either the α (HCoV-229E and NL63) or β (MERS-CoV, SARS-CoV, HCoV-OC43, and HCoV-HKU1) genera (Perlman *et al.,* 2009). On the basis of sequence homology, all human coronaviruses have animal origins: SARS-CoV, SARS-CoV-2, MERS-CoV, HCov-NL63 and HCoV-229E are considered to have originated from bats,1 whereas HCoVOC43and HKU1 likely originated from rodents (Cui et al., 2019). SARS-CoV-2 has a significant structural similarity to SARS-CoV and MERS-CoV and other human and animal coronaviruses (Zhang et al., 2020; Wu *et al.,* 2020). Coronaviruses have a high mutation rate and a high capacity to act as pathogens when present in humans and various animals presenting with a wide range of clinical features. The disease characteristics can range from an asymptomatic course to the requirement of hospitalization in an intensive care unit. *Coronaviruses* cause infections of the respiratory, gastrointestinal, hepatic, cardiac, renal and nervous systems and exacerbations of lung diseases, croup and bronchiolitis (Mortaz et al., 2020).

Angiotensin converting enzyme (ACE) catalyses the formation of angiotensin II from angiotensin I and, thereby, plays a key role in the control of cardio-renal function and blood pressure (Tikellis and Thomas, 2012). ACE2 is highly expressed in the lungs, small intestine, kidney and heart, but it is not expressed on innate and adaptive immune cells (Qi *et al.,* 2020). It has been shown that SARS-CoV-2 can also use CD147 to enter T-cell lines and cells of epithelial origin. CD147 is also expressed in epithelial cells in human airway and kidney. Moreover, CD147 is also found in granulocytes, macrophages, dendritic cells (DC), innate lymphoid cells (ILCs) and lymphocytes. Besides ACE 2 and CD 147, other receptors potentially utilized by SARS-CoV-2 are CD26 (encoded by *DPP4*; a receptor for MERS-CoV), an important T cell and also epithelial cell receptor, amino peptidase N (ANPEP; a receptor for human and porcine coronaviruses), ENPEP and a glutamyl aminopeptidase, as well as DC-SIGN (Sokolowska *et al.,* 2020). After entering into target cell virus replicates and produce its polyproteins and these proteins are then processed and presented to immune cells which in turn stimulates host immune mechanisms. Viruses elicit several key host immune responses such as increasing the release of inflammatory factors, induction and maturation of dendritic cells (DCs) and increasing the synthesis of type I interferons (IFNs), which are important in limiting viral spread. Both the innate and acquired immune response are activated by SARS-CoV-2.

Being a global health issue, COVID-19 urges scientists to put a lot of effort into developing effective therapeutic strategies for treating and saving lives. Further research on the detailed understanding of SARS-CoV-2 infection would be of great significance for the development of effective therapeutic strategies. Immunological aspects of the disease reflect the importance of the immune system to inhibit the viral factors and to control and regulate the pathophysiological processes during SARS-CoV-2 infection.

IMMUNOLOGICAL MECHANISMS ASSOCIATED WITH COVID-19

SARS-CoV-2 receptors

SARS-CoV-2, like SARS-CoV, utilises the membrane bound form of angiotensin converting enzyme 2 (ACE2) to enter human cells via its spike protein (S). After binding with spike protein S of SARS-CoV-2, ACE2 gets internalized and this in turn decreases its membrane expression. ACE2 is

an important regulator of bradykinin. So its reduced expression results in local vascular leakage leading to angioedema in the affected lung tissue. TMPRSS2, the host serine protease, cleaves spike protein into S1and S2 fragments. These fragments enable fusion with the cellular membrane and this in turn enables the viral entry to the cell and as a result viral replication starts (Hoffmann *et al.,* 2020). In addition to TMPRSS2, other proteins such as furin or human endosomal cysteine proteases are potentially capable of cleaving S, such as cathepsin L (CTSL) and cathepsin B (CTSB) (Shang *et al.,* 2020). ACE2 is highly expressed in the lungs, small intestine, kidney and heart, but it is not expressed on innate and adaptive immune cells (Qi *et al.,* 2020). As recently shown, SARS-CoV-2 can also use CD147 (also called basigin (BSG) or extracellular matrix metalloproteinase inducer (EMMPRIN), to enter T-cell lines, as well as cells of epithelial origin. CD147 is expressed in human airway and kidney epithelium, as well as ininnate cells (granulocytes, macrophages, dendritic cells (DC), innate lymphoid cells (ILCs) and lymphocytes. Other receptors potentially utilized by SARS-CoV-2 are CD26 (encoded by *DPP4*; a receptor for MERS-CoV), an important T cell and also epithelial cell receptor, amino peptidase N (ANPEP; a receptorfor human and porcine coronaviruses), ENPEP and a glutamyl aminopeptidase, as well as DC-SIGN30 (Sokolowska *et al.,* 2020).

Entrance of the virus through epithelial barriers

ACE2 and TMPRSS2 are highly co-expressed in the upper and lower respiratory tract, but there is no expression of SLC6A19, which potentially blocks the access of TMPRSS2 to ACE2 and subsequently reduces active infection. In the nasal and the pharyngeal epithelium, in goblet and ciliated cell, ACE2 is expressed at high levels and co-expressed with TMPRSS2 representing the sites of initial viral replication and a main source of infectious particles. The lower airways, bronchial epithelium and type II pneumocytes (AT2cells) highly express ACE2 and TMPRSS2, which may provide virus entrance to the lung and lead to COVID-19 pneumonia. Moreover, CD147, CD26, ANPEP and ENPEP are also expressed in the airway epithelium,as well as in many innate and adaptive immune cells (Sokolowska *et al.,* 2020).

Once the virus enters the host cell, it releases its RNA into the cytoplasm and uses the host translation machinery to translate its polyproteins pp1a and pp1b, also known as replicases and viral essential proteases 3CLpro and PLpro. After protein translation, they traffic through the ER to the Golgi apparatus, where the mature virions are assembled in budding vesicles and are exocytosed from the cell. Inside infected cells, there are several innate immune mechanisms responsible for recognizing the virus at different stages of its replication and leading to the production of interferons type I (IFNα and β), type III, and proinflammatory cytokines (Prompetchara *et al.,* 2020). Viruses use various strategies to evade these mechanisms (Finlay *et al.,* 2006). Very little information is known about SARS CoV-2 antiviral responses. Epithelial cells produce type I and type III IFNs upon viral infection. Type I IFN act through receptors expressed in a vast number of cells. On the other hand, type III IFNs seem to exert their effect mostly on epithelial cells, are less inflammatory and are activated faster than type I IFN (Prokunina-Olsson *et al.,* 2020). IFNs are one of the most potent antiviral components of the innate immune response. They work on various levels i.e. blocking viral attachment, entry, trafficking, protein production and genome amplification and also viral assembly. Moreover, IFNs also activate other innate and adaptive immune responses. However, in case of COVID-19 these responses seem to be diminished or dysregulated (Channappanavar *et al.,* 2016). SARS-CoV and MERS-CoV inhibit IFN signaling on various levels (Kindler *et al.,* 2016). The nsp 16 mediated 2'O methylation of viral mRNA cap structure prevents coronaviruses recognition by MDA5 (Menachery *et al.,* 2014). The sequestration of viral dsRNA within double membrane vesicles (DMVs) also protects coronaviruses from detection through cytosolic PRRs (Versteeg *et al.,* 2007). Moreover, coronaviruses produce many non-structural proteins which inhibit induction of IFNs (inhibition of IRF3 and IRF 7) and/or interferon signaling (inhibition of STAT 1 signaling) (Kindler *et al.,* 2016). A reduced antiviral response via IFN pathway inhibition, together with an ongoing pro-inflammatory response, presumably heightened by increased viral load, may lead to excessive inflammation and worsening of the disease. In an animal model of SARS-CoV, a delayed type I interferon response resulted in accumulation of inflammatory monocytes/macrophages, leading to elevated lung cytokine/chemokine levels, vascular leakage and impaired virus-specific T cell responses (Channappanavar *et al.,* 2016).

Based on the current knowledge of SARS-CoV-2 receptors' expression on the epithelial barrier sites, the gastrointestinal tract requires special attention (Sokolowska *et al.,* 2020). Human ACE2 is homogeneously distributed on the brush border of enterocytes across the small intestine and in the lung epithelium. TMPRSS2 and TMPRSS4 mediate infection of small intestinal epithelial cells. These enzymes might additionally be an interesting target for therapeutic intervention, since a clinically approved protease inhibitor is available. Less is known regarding the gastrointestinal distribution of CD147. CD26 expression was reported to be high in ileum and jejunum, low in duodenal samples and not detectable in colon epithelial cells (Sokolowska *et al.,*2020). Gastrointestinal symptoms like vomiting and diarrhea in COVID-19 are gaining attention (Pan *et al.,* 2020).

Innate and adaptive immune mechanisms associated with Covid 19

Innate immune responses in COVID-19

Monocytes/macrophages and DCs play a crucial role in anti-viral responses by linking innate and adaptive immunity. In COVID-19 patients, ACE2 expression was detected on both lymph node-associated CD68+ macrophages and tissue-resident CD169+ macrophages. SARS-CoV-2 particles were found in macrophages. It is reported that SARS-CoV-2, similarly to HIV,can use macrophages as a Trojan horse contributing to viral spread (Park, 2020). SARS-CoV-2 can trigger NLRP3 inflammasome activation in monocytes/macrophages, production of high levels of proinflammatory mediators such as IL-6, GM-CSF, IL-1β, TNF, CXCL-8 or CCL-3, enhanced cell death and lead to the cytokine storm also known as Cytokine release syndrome (CRS) (Ratajczak and Kucia, 2020). Some of these cytokines (i.e. IL-6) are mainly secreted by macrophages and the evidence of macrophage activation syndrome has been reported (McGonagle, 2020). Overloaded, activated and subsequently dying macrophages might contribute to an increase in the levels of plasma ferritin and profound dysregulation of iron metabolism (Nairz *et al.,* 2017). High ferritin levels are common clinical findings in patients with severe COVID-19 (Velavan and Meyer, 2020).

Neutrophils are one of the predominant lung infiltrating leukocytes in severe SARS-CoV-2 infection, and neutrophilia predicts poor clinical outcome. 84 Post-mortem analysis of lung samples from COVID-19 patients showed neutrophil infiltration in pulmonary capillaries and neutrophil extravasation into the alveolar space (Barnes *et al.,* 2020).

The complement system is engaged in both coagulation and inflammatory pathways. Histologic and immunohistochemical analysis of lung and skin have been conducted in patients with COVID-19-induced ARDS. The typical pulmonary findings for ARDS were accompanied with significant deposits of terminal complement components C5b-9 (membrane attack complex), C4d, and mannose binding lectin (MBL)-associated serine protease (MASP) 2, in the microvasculature (Magro *et al.,*2020).

Adaptive immune responses in COVID-19

Humoral immune mechanisms

Human SARS-CoV-2 infection activates mechanisms of B and T cell immunity that result in the generation of neutrallizing antibodies (Thevarajan *et al.,* 2020). At first, B cells appear to recognize SARS-CoV-2 through the nucleocapsid protein, which induces their activation and subsequent interaction with cognate CD4+ T cells. The antibody response is obtained 4-8 days after the onset COVID-19 symptoms and dominated by IgM. This initial IgM-response is followed by IgA and then IgG production (10-18 days). The development of mucosal IgA mostly prevents SARS-CoV-2 re-infection. On the other hand circulatory IgA may contribute to systemic SARS-CoV-2 neutralization and to dampen inflammation during active infection (Breedveld and van Egmond, 2019). SARS-CoV-2-neutralizing IgG antibodies should be specific for the S protein and detected in serum at 2-3 weeks post-infection. For this reason, human convalescent serum transfer has been proposed for the prevention and treatment of COVID -19 patients (Casadevall and Pirofski, 2020). In fact, and a number of clinical trials have recently reported its therapeutic value in COVID-19 (Ahn *et al.,* 2020). However, low affinity or suboptimal IgG levels may enhance viral entry into Fcγ receptor-expressing cells through IgG binding. This mechanism may induce the release of inflammatory cytokines and contribute to the CRS reported in some severe COVID-19 patients (Iwasaki and Yang, 2020).

CTL related mechanisms

T cells are instrumental in developing immunological memory in the form of virus specific CD8+ and CD4+ T

cells as shown in case of SARS-CoV (Ng *et al.,* 2016). CD4+ T cells responded to spike (S) protein, which correlated with the magnitude of the anti-SARS-CoV-2 IgG and IgA titers. Prominent lymphopenia, with the subsequent shifts in the T cell subsets composition, is often observed in SARS-CoV-2 infection, similarly to SARS-CoV and some other viruses (Xu *et al.,* 2020). Total numbers of CD4+ T cells and CD8+ Tcells are below normal levels in most COVID-19 patients, with the lowest numbers in the severe cases. The mechanisms involved in the lymphocytopenia are still not known in SARS-CoV and SARS-CoV-2 patients. In severe pneumonia in COVID-19 patients, it has also been shown that highly cytotoxic, activated CD8+ T cells and Th17 cells, can also participate in the CRS, together with macrophages and epithelial cells (Bermejo-Martin *et al.,* 2020). Highly activated T cells participating in viral infection often acquire an exhausted phenotype. Surviving T cells appear functionally exhausted with elevated levels of PD-1 (Diao *et al.,* 2020). The increased expression of PD-1 and Tim-3 on CD8+ T cells was found to progress with the infection.

PATHOPHYSIOLOGICAL MECHANISMS ASSOCIATED WITH COVID-19

Lung pathologies in COVID-19

COVID-19-associated viral pneumonia gets complicated by ARDS. In severe COVID-19 patients postmortem analysis showed extensive alveolar damage along with the formation of hyaline membranes, diffuse remodeling of alveolar wall and accumulation of immune cells like macrophages into the airspaces (Tian *et al.,* 2020). Macrophages accumulating in lungs secrete type I and type III IFNs which induces local antiviral defenses in surrounding epithelial cells. Lung-associated macrophages are responsible for the development of CRS by producing IL-6 and IL-1β, cytokines promoting further recruitment of cytotoxic T-cells and neutrophils. As a result, activated neutrophils produce reactive oxygen species and leukotrienes that directly contribute to acute lung injury (Vardhana and Wolchok, 2020).

Myocardial and endothelial damage

Cardiac injury is a prominent feature in severe COVID-19 patients and is associated with an increased mortality (Liu PP *et al.,* 2020). The pathogenesis of COVID-19 in the cardiovascular system likely results from a combination of several mechanisms such as direct viral toxicity, systemic CRS mediated and stress-related injury. These mechanisms induce cardiomyocyte and endothelial apoptosis, endothelial shedding, plaque destabilization and increase wall shear stress, leading to myocarditis, endotheliitis, ischemia, cardiac arrhythmias and hypercoagulability. ACE2 is highly expressed on cardiomyocytes and endothelial cells, possibly facilitating direct cardiac damage (Liu PP *et al.,* 2020).

COVID-19-related kidney failure

ACE2 is highly expressed on renal tubular cells (Magrone *et al.,* 2020). It has been shown that SARS-CoV-2 can directly infect human kidney cells (Monteil *et al.,* 2020). Other than ACE2, CD147 has also been found to be highly expressed on proximal tubular epithelium.CD147 together with one of its ligands, cyclophilin, plays a crucial role in renal inflammation and renal fibrosis (Qu et al*.,* 2014). Moreover, cyclophilins efficiently control the process of coronavirus replication (Pfefferle *et al.,* 2011). Thus, therapeutic strategies could aim at breaking the CD147-cyclophillin complex.

Pathophysiological mechanism in CNS in COVID-19

The blood-brain-barrier along with the choroid plexus protects the brain from invading microorganisms. Viruses, are still able to traverse the barriers, especially in cases of systemic inflammation causing potential alterations of the central nervous system (CNS).Coronaviruses might exhibit neurotropic properties, and SARS-CoV was detected in human brain (Wu *et al.,* 2020). Moreover, ACE2 is also expressed in the human brain. SARS-CoV can enter the brain via the olfactory nerve leading to a rapid, transneuronal spread to connected areas of the brain (Netland *et al.,* 2008). As SARS-CoV infects immune cells, the virus might penetrate the CNS also via the hematogenous route. Few reports described COVID-19 associated meningitis/encephalitis. COVID-19–associated acute necrotizing hemorrhagic encephalopathy with or without SARS-CoV-2 RNA in the cerebrospinal fluid has also been described (Poyiadji *et al.,* 2020; Zhou *et al.,* 2020). In addition, olfactory and gustatory dysfunctions are often found in patients with COVID-19, which might be due to direct effects on the nervous system (Lechien *et al.,* 2020).

Coagulation parameters in COVID-19 patients

Abnormal coagulation parameters such as mild thrombocytopenia, prolonged prothrombin time, disseminated intravascular coagulation and elevated D-dimers are seen in 36% to 43% of COVID-19patients (Liu *et al.,* 2020; Lippi and Favaloro, 2020).

MULTI-MORBIDITIES AS A RISK FACTOR FOR SEVERE COVID-19

Multi-morbidities are associated with the severe course of COVID-19. In a recent study, patients with COVID-19 showed chronic obstructive pulmonary disease (COPD), cerebrovascular disease, type 2 diabetes mellitus (T2DM), and hypertension as independent risk factors (Wang *et al.,* 2020).

Sex and ageing as a risk factor for COVID-19

The increased vulnerability of males compared to females to severe COVID-19 has been reported during the pandemic. A direct endocrine link is involved as androgen receptor activity is required for the transcription of TMPRSS2 gene (Wambier and Goren, 2020). Male vulnerability may be further enhanced by X-linked inheritance of genetic polymorphisms as both the androgen receptor and the ACE2 genes loci are on chromosome X. Old age was also associated with an increased risk of infection and worse outcome. The aged immune system is characterized by a low-grade chronic systemic inflammatory state marked by elevated inflammatory markers such as IL- 6 and C-reactive protein and an increased susceptibility to infection (Franceschi *et al.,* 2018).

IMMUNOLOGICAL BIOMARKERS OF COVID-19

The list of markers related to severe disease condition. In ICU-admitted COVID-19 patients, significant increases of D-dimer, ferritin, LDH, IL-6, high sensitivity cardiac troponin, IL-2, IL-7, G-CSF, MCP-1, MIP-1α and TNF-α were reported (Huang *et al.,* 2020). Differences in the biomarkers described are most probably due to the different sampling time during disease and the large heterogeneity between the patients (Huang *et al.,* 2020). Single biomarkers will not be predictive only a combination of markers (a biosignature) will help in patient stratification and may even guide patients-tailored therapy.

IMMUNOLOGICAL TREATMENT APPROACHES

Immunological treatment approaches include targeting the CRS and hyperinflammatory status of lung destruction via anti-IL-6R antibodies, IL-1R antagonists, JAK-STAT inhibitors. Other approaches are inhibition of entrance by anti CD147 antibodies and destruction of the virus via protective antibody delivered with convalescent plasma (Sokolowska *et al.,* 2020). Eculizumab targets complement protein C5 and prevents activation of complement terminal complex (Diurno *et al.,* 2020). In addition, clinical trials with type I and III interferons in COVID-19 are currently conducted (Sallard *et al.,* 2020). Targeting T cell exhaustion to reverse the dysfunctional state and restore immune responses can be achieved by anti-PD-1 and LAG-3 therapies (Nguyen and Ohashi, 2015), revealing novel therapeutic opportunities for persisting infections.

CONCLUSION

Since the novel coronavirus disease 2019 (COVID-19) results from the interaction between the SARS-CoV-2 virus and the patient's immune system, it can be assumed that its onset and development significantly depend on this communication. Being a global health issue, COVID-19 urges scientists to put a lot of effort into developing effective therapeutic strategies for treating and saving lives. Further research on the detailed understanding of SARS-CoV-2 infection would be of great significance for the development of effective therapeutic strategies. Immunological aspects of the disease reflect the importance of the immune system to inhibit the viral factors and to control and regulate the pathophysiological processes during SARS-CoV-2 infection. Hence more and more new research on immunological mechanisms associated with COVID-19 is thus important in determining drug targets and developing therapies against this deadly disease.

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