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Understanding of SARA-CoV-2(Covid-19) Immune Response

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Abstract
Pandemic of novel coronavirus disease 2019 (COVID-19)started in December 2019 in Wuhan (China) and rapidly expanded,until it became the biggest global sanitary and economic emergency problem. The causative agent is the severe acute respiratory syndrome coronavirus 2(SARS-CoV-2).Mostly around 80% of COVID-19 patients are exhibits mild to moderate symptoms, but almost 15% of all lead to severe pneumonia and about 5% ultimately develops acute respiratory distress syndrome (ARDS), then death. All immune system components; innate and acquireddefense lines,fight together to encounter the new invader COVID-19virus. Pro-inflammatory host response has been hypothesized to induce an immune pathology resulting in the rapid course of acute lung injury (ALI) and ARDS occurring in covid-19 infected patients. It has been found that the lymphocytopenia and a modulation in total number of neutrophils are common hallmarks and seem to be directly correlated with disease severity and death.As well as a marked decrease in the levels of Blymphoscytes cell and natural killers(NK)cells is reported. Moreover most significantly high serum levels of pro-inflammatory cytokines such as (IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GMCSF, IP-10, MCP-1, CCL3, and TNFα) are relatedwith severe COVID-19. Also C-reactive protein (CRP)and procalcitonin serum levels also affected at covid-19 illness onset.Moreover is found a significantly lower number of total T cells, both T helper (CD4) and T suppressor (CD8) cells during COVOD-19 illness..So this article will highlight of important immune responses during COVID-19 disease.

Key Words: *COVID-19, Immune, Response, SARS-CoV2.*

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I. Introduction

In the 1930s it was the first discovery ofcoronaviruses (CoVs) when an acute respiratory infection of domesticated chickens was diagnosed, whereas human coronaviruses were first reported in the 1960s' .In 2002, the first known case of severe acute respiratorysyndrome (SARS) occurred in China and SARS coronavirus (SARS-CoV) wasidentified in 2003. Before SARS pandemic was declared to be over in summer of 2003, about 8500 cases were reported, including almost 900 deaths in 32 countries[1,2]. Ten years later, in 2012, a novel coronavirus, Middle East respiratory syndromecoronavirus (MERS-CoV), was isolated and was proven to be associated withseveral clusters of cases, first in the Arabian Peninsula and then in other countries.As a result, almost 2500 cases including more than 850 deaths in 27 countries havebeen reported[2]. At that time just four types were identified as well as are circulated in the global human population and contribute to ~30% of common cold infections and mild respiratory symptoms and include the coronaviruses NL63,229E,OC43 and HKU1.5 There are three additional types of coronavirusesrecently known to cause disease in humans areMiddle East Respiratory Syndrome(MERS-CoV), SARS-CoV-1 and SARS-CoV-2 (or COVID-19), are more severe than the four relatively benign earlier counterparts. Although SARS-CoV-1 and SARS-CoV-2 share the same host receptor the human angiotensin-converting enzyme 2 (ACE2), and in spite of ~80% genetic identity between SARS-CoV 1 and 2, these coronaviruses are different in several epidemiologic and biologic characteristics[3,4,5].

In the end 2019 and the beginning of 2020, many human cases of novel coronavirus infection were reported in relation to the Huanan Seafood Wholesale Market (South China Seafood City Food Market) in Wuhan, China. At 9 O'clock, 7 January 2020, the virus was identified as a novel coronavirus and officially named by the WHO as SARS-CoV-2 (or COVID-19). As of 22 June 2020, 8,860,331 confirmed cases and 465,740 confirmed deaths with COVID-19 have been reported globally among 216 countries[4,5]. Already in 2012 the first observations of middle east respiratory syndrome coronavirus (MERS-CoV) was identified. It was found that total of 1401 MERS-CoV-1 infections, and 543 (~39%) of which are died. Since then, it has realized that the CoV is a real threat to humans and the economy as they emerge unexpectedly, spread easily, and lead to catastrophic consequences[6,7,8].

Coronavirus (CoV) are the largest known viral RNA genome. It is enveloped, nonsegmented,positive-sense single-stranded RNA virus genomes in the size ranging from 26 to 32 kilobases, The virion has a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein, which is buried inside phospholipid bilayers and covered by two different types of spike proteins: the spike glycoprotein trimmer (S) tha\at can be found in all CoVs, and the hemagglutinin-esterase (HE) that exists in some CoVs. The membrane (M) protein (a type III transmembrane glycoprotein) and the envelope (E) protein are located among the S proteins in the virus envelope. CoVs were given their name based on the characteristic crown-like appearance. The structure of CoVvirion is shown inFigure 1.

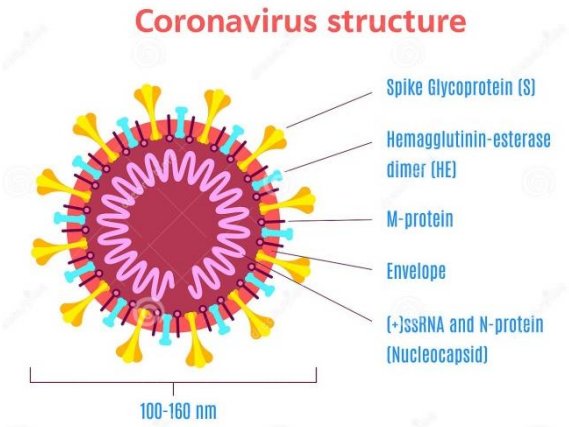

Fig.1 : Coronavirus virion structure diagram isolated on white background. Infographic template. Stock vector illustration in flat style

Temperton and Ho in 2005 have been reported that most recovered SARS-CoV patients have higherand sustainable antibody responses compared to those observed in fatal cases[9,10]. This suggests showed that antibodyresponses are likely to play an important role in determining the ultimate diseaseoutcome of SARS-CoV infection. Several forms of possible vaccines, such as attenuatedor inactivated SARS-CoV, have been evaluated in animal models but it is difficult to evaluate whether these vaccines will prevent the disease in humans; may due tothese animal models, including nonhuman primates, lack the severe clinical features observed in humans[11,12,13]. As the inflammatory response is strongly implicated in the pathogenesis of SARS-CoV, a full understanding of the mechanism of protective immunity against SARS-CoV in humans is critical in the development of a safe prophylactic vaccine for use in humans[14,15,16].

II. Innate Immune Response

large-scale experimental analysis of plasma from SARS-CoVs patients shows activation of innateimmune responses and demonstrated increased acute phase proteins such as serum amyloid A (SAA) and Mannose-binding lectin (MBL)[17].Early study in 2005 showed that MBL could bind to SARS-CoVand inhibit virus infectivity by blocking the carbohydrate-recognition domains of the S protein[16]. As well as observed, that low MBL serum concentrations andhaplotypes associated with MBL deficiency have been observed in SARS patients[18].

On the other hand several studies shown sever reduction in the total number of natural killer(NK) cells like CD3, CD56, CD16, CD158b were detected during the course of SARS-CoV infection, and reported that such reduction is associated with the severity of disease[19,20]. However, the significance of thesechanges in SARS-CoV pathogenesis is not clear. In a C57BL/6 mouse model of SARS infection, NK and NKT cells are not required for viral clearance in beige and CD1/mice[21,22].

Regarding of cytokines and chemokinesdrastic elevation (known as a cytokine storm)is observed in the tissues and serum is a classical feature with acute coronaviruses infection[23,24,25] .Recent above studiesdemonstrated that during the first 14 daysof infection onset, concentration of IL1b, IL-6, IL-12, IFN-g, IL-8, IP-10, and MCP-1 aremarkedly up-regulated; then reduction in the level of these interleukins isassociated with recovery from coronaviruses pneumonia[26,27,28]. These interleukins are predominantly pro-inflammatory cytokines and represent mainly the innate immuneresponses such as monocytes/macrophages and NK cells against viruses[27]. The predictive valueof cytokines in covid-19 disease outcome is still limited. IL-6 has been strongly associatedwith radiographic score, and increased Thelper cell cytokines are observed in patients witha fatal outcome[27,29]On the other hand reported that some of immunosuppressive factors like IL-10,TNF-b,and prostaglandin E2 (PEG2) are presented in the serum with coronaviruses cases such, observations may provide an alternative explanation for prolonged andsevere clinical outcomes[25,26,30]. As well as other surveillances

suggested that there is dysregulation of type I and II interferon responses was associatedwith defective adaptive immunity and a severe disease outcome for SARS-CoV patients[31].

III. Antibody and B-Cell Responses

IgG Serum immunoglobulin against N protein,in patients with SARS-CoVare present after primary infection. By using of immunofluorescence assays and ELISA technique, also canbe detected as early as four days after illness onset. In addition serum IgM, and IgAresponses to SARS-CoV are present around the same time, with most patients seroconverted by day 14 after illness onset[32]. Through the study of 56 cases with corona viruses reported that SARS-specific IgG and neutralizingantibodies peaked at month 4 and decreased thereafter[33,34]. In a large study of 623coronaviruese patients, antibodies were able to neutralize pseudotyped viruses bearing Sproteins from four different SARS-CoV strains, suggesting that these antibodies arecross-reactive[35]. Among structural proteins, only the S protein elicitsneutralizing antibody[36]. The major immunodominant epitopein S protein lies between 441 and 700 amino acids[37].

IV. Immunopathology of Covid-19

Mostly around 80% of COVID-19 patients are asymptomatic or exhibits mild to moderate symptoms, but almost 15% of all lead to severe pneumonia and about 5% ultimately develops acute respiratory distress syndrome (ARDS), septic shock and/or multiple organ failure then death[37,38]. As for SARS and MERS-CoVs, the most common symptoms of SARS-CoV or COVID-19 are fever, fatigue, and respiratory symptoms, including cough, sore throat and shortness of breath[38,39].

Mostly, covid -19 infection stimulate the innate and acquired immune response, and exaggerated inflammatory innate response and dys-regulated acquired host immune defense may cause harmful tissue damage at both at the site of virus entry and at systemic level. Several studies reported that the excessive pro-inflammatory host response has been hypothesized to induce an immune pathology resulting in the rapid course of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) occurring in covid-19 infected patients[38,39]. The so-called "cytokine storm" is a perfect example, and reflecting of a widespread uncontrolled dysregulation of host immune defense. Like such situation given the key role of the immune system in COVID-19 illness, a deeper understanding of the mechanism behind the immune dysregulation, as well as of SARS-CoV-2 immune-escape mechanisms might give us clues for the clinical management of the severe cases and for preventing the transition from mild to severe stages[38,39].

V. Immune response to SARS-CoV-2 (COVID-19)

Very recently studies highlightedon the criticalchanges that occurringinboth innate and adaptive immune system during COVID-19 infection. It has been found that the lymphocytopenia and a modulation in total number of neutrophils are common hallmarks and seem to be directly correlated with disease severity and death[39,40].On the other hand several studies showeda marked decrease in the levels of CD4+, CD8+, B cell and natural killers cells[41] as well as in monocytes, eosinophils and basophils has been reported in cases with severe COVID-19.Moreover mostsignificantly high serum levels of pro-inflammatory cytokines such as (IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GMCSF, IP-10, MCP-1, CCL3, and TNFα) are reportedof patients with severe COVID-19[42,43,44].Also reported that C-reactive protein (CRP) also affected during covid-19 illness onset, it was found that highCRP and procalcitonin serum levels are displayed[45].

Noteworthy, that ACE2 receptorwhich is the preferred receptor of coronaviruses is only expressed in monocytes, macrophages, and T cells in the lung, hence, the mechanism by which how coronaviruses directly infects immune cells is still unknown[46].Since the covid -19 belongs to coronaviruses. the question remains by which mechanism exactly covid-19 infect monocytes and macrophages;present and future studies will be answered.Guesses in this regard, it may be that covid-19 capable to bind other specific receptors and/or other mechanisms of viral entry mode can be exploited by the virus. As far as concerns the acquired immunity, the novel covid-19 has been demonstrated to mainly affect lymphocyte counting and balance.In particular, Li et al. reported that, compared with survivors, dead COVID-19 patients showed lower percentage and count in CD3+, CD4+, and CD8+ lymphocytes populations, strong predictive values for in-hospital mortality, organ injury, and severe pneumonia[45]

During illness with coronaviruses that can cause fatal lowerrespiratory tract infections and extrapulmonary manifestationsit was found that CD4 Thelper, and CD8+ T suppressor cells particularly play a significantantiviral role by balancing the combat against pathogens and the risk ofdeveloping autoimmunity or overwhelming inflammation[47,48,49]. CD4+T cells induce the production of virus-specific antibodies by activatingT-dependent B cells. However, CD8+ T cells are cytotoxic and can killviral infected cells. CD8+ T cells account for about 80% of total infiltrative inflammatory cells in the pulmonary interstitium in coronaviruses infected patients and play a vital role in clearing coronaviruses in infected cellsand inducing immune injury[50,51].

In 2020 Qin and his colleagues in Wuhan city displayed a significantly lower number of total T cells, both T helper and T suppressor cells[40].As it's known that T cells are essential immune components, whose balance is crucial for maintaining a highly efficient defensive response. Naïve T cells enable the defenses against new and previously unrecognized infection by a massive and tightly coordinated release of cytokines, whereas memory T cells mediate antigen-specific immune response. A dysregulation in their balance, favoring naïve T cells activity compared with regulatory T cells, could highly contribute to hyper inflammation. A reduction in memory T cells on the other hand could be implicated in COVID-19 relapse, since a number of recurrences has been reported in recovered cases of COVID-1950. These data are consistent with results reported by Tan et al.29 Overall, the lymphopenia observed in COVID-19 patients may depend on the fact that SARS-CoV-2 may directly[52,53].

Usually lymphocytes expressing ACE2receptors; which is the preferred receptor of coronaviruses, So it will be infected duringcovid-19 illness and subsequently death.Lymphocyte it will be the inevitable resultor, alternatively, may directly damage lymphatic organs since they express ACE2 receptors. However, to date no data are available on lymph nodes and spleen shrinking and lymphocytes functionalities, hence such speculations need to be further investigated to confirm these hypotheses[54].

Regarding B lymphocytes and antibody-secreting cells during coronaviruses infection. The antigen stimulation of coronaviruses was clarifiedby using the specific 9-mer peptide "CYSSLILDY", which located atposition 437 to 445 within the region of the S glycoproteinon the envelop of coronaviruses[55,56]. Thesequence has the highest B cell antigenicity plot and has the ability toform the greatest number of interactions with MHCI alleles in acomputerized simulation. Reports show that humoral immunity isessential to control the persistent phase of coronaviruses infection. Moreantibodies isolated from patients who have survived MERS-CoVinfection have been described, including MCA1, CDC-C2, CSC-C5,CDC-A2, CDC-A10, MERS-GD27, and MERS-GD33[57,58]

Very recent studies concerning of B cells, reported that there is found significant changes in B cells. In particular, while the naïve B cells have been reported to be decreased, the plasma cells have been found remarkably increased in peripheral blood mononuclear cells[59]. Moreover, several new B cell-receptor changes have been identified (e.g. IGHV3–23 and IGHV3–7). In addition, isotypes, including IGHV3–15, IGHV3–30, and IGKV3–11, previously used for virus vaccine development have been confirmed[57]. The strongest pairing frequencies, IGHV3–23-IGHJ4, has been suggested to indicate a monoclonal state associated with SARS-CoV-2 specificity. InCOVID-19 patients, it is found that 100% of patients had positivevirus-specific IgG approximately 17 - 19 days after symptomonset. Instead, 94.1% patients showed positive virus-specificIgM approximately 20-22 days after symptom onset[59,60] .

In addition to these observations about host immune responses,there is a critical point has to be raised concerning the ability to escape from antiviral host defense lines. Viral evasion from host immune system is in fact believed to play a major role in disease severity[61].Previous study suggested that coronaviruses escape and suppress the signaling pathways mediated by type I Interferon (IFN); a key cytokine secreted by virus-infected cells to protect nearby cells to heighten their anti-viral immune defenses. So based on genomic sequence comparison and on partial identity of covid-19 with other coronaviruses , it is speculative that covid-19 can adopt similar strategies to modulate the host innate immune response, thus evading immune detection and dampening human defenses[62].

VI. Inflammatory cytokine storm and lung damage

When a virus invades the host,pathogen-associated molecular patterns(PRRs) initially recognize the viralnucleic acid, collect the specific signal adapter protein, activate Interferon regulatory factor 3 (IRF3)andInterferon regulatory factor 7(IRF7). before being translocated to the nucleus and promote thesynthesis of type I interferons (IFNs). Type I IFNs subsequently activate the downstream Janus kinases (JAKs), signal transducer and activator of transcription proteins (STATs), JAK-STAT signal pathway, promote the expression of IFN-stimulated genes (ISGs)[63,64]. It is reported thatIFNs limit virus spread, and play an immunomodulatory role to promote macrophage phagocytosis of antigens, as well as NK cells restriction of infected target cells and T/B cells. Thus, blocking the production of IFNs has a direct effect on the survival of the virus in the host[65,66]. It has reported that patients with severe COVID-19 suggested that extensive changes in the serum levels of several cytokines play a pivotal role in the pathogenesis of COVID19[44,67,68].Such hyper-cytokinemia, the so-called "cytokine storm," has been proposed as one of the key leading factors that trigger the pathological processes leading to plasma leakage, vascular permeability, and disseminated vascular coagulation, observed in COVID-19 patients, and accounting for life-threatening respiratory symptoms[39]. On the other hand demonstrated that plasma concentrations of IL-1β, IL-1ra, IL-7, IL-8, IL-9, IL-10, basic FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, TNFα, and VEGF were higher in both ICU (intensive care unit) patients and non-ICU patients than in healthy adults. Moreover, when comparing ICU and nonICU patients,

plasma concentrations of IL-2, IL-7, IL-10, G-CSF, IP-MCP-1, MIP-1α, and TNFα were higher in ICU patients thannon-ICU patients, thus indicating that the cytokine storm might becorrelated with disease severity[38].

Another confirmatory study showed that found 15 cytokines (IFN-α2, IFN-γ, IL-1ra, IL-2, 4, 7, 10, 12 and 17, chemokine IP-10, as well as G-CSF and M-CSF) are associated with lung injury based on murray scorewith severe COVID-19 pneumonia[68].

VII. SARS-CoV-2/or (Covid-19) Vaccines

Any vaccine of covid-19 will be withina biotechnology technique to provide acquired immunity against coronavirus disease 2019 (COVID‑19). In the end of July 2020, there was around 218 vaccine candidates were indevelopment around the world.although there is no candidate vaccine has been completed clinical trials to prove its safety and efficacy[69,70].Previous attempts to develop a vaccine against the coronavirus diseases SARS-CoV and MERS-CoV established considerable knowledge about the structure and function of coronaviruseswhich accelerated rapid development during early 2020 of varied technology platforms for a COVID‑19 vaccine.But all the previous coronavirus vaccine candidates failed in early-stage clinical trials, with none being advanced to licensing[71].The Coalition for Epidemic Preparedness Innovations (CEPI) CEPI classifies development stages for vaccines as either "exploratory" (planning and designing a candidate, having no evaluation in vivo), "preclinical" (in vivo evaluation with preparation for manufacturing a compound to test in humans), or initiation of Phase I safety studies in healthy people[72,73].

VIII. Conclusion Remarks

SARS-CoV-2/covid-19 pandemic considered one of the biggest global challenges for the WHO, since the pandemic influenza outbreak of 1918 and provides an unprecedented challenge for the identification of both preventive and therapeutic drugs. There is an urgent neededto effortsuniteto provide effective vaccines and treatments to counter this hateful virus. But fortunately, and by virtue of biotechnology, there are a good newsto manufacture an effective vaccine of several RNA and DNA vaccine candidates, licensed vectored vaccines, recombinant proteins and cell culture-based vaccines for many indications to ends the devastating effects of this Infinitesimal creature.

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