Current Scenario: Covid-19 and Host Innate Immune Response

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Abstract - The respiratory disorders, the caused by novel corona virus covid-19 (SARS-CoV-2) is a highly contagious disease. The ongoing outbreak has declared as pandemic by World Health Organization (WHO) and it is a global public health emergency. Corona viruses (CoV) belong to the family Coronaviridae with its high mutation rate .The covid19 virus is differ from other corona viruses in an inducing the potent storm of pro inflammatory cytokines that causes the exhaustion of T cells , a state of poor effectors function. The innate and adaptive immune system responds vigorously to get rid of Covid-19 infection. The infection becomes severe where immune system is compromised especially in the elderly individuals if having diabetes, tuberculosis or cancer and are more prone to severe infection. Currently, enormous efforts in the research on novel corona virus are in progress. This review is in the ancipitation to understand better the interaction of human innate immune system to COVID-19 which is a nonspecifically act to combat the infection and act as a first line of defense mechanism by reviewing the different tools of adaptive immune response so that it could help to design effective immunotherapy against the COVID-19.

Keywords: SARS-CoV-2; COVID-19; coronavirus; pneumonia; respiratory infection, innate, adaptive

I. INTRODUCTION

A case of unidentified Pneumonia in Wuhan, Hubei Province, People's Republic of China was reported on 31st December 2019[1].The cluster of patients indicated symptoms as fever, breathing difficulty, and lung infection. These symptoms were similar to viral pneumonia and accordingly this was linked to a local Huanan South China Seafood Market in Wuhan, Hubei Province, China and confirmed by WHO also but no specific animal association was identified[2].The virus was isolated and the virus genome sequence was published on 7th January [3].
The outbreak was declared as public health emergency on 30th January 2020 by WHO when there were 7711 confirmed and 12167 suspected cases throughout the country .At the time of writing this paper the disease is spread in 213 countries and there are 23 M confirmed cases,15M recovered and 807K deaths .The data is changing day per day as number of confirmed cases are increasing day by day. WHO officially named the disease COVID-19. International Committee on Taxonomy of Viruses (ICTV) named the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]. Due the recent advanced techniques like next generation sequencing (NGS) and open access information, scientists started the comparative and core information studies on the clinical aspects of infected patients and the host immune responses to explore the various strategies for treatment of the pandemic infection[5].The review aims to provide meaningful information with respect to the immune response against this COVID-19 for future research to explore more drug target receptors to fight against this Epidemic.

II. VIRAL KEY FACTORS AND TRANSMISSION

The corona virus belongs to coronaviridae family, sub family orthocoronavirinae and order virinals. The orthcoronavirinae are further subdivided into four groups initially sorted on the basis of serology but now divided by phylogenetic clustering into alpha, beta, gamma and delta [6].The 2019 novel CoV (SARS-CoV-2) is the newest addition to human CoVs (HCoVs) that also include 229E, OC43, HKU1, NL63, severe acute respiratory syndrome (SARS) CoV, and Middle East respiratory syndrome (MERS)CoV. The 229E and NL63 belong to Alpha coronavirus, others are members in the genus of Beta coronavirus[5].The corona virus consists of non segmented, positive RNA genome of ≈ 30 kb. The corona virus RNA genome was fully sequenced [7]can act as m RNA having 5'cap and 3'poly A tail for translation of replicase polyproteins [8].

The four HCoVs cause common cold only, but could become the cause of pandemics of highly contagious respiratory diseases when they crossed species barrier and are able to infect humans. The existing all seven HCoVs are having zoonotic origin from bats, rodents or domestic animals[9].Based on covid-19 RNA genome sequence ,comprehensive sequence analysis with relative synonymous codon usage (RSCU) among different animal species

showed that virus to be a recombinant virus between the bat corona virus and another corona virus with unknown origin[10].Ji and colleagues suggested that snake could be the most probable animal reservoir as the RSCU usage sequence analysis found to be the closest to snake. By using deep learning algorithm for the analysis of gene sequences of novel corona viruses and other corona viruses to predict viral host indicated that bats and mink could be the two potential hosts out of which the intermediate host may be the mink for the new corona virus[11].The reservoir hosts for these corona viruses are selected through evolution. Due to evolutionary selection and mutual adaptation, the virus usually becomes non pathogenic or cause very mild disease. However, when they cross the animal species barrier as SARS-CoV-2and enters into a new host such as human initially the due to due to a new round of adaptation the intensity of the disease is significant. The infection outcome is governed by the tug of war of host antiviral defense strategy and virus.

During the Covid-19 infection this host immune response become out of control and is associated with pulmonary tissue damage, respiratory functional impairment and reduced lung capacity. The cytokines and chemotactic functions which are essential to regulate the dilation and directing the leukocyte traffic in the host lungs. The immune insufficiency or misdirection causes tissue damage and virus got opportunity for replication. Besides that overactive response of immune system the situation further worsens due to cytokines storm in Covid-19 infection

The corona viruses are enveloped polycistronic, non-segmented positive single strand RNA genome about 30 kD in size. The virus has a nucleo capsid consisting of a RNA positive RNA genome and the phosphorylated N(nucleocapsid) protein located inside the phospholipid bilayers and also covered by a glycol protein trimmer; the S (spike) and HE (hemagglutinin-esterase) [12,13].The M (membrane) protein and E (envelope) are situated among the S proteins in the virus envelope The life cycle of corona virus begins in the host by the binding of corona surface spike protein to the specific receptor on the cell and fusion of viral envelop and host cell membrane take place [14-16].Different receptors are used by different types of corona viruses such as SARS-CoV and HCoV-NL63 from beta and alpha genera respectively recognize angiotensin-converting enzyme2(ACE2) [17-19]. The HCoV-229E of alpha genus found to be recognized aminopeptidase(APN) [20]. The Dipetidyl peptidase4 (DPP4), another surface receptor recognized by MERS-CoV [21]. This virus and host cell membrane fusion dictates species–specific entry of virus in the cell[22].The activity of CoV S protein initiate the viral interference including cytokines and IFN production[23,24].

III. INTERACTION COVID-19 TO IMMUNE RESPONSE

3.1.Covid 19 and Innate Immune system

The invasion of virus is first encountered by innate immune system.The soldiers of innate immune systems are virus specific pathogen associated molecular pattern recognition assembly system known as Toll –Like receptors,Complement system,Interferons,macrophages and neutrophils and imflammatory cytokines.

The virus could be identified by recognizing virus specific pathogen associated molecular patterns (PAMPs). Pattern recognition receptors(PRRs) which are the family of 11 proteins that reconized the unique sequence that is from conserved non self molecules called PAMPs that could activate the host innate immune defense mechanism[25].

The two more pivotal importance pattern recognition receptors are Tol-like receptors(TLRs) and retinoic acid-inducible gene I(RIG-I)-like receptors (RLRs) in Co V infections [26,27].These recognized both the intermediate of RNA replication and viral RNA. There are two sensors present one is in the alveolar epithelium and another one is in cytosol as TLR 7/8 and RIG-I/MDA-5 respectively[28,29].when the virus entered into the alveolar epithelium it is sensed by the TLR 7/8 which is a single stranded RNA sensor and the double stranded RNA sensor RIG-I/MDA-5 .After the virus recognition both the sensors induce down regulation by recruiting the MyD88 and MAVS adapter proteins.

The recruitment of these adapter proteins leads to the activation of two transcription factor IRF3/7 and NK-κ respectively and also activate the production of Interferon alpha and beta along with IL6 and TNFα which are proinflammatory cytokines[30].Along with the activation of the proinflammatory cytokines, additionally the virus activate the inflammasome sensors NLRP3.In response to the viral recognition pattern the inflammasome complex assemble in the cytoplasm of macrophages.The previous study showed the activation of inflammasome by SAR Co V virus envelope protein E and another protein 3a[31,32].

3.1.1 Interferons

The Interferons which are signal proteins formed in response to the infection and play very important role in controlling the covid -19 infection. There are three types of Interferons .Type I consists of INF α,κ,€ and ,ω. Infected cells produce Type I interferons. The Type II has Interferon γ as only one member and Type III Interferons are produced by some immune cells and epithelial cells [33,34]. Two cytosolic recognition receptor protein Melanoma differentiation –associated protein 5(MDA5) and retinoic acid-inducible gene)(RIG) causes activation of IRF3 and results in activation of the transcription factor of Interferon Type I. The Type I interferon play a crucial role in the early phase of corona infection resolution [35]. The effectiveness of the typeI interferon was established by a number of research studies such as the study which was done by Higgins et al2018 on examining the efficacy of the recombinant Type I interferon alpha through nasal administration by comparing between the healthy volunteers and patients infected by corona virus for the protection against respiratory viral infection .The severity of the disease and virus load were found to be significant lower in the interferon alpha treated group [36]. As Type I interferon is very crucial and appears to play its first line of defense role in protection against virus. There are many SAR- CoV -2 virus proteins that act on either the effectors functions of the interferon alpha or by inhibiting the transcription factor .The corona proteins nsp1,nsp3,nsp16,ORF3b, ORF6 and M and N proteins[37,38].The ability to inhibit the various interferon vary among Corona virus family. For example HKU1 causes mild flu infection while SARS-CoV and MERS CoV are very potent in inhibiting the interferon activity and modification in the interferon activity results in the cytoplasmic storm that causes severe respiratory disorder [39].

3.1.2 Complement system

The complement system is a very important part of the innate immune defensive system. The complement system consists of a groups of serum proteins which are present in an inactive state in the serum. They become activated and act in a cascade manner to work against the nonself molecules following the recognition the DAMPS(Danger Associated Molecular Patterns) and PAMPS(Pattern Associated Molecular Pattern) . There are three ways which the complement system could be activated in blood. The classical pathway is activated by recognizing uncoated or coated immunoglobulin antigens. It initiated with C1 that consist of three subunits CIq,C1r and C1s[40]. The alternative pathway activated by microbial cell wall components and the lectin pathway is triggered by the presence of the bacterial carbohydrates that bind to mannose binding lectin(MBL) .Once recognized cascade of reaction occurs in which every protein component breakdown in the two unequal components. The bigger one act as an enzyme whereas the smaller one can cause inflammation reaction[41,42].As complement is a very integral part of innate immune response and classic pathway play a very important role in viral infection[43].

A study carry out recently suggest that in the Acute Respiratory Distress Syndrme (ARDs) due to closely related corona virus named SARS-CoV infection become worsen due the activation of complement C3[44]. The study suggest the use of C3 inhibitor that also cause the inhibition of C5a could be effective in reducing the inflammatory cytokines .Although there are studies to indicate that complement play a very important role with respect to exaggerate the ARDs but data for the effectiveness on SARS-CoV2 is less[45].

A recent study indicate that the biopsy taken from lungs of the SARS CoV 2 infected patients show the elevated levels of the complement proteins[46].The inhibition of the complement components specifically C3 and C5a could proof to be effective therapy that need to be investigated in detail as inhibition ofC5a by using different inhibitors in many respiratory infections have in use from last 15 years [47].The inhibition of classic or alternative pathway by using different inhibitor components need to be studied.

3.1.3 Immune Cells

Neutrophils

Neutrophils are first line of phagocytic immune cells. Their numbers were found to be increased in blood of Covid-19 patients with lymphopenia. Infiltration of neutrophils observed in lungs of the patients died due to covid 19 .More studies on its pathophysiological aspect are required to define the role of neutrophils in the disease [48-50]. When viral infection occurs and the expression of the viral specific protein occur this leads to the damage of the epithelial cells resulting in the infiltration on Neutrophils at the site of infection .This causes the release of the cytokines[51].The in-vitro study demonstrated that the corona virus infected lung's Type I alveolar cells linked with the neutrophils had an increased m RNA expression of CC chemokines (CCL-2,CCL-4,CCL-7,CCL-9,CCL-12 and CCL-22),CXC chemikines (CXCL-1,CXCL-2,IP-10,and CXCL-11) and the proinflammatory chemokines(IL-18,IL-1a,IL-1b and TNF-a) [52].More studies required to establish a certail role of neutrophils in tissue damage and in the recruitment of immune cells at the of early infection[53].

3.1.4 Monocytes and Macrophages

The monocytes cells are the commited phagocytic immune cells that play a veryimportant role as opsonin. These cells are having kindney shaped nucleus called monocytes when present in blood. In blood these monoctytes have the life span about 7 days but when these cells enter in tissues and reside there then called macrophages. The

macrophages have different names according to the tissue in which they reside.The studies on the covid -19 patients's autopsies showed that tere were intensive infiltration of monocytes and macrophages along with other immune cells[54].
The macrophages active involvement in Covid 19 infection can be inferred by studying the immune response of hosts from other closely related SARS CoV virus.In SARS CoV infection the interaction between Inflammasome ,which is big molecule of multiple subunits and an integral part of the innate immune response and Open Read Frame 8 (ORF-8) ,a accessory protein involved in the activation of the stress at the intracellular level resulting in the lysosome damage and cell autophagy occur ,through a series of reactions[55].RF8 first interaction with a structural protein ,crypyrin(NLRP3) of inflammasome forms intracellular aggregates .This results in a conformation change and activation of inflammasome. The Pro- caspase-1,a proteolytic enzymes act on two proteolytic proinflammatory cytokines pro-IL-18 and pro-IL-1-β[56].When these two proinflammatory cytokines activated this leads to the cascade of reactions causes a special type of programme cell death named pyroptosis. In pyroptosis ,the cell recognizes the intracellular pathogen and release cytokines,chemokines and by itself undergo programmed cell death as a result the chemotaxis of the circulating immune cells at the site of infection take place.
The pyroptosis is a important link between the innate and adaptive response.IL-18 play a important role as once it releases it stimulates the production of IFN γ .T helper cell type1 development and polarization take place a adaptive response take place [57-62].This could be suggested that due the high analogy between SARS CoV2 and SARS Co V virus in ORF-8,the same events could be happen in SARS CoV2[63,64].

Another important cytokines which is released from the macrophages is IL-1 , one the key cytokines leads to cytoplasmic storm.The aggrecive form of ctopasmic storm is very much like the hemophagocytic lymphohistiocytosis[65].There are many clinical trials on by using various IL-1 receptor antagonists to block the cytokine storm [66]. There is a IL-1 antagonist ,Anakinra reported to be a effective in Covid-19 pneumonia [67].More clinical trials and study are in a process to determine the efficacy of the Anakinra and other antagonist.

3.2 Covid-19 and Adaptive Immune Response

Host adaptive immune response that consists of T cells and antibodies also play a important role to control the Covid-19 infection. When Covid -19 gets entry inside the cell through the binding to the ACE-2 receptor via spike protein it takes over the control over cell machinery. Once the virus is inside the cell it replicates in the cell cytoplasm by using viral RNA –dependent –RNA polymerase.When the progeny will mature,they will not kill the host cell instead of release through the budding[68-70].Recent work in cellular immunology has uncovered the T subset involvement as in high grade chronic viral infections, CD8+ T cells cannot sustain long term activation and enter a stage of 'exhaustion'. Exhausted T cells (Tex) are epitope-specific, and different and distinct from anergic T cells. High-grade chronic viral infections may lead to depletion of specific Tex subpopulations via apoptosis. Tex express certain specific markers, including CD279 (programmed cell death marker-1, PD-1) and CD366 (T cell immunoglobulin & mucin domain-3, Tim-3) and either produce or are modulated by certain cytokines, including IL-10.The dysregulation in metabolism and inhibitory expression of receptor with very poor memory , inefficient self –renewal and epigenetic programs are the characteristics of Tex cells Programmed cell death protein1PD-1 (CD279) and T-cell immunoglobulin and mucin-domain containing-3 (Tim-3) (CD366) expression are critical checkpoints for T cell exhaustion [71-75].More studies are required on the T cell receptor agonist to target a potential therapeutic candidate.
In Covid -19 ARD,it is the cytokine storm released by immune system that damage the lungs and other organs. The activated immune defensive system attack on the virus infected cells to kill them to get rid from virus inside. This cytokine storm is mediated by one of the arm of immune system i.e cell –mediated immune while another humoral immune arm through neutralizing antibodies prevent them from entering into the uninfected cells by neutralization process [76]. In neutralization, the host cell antibodies recognize the nonself antigen on the virus protein called spike which protrude out from the envelope of virus. Blocking the attachment site of the spike protein prevent the binding of virus to the healthy cells as virus bind to the host cell via the spike which binds to AnG2 receptor on the host cell. Therefore, there is cooperation between the innate and adaptive defense immune response. In individuals where immune system is weak or suppressed the virus overcomes the defensive mechanism and results in severe consequences. Actually, more research on immunopathogenes is needed so that the cytokine cyto- storm that cause lung damage could be prevented by applying the immunomodulatory effects of many cytokines such as use of IL-10 which inhibit the IL-12,TNF –alpha and IFN –gamma and could inhibit the Th1 response[77] .

IV. CONCLUSION

The pandemic cause by SARS-CoV2 virus created both the state of immediate uncertainty for the treatment as well as residing the trust on the science and scientist to come back with the effective treatment as well vaccine against it. There are ample of new knowledge and options available for research based on genomics and proteonomics. The immune system play a very crucial first line of defense against corona virus. Both innate and adaptive immune response involved aggressively against it. More research study required with respect to innate and adaptive immune response to study antagonists against crucial cytokines play a role in the induction of cytokine storm and development of vaccine and use of plasma therapy for Covid-19 patients.

Compliance with Ethical Requirements
Author declares no conflict of interest and ethical statements.

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