Immunology of COVID-19 and its clinical implications for therapy

The world has already experienced several viral attacks in the 21st Century (Christou, 2011) have affected millions of people globally and caused substantial mortality and morbidity (Sutton, 2018). One that caused global pandemic and fear is newly emerged novel coronavirus (COVID-19) (Wilder-Smith *et al.*, 2020). It is highly contagious, large enveloped, single-stranded, non-segmented, positive-sense RNA virus that belong to coronaviridae family and genus Beta coronavirus (Yan *et al.*, 2020). The viruses of coronaviridae family are further divided into two subfamilies; Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) (Kindler *et al.*, 2016). COVID-19 show close similarities to SARS-CoV due to phylogenetic relationship and genome structure. World Health Organisation (WHO) has designated the current pandemic of SARS-CoV-2 infection as COVID-19 (Sohrabi *et al.*, 2020). The virus shows high infectivity and mainly transmitted in the form of droplets with an incubation period of about 4-5 days. The onset of symptoms in patients is usually within 11-12 days (Linton *et al.*, 2020). The most prominent symptoms seen in almost every patient includes dry cough, fever, fatigue, sore throat, lack of smell and taste, and severe patients suffer from breathing difficulties (Guan *et al.*, 2019). We do not have any effective therapeutics or drugs approved by the U.S. Food and Drug Administration (FDA) to prevent or treat COVID-19 infections presently. The only treatment available for patients with COVID-19 is supportive care, including supplement oxygen and mechanical ventilator support. Therefore, there is an urgent need to develop an effective therapy to treat patients infected with COVID-19. The present situation calls much attention on prophylactics and therapeutics approach.

This virus contain four structural proteins viz. the spike (S), membrane(M),envelop (E) and nucleocapsid (N).The S protein is considered to be highly immunogenic and contribute protective immunity in contrast to N, M and E proteins(Saha *et al.*, 2020). Many laboratories have confirmed the entry of virus into human cells after its fusion with cell membrane of target tissues. After fusion, the S protein undergoes proteolysis by host proteases and give rise to S1 and S2 fragments. Thus, S1 protein is ready to interact with angiotensin converting 2 (ACE2) receptors present on respiratory and intestine epithelia besides alveolar macrophages present in the lungs(Cheng *et al.*, 2020). Few studies have confirmed that ACE2 receptors are present in other cells too. S1 protein has a domain that interacts specifically with a domain on the ACE2 receptor. This interaction is must to produce the symptoms of disease (Nadeem *et al.*, 2020).One must understand the role of chloroquine analogues works here by inhibiting virus fusion into the cell membrane. Some laboratories have generated both polyclonal and monoclonal antibodies against S1 domain and inhibited the interaction (Ravichandran *et al.*, 2020; Zhao *et al.*, 2020). This is one of the areas of immunotherapy. Some key amino acids present on the S1 domain initiate this interaction with high affinity (Saha *et al.*, 2020). If these amino acids are blocked by monoclonal antibodies or lacked by chance due to mutation, the rate of infection would be reduced and patients may show minimal symptoms. This protective effect can be seen by reduced affinity of viruses to ACE2 receptor that would result in decreased infection.

As the virus is getting mutated, some infected persons shown critical symptoms and other escape the disease severity. If the virus continues to mutate to lower its pathogenicity, there is a high possibility that it might coexist with humans. Using computational and bioinformatics, few laboratories have predicted B cells, T cells and cytotoxic T cells epitopes on S protein as well as other structural proteins(Baruah *et al.*, 2020). This will help us to develop virus specific neutralizing antibodies by gene cloning or peptide synthesis-based approach. We personally feel if we have antisera from recovered patients of COVID-19 infection, using panel of peptides from different regions of viral proteins will help us to develop diagnosis kits and peptide-based vaccine. Since immune response is based on individual Human Leukocytes Antigens (HLA), the above approach will help to identify immunodominant regions on viral proteins. In addition, we can identify the polymorphic loci on HLA genes among infected persons showing clinical symptoms and others escape the disease severity to confirm the susceptibility towards infection, immunity and outcomes.

COVID-19 infection has led to inflammatory storm due to presence of hyper activated immune cells and over-production of pro-inflammatory cytokines that may determine the outcome (Ye *et al.*, 2020). Several studies have shown the presence of elevated levels of

serum pro-inflammatory cytokines (IL-6, IL-1 β and TNF- α) and increased immune inflammatory cells leading to cytokine storm, which could be partially responsible for immune mediated problems in the lungs of the patients (Ye *et al.*, 2020; Felsenstein *et al.*, 2020). Immune mediated, acute respiratory distress syndrome (ARDS) are commonly seen in ICU that are associated with poor outcome in patients with COVID-19 (Zhang *et al.*, 2020). Therefore, specific blockade of inflammatory storm associated with hyper-inflammation during COVID-19 is an important therapeutic approach when compared to the systemic immunosuppression. To our knowledge, few clinical trials are ongoing to test the safety and efficacy of targeted therapies associated with IL-6, IL-1 receptor and Janus kinases (JAK) blockade in severe COVID-19 patients (Neurath, 2020; Russell *et al.*, 2020). Like targeted therapies, several clinical trials of anti-viral drugs therapies such as Remdesivir, Lopinavir and Favipiravir are ongoing study (Şimşek and Ünal, 2020; Cao *et al.*, 2020). The safety and efficacy of these trials are still unclear which need furthermore investigations in patients across the globe. Recently, few studies have confirmed blood clots in lungs and heart of patients with COVID-19 (Connors and Levy, 2020). We feel that treatment with blood thinner or low molecular weight heparin can reduce the problems of blood clots.

Development of animal models of coronavirus infection are useful for testing vaccines and antiviral drugs. However, currently available animal models do not reproduce the inflammatory storm or pulmonary disease observed in individuals infected with SARS-CoV (Cleary *et al.*, 2020). SARS-CoV viruses has been found to replicate in the lungs of domestic cats, hamsters, and mice. These animal models remain symptomatic (Tiwarei *et al.*, 2020). Therefore, we believe that development of animal models that establishes COVID-19 infections can show symptoms require a transgenic animal approach. The knowledge obtained from the study of animal models will help us in developing specific therapies, and vaccine would minimize pulmonary disease and optimise the inflammatory storm. Finally, we conclude that vaccine is the best for protection against COVID-19 infections, but development of antiviral drugs or targeted therapies are urgently required to cure COVID-19 patients.

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