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Covid19 the Virus Immunology and Blood Coagulation, a Positive Feedback Cycle with Resultant Pathogenesis: A Perspective

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Perspective

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Perspective

Covid 19 is a new beta corona virus which is driving the present pandemic across the world. The virus is highly transmissible through respiratory route with a Ro value varying between1.3-2.0. The virus is a direct strand RNA virus and is one of the largest viruses of RNA virus group. It has 11 open reading frame of which ORF 9-11 is involved in translation of structural S (Spike), E (Envelop), M (Matrix) and N (Nucleocapsid) glycoproteins. Of these S protein is very important from the point of view of virus engagement with the host cell and its infectivity. S protein (Spike) is responsible for the corona of the virus and its receptor binding domain is the principal target for developing vaccine derived immunity. However other structural proteins and many of the Functional/enzymatic/polymerase/Gyrase/ Endoribonuclease/and proteases required for replication, processing of the virus proteins and its assembly to produce virus structure has important infection and immunological consequences and some of them are obvious targets for future drug development. Detailed virus structure has been reviewed [1]. The virus does not enter the nucleus of host cell and most of the virus replication and assembly takes place in the cytoplasm.

While this enveloped virus can be easily inactivated by detergent, heat etc., it can tolerate some amount of drying and lives long on metallic surfaces. The virus though spread by respiratory route has been detected on the surfaces of fruits, vegetables and sewage effluents. In fact viral load in sewage effluents has been used to calculate the number of infected person in the drainage area [2]. Surprisingly just before the first case was diagnosed in the community N1 nucleocapsid sequences were detectable in the sewage in low numbers.

Covid 19 (SARS2 Corona Virus) like its cousin SARS utilizes similar receptors to gain entry into the host cell. Both the viruses utilize ACE2 (an enzyme) receptor to cause the infection. ACE 2 is a carboxyl peptidase which is capable of converting Angiotensin I and Angiotensin II to a vasodilator heptapeptide. Hence ACE1 for which many inhibitors ate available to treat hypertension, together with ACE2 maintains vasodilators and vaso constrictor balance in the system. Moreover angiotensin has innumerable biological effects including growth of fibroblasts and attendant fibrosis. Hence this unbalance in microcirculation of lungs can be one of the reasons of delayed pulmonary fibrosis seen in this disease. In addition to ACE2 Covid 19 also utilize CD147 (Basignin/ EMMPRIN) as its alternative receptor for entry into target cells. Both the receptors are now targets of COVID19 therapeutic development. Commonly available drug Azithromycin interferes with interaction of the virus with this target. Chiloquin/ Hydro chloroquin were seen to interfere with attachment of Covid19 with ACE2 receptor. Doxycycline down regulates CD147 receptor density and using this pathway reduces the matrix metalloprotease production. Details of these interactions have been described by Ulrich, et al. [3].

S protein in its native state cannot engage with its cognate receptors and needs to be activated by proteolysis digestion. Presence of TMPRSS2 on the surface of the cell des the job and may also be induced by CD147. Other metalloproteases and fibrinolysis enzymes from endothelial cells can also perform the job and induces a positive feedback loop of heavy infection and its integration with blood coagulation [4].

Though the virus initially infects epithelial cells of the nasal epithelium and then goes down the throat and finally lungs where type 2 pneumocystis and pulmonary

macrophages having a high density of ACE 2 receptors get infected produce all the pulmonary complications and even death in this condition. However studies have shown the virus can infect a large variety of cells ie epithelial cells, Reticuloendothelial cells, T, B, NK cells, myocardial cells and Nerve cells [5]. It also engages TLR 3, TLR 7 activating innate immunity through cytokine generation and activation of cellular proteases and its apoptotic path ways [6]. Large number of cell death particularly activation of neutrophil elastase produce Neutrophil Extra cellular traps and also activates complement which along with its myriads of activities activates blood coagulation [7,8].

Corona virus with its multitudinal structural and nonstructural proteins induces immune response in the host which is often deregulated and leads to CD4, CD8, NK cell lymhocytopenia, Neutrophil leukocytosis, mono cytosols. Loss of lymph node architecture and germinal center formation due to loss of Follicular helper T cells which secretes Bcl6 and helps to produce germinal center. B lymphocytes are not greatly affected. Degree of lymhocytopenia correlates with clinical picture and altered lymphocyte neutrophil ratio is related to cytokine storm and deterioration of clinical picture in Covid19 cases [6,9].

Initially starting with endothelial injury and vasculopathy, the disease progresses with complement activation, Platelet activation and cytokine induced derangement of coagulation leading to microvascular and peripheral thrombosis [10,11].

This is reflected in the laboratory by very high level of clotting factor levels specially fibrinogen, factor VIII and D-Dimers as an indicator of coagulation activation. Extensive micro thrombosis in the pulmonary capillaries triggers severe hypoxia and lactic acidosis. Many patients develop myocardial infarction and peripheral venous thrombosis. Cytokine storm in some patient produce macrophage activation syndrome providing the rationale of anti IL6 therapy in this condition [12].

In the management of Covid19 pneumonia in addition to supportive and general management ensuring adequate tissue oxygenation and prevention of secondary infection, down regulation of in appropriate inflammatory state and managing the in appropriate prothrombotic state takes great precedence [13].

Considering the ongoing pandemic and different strains of virus circulating across the world a good and safe vaccine has been considered by many to be an ideal answer to produce herd immunity and stop the epidemic. More than 100 companies are trying to produce the vaccine and some of them are already entering the phase 3 clinical trial. Initial results seem to be encouraging. But doubt remains as to the possible efficacy of the vaccine due to evanescent immune response with this infection, multiple strain and antibody dependent enhancement of infection as is seen with dengue and Ebola fevers [14,15].

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