Review Article

Virology and Pathogenesis of COVID-19

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After the discovery of human coronavirus from the samples of human respiratory tract in 1960 by Dr June Almeida several years elapsed before epidemics occurred in China in 2002-2003 as SARS-CoV and epidemics in Middle East countries in 2012-2014 as MERS-CoV. But recently in December, 2019 in Wuhan in China the novel coronavirus started its journey and ultimately spread worldwide to involve millions of people and took the life of more than 1.25 lakh of affected patients. There are recurrent antigenic changes in this virus, SARS-CoV-2, which has to be determined by the scientists all over the world to discover the definite medicine as well as vaccines for prevention.

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Discovery of Human Coronavirus :

History of human coronavirus,started in 1960 when Tyrrell and Bynoe found a virus in embryonic tracheal organ culture received from adult respiratory tract of a patient in the cold unit in Salisbury in Wiltshire. They sent several samples to virologist, June Almeida, who demonstrated the particles under electron microscope. She also saw this type of particle while investigating mouse hepatitis. She wrote a research paper but was rejected by one peer-reviewed journal. In 1965, British Medical Journal published the new discovery of thevirus B814. The photograph of this B814 particle was exactly like that what Dr. Almeida demonstrated previously and ultimately her article was accepted and published two years later. Now she is no more (died in 2007 at the age of 77 years) but corona virus remains and responsible for this huge pandemic.

Taxonomy and description of onset of pandemic of COVID-19 :

Order Nidovirales has four families, namely Coronaviridae, Arteriviridae, Roniviridae. Coronaviridae, largest of all the above families has two sub-families—Coronavirinae and Torovirinae, former one is subdivided into four sub-groups – alpha, beta, gamma and delta coronaviruses. These viruses are divided according to the phylogenetic clustering. Coronaviruses are the main pathogen of human being and vertebrates, like birds, bats, mouse and many other wild animals attacking respiratory, gastrointestinal, nervous and hepato-biliary systems[1,2,3]. Since the primary reservoir of COVID-19 is bats, ICMR started to gather evidence of any presence of virus from different types of Indian Bats. Very recently ICMR reported there is presence of COVID-19 in two types of bat, one is Pteropas (Indian Flying Foxes and the other is Rousettus (Fruit Bats) collected from different regions of India. They have tested for COVID-19 in 508 flying foxes and 78 Rusetus and recovered the viruses from 21 flying foxes and 4 Rusetus.

Editor's Comment :

- **SARS-CoV-2 has a complex protein structure that helps in entry, incorporation into host cell and replication.**
- **Clinical outcome depends on cytokine activation, immune evasion and coagulopathy**
- **Knowledge of structure and pathogenesis of SARS-CoV-2 infection will help in devising therapy and preventive measures.**

The primary target of coronaviruses is respiratory system of human being. Almost 50 years ago coronaviruses started producing mild respiratory symptoms by the four coronaviruses. HCoV-229E and HCoV-NL63 are alpha-coronaviruses and HCoV-OC43 and HCoV-HKU1 are beta-coronaviruses responsible for producing respiratory symptoms. HCoV-229E and HCoD-OC43 were isolated 50 years ago but the other two were identified in recent coronaviruses outbreak[4,5,6,7,8]. In 2003-2004 in Guandong province of China, a virus, SARS-CoV, was isolated from patients with severe respiratory tract infection, i.e. group 2b beta-coronavirus. It was responsible for 8098 cases with death of 774 having higher mortality rate of about 50% above 60 years of age and loss of 40 billion dollar activity. It started in a hotel in China and ultimately spread into two dozen of countries. During that time this SARS-CoV was originated in bats and Chinese horse shoe bats[9].

Again in 2012, another coronavirus was isolated from patients of Middle-East including Saudi Arabia and other

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countries, who suffered from severe respiratory tract infections with mortality of nearly 50% at early stage—it was known as Middle-East respiratory syndrome Virus or MERS-CoV[10]. Though this outbreak decelerated in 2013 but again a small peak occurred in 2014 which gave rise to 200 cases with death of 40 patients – this resulted from seasonal increase in birth of camel, improved detection methods as well as good reporting. MERS-CoV is group 2c beta-coronavirus believed to be originated form bats but also camels in middle East as viral antibodies was detected in these animals[11].

Ultimately in last week of December, 2019, patients wereadmitted in hospitals with symptoms of respiratory tract infections of unknown etiology[12]. These patients were directly related to wet animal wholesale market in Wuhan, in the province of Hubei, China. On the same day International virus classification declared that the name of the new virus as Severe Acute Respiratory Syndrome Virus 2 (SARS-CoV-2)[13]. Within 18th to 29th December, 2019, total 5 patients were admitted with same infection and one of them died[14]. Again, according to a report, by 2nd January 41 patients admitted in hospitals with confirmed SARS-CoV-2 positive respiratory tract infections half of them having comorbidities, like, diabetes mellitus, hypertension, cardiac diseases helped to come to a conclusion that these patients may be infected by nosocomial infection by unknown mechanism during hospital stay in various locations throughout the hospital rather than in a single hall[15]. It should be remembered also that during that time those who were clinically infected were tested but not mildly symptomatic or asymptomatic patients. Till 20th January, 2020,291 clinically and sequence analysis proved cases were recovered of which 270 were from Wuhan and rest 21 from Beijing, Shanghai and Guangdong. In addition four more cases were confirmed of which one from South Korea, one from Japan and rest two from Thailand, but all these patients went as visitor in Wuhan 2 weeks back. By 22nd January, 2020, 571 more cases were recovered from 25 Provinces covering districts and cities of China[16]. First 17 deaths were reported in detail by China National Health Commission, some of them had some comorbidities, like, cardiovascular diseases, renal dysfunction, liver disease and abdominal tumor. By 25th January, 2020 total confirmed cases were 1975 with total death of 56, where as in another report on 24th January, 2020total COVID -19 positive cases were 5502[17,18]. Ultimately it spilled over the several countries worldwide to reach a recent pandemic stage. As per report of 30th January, 2020 total case cases from china was 7734 and from other countries, worldwide , 90 cases were recovered as COVID-19 positive with case fatality rate of 2.2%[19].

After recovery of the first case from United States, proper description of the illness came across, which was characterised by mild presenting symptoms, like, cough, fever followed by progression to pneumonia within 9 days of illness[20]. On 30th January, 2020 first case of human to human transmission was identified in United States. According to a report of 7th February, 2020, in Nature Journal total infected patients in China was 31161 with death of more than 630 (http://www.nature.com/articles/d41586-020-00154). In 11th February, 2020 World Health Organization gave the new name of this corona virus as COVID-19 (Fig 1).

Structure :

This virus is non-segmented positive sense single stranded RNA of 30 kb containing 5xþ cap structure and 3xþ poly tail. It has ten open reading frames; out of which first frame (ORF 1a/1b) contains two third of viral RNA of 20 kb which will be translated into two polyproteins, pp1a and pp1ab by the method of -1 frame shift between ORF1 and ORF2 which will be processed into 16 non-structural proteins (nsp1 – 16) leading to formation of replicase transcriptase complex[21,22]. These non-structural proteins rearrange the membrane starting from rough endoplasmic reticulum into double membrane vesicles[23]. Since the length of RNA is small as compared to DNA viruses hence the replication and mutation rate of the former is much higher. But human coronavirus being largest RNA virus (30 kb in length) maintains this genomic structure due to presence of unique RNA processing enzymes, like, 3xþ-5xþ exoribonuclease of non-structural protein 14 which provides proof reading function of replicase-transcriptase complex[24] (Fig 2).

The main functions of nonstructural proteins are degradation of cellular RNA,inhibition of interferon signalling, cleaving of polypeptideand blocking of host innate immune response. They promote expression of cytokines and formation of double membrane vesicles[25,26].

There are four structural proteins. These proteins serve many functions. These are the following (Fig 3) :

(A) Spike protein(S) : These proteins are responsible for attachment to the host receptors.

(B) Membrane (M) protein :

1. It will give shape to the virions
2. It promotes the curvature of membrane of the virus.
3. It will bind to nucleocapsid.

(C) Envelope (E) protein :

1. It helps in assembling of the virus.
2. It will help in release of virus.
3. It will take part in pathogenesis.

(D) Nucleocapsid (N) protein: It has two domain which binds viral RNA genome through different mechanisms.

1. It can bind to nsp3 protein to help tether the genome

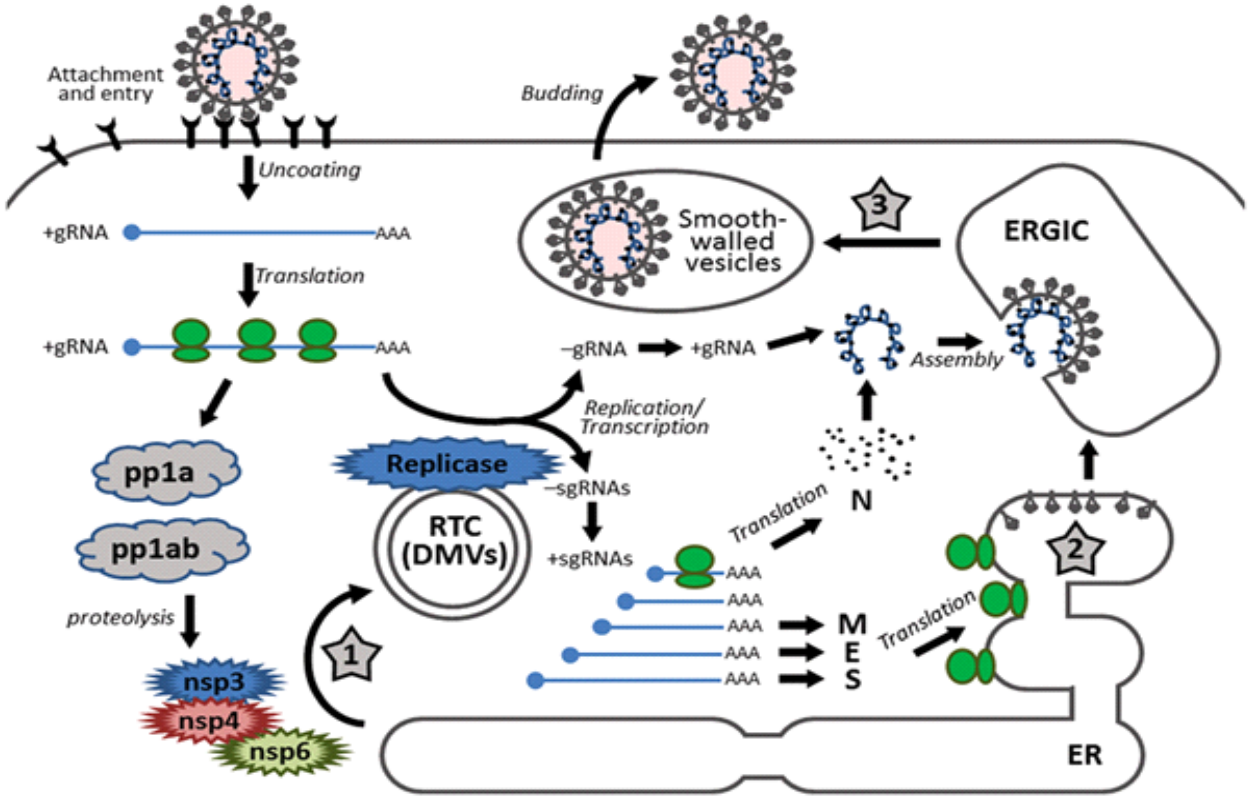

Fig 1

to replication-transcription complex.

2. It helps in encapsulating the genome into the virions.

3. It acts as antagonist of interferon as well as viral encoded repressor of RNA interference – it is beneficial for viral replication (Fig 3).

Pathogenesis of COVID-19 :

Entry of coronavirus and its replication:

Spike protein (S) is responsible for attachment to the host cell receptor[27] that is the ACE2 receptor for SARS-CoV, SARS-CoV-2 (COVID-19).

After entry of the virus there will be fusion between virus and plasma membrane followed by viral infectivity due the occurrence of a proteolytic cleavage at position 2xþof S protein 28,29. There is another process of entry of SARS-CoV2 through clathrin-dependent as well as clathrin-

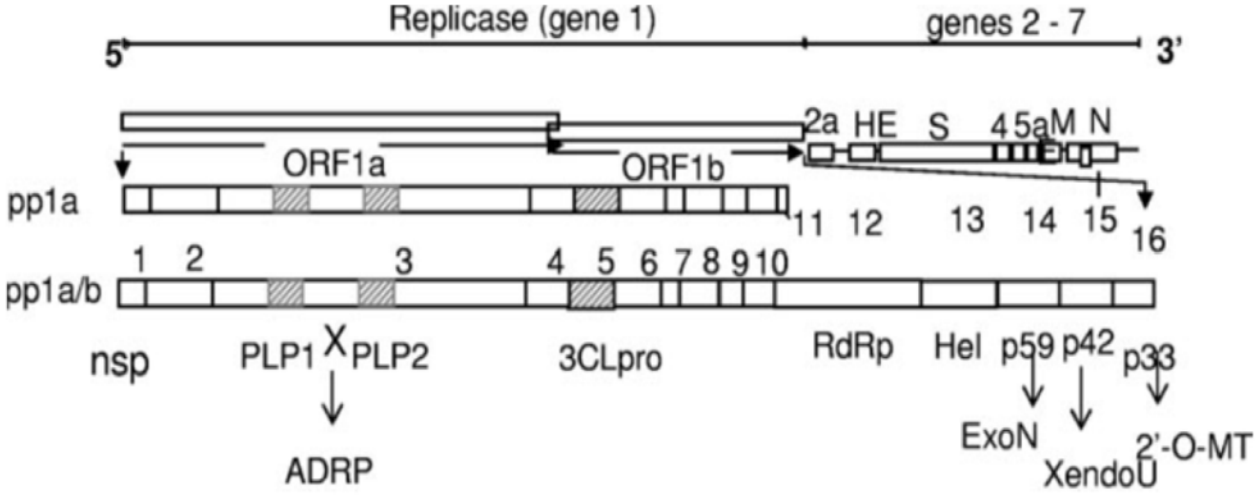

Fig 2

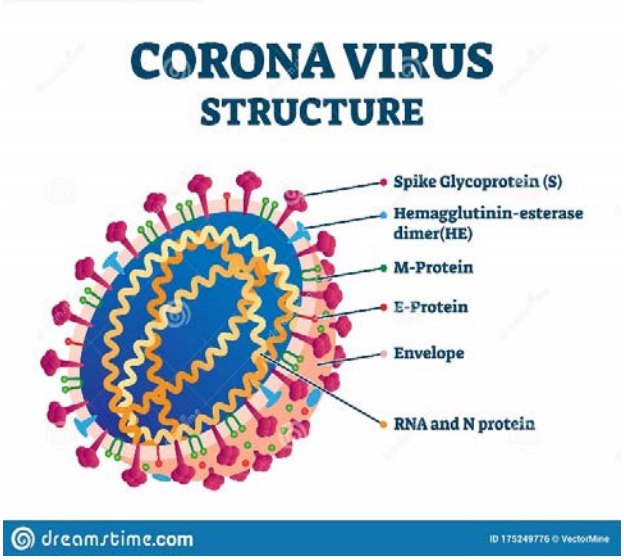

Fig 3

independent endocytosis[30,31]. After gaining entry into the cells viral RNA is released in to the cell cytoplasm which will be translated into two polyproteins as well as structural proteins followed by viral genome replication[32]. Then newly formed envelope glycoproteins are inserted into endoplasmic reticulum and golgi apparatus and genomic RNA and nucleocapsid protein are combined to form nucleocapsid. Then small viral particle will germinate into the endoplasmic reticulum-golgi intermediate compartment and small vesicle containing viral particles will be formed. Lastly this vesicle will fuse with the plasma membrane followed by the release of full-blown virus into the circulation.

Presentation of Antigen in COVID-19 Infection :

After entry viral antigenic peptides will be presented to antigen presentation cells by major histocompatibility complex or human leukocyte antigen which will be subsequently recognized by virus-specific cytotoxic T lymphocytes, hence antigen presentation is of prime importance in pathogenesis as well as development of viral specific immunity. In case of SARS-CoV MHC I and to some extent MHC II are responsible for antigen presentation[33,34]. Again, genetic polymorphism of mannose binding lectin (MBL) are also related to risk of SARS-CoV infection. But there is no specific information regarding pathogenesis of COVID-19.

Different Types of Immunity :

As a result of antigen presentation T and B cells are stimulated leading to development of cellular as well as humoral immunity. Like other viral infection SARS-CoV develops IgM of acute phase response and IgG antibody corresponding to chronic phase response. IgM develops within 5 to 7 days and persists for another 5 to 7 days followed by disappearance. On the other hand T and N protein SARS-CoV specific IgG antibodies persist for years which has protective role[35,36]. But as compared to humoral immunity cellular immunity is greatly depressed in SARS-CoV-2 positive individuals as evidenced by severely decreased in number of CD4+ T and CD8+ T cells in acute phase response but its status is excessive activation as evidenced by high proportion of HLA-DR and CD38 double-positive fractions[37].

But there is increase in neutrophil count along with neutrophil/lymphocyte ration will be increased indicating severe form of disease with poor outcome[38,39]. In addition, in COVID-19 patients exhaustion markers, like, NKG2A present on cytotoxic T lymphocytes, natural killer cells, CD8+ T cells are up-regulated but on the other hand in convalescent or recovered patients thesecells will be normalized along with detection of SARS- specific antibodies in the blood.

In case of COVID-19 patients there are two phases of immune responses. In the incubation period i.e. in the non-severe stage an adaptive response is required to prevent progression into the severe stage. So boosting of immune response by several means, like, pegylated interferon or anti-sera are required along with good health and good genetic background. But if the protective response is impaired COVID-19 virus will propagate, invade into different tissues mainly affecting those having high ACE2 receptors, like, intestine, kidney and destroy them. Damaged tissue produces innate inflammatory response mediated by inflammatory macrophages as well as granulocytes leading to severe respiratory disorder in severe stage. After discharge from the hospital some patients are unable to eliminate the Virus-eliminating immune response of SARS-CoV-2 from the body and in these patients, vaccine will not work as the immune system is probably very weak in these patients. Already recovered patients from the early non severe stage should be monitored for T/B cell response. [40,41]

Cytokine Response in COVID-19 :

In early stage of outbreak, amongst 41patients with COVID-19 six patients died of acute respiratory distress syndrome. The most common immunopathological event is cytokine storm, the uncontrolled systemic inflammatory response releasing large amount of pro-inflammatory cytokines, like, interferon-α, interferon-, interleukin-1β, interleukin-6, interleukin-12, interleukin-18, interferon-33, tumor necrosis factor-α, tumor growth factor-β and chemokines, like, CCL2, 3, 5, CXCL8, 9, 10 etc by effector immune cells in COVID-19 infection This storm ultimately triggers the immune system of the body to attack different

organ systems leading to multi-organ failure followed by death in COVID-19 infection as occurred in case of SARS-CoV and MERS-CoV epidemic. Cytokine release syndrome in severe patients with leucocytosis with lymphopenia is mediated by leukocytes other than T cells.[42]

Immune Evasion by Coronavirus :

Like SARS-CoV or MERS-CoV, COVID-19 avoids immune response. Pattern recognition receptors (PPRs) recognize pathogen-associated molecular pattern, evolutionarily conserved microbial structure. But SARS-CoV, MERS-CoV and COVID-19 are bound by double-membrane vesicle thus host immune cells cannot detect microbial dsRNA .Interferon á and â are protective in coronavirus infection. But by the following methods coronavirus SARS-CoV, MERS-CoV prevent interferon from preventive actions:

(A)Accessary protein 4a blocks the induction of interferon in MERS-CoV infection at the level of MDA5 through direct interaction with double stranded RNA.

(B) Accessary proteins, like, 4a, 4b, ORF5, membrane protein of MERS-CoVprevents activation of interferon â promoter by inhibiting nuclear transport of interferon regulatory factor 3. [42,43]

So, destruction of this evasion of immune system is a way by which one can treat COVID-19.

Effect on Coagulation and Heme Metabolism :

It has been documented that SARS-CoV-2 causes intense epithelial viral cytopathic effects involving alveolar and small airway epithelium with variable number of small fibrinous thrombi in small pulmonary arterioles in areas of damaged and preserved lung parenchyma.Endothelial tumefaction (swelling) and large numbers of pulmonary megakaryocytes in pulmonary capillaries due to activation of coagulation cascade, and small foci of alveolar hemorrhage and pulmonary infarctions are seen. This supports the concept of hypercoagulative status, showing high frequency of pulmonary microthrombosis. The most common pattern of coagulopathy observed in patients hospitalized with COVID-19 is characterized by elevations in fibrinogen and D-dimer levels. This correlates with parallel rise in markers of inflammation (e.g. CRP). Unlike the pattern seen in classic DIC from bacterial sepsis or trauma, the degree of aPTT elevation is often less than PT elevation (likely due to increased factor VIII levels), the thrombocytopenia is mild (platelet count ~100 x 10^9/L), and microangiopathy is not present.Some patients with severe COVID-19 infection can develop a coagulopathy meeting criteria for DIC per ISTH criteria with fulminant activation of coagulation and consumption of coagulation factors[44.]

Moreover ,ORF8 protein and surface glycoprotein of the virus bind to porphyrin respectively and Orf1 ab, ORF10, and ORF3a proteins attack the heme on the 1-beta chain of hemoglobin to dissociate the iron to form porphyrin. This reduces hemoglobin's ability to carry oxygen and carbon dioxide.O2 dissociation curve shifted to right -> release of O2. But this hypothesis has been challenged on the grounds that RBCs have no DNA and it is unclear how SARS-CoV-2 would enter RBCs[45].

Conclusion :

To conclude, knowledge about the structure and function of the virus as well as its complex interaction with host will hopefully help us to device new therapeutic and preventive strategies in the future.

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