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# Pathogenesis of COVID-19

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**Abstract:**

The coronavirus disease 2019 (COVID-19) is a very contagious infectious disease which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus is first identified in Wuhan city of China in December 2019 and in a short time dispersed to rest of the World. Animal to human transmission of the virus happened by eating of an infected animal and then the virus is transmitted to healthy persons by close contact. Coronaviruses attach and enter to the host cells by means of the spikes on the cell membrane. The type 2 pneumocytes are the primary target of the virus. The aim of this report is to review the immunopathogenesis of COVID-19 in the light of current literature.

**Keywords:**

Coronavirus, COVID-19, pathogenesis

## Introduction

The coronavirus disease 2019 (COVID-19) is a very contagious infectious disease which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus is first identified in Wuhan city of China in December 2019 and in a short time dispersed to rest of the World.[1] Novel coronavirus (nCov) induced pneumonia named as COVID-19 by the World Health Organization on February 11, 2020.[2] In this article, pathogenesis of COVID-19 was reviewed in the light of current literature.

## Taxonomy of SARS-CoV-2

Coronaviruses are in diameter between 65 and 125 nm and contain a single-stranded RNA with a length about 30 kbs as a nucleic acid. All coronaviruses contain specific genes encoding replication proteins, nucleocapsid, and spike (S) protein.[3] SARS-CoV-2 has the typical coronavirus structure with S protein, nucleoproteins, and membrane proteins.[4] The structure of SARS-CoV-2 is shown in Figure 1.

The coronaviruses are divided into the subgroups named as alpha (α), beta (β), gamma (γ), and delta (δ) coronavirus. The Chinese scientists described the novel virus as 2019-nCov. Formerly, six coronaviruses were reported as a causative agent of an infectious disease in humans, SARS-CoV-2 is the seventh one following SARS-CoV and Middle East respiratory syndrome-CoV (MERS-CoV.[5] Furthermore, this new virus also was defined as a member of β coronaviruses similar to SARS-CoV and MERS-CoV. The International Committee on Taxonomy of Viruses named the virus as SARS-CoV-2 and the disease as COVID-19.

## Transmission

The nCov arised from the live animal market at Wuhan city of China where wild animals such as bats, snakes, raccoon dogs, palm civets are present, and then quickly scattered to 109 countries. The origin of SARS-CoV-2 is not exactly confirmed, nevertheless, sequence-based analysis estimated that bats might be the key reservoir. Furthermore, pangolins and snakes are supposed to be the intermediate hosts.[6] A study using genetic sequencing revealed that gene sequence of SARS-CoV-2 and bat coronavirus were

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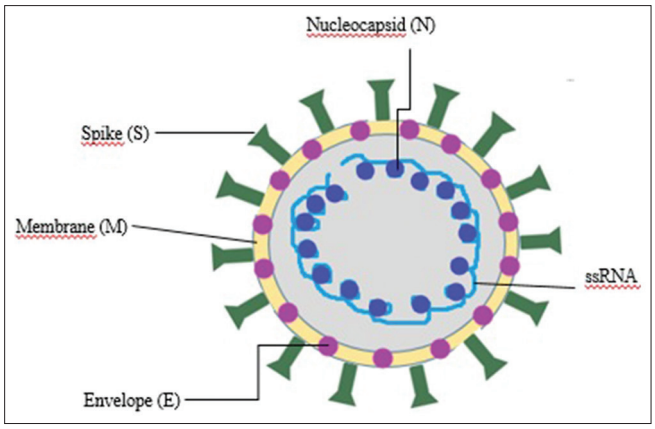


**Figure 1:** The structure of SARS-CoV-2, ssRNA: Single-strained ribonucleic acid

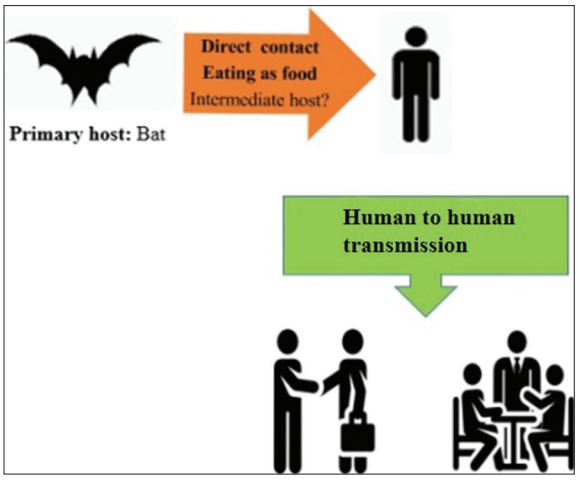


**Figure 2:** The key reservoirs and mode of transmission of SARS-CoV-2, major cause of the animal to human transmission is eating of infected animal and the virus is further transmitted to healthy persons by close contact with an infected person, pangolins, and snakes are suspected intermediate hosts

similar in proportion of 96%.[7] Besides, Xu *et al*. reported that SARS-CoV-2 originated from pangolin were almost identical (99%) in genomic sequencing with the virus strains infecting humans. The researchers demonstrated the typical nCov granules and suggested that pangolin might be the intermediate host of the SARS-CoV-2.[8]

Animal to human transmission of the virus happened by eating of an infected animal and then the virus is transmitted to healthy persons by close contact with a patient carrying the virus[2,4,8] Respiratory droplet nuclei spreading while coughing, sneezing and even speaking of an infected person and contact to the contaminated surfaces are the major transmission ways of the virus. Figure 2 summarizes the key reservoirs and transmission ways of SARS-CoV-2.

Interestingly, SARS-CoV-2 RNA was shown in various secretions of the body such as saliva, urine, tears and even in gastrointestinal tissues and stool of COVID-19 patients.[8,9] Fortunately, intrauterine vertical transmission was not revealed in a small series of pregnant women with COVID-19.[10]

## Virus Entry to the Host Cell

Coronaviruses attach and enter to the host cells by means of the S proteins on the cell membrane. S protein which determine virus entry into host cells, notices the related receptor on the target cell. The life cycle of the virus starts subsequent to the binding of S protein to angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface. The conformation of S protein changes following the binding to ACE2 receptor. So that the virus easily envelope and fused to the cell membrane. Then the viral RNA is released into the host cell. Further steps are translation of RNA into viral replicase polyproteins and division into small parts via viral proteinases. A series of messenger RNAs are synthesized by polymerase chain reaction as a result of intermittent transcription and after that translation into appropriate viral proteins comes true. Viral proteins and genome RNA are consequently collected into virions in the endoplasmic reticulum and Golgi aparatus and then carried through vesicles and excreted out of the cell.[1]

The S protein of SARS-CoV-2 which is a combination of bat SARS-CoV and an unknown Beta-CoV, contains a 3-D structure in the receptor binding domain (RBD) region to preserve the van der Waals forces.[7,11] The type 2 pneumocytes are the main target of the virus. The lysine 31 residue on the human ACE2 receptor notices the 394 glutamine residue in the RBD region of SARS-CoV-2.[12] Recently, the researchers demonstrated that the SARS-CoV-2 resembles to SARS-CoV, because it enters into the host cell following the binding the same ACE2 receptor by using similar mechanism.[7,13]

Although the affinity of SARS-CoV-2 to ACE2 receptor was found to be higher than 10 folds compared with SARS-CoV, the threshold required to begin infection with SARS-CoV-2 is more than that of SARS-CoV.[14] The detailed pathological mechanisms causing multisystemic organ damage of the SARS-CoV-2 is not yet clear. Future studies will help to clarify the higher contagious capacity of the SARS-CoV-2 in humans than SARS-CoV, and also the higher level of affirmed COVID-19 cases than the amount of infectious disease by SARS-CoV. Furthermore, soluble ACE2 might be a possible molecule for COVID-19 treatment due to the higher affinity of SARS-CoV-2 to ACE2 receptor.

## Antigen Presentation in Coronavirus Infection

Antigen presentation cells present the viral antigens following the virus entry to the host cell. Major

histocompatibility complex (MHC; or human leukocyte antigen in humans) is responsible for presentation of antigenic peptides and then cytotoxic T lymphocytes specifically notice these antigens. Unfortunately, there is not enough data about antigen presentation of SARS-CoV-2. For now, previous reports on SARS-CoV and MERS-CoV are giving us information about it. Nevertheless, SARS-CoV presents its antigens mainly via MHC I,[15] MHC II also takes role in this process.

## Humoral and Cellular Immunity against Coronavirus

Specific B and T cells mediated humoral and cellular immunity are stimulated following antigen presentation. Subsequently, virus-specific immunoglobulin M (IgM) and IgG are produced like in other acute viral infections. The SARS-CoV-2-specific IgM antibodies detected between 7 and 21 days of infection, while the IgG antibody production starts on day 14, and can last for a long time and may have protective role.[16] Recently, it was reported that the count of T helper 1 and 2 cells in the peripheral blood of SARS-CoV-2-infected patients decreases significantly, but they are over activated.[17]

## Cytokine Storm in Coronavirus Infection

The cytokine storm is the intense, unrestrained multisystemic inflammatory response. It turns out the excretion of huge amounts of pro-inflammatory cytokines (interferon [IFN]-α, IFN-γ, interleukin-1 [IL-1] β, IL-6, etc.) and chemokines (CCL2, CCL3, CCL5, etc.). It causes ARDS and multiple organ failure, and finally to death in severe cases of SARS-CoV-2 infection, similar to SARS-CoV and MERS-CoV infection.[17] The report in Lancet showed that 14.6% (6/41) of the included COVID-19 patients died due to ARDS.[18] ARDS is the common course of severe infection in SARS-CoV-2-, SARS-CoV-, and MERS-CoV-related diseases.[17]

## Avoidance of Coronavirus from Immune System

SARS-CoV and MERS-CoV use several methods to avoid immune responses and keep going on to live in host cells. SARS-CoV and MERS-CoV can induce the production of double-membrane vesicles that can escape from control of immune system of the host. Then they continue to replicate in these vesicles by means of avoiding the host detection.[19] The coronavirus also can disturb antigen presentation. For example, gene expression related to antigen presentation is down-regulated after MERS-CoV infection.[20] So that, destroying the immune evasion of SARS-CoV-2 is obligatory to develop specific drug.

In conclusion, although every step of pathogenesis of COVID-19 is not yet clear, similarities in genetic sequencing and mechanisms of action of SARS-CoV-2 with SARS-CoV and MERS-CoV will provide leadership for the studies to clarify the details of immunopathogenesis of COVID-19 and also to develop vaccine and drugs for the disease.

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## Conflicts of interest
There are no conflicts of interest.

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