**ASSIGNMENT ON COVID-19.**

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***ETIOLOGY OF COVID-19***.

Covid-19 is a strain a particular type of virus called *Corona viruses*. They belong to the *Coronaviridae* family in the *Nidovirales* order. They are enveloped single-stranded RNA viruses that are zoonotic in nature and causes symptoms ranging from those similar to the common cold to more severe respiratory, enteric, hepatic, and neurological symptoms. It was discovered in 2019 originally in a marketplace in Wuhan, China; where it caused so many illnesses and deaths.

The covid-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it’s important that individuals practice respiratory etiquette e.g.: coughing into a flexed elbow. Transmission may also occur when an individual touches a surface or object contaminated with the virus and subsequently touches their mouth, nose or eyes. This virus can be viable for as long as 6 to 12 hours on surfaces; and for 5 to 10 minutes on the skin. Aerosol transmission may occur when respiratory droplets mix into the air, forming aerosols and may cause infection when inhaled.

***ORIGIN.***

Recently at the end of 2019, Wuhan a city in china experienced an outbreak of a novel corona virus that killed more than 1,800 and infected over 70,000 individuals within the first 50days of the epidemic; although many more mild cases have likely gone undiagnosed. This virus was reported to be a member of the β group of corona viruses. The novel virus was named as Wuhan corona virus or the 2019 novel corona virus by the Chinese researchers. The virus caused several cases of pneumonia with unfamiliar etiology.

The outbreak was initiated from the Hunan seafood market in Wuhan city and rapidly infected more than 50 peoples. The live animals are frequently sold at the Hunan seafood market such as bats, frogs, snakes, birds, marmots and rabbits. Initially, it was suggested that the patients infected with Wuhan corona virus induced pneumonia in china may have visited the seafood market where live animals were sold or may have used infected animals or birds as a source of food. However, further investigation revealed that some individuals contracted the infection even with no record of visiting the seafood market. These observations indicated the human spreading capability of this virus, which was subsequently reported in more than 100 countries in the world.

It is believed that the virus evolved to its current pathogenic state through natural selection in a non-human host and the jumped to humans. This is how previous corona virus outbreaks have emerged, with humans contracting the virus after direct exposure to Pangolins or bats. The researchers proposed bats as the most likely reservoir for corona viruses. There are no documented cases of direct bat-human transmission, however, suggesting that an intermediate host was likely involved between bats and humans (most likely Pangolins or camels). Both of the distinctive features of COVID-19’s spikes protein:

1. the RBD portion that binds to cells and
2. the cleavage site that opens the virus up;

would have evolved to their current state prior to entering humans. In this case, the current epidemic would probably have emerged rapidly as soon as humans were infected, as the virus would have already evolved the features that make it pathogenic and able to spread between people.

***STRUCTURE.***

All corona viruses contain specific genes in ORF1 downstream regions that encode proteins for viral replication, nucleocapsid and spikes formation. The glycoprotein spikes on the outer surface of the corona viruses are responsible for the attachment and entry of the virus to host cells. The receptor-binding domain (RBD) is loosely attached among virus, therefore, the virus may infect multiple hosts. Other corona viruses mostly recognize amino peptidases or carbohydrates as a key receptor for entry to human cells while SARS-CoV and MERS-CoV recognize exopeptidases. The entry mechanism of a coronavirus depends upon cellular proteases which include human airway trypsin-like protease (HAT), cathepsins and transmembrane protease serine (TMPRSS2) that split the spike protein and establish further penetration changes. MERS-coronavirus employs dipeptidyl peptidase 4 (DPP4), while HCoV-NL63 and SARS-coronavirus require angiotensin-converting enzyme 2 (ACE2) as a key receptor.

Covid-19 possesses the typical coronavirus structure with spike protein and also expressed other polyproteins, nucleoproteins, and membrane proteins, such as RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins. The spike protein of Covid-19 contains a 3-D structure in the RBD region to maintain the van der Waals forces. The 394 glutamine residue in the RBD region of SARS-CoV-2 is recognized by the critical lysine 31 residue on the human ACE2 receptor.

***PATHOGENESIS.***

Patients with COVID-19 show clinical manifestations including fever, nonproductive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia, which are similar to the symptoms of SARS-CoV and MERS-CoV infections. Hence, although the pathogenesis of COVID-19 is poorly understood, the similar mechanisms of SARS-CoV and MERS-CoV still can give a lot of information on the pathogenesis of SARS-CoV-2 infection to facilitate our recognition of COVID-19.

Corona virus S protein has been reported as a significant determinant of virus entry into host cells. The envelope spike glycoprotein binds to its cellular receptor which is ACE2. The entry of covid-19 into cells was initially identified to be accomplished by direct membrane fusion between the virus and plasma membrane; besides membrane fusion, the clathrin-dependent and independent endocytosis mediated its entry too. After the virus enters the cells, the viral RNA genome is released into the cytoplasm and is translated into two polyproteins and structural proteins, after which the viral genome begins to replicate. The newly formed envelope glycoproteins are inserted into the membrane of the endoplasmic reticulum or Golgi body, and the nucleocapsid is formed by the combination of genomic RNA and nucleocapsid protein. Then, viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). At last, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus.

While the virus enters the cells, its antigen will be presented to the antigen presentation cells (APC), which is a central part of the body’s anti-viral immunity. Antigenic peptides are presented by major histocompatibility complex (MHC); or human leukocyte antigen (HLA) in humans and then recognized by virus-specific cytotoxic T lymphocytes (CTLs). The antigen presentation of Covid-19 mainly depends on MHC I molecules, but MHC II also contributes to its presentation.

Antigen presentation subsequently stimulates the body’s humoral and cellular immunity, which are mediated by virus-specific B and T cells. Similar to common acute viral infections, the antibody profile against Covid-19 has a typical pattern of IgM and IgG production. The Covid-specific IgM antibodies disappear at the end of week 12, while the IgG antibody can last for a long time, which indicates IgG antibody may mainly play a protective role, and the Covid-specific IgG antibodies primarily are S-specific and N-specific antibodies. Comparing to humoral responses, there are more researches on the cellular immunity of corona virus. Even if there is no antigen, CD4+ and CD8+ memory T cells can persist for four years in a part of Covid-19 recovered individuals and can perform T cell proliferation, DTH response and production of IFN-γ.

The report in Lancet shows ARDS is the main death cause of COVID-19. Of the 41 SARS-CoV-2-infected patients admitted in the early stages of the outbreak, six died from ARDS. ARDS is the common immunopathological event for SARS-CoV-2, SARS-CoV and MERS-CoV infections. One of the main mechanisms for ARDS is the cytokine storm, the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, TNF-α, TGFβ, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells in β corona viruses infection. Similar to those with SARS-CoV, individuals with severe MERS-CoV infection show elevated levels of IL-6, IFN-α, and CCL5, CXCL8, CXCL-10 in serum compared to those with the mild-moderate disease. The cytokine storm will trigger a violent attack by the immune system to the body, cause ARDS and multiple organ failure, and finally lead to death in severe cases of Covid-19 infection, just like what occurs in SARS-CoV and MERS-CoV infection.

To better survive in host cells β corona viruses use multiple strategies to avoid immune responses. The evolutionarily conserved microbial structures called pathogen-associated molecular patterns (PAMPs) can be recognized by pattern recognition receptors (PRRs). However, these viruses can induce the production of double-membrane vesicles that lack PRRs and then replicate in these vesicles, thereby avoiding the host detection of their dsRNA. IFN-I(IFN-α and IFN-β) has a protective effect on SARS-CoV and MERS-CoV infection, but the IFN-I pathway is inhibited. Accessory protein 4a of MERS-CoV may block the induction of IFN at the level of MDA5 activation through direct interaction with double-stranded RNA. Besides, ORF4a, ORF4b, ORF5, and membrane proteins of MERS-CoV inhibit nuclear transport of IFN regulatory factor 3 (IRF3) and activation of IFN β promoter. The antigen presentation can also be affected by the corona virus; for example, gene expression related to antigen presentation is down-regulated after MERS-CoV infection. Therefore, destroying the immune evasion in Covid-19 is imperative in its treatment and specific drug development.

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