Name- Sanda Fatima Umar

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Course -virology

Questions

Discuss the etiology,origin,structure and pathophysiology of COVID-19

Answer

Etiology

The coronavirus disease (COVID-19) has been identified as the cause of an outbreak of respiratory illness in Wuhan, Hubei Province, China beginning in December 2019. As of 31 January 2020, this epidemic had spread to 19 countries with 11 791 confirmed cases, including 213 deaths. The World Health Organization has declared it a Public Health Emergency of International Concern. Coronaviruses are enveloped single-stranded RNA viruses that are zoonotic in nature and cause symptoms ranging from those similar to the common cold to more severe respiratory, enteric, hepatic, and neurological symptoms .Other than SARS-CoV-2, there are six known coronaviruses in humans: HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU1, and MERS-Cov . Coronavirus has caused two large-scale pandemics in the last two decades: SARS and MERS . To detect the infection source of COVID-19, China CDC researchers collected 585 environmental samples from the Huanan Seafood Market in Wuhan, Hubei Province, China on 1 January and 12 January 2020. They detected 33 samples containing SARS-CoV-2 and indicated that it originated from wild animals sold in the market . Then, researchers used the lung fluid, blood, and throat swab samples of 15 patients to conduct laboratory tests. These laboratory tests found that the virus-specific nucleic acid sequences in the sample are different from those of known human coronavirus species. Laboratory results also indicated that SARS-CoV-2 is similar to some of the beta (β) coronaviruses genera identified in bats which is situated in a group of SARS/SARS-like CoV .To conduct next-generation sequencing from bronchoalveolarp lavage fluid and cultured isolates, researchers enrolled nine inpatients in Wuhan with viral pneumonia and negative in common respiratory pathogens. The results of this next-generation sequencing indicated that SARS-CoV-2 was more distant from SARS-CoV (with about 79% sequence identity) and MERS-CoV (with about 50% sequence identity) than from two bat-derived SARS-like coronaviruses – bat-SL-CoVZC45 (with 87.9% sequence identity) and bat-SL-CoVZXC21 (with 87.2% sequence identity) .Studies also reported that COVID-19 S-protein supported strong interaction with human ACE2 molecules despite the dissimilarity of its sequence with that of SARS-Cov

Many domestic and wild animals, including camels, cattle, cats, and bats, may serve as hosts for coronaviruses . It is considered that, generally, animal coronaviruses do not spread among humans . However, there are exceptions, such as SARS and MERS, which are mainly spread though close contact with infected people via respiratory droplets from cough or sneezing. With regard to COVID-19, early patients were reported to have some link to the Huanan Seafood Market in Wuhan, China, suggesting that these early infections were due to animal-to-person transmission. However, later cases were reported among medical staff and others with no history of exposure to that market or visiting Wuhan, which was taken as an indication of human-to-human transmission. The latest guidelines from Chinese health authorities described three main transmission routes for the COVID-19: 1) droplets transmission, 2) contact transmission, and 3) aerosol transmission. Droplets transmission was reported to occur when respiratory droplets (as produced when an infected person coughs or sneezes) are ingested or inhaled by individuals nearby in close proximity; contact transmission may occur when a subject touches a surface or object contaminated with the virus and subsequently touch their mouth, nose, or eyes; and aerosol transmission may occur when respiratory droplets mix into the air, forming aerosols and may cause infection when inhaled high dose of aerosols into the lungs in a relatively closed environment . In addition to these three routes, one study also indicated the digestive system as a potential transmission route for COVID-19 infection. Since patients had abdominal discomfort and diarrhoea symptoms, researchers analyzed four datasets with single-cell transcriptomes of digestive systems and found that ACE2 was highly expressed in absorptive enterocytes from ileum and colon.

Origin

In December 2019, a cluster of pneumonia cases, caused by a newly identified β-coronavirus, occurred in Wuhan, China. This coronavirus, was initially named as the 2019-novel coronavirus (2019-nCoV) on 12 January 2020 by World Health Organization (WHO). WHO officially named the disease as coronavirus disease 2019 (COVID-19) and Coronavirus Study Group (CSG) of the Inter-national Committee proposed to name the new coronavirus as SARS-CoV-2, both issued on 11 February 2020. The Chinese scientists rapidly isolated a SARS-CoV-2 from a patient within a short time on 7 January 2020 and came out to genome sequencing of the SARS-CoV-2 . As of 1 March 2020, a total of 79,968 cases of COVID-19 have been confirmed in mainland China including 2873 deaths. Studies estimated the basic reproduction number (R0) of SARS-CoV-2 to be around 2.2 , or even more (range from 1.4 to 6.5) , and familial clusters of pneumonia outbreaks add to evidence of the epidemic COVID-19 steadily growing by human-to-human transmission

origin and transmission of SAR-Cov-2

The SARS-CoV-2 is a β-coronavirus, which is enveloped non-segmented positive-sense RNA virus (subgenus sar-becovirus, Orthocoronavirinae subfamily) . Corona-viruses (CoV) are divided into four genera, including α−/β−/γ−/δ-CoV. α- and β-CoV are able to infect mammals, while γ- and δ-CoV tend to infect birds. Previously, six CoVs have been identified as human-susceptible virus, among which α-CoVs HCoV-229E and HCoV-NL63,and β-CoVs HCoV-HKU1 and HCoV-OC43 with low pathogenicity, cause mild respiratory symptoms similar to a common cold, respectively. The other two known β-CoVs, SARS-CoV and MERS-CoV lead to severe and potentially fatal respiratory tract infections . It was found that the genome sequence of SARS-CoV-2 is 96.2% identical to a bat CoV RaTG13, whereas it shares 79.5% identity to SARS-CoV. Based on virus genome sequencing results and evolutionary analysis, bat has been suspected as natural host of virus origin, and SARS-CoV-2 might be transmitted from bats via unknown intermediate hosts to infect humans. It is clear now that SARS-CoV-2 could use angiotensin-converting enzyme 2 (ACE2), the same receptor as SARS-CoV , to infect

Structure

Genome structure and key viral factors

Isolated from a COVID-19 pneumonia patient, a worker in the Wuhan seafood market, the complete genome of Wuhan-Hu-1 coronavirus (WHCV), one strain of SARS-CoV-2, is 29.9 kb . While SARS-CoV and MERS- CoV have positive-sense RNA genomes of 27.9 kb and 30.1 kb ,respectively . It has been shown that the genome of CoVs contains a variable number (6–11) of open reading frames (ORFs) . Two-thirds of viral RNA, mainly located in the first ORF (ORF1a/b) translates two polyproteins, pp1a and pp1ab, and encodes 16 non-structural proteins (NSP), while the remaining ORFs encode accessory and structural proteins. The rest part of virus genome encodes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein ,and also several accessory proteins, that interfere with the host innate immune response. Wu et al have recently performed deep meta-transcriptomic sequencing on WHCV, which contained 16 predicted NSP. WHCV exhibits some genomic and phylogenetic similarity to SARS-CoV, particularly in the S-glycoprotein gene and receptor-binding domain (RBD), indicating the capability of direct human transmission. Compared with the known SARS-CoV and MERS-CoV genome, SARS-CoV-2 is closer to the SARS-like bat CoVs in terms of the whole genome sequence. Most genomic encoded proteins of SARS-CoV-2 are similar to SARS-CoVs, as well as exist certain differences. At the protein level, there are no amino acid substitutions that occurred in NSP7, NSP13,envelope, matrix, or accessory proteins p6 and 8b, except in NSP2, NSP3, spike protein, underpinning subdomain ,i.e., RBD . Another recent research suggested that the mutation in NSP2 and NSP3 play a role in infectious capability and differentiation mechanism of SARS-CoV-2.This provokes people to explore the difference of the host tropism and transmission between SARS-CoV-2 and SARS-CoV or conduct further investigations on the potential therapeutic targets. Zhang et al. analysed the genotypes of COVID-19 in different patients from several provinces and found that SARS-CoV-2 had been mutated in different patients in China. Although the degree of diversification of SARS-CoV-2 is smaller than the mutation of H7N9 avian influenza . Tang et al. [26] conducted a population genetic analyses of 103 SARS-CoV-2 genomes and classified out two prevalent evolvement types of SARS-CoV-2, L type (~ 70%) and S type (~ 30%). The strains in L type, derived from S type, are evolutionarily more aggressive and contagious. Thus, virologists and epidemiologists need to closely monitor the novel corona-virus, in order to inspect the virulence and epidemic.

Pathophysiology

Different CoVs display diverse host range and tissue tropism.Usually, alphacoronaviruses and beta coronaviruses infect mammals. In contrast, gamma coronaviruses and delta coronaviruses infect birds and fish, but some of them can also infect mammals.4,60 Before 2019,there were only six CoVs that were known to infect human and cause respiratory diseases. HCoV‐229E, HCoV‐OC43, HCoV‐NL63, and HKU1 cause only mild upper respiratory disease, and in rare cases some of them can cause severe infection in infants, young children and elders. SARS‐CoV and MERS‐CoV can infect lower respiratory tract and cause severe respiratory syndrome in human.56,61 Some CoVs can infect livestock, birds, bats, mice, whales, and many other wild animals, and they can cause great economic loss. For example, in 2016, an HKU2‐related bat CoV, swine acute diarrhoea syndrome CoV, caused a large‐scale outbreak of fatal disease in pigs in Southern China, and more than 24 000 piglets were dead.62 This is the first documented spill over of a bat CoV that caused severe disease in livestock.4,63 The new CoV, 2019‐nCoV, which belongs to betacoronaviruses based on sequence analysis , can also infect the lower respiratory tract and cause pneumonia in human, but it seems thatthe symptoms are milder than SARS and MERS. Up to 20 January 2020, 291 cases in total have been confirmed in China by sequence analysis, clinical diagnosis and epidemiological examination, including 270 cases in Wuhan . In addition, four cases were confirmed in three other countries, including two cases in Thailand, one case in Japan, and one case in South Korea; all these patients had stayed in or visited Wuhan 2 weeks before the onset of the symptoms. Six deaths and 63 patients with severe symptoms were reported in Wuhan . Among the six death cases, four patients with published information are elder people of over 60 years old and have other illnesses before the infection, such as abdominal tumour and chronic liver disease, myocarditis and renal dysfunction, and cardiovascular disease.Many of the patients have direct or indirect contact with the Wuhan Hunan Seafood Wholesale Market that is believed to be the original place of the outbreak of the 2019‐nCoV. However, transmission of 2019‐nCoV from fish to human is unlikely. The 2019‐nCoV and fish CoVs such as Beluga Whale CoV/SW1 belong to different genera and apparently have different host ranges. As the Wuhan seafood market also sells other animals, the natural host of 2019‐nCoV awaits to be identified. Due to the possibility of transmission from animal to human, CoVs in livestock and other animals including bats and wild animals sold in the market should be constantly monitored. In addition, more and more evidence indicate the new virus 2019‐nCoV is spread via the route of human‐to‐human transmission because there are infections of people who did not visit Wuhan but had close contact with family members who had visited Wuhan and got infected. The major pathogenic CoVs are listed in Table 2 for better understanding the pathogenesis of CoVs.

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