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Human coronaviruses: Origin, host and receptor

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Keywords: Human coronavirus, Emerging coronavirus, Host, Receptor, SARS-CoV-2, COVID-19

Abstract

Coronavirus is a type of RNA-positive single-stranded virus with an envelope, and the spines on its surface derived its official name. Seven human coronaviruses 229E, OC43, NL63, HKU1, MERS, SARS-CoV-2 can cause both a mild cold and an epidemic of large-scale deaths and injuries. Although their clinical manifestations and many other pathogens that cause human colds are similar, studying the relationship between their evolutionary history and the receptors that infect the host can provide important insights into the natural history of human epidemics in the past and future. In this review, we describe the basic virology of these seven coronaviruses, their partial genome characteristics, and emphasize the function of receptors. We summarize the current understanding of these viruses and discuss the potential host of wild animals of these coronaviruses and the origin of zoonotic diseases.

1. Introduction

In the past sixty years, the coronavirus has caused two large-scale public health incidents and several regional influenza incidents. The current epidemic of the new coronavirus has also posed an unprecedented challenge to global health. Many experts in public health hold the unanimous view that the coronavirus lurking in bats may cause large-scale disease outbreaks in the future. This review summarizes the current understanding of coronavirus such as 229E, OC43, SARS, NL63, HKU1, MERS, SARS-CoV-2. Based on recently published studies, this review covers the basic research of the origin, host, isolation, and identification of the coronavirus infected human being, including the intermediate host, the epidemiology, and receptor binding. Furthermore, we will discuss the clinical and other features.

1.1. The coronavirus: classification and origin

In 1966 Human respiratory virus 229E was discovered. In 2007, a homologous sequence of 229E was founded in a kind of alpaca in California. It named Alpaca Coronavirus (ACoV). The ACoV was genetically most similar to the common human coronavirus (HCoV) 229E with 92.2% nucleotide identity over the entire genome [1].

Follow-up research about the virus carried by Adrian bats demonstrated that 229E also has a high degree of similarity with the coronavirus in bats [2]. It means alpaca is likely to be the intermediate host of the original strain of the 229E virus from bats to humans [3].

Human coronavirus OC43 is a kind of β-coronavirus [4,5]. Also, an analysis of the molecular clock suggested that the recent common ancestor of OC43 and bovine coronavirus (BCoV) was isolated from 1890. It means that around 1890, BCoV has jumped the species barrier and infected humans. It could be the origin of the birth of OC43 [6].

SARS-CoV causes severe acute respiratory syndrome. This kind of disease was named SARS by World Health Organization in 2003. The research found that the pandemic was caused by a coronavirus which was the first coronavirus to result in severe public health events, and its natural origin could be the civet because the sequence of virus isolated from them is a similarity to the human SARS virus as high as 99.8%. Therefore, human SARS-CoV seems to be an animal virus that crosses the barrier of the intermediate host to infect human beings [7]. Seroepidemiologic data also proved this argument [8-10].

In January 2003, a 7-month-old kid was sent to the hospital in Amsterdam for fever, conjunctivitis, and coryza [11]. After the first description of HCoV-NL63, a second research group described the same virus named HCoV-NL63 in Vero-E6 cell culture supernatant [12,13].

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Human coronavirus HKU1 (Hong Kong University) was discovered in 2004 in a patient infected by the virus. There is no specific sequence from any other member of the same species [14].

On June 13, 2012, a local private hospital in Jeddah received a man. After 11 days of admission, the infected patient died from renal failure and progressive respiratory [15]. In an outbreak of a hospital in 2013 in Al-Hasa, Saudi Arabia, 23 patients were infected by a novel virus. In 1983, MERS-CoV infection was detected in camel serum samples, which means MERS-CoV could present in camels 30 years ago. [16] The genomic sequence analysis revealed that the MERS-CoV, Pipistrellus bat coronavirus HKU5 and Tylonycteris bat coronavirus HKU4 are phylogenetically related (denoted as betacoronavirus lineage C). The structure of the virus isolated from bats has a high correlation with MERS-CoV. It supports the hypothesis that MERS-CoV originated from bats.

In December 2019, a case of pneumonia was reported. After the report, the local hospital used the surveillance mechanism to identify 4 cases of novel pneumonia. All of them are originated from the Huanan (the southern area of China) seafood market and had direct contact with the trade in the market.

In 2018, researchers analyzed nasal swabs from 301 pneumonia patients treated in a hospital in East Malaysia. It was found that eight patients, except for one child, were infected with the newly discovered coronavirus, which the researchers of the study named CCOV-HuPn-2018. In a study on May 20, 2021, researchers described the genetic characteristics of CCOV-HuPn-2018, indicating that it is a new coronavirus that has been transferred from infected dogs to infected people [17] (Fig.2).

1.2. Animal host and its spillover

Follow-up research about the virus carried by Adrian bats demonstrated that 229E also has a high degree of similarity with the coronavirus in bats. [2]. Furthermore, it means alpaca is likely to be the intermediate host of the original strain of 229E virus from bats to humans, but the specific role in human infection is unknown [3].

An analysis of the molecular clock suggested that the recent common ancestor of OC43 and bovine coronavirus (BCoV) was isolated from 1890. It means that around 1890, BCoV has jumped the species barrier and infected humans. The supporting evidence of this kind of hypothesis is the finding of the absence of 290-nucleotide compared with BCoV because this extra sequence fragment is present in murine hepatitis virus (MHV) and rat sialodacryoadenitis virus (SDAV). Therefore, the assumption that the spread from bovines to humans sounds like much credibility [6].

What is the actual host of SARS? A study unveils this secret. From the study of Wendong Li, his team reported that ‘species of bats are a natural host of coronavirus closely related to those responsible for the SARS outbreak. In 2017, a team found all the genomic components of the SARS virus in two caves (Swallow Cave and Stone Cave) in Xiyang Yi Township, Jinjing County, Yunnan Province, China, and pinpointed the source. They also Visited 218 villagers in Xiyang Yi Township, 81.2% raised or owned livestock or pets, and 9.1% witnessed bats flying near houses [14,18-20].

Up to date, some researchers found three different sequences of CoVs (family Hipposideridae) from Kenya that related closely with HCoV-NL63. The report also includes one strain (BtKYNL63–9a, GenBank ACC no. KY073744) with more than 90% similar amino acid sequence identity threshold about species typing in three of seven conserved domains [21]. Significantly, HCoV-229E and HCoV-NL63 could be from sister species. The recombination procedure involved the spike gene through two breakpoints. One is located near the gene’s 5’-end and another near 200 nucleotides upstream of the 3’-end [21]. Among SARS-and SARS-like CoV and HCoV-OC43 have shown similar breakpoints.

According to the modification of genus of the virus of classification report of 10th ICTV, the coronavirus suborder divides into four-part: α coronavirus, β coronavirus, γ coronavirus, δ coronavirus. The first two only infect mammals, and the latter two mainly infect birds or a few mammals.
The existence of recombination could implicate incomplete speciation; therefore, the existence of BtKYNL63-9a could be regarded as evidence of the primordial host of HCoV-NL63. Its ancestor could exist in hipposiderid or rhinolophid bats. The exact source of MERS transmission to human beings remains unknown. Initial investigation revealed that MERS-CoV could originate from bats: some MERS-CoV-related sequences were founded from several bat species [25, 26]. However, MERS-CoV has never been isolated directly from bats. Therefore if MERS-CoV was transmitted to people directly or indirectly is unknown. From an early study, all of the dromedary camels in Oman and 14% in the Canary Islands (in Spain) suggested positive anti-MERS-CoV antibodies [27]. Although the bats are significant, some facts revealed that some other animals play the role of intermediate host between humans and bats. First of all, when the pandemic was reported (in the winter of 2019), most bats were hibernating. Secondly, non-aquatic animals are sold at the Huanan seafood market, not including bats. Finally, bats are the natural host between MERS-CoV and SARS-CoV. Masked palm civet is the intermediate host of SARS-CoV, and dromedary camels are the intermediate host for MERS-CoV; humans are their terminal hosts [7, 28]. Since the high sequence similarity between SARS-like bats coronavirus (Hipposideros bats in China) and SARS-CoV-2, it seems verified this hypothesis that the natural host of SARS-CoV-2 could be the Hipposideros bat. Another discovery also revealed that the coronavirus genomes of Malayan pangolin have 85.5~92.4% sequence similarity to SARS-CoV-2. It also represents two sub-lineages of the related viruses of...

**Fig. 2.** It is the timeline of coronavirus that was first discovered in human history. The 229E was first founded in 1966, and it was the first invented coronavirus of which seven ones could infect people. Secondly is OC43, which was isolated from patients with cold. The next one is SARS, the outbreak of SARS was discovered in November 2002 and ended in 2003. In the same year, NL63 was detected using the VIDISCA and PCR method. In 2004, HKU1 was reported by HKU and named. Seven years later, an outbreak was founded in the Middle East, caused by a novel coronavirus named MERS-CoV. In 2018, researchers surprisingly analyzed nasal swabs from 301 pneumonia patients treated in a hospital in East Malaysia. It was found that eight patients, except for one child, were infected with the newly discovered coronavirus, which the researchers of the study named CCoV-HuPn-2018. In December 2019, a case of SARS-CoV-2 was reported in Asia. Nevertheless, there is also evidence in NEJM that revealed that the 2019-nCoV infection could be diagnosed in Germany and transmitted outside to Asia. The authentic original place of SARS-CoV-2 is still unknown.

**Fig. 3.** Origins of human coronavirus. Severe acute respiratory syndrome coronavirus is a novel coronavirus related to bats with recombination. Before the SARS epidemic outbreak, the bats’ virus infected civets and evolved to adapt to infect humans. The MERS-CoV could be originated from bats and spread to camels about 30 years ago and has been prevalent in dromedary camels. HCoV-NL63 and HCoV-229E, these two viruses do not cause severe respiratory damage and usually only bring a mild cold. The ancestor of both of them has been founded in African bats recently, and the camels could be the intermediate host of HCoV-229E. Discovery revealed that the coronavirus genomes of Malayan pangolin have high sequence similarity to SARS-CoV-2. It means that Malayan pangolins could be thought to be the possible intermediate host. HCoV-OC43 and HCoV-HKU1 could be originated from rodents. Black arrows showed the direction of propagation. In this figure, humans are the ultimate hosts of transmission.
related bat, camel, and alpaca 229E viruses are transmitted to the cor
SARS, and SARS-CoV-2) exchange of various viral ancestors, including the strains isolated from
transmission. It means MERS-CoV could originate from the differential
could endow the ability to adapt to new environments and cross-species

The nature of the interaction between various RBDs and hAPN also provides clues for the in-depth understanding of how HCoV-229E and related bat, camel, and alpaca 229E viruses are transmitted to the corresponding hosts [62].

1.3.2. DPP4 receptor (HCoV-MERS)
The length of 30–31 kb genome could encode many proteins, which could endow the ability to adapt to new environments and cross-species transmission. It means MERS-CoV could originate from the differential exchange of various viral ancestors, including the strains isolated from the camels and its assuming natural host: bats. Since the outbreak of 2012, MERS-related virus (such as HKU4 and HKU5) has been found in different kinds of bats. The ORF1ab of these viruses are highly similar to MERS-CoV’s. Some MERS-related viruses could even use the same receptor (DPP4) of MERS-CoV [63–65].

1.3.3. ACE2 receptor (The similarities and differences between NL-63, SARS, and SARS-CoV-2)
The human ACE2 receptor is a crucial target of the NL-63, SARS-CoV, and SARS-CoV2 spike (S) protein receptor-binding domain (RBD) that facilitates viral entry into host cells. The S protein drives the infection between coronaviruses of the target cell. The S protein could promote the entry of SARS-CoV-2 into the target cell. Depending on the S1 unit of the surface of S protein can facilitate the combination with the ACE2 receptor. S protein of SARS-CoV-2 shares about 76% amino acid identity with SARS-CoV’s. Since SARS-S uses ACE2 as a receptor for cell entry and uses the cellular serine protease Tmprss2 for S protein initiation, it is not difficult to deduce that SARS-CoV-2 has also a similar effect. This mechanism makes the degree of fusion of ACE2 and SARS-CoV a decisive factor in virus transmission [66]. During the infection of SARS-CoV, S protein plays a significant role in mediating the production of neutralizing-antibody and T-cell responses, also protective immunity [67]. In addition, the RBD in S1 is responsible for the recombination between virus and host cells [68, 69]. It means ACE2 is the functional receptor of SARS-CoV [69, 70]. Compared with SARS-CoV, ACE2 is also the docking point, but SARS-CoV-2 binds to ACE2 is more robust 2–4 times than SARS-CoV because the changes in RBD stabilize the virus-binding hotspots [69,71,72]. From the sequence analysis, although the SARS-CoV-2 genes shared less than 80% identity of the sequence of nucleotide to SARS-CoV, the amino acid sequences of seven conservation replicate domains in ORF1ab for classification shared 94.4% identification between SARS-CoV-2 and SARS-CoV. That is to say, both of them belong to one same species, SARSr-CoV. From the study, it is said that a short paragraph of the RNA-dependent RNA polymerase (RdRP) of a kind of coronavirus (BatCoV RaTG13) isolated from bats has the identification of sequence to SARS-CoV-2 highly. After the full-length sequencing of the sample, the result revealed that the SARS-CoV-2 is highly similar to RaTG13 in the whole genome sequence. The identity between them is as high as 96.2%. In addition, the known virus in bat SARS-CoV-2 lineage has not used the ACE2 of humans efficiently compared with the SARS-CoV-2 from pangolin or SARSr-CoV-1 lineage viruses [73]. Compared with SARS-CoV, the amino acid sequence identity between the S protein of them is 76.47% [74]. It is evident that SARS-CoV-2 is a high-speed virus; it could prevent our immune system from identifying and fighting for the infection with its unique ability. When our immune system realize there is virus survives, the immune-response proteins would swarm into the bloodstream with high speed than normal condition and could cause damage. Some infected patients become deteriorate by the overactive immune response to SARS-CoV-2 and the toxic effects of the virus itself [72,75].

From the study, the genome sequence level of SARS-CoV-2 is closer to bat-SL-CoVZXC21 and bat-SL-CoVZC45, but from the receptor-binding domain and external subdomain, it is closer to SARS-CoV. Isolated from the patient species of Wuhan, China, the phylogenetic analysis suggested that SARS-CoV-2 belongs to the Sabeovirus. Although specific antibodies in patients with SARS-CoV can be maintained for two years after infection, the difference is that despite being vaccinated with specific vaccines, SARS-CoV-2 patients still have a greater possibility of re-infection after recovery [76]. Interestingly, Marlin et al. described in the macaque (humanoid) model that infected and convalescent macaques were still at risk of reinfection at six months. This result also means that the levels of neutralizing antibodies in the body tend to weaken over time [77]. Studies have shown that soluble ACE2 (sACE2) can bind to the viral S protein. The sACE2 released from the human airway epithelium will limit the binding of the above virus to the ACE2 receptor on the cell surface, preventing the virus from further replicating in the human body [78,79]. Secondly, studies have shown that CD40L expressed on T cells can be activated and interacted with by expressing CD40. And then regulating the immune function of B cells and T cells, improving the recovery period of patients with secondary infection and effectively increasing the level of neutralizing antibodies. These two mechanisms may serve as a new direction for vaccine development [77, 80]. Vaccines at the current stage can only prevent major complications after infection but cannot prevent re-infection and secondary transmission. Many virus spreaders are vaccinated, but they remain asymptomatic and can continue exporting the virus. While building herd immunity, we also need to prevent asymptomatic infections from becoming a source of infection again.

2. Conclusions
To sum up, it is not difficult to conclude that the SARS-CoV-2 could be more infectious than SARS-CoV and MERS-CoV. Is this related to other unknown receptor interactions? Will 2019-nCoV produce adaptive mutations in human-to-human transmission? These issues are still worthy of our in-depth study. Both SARS-CoV-2 and SARS-CoV can activate the body’s antiviral immune response and cause uncontrolled inflammatory responses in critical patients. It is characterized by the release of proinflammatory cytokines, leading to lymphopenia, lymphocyte dysfunction, and granulocyte and monocyte abnormalities. The clinical characteristics of the two are different, but the difference lies in the longitudinal factors such as the severity of the onset, the fatality rate, and the infection rate. For their pathological manifestations in the respiratory tract, there seems to be a specific correlation with the utilization rate of ACE2 receptors. In terms of virus grouping, MERS-CoV, which belongs to Betacov, is quite different from the above two viruses in lung manifestations; this is also related to the utilization of the receptor DPP4 of MERS-CoV. The origin of coronaviruses is relatively simple compared to other viruses, but its hosts are primarily distributed in mammals. This result should arouse our attention more than other phenomena because humans are mammals and advanced mammals. The relationship is self-evident. Whether one-day humans will be infected with a new type of virus through excessive contact with mammals, no
Table 1
Summary of discussed coronaviruses.

| Virus     | Virus species | Natural host | Intermediate host | Receptor | Clinical manifestation                                                                 | Tropism | Available vaccine and reference |
|-----------|---------------|--------------|-------------------|----------|---------------------------------------------------------------------------------------|---------|---------------------------------|
| TGEV      | Alpha-CoV     | unknown      | Pig               | APN      | /                                                                                    | enteric | LAV, PRCV as natural vaccine    |
| BCoV      | Beta-CoV      | unknown      | Bovine            | SIALIC   | /                                                                                    | Enteric, respiratory | Inactivated virus, live attenuated vaccine |
| MHV       | Beta-CoV      | unknown      | Mice              | CEACAM1  | /                                                                                    | Strain dependent (enteric, hepatic, respiratory, CNS) | / |
| HCoV-229E | Alpha-CoV     | bats         | Alpaca            | APN      | General malaise, headache, nasal discharge, sneezing, sore throat, fever and cough  | /       | [34, 35]                        |
| HCoV-NL63 | Alpha-CoV     | bats         | Unknown           | ACE2     | cough, fever, sore throat, rhinitis, expectoration, and upper and lower respiratory tract infection, such as bronchitis, bronchiolitis or pneumonia | respiratory | / |
| HCoV-OC43 | Beta-CoV      | mice         | Bovine            | SIALIC   | Upper respiratory tract infection, headache, rhinorrhea and sore throat, coughing and fever | respiratory | / |
| HCoV-HKU1 | Beta-CoV      | mice         | Unknown           | SIALIC   | Rhinorrhea, fever, coughing, and wheezing, and can result in bronchiolitis and pneumonia | respiratory | / |
| SARS-CoV  | Beta-CoV      | bats         | Civet cats        | ACE2     | ARDS, DAD, pulmonary fibrosis, Fever, Myalgia, Headache, Malaise, Chills, Nonproductive cough, Dyspnea, Respiratory distress | respiratory | multiple phase 1 trials |
| MERS-CoV  | Beta-CoV      | bats         | Camels            | DPP4     | ARDS, multi-lobar airspace disease, pulmonary fibrosis | respiratory | three recently concluded phase 1 trials |
| SARS-CoV-2| Beta-CoV      | bats         | Pangolins         | ACE2     | ARDS, DAD, pulmonary fibrosis, fever, myalgia, headache, malaise, Chills, nonproductive cough, dyspnea, respiratory distress fatigue, chest pain, cognitive disturbances, arthralgia | respiratory | several ongoing clinical trials, RNA-based vaccine, Adenovirus vector (nonreplicating), protein subunit |
| CCoV-HuPn-2018 | Alpha-CoV | unknown     | canine            | APN      | Respiratory illness that does not include the gastrointestinal issues | respiratory | / |

HCoV, human coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MERS-CoV, Middle East respiratory syndrome coronavirus; CCoV-HuPn-2018, Canine coronavirus HuPn-2018; DAD, diffuse alveolar damage.
one will know. We can draw some conclusions from the coronavirus we mentioned above. First of all, from the lessons of MERS-CoV and SARS-CoV-2, promoting early intervention and identification plays a significant role in protecting from deteriorating and preventing aberrant proinflammatory response even if the vaccination strategy is not mainstream. However, form using the strategies of immune evasion could prevent the identification by pattern recognition receptors. Secondly, neutralizing antibody responses exhibit its protection during the infection of coronavirus. It could be considered as the critical point for vaccine strategies. Also, the studies of animals and humans show that vaccines should strongly induce humoral responses and cellular adaptive immune responses because they are the utmost essential mediators of protection. Last but not least, we should also pay more attention to the potential variants of the virus.

3. Future Outlooks

Although the death of SARS-CoV-2 is less than MERE-CoV and SARS, the rapid pandemic outbreak has posed the severest threat to the public health of our world. The pandemic has lasted over two years. when will it end? Nobody knows. The vaccine for the current epidemic has been developed, but the real question is, how should we face the next pandemic of the zoonotic coronavirus? Will the next global pandemic be in 5 years? Ten years? Or did it appear earlier? After we control the pandemic, the next step should focus on virus screening, identification, isolation, and further detecting coronaviruses’ presence in wild animals, especially bats. At the same time, researchers should find suitable animal models to conduct in vitro and in vivo studies to assess the risk of future epidemics. Therefore, we may build up appropriate animal models of COVID-19, which could be used to understand the immune operational mechanism. Non-human primates could be best. Due to non-human primates being humans’ closest relatives in evolution, they may provide the most relevant data for pathological alteration, the safety and effectiveness of the vaccine, therapy, and preclinical experiment. However, the availability and expense of the non-human animal model should also be taken into account. Finally, the persistent analysis of the full-length genome is necessary because of the high mutability of coronavirus. At present, the novel coronavirus epidemic is undergoing mutations at a high rate; before the arrival of a new round of the epidemic, we must take measures to prevent the occurrence of a new pandemic. It seems to be an excellent decision to choose cd40 or sACE2 as the new direction for vaccins. Under the epidemic prevalent in the world, addressing the problematic issue requires the efforts of every people, government, and nation. Only through cooperation can we overcome common difficulties.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was sponsored by the National Natural Science Foundation of China (81770683), Guangzhou Science and Technology Program Project (202102010343), Health and Medical Collaborative Innovation Project (201704020225), the grant of the State Key Laboratory of Respiratory Disease, Guangdong-Hong Kong-Macao Joint Laboratory of Respiratory Infectious Disease (GJMHLRID-Z-202104) and Guangdong Basic and Applied Basic Research Foundation (2021A1515110550).

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