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Review Article

Spotlight of Twenty First Century Betacoronaviruses

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Abstract

Coronavirus (CoV) have previously been considered as relatively non-virulent respiratory pathogens to human. Beginning of the 21st century, three CoV's have crossed the species barrier to cause high pathogenic and mortality rates in human populations. However, two epidemic of severe respiratory tract infection caused by severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) deadly diseases in human. Another one, named SARS-CoV-2 is ongoing outbreak of atypical pneumonia and pandemic to global population. This brought CoV alert and highlighted the importance of controlling infectious pathogens at worldwide. In this review, we focus on present understanding of the epidemiology, pathology, transmission, prevention, and treatment of SARS-CoV, MERS-CoV and SARS-CoV-2.

Keywords: Coronavirus; SARS-CoV; MERS-CoV; SARS-CoV-2; COVID-19

Introduction

Coronavirus (CoV) is considered of high veterinary impact exclusively, now recognized as zoonotic threats of pandemic potential to world population. CoV is crown like morphology, enveloped and single strand RNA genome virus, are 80 to 160 nm in size. It can be classified into four genera: alpha, beta, gamma, and delta CoV [1]. Previously identified alpha CoV: hCoV-NL63 and hCoV-229E and beta CoV (βCoV): HCoV-OC43, HKU1 cause self-limiting common cold-like illnesses [2]. However, other βCoV's are Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East respiratory syndrome Coronavirus (MERS-CoV) and SARS-CoV-2 infection leads to life threatening disease and have pandemic potential.

SARS-CoV is transmission from bats to human and nosocomial communication between individuals, accompanied by high fatality rates. It's emerged from Guangdong province of southern China in 2002 and spread to 33 countries [3]. Combined global attempt led to fast identification of SARS-CoV and remarkable scientific advancements in epidemic prevention. Remarkably, SARS-CoV epidemic was ended in 2004 and infections controlled. One decade later in 2012, another zoonosis and virulent pathogenic virus, MERS-CoV was identified in Saudi Arabia [4] and spread 27 countries. MERS-CoV infected the humans through direct or indirect contact with infected dromedary camels [5].

Recent emergence of SARS-CoV-2 is significant threat to global public health. SARS-CoV-2 reported a cluster of human population in Wuhan City, China on 2019 [6], and designated as CoV disease 2019 (COVID-19). The SARS-CoV-2 origin is under investigation but associated to a wet animal market [7]. All three βCoV's are share common features contribute to nosocomial transmission, viral replication, immunopathology and cause lower respiratory tract infection. Infection is begins with binding of viral particles to host surface cellular receptors called spike (S) glycoprotein [8]. Angiotensin Converting Enzyme 2 (ACE 2) binds with S protein and gets conformational changes for membrane fusion [9]. This review highlights the epidemiology and pathogenesis of βCoV, including our current understanding of their biological characteristics, transmission, replication, prevention and treatments.

Human epidemiology

The transmission mechanism and epidemiology character of SARS-CoV, MERS-CoV and SARS-CoV-2 are tabulated (Table 1). Transmission from animals to human, direct contact with intermediary host might be one route. In twenty first century, first βCoV causing infectious disease, SARS-CoV originated in Foshan, Guangdong province in China at November 2002, resulted in 813 deaths among more than 8447 patients in 33 countries [3]. SARS-CoV was outbreaks in two times, 1) First outbreak begins in Guangdong province in late 2002. 2) Second outbreak during in late 2003 to early 2004, again reported from Guangdong province, in individuals with animal contacts with different SARS-CoV strains [10].

The second βCoV, MERS-CoV emerged in June 2012 in Jeddah, Saudi Arabia when a 60 year-old man presented with severe pneumonia [11]. MERS-CoV spread around 27 countries but around 80% of cases have occurred in Saudi Arabia. The consumption of camel milk, urine, or uncooked meat may be conducive to transmission. It's rarely transmitted among people and mostly occurs in family members and health care workers. Nosocomial infections were reported, and overseas travel led to the transmission of MERS-CoV to Middle East/North Africa, causing it to become a global pathophoresis [12]. MERS-CoV affects 2519 people and approximately 35% of patients were died (WHO).

Ongoing outbreak of SARS-CoV-2 is pandemic to world population and biological characters close resemblance to SARS-CoV. SARS-CoV-2 was reported from wet seafood market in Wuhan City, Hubei Province of China in December 2019. The SARS-CoV-2 source of transmission still unknown but linked to a wet animal market [7]. It has a 96% similarity to a bat CoV and 70% genetic similarly with SARS-CoV [13-15].

	SARS-CoV	MERS-CoV	SARS-CoV-2
Possible Natural Reservoir	Bat	Bat	Under investigation
Possible Intermediary Host	Palm civet	Dromedary camel	
Affected countries	33	27	215
Transmission region	Globally	Regionally	Globally
Mortality	9.6%	34.3%	1.38% to 3.4%
Mode of transmission	Droplets produced by coughing, sneezing, talking, or breathing	Droplets from person to person, unclear from camels to humans	Droplets produced by coughing, sneezing, or talking
Mean incubation period	5 days	6 days[¥]	5 days
Key symptoms	Dry cough, fever, diarrhea	Fever, cough, shortness of breath	Fever, dry cough, shortness of breath
At risk groups	People with underlying medical conditions	Men above the age of 60 (diabetes, high blood pressure, kidney failure)	Adults aged 65 and over, people of all ages with medical conditions
Treatment	No specific treatment	No specific treatment	No specific treatment

Table 1: Epidemiology characteristics of the βCoV's.

Reference: Assiri., *et al*. [12]; Song., *et al*. [49].

Pathogenesis of βCoV's

Our existing knowledge of the pathogenesis of CoV's infection still unclear, we tabulated what is presently CoV's are the single strand (positive sense) RNA viruses (26 - 32 kb) as they are about 125 nm in diameter. Based on its phylogenetic relationships and genomic structures the three CoV's are belongs to genera Betacoronavirus. βCoV have largest genomes (26.4 - 31.7 kb) among all known RNA viruses, with G+C contents varying from 32% to 43% [16]. Genetically, SARS-CoV-2 is similar to SARS-CoV (about 79%) and MERS-CoV (about 50%) (Figure 1). βCoV's contain structural protein are S protein, nucleocapsid protein (N), envelope protein (E), and membrane protein (M). The S protein major role is receptor binding and following viral entry into host cells, therefore a major therapeutic target. The N protein is necessary for

RNA synthesis, M and E proteins play vital roles in viral assembly [14]. Accessory proteins are help the virus escape the immune system by being harmful to the innate immune response [17]. Hemagglutinin esterase contributes to virion adhesion, and same time enhances sialate o-acetylesterase activity towards clustered sialoglycotopes [18].

Life cycles of βCoV's

βCoV's are emerging communicable viral disease characterized by severe clinical demonstration of the lower respiratory tract, resulting in diffuse alveolar damage. βCoV's enter target cells through an endosomal pathway. Viruses are binds to human cell by receptor protein and allow virus to enter and infect the cells. SARS-CoV and MERS-CoV source of transmission are tabulated (Table 1), SARS-CoV-2 source is still unknown. Three βCoV's are spreads through respiratory secretions, such as droplets, via human to human contact. S proteins of SARS-CoV and SARS-CoV-2 are binding to ACE2 of human cells followed by membrane fusion [19] (Figure 1). The SARS-CoV-2 S protein has a higher affinity for ACE2, while lower affinity for SARS-CoV [20]. In respiratory tract, ACE2 is widely expressed on the epithelial cells of alveoli, trachea, bronchi, bronchial serous glands, and alveolar monocytes and macrophage [21]. After virus enters the human cell and uncoats, genome replication and transcription takes place at cytoplasmic membranes. The mature virions are forms by budding then released from primary cells and infect new target cells [22].

		SARS-CoV	MERS-CoV	SARS-CoV-2
Virus particle size (in nm)		80-90	118-136 nm	60 to 140 nm
Length of nucleotides		29,727	30,119	29,844
Open reading frames		11	11	11
Structural protein		4	4	4
Spike protein (length of amino acids)		1255	1353	1273
S1 subunit	Receptor-binding domain	318-510	367-588	331-524
	Receptor-binding motif	424-494	484-567	437-509
S2 subunit	Heptad repeat 1 domains	892-1013	984-1104	894-966
	Heptad repeat 2 domains	1145-1195	1246-1295	1145-1195
Non-structural proteins (NSPs)		5	16	14
Accessory proteins		8	5	6
A characteristic gene order		50-replicase ORF1ab, spike (S), envelope (E), membrane (M), and nucleocapsid (N)-30		

Table 2: Genomic characteristics of βCoV's.

Reference: Mousavizadeh and Ghasemi, [14]; Neuman., *et al.* [51].

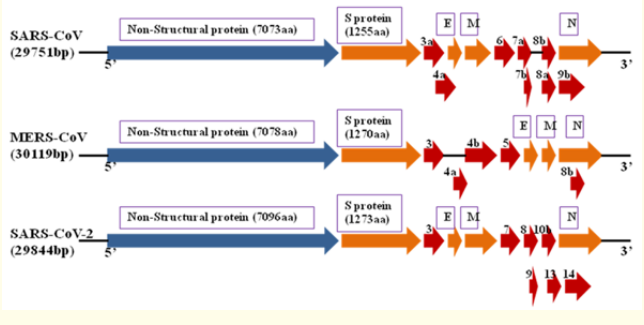

Figure 1: The coding and non-coding region of SARS-CoV, MERS-CoV and SARS-CoV-2. The numbers of base pairs among coronaviruses are shown. The differences in the arrangement of structural protein: envelope (E), membrane (M), and nucleoprotein (N) among βCoV.

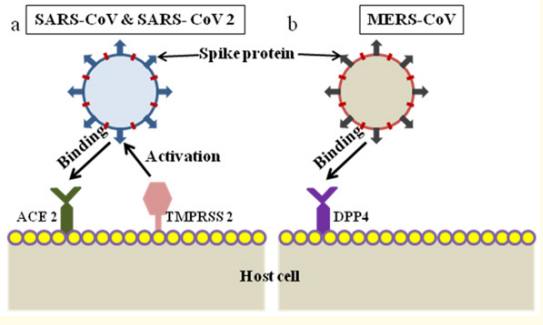

Figure 2: a) SARS-CoV and SARS-CoV-2 S protein are binding with ACE2 and cellular protease TMPRSS2 for their activation. b) MERS-CoV S protein is binding with DPP4. ACE2: Angeiotensin converting enzyme 2; TMPRSS2: Transmembrane protease, serine 2; DPP4: Dipeptidyl peptidase 4.

MERS-CoV infect to human cell by multifunctional cell surface receptor protein, dipeptidyl peptidase 4 (DPP4), which is expressed on epithelial cells in the kidney, alveoli, small intestine, liver, and prostate, and on activated leukocytes [23]. MERS-CoV S protein bind to DPP4 of epithelial cells, forming the double membrane vesicle in host cell, and releasing the RNA enclosed in nucleocapsid. The viral RNA replicate, transcript followed by translation; endoplasmic reticulum support the assembly of virus particle and MERS-CoV is released out of the host cell by exocytosis [24].

βCoV's spike protein

βCoV's transmembrane S glycoprotein is forms homotrimers protruding from the viral surface. S protein comprises two functional subunits responsible for binding to host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). In many βCoV's S protein is cleaved at the boundary between the S1 and S2 subunits, which remain non-covalently bound in prefusion conformation [25]. All βCoV's S is cleaved by host proteases at S2` site located next to upstream of the fusion peptide. This cleavage is activating the protein for membrane fusion through extensive irreversible conformational changes [26].

SARS-CoV, MERS-CoV and SARS-CoV-2 S proteins emphasize the close relationship in structural similarity and sequence conservation. S protein is approximately 180 kDa glycoprotein and it is composed of two domains, S1 and S2 [27]. S1 contain the receptor binding domain, which binds to peptidase domain of ACE 2, and S2 is responsible for membrane fusion [28]. S1 subunit is recognizing a variety of binding and entry receptors, depending on the viral species. When S1 binds to ACE2 receptor, S2 is cleaved by host proteases, process that is critical for viral infection. S2 subunit contains two regions with 4,3 heptad repeat (HR), designated as HR1 and HR2. Both are conserved in position and sequence among the members of three βCoV antigenic clusters. A number of studies have shown that HR1 and HR2 regions are involved in viral fusion [29].

Antiviral drugs

During the SARS-CoV-2 epidemic, clinical studies show that the lopinavir-ritonavir combination therapy with ribavirin in SARS patients decreased the virus load and clinical symptoms when compared with standard treatment cases [30,31]. Lopinavir–ritonavir was an HIV-1 protease inhibitor but it was reported to target SARS-CoV-2 nonstructural protein 3CLpro [31]. Similarly during the MERS-CoV outbreak, MERS patient treated with lopinavir–ritonavir showed virus replication decreased, viral clearance from sputum and serum, and increased immune response [31]. Other clinical study from Korea also reported that the lopinavir–ritonavir combination therapy is showing antiviral activity [32]. Later, a combination treatment of Interferon/ribavirin/ lopinavir-ritonavir was recommended officially for MERS therapy in South Korea during the 2015 disease spread [33]. Ribavirin is a guanosine analog, which inhibits RNA synthesis by viral RdRp as well as inhibits mRNA capping. Ribavirin was primarily used as a treatment option in Saudi Arabia and UAE [34,35]. Interferon (IFN) is a group of low-molecular glycoproteins mainly shows antiviral acidity by inducing antiviral production effector proteins, inhibits viral replication and activates cellular. The same was further recommended in the Saudi Arabia for MERS treatment [36]. In the case of COVID-19, Clinical trial study from China shows that no improvement was observed with lopinavir-ritonavir treatment compared to the standard care [37]. Hydroxychloroquine a well-known anti-malarial drugs was reported to show antiviral activity in small non-randomized French population study [38]. However, other study from the French population showed no improvement after hydroxychloroquine treatment compared to standard care [39]. Remdesivir is a nucleotide analogue prodrug that inhibits viral RNA polymerases. Non-randomized clinical study including COVID 19 patients form US, UK and Japan shows a 68% of clinical improvement compared to the standard care, the study funded by Gilead Sciences [40]. Gilead Sciences stated that they are conduction large scale study in 180 trail sites with 5,600 patient enrollments from various part of the world.

Vaccine development

To date, there is no specific treatment proven effective against this SARS-CoV and MERS-CoV disease. In addition, no vaccine has been licensed to prevent this viral infection so far. In 2002 - 2003, during the SARS-CoV outbreak, in four months the genome sequence of the coronavirus was sequenced to develop antigens. Many pharma companies and laboratories started to develop vaccine against the SARS-COV. Various vaccines based on inactivated virus, recombinant viral vectors, DNA, virus-like particles, soluble proteins and DNA vaccines were studied. But, vaccines based on an inactivated SARS virus, DNA vaccine and soluble proteins were entered the phase I clinical stages [41-43]. The first human trial of an inactivated SARS vaccine was conducted in Beijing (December, 2004), but by that time the epidemic had ended and research into other diseases had been prioritized so that it had been dropped

[44]. Similarly, for MERS outbreak in Saudi Arabia (2012), similar vaccine strategies were considered for vaccination, including an inactivated virus vaccine, a live-attenuated vaccine, a viral vector such as adenovirus, bacterial vectors, recombinant MERS-CoV proteins, MERS-CoV DNA vaccines [45]. Among that, adenovirus vaccine (ChAdOx1 MERS, which uses a replication-deficient chimpanzee adenovirus) was in Phase 1 human clinical trials in the United Kingdom and Saudi Arabia. However, the other vaccines are in development and clinical trial phases, so far, no vaccine was licensed for MERS therapeutics yet. As compared to SARS-CoV and MERS-CoV, SARS-CoV-2 is a pandemic disease, infected more than 3.4 million people worldwide. Hence, finding a safe and effective vaccine to prevent SARS-CoV-2 infection is a crucial public health importance. China successfully sequenced SARS-CoV-2 genome and submitted to GenBank on 5 January 2020 [46]. As, SARS-CoV-2 'S' glycoproteins is responsible for virus binding and host cell entry [47]. The glycoprotein is cleaved into 'S1' and 'S2' subunit, 'S1' and 'S2' subunit shares 70% and 99% similarity with SARS-CoV, respectively [48]. Hence, developing a new vaccine targeting the 'S' glycoprotein may enhance the antiviral effect against SARS-CoV-2.

Conclusion

COVID-19 has attained the status of a global pandemic over a short period. A proper understanding of the pathogenesis of CoV's are indicated in this study and related molecular mechanisms will definitely help in the development of therapeutics against the novel CoV's.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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