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Review Article

Current Insights into the Genomics of Novel Coronavirus: SARS-Cov-2

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Abstract

Coronavirus (2019 nCoV)- a deadly virus which causes panic throughout the world particularly in Wuhan region of China in 2020 affecting more than 12000 people as on 02-02-2020. Coronaviruses belong to a class of single stranded RNA viruses from the order Nidovirales. The word "Corona" itself means crown taken from its structure due to its large bulb like outgrowths, known to be among largest RNA virus, size ranging from 27 to 32 Kb. This virus is known to have unique strategy for replication. This review will lay emphasis on various animal coronaviruses and their pathogenesis, and the newly discovered human emerging pathogen 2019 - nCoV, no treatment i.e. no vaccines or antiviral drugs are approved for its prevention or treatment. This review will help understand the biology and potential risk of coronaviruses.

Keywords: *Coronavirus; Wuhan; Vaccine; 2019-nCoV*

Introduction

Dated back from 1972 - 1982, the human coronavirus (HCoV) were analysed in London by using ELISA technique [1]. HCoV's were known to cause respiratory tract infections [2]. HCoV-229E and HCoV-OC43 discovered in 1960 were only known before emergence of Severe acute respiratory syndrome-related coronavirus (SARS-CoV) in 2003 and of Middle East respiratory syndrome-related Coronavirus (MERS-CoV) in 2012: HCV's originated from animals [3-6]. All types of emerging HCoV's are known to have their origin from bats but only lineage A beta CoVs have in rodents [7]. Then with the discovery of more strains of HCV: HCoV-NL63 and HCoV-HKU1, in 2004 - 2005 were isolated from nasopharyngeal aspirates and more information about HCoV's was gained. These HCoV's were originated from bats and with time the other animal species also contains its various forms [8]. Even SARS was first reported in Guangdong Province, China, like 2019-CoV and then disease quickly spread worldwide, causing nearly 800 deaths [9]. MERS in the same way leads to 48 deaths due to respiratory distress, renal failure in 2012 [10,11]. Different HCoV'S uses various receptors like SARS uses angiotensin-converting enzyme 2 (ACE2) while as MERS-CoV uses dipeptidyl peptidase 4 (DPP4) [12]. MERS-CoV transmits between both human to animals and animals to animals [13]. Besides humans, camels also are seropositive to this virus. Figure 1 represents different receptors used by different types of HCoV's [14].

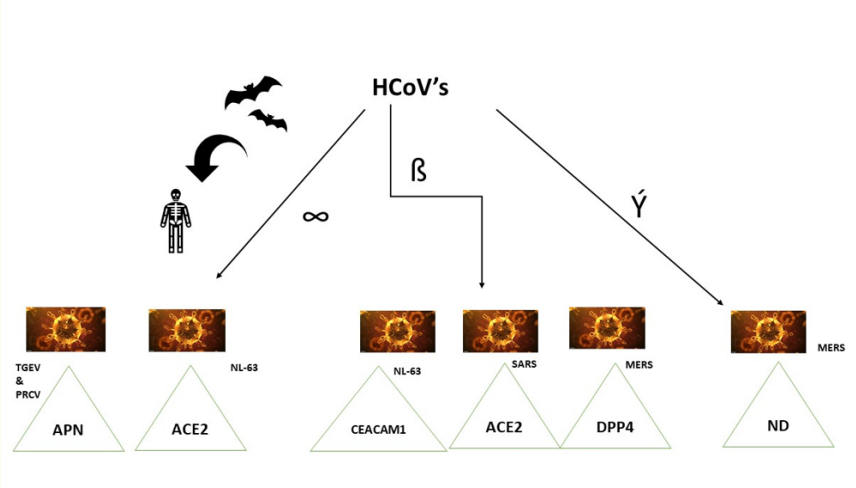

Figure 1: *Representative picture shows various different receptors of corona viruses.*

2019-nCoV virus

2019-nCoV virus also known by the name Wuhan virus [15]: a positive ss RNA virus shows similarities to beta coronavirus (subgenus sarbicovirus), 79.5% similarities with SARS-CoV and 88% with bat derived corona viruses bat-SL-CoVZC45 and bat-SL-CoVZXC21 and 50% similarity with MERS virus [16,17]. 28 genomes of this lethal virus, which transmits from humans to humans have been isolated [18]. 2019-nCoV virus is the seventh known coronavirus to infect people, after 229E, NL63, OC43, HKU1, MERS-CoV and SARS-CoV [19].

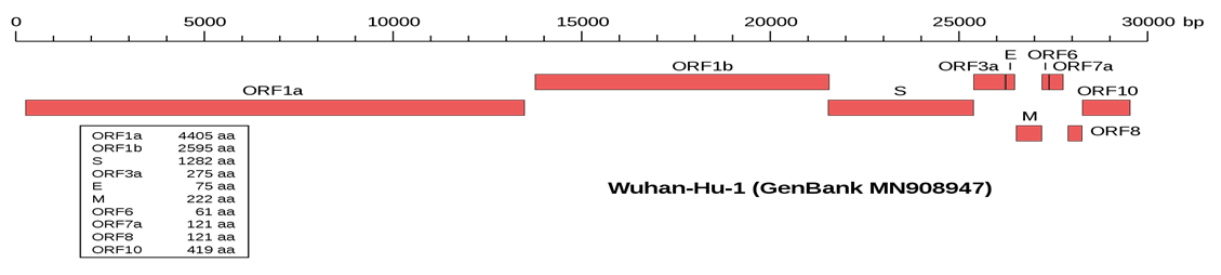

Figure 2: *Representative picture shows the 30,473 bp length RNA of Wuhan virus (NCBI Genome ID MN908947).*

2019-nCoV virus is the known cause of more than 259 deaths in China alone as on 02-02-2020, most of which involved people living in or visiting Wuhan, and human-to-human transmission has been confirmed. Outside China, Philippines reported first confirmed death on 02-02-2020. Besides 11,949 infected cases Coronavirus cases have been reported in the following continents but deaths have been only reported in China and one in Philippines (Table 1).

Continent	Countries	Number of cases
Asia	China	11000+
	Thailand	14
	Japan	14
	Singapore	13
	Taiwan	9
	Malaysia	8
	Korea	7
	UAE	5
	Vietnam	6
	Hongkong	13
	Cambodia	1
	Nepal	1
	India	1
	The Philippines	1
	Srilanka	1
Europe	France	6
	Germany	7
	Italy	2
	Finland	1
	UK	2
America	USA	6
	Canada	3
Oceania	Australia	9

Table 1: *Number of coronavirus cases till 2-02-2020.*

Structure and genomics of coronavirus

Recently discovered 2019-NcoV is a single stranded linear RNA virus having 29903 bp length with 3' poly A tail and 5' cap GenBank: MN908947.3; Locus MN908947 [20] and its having 38 aa protein sequence; Locus QHI42199 [21]. Figure 3 shows electron microscopic structure of Coronavirus [22].

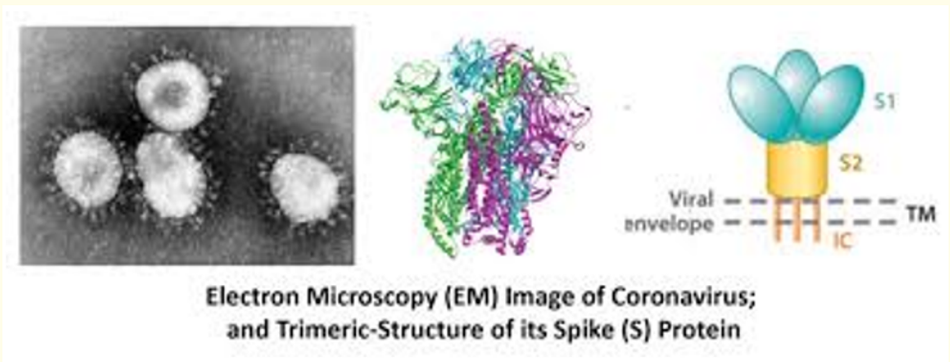

Figure 3: *Represents structure of Coronavirus and trimeric structure of its Spike proteins. Reproduced from reference 22.*

In general, RNA of coronavirus codes for four major structural proteins which are required not only for its complete structure but also for its replication includes spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein [23-26]. S protein is required for the attachment and subsequently the entry of virus to host cell surface [27,28]. N protein is required to make up

the nucleocapsid part of virus and replication s well [29,30]. Among 4, M protein is the most abundant structural protein and mediates interface with other structural proteins by homotypic interactions of the virus [31-34]. S interaction with M proteins in the virus is needed for the retainment of S proteins with Golgi apparatus so helps in its new incorporation into new virions [35,36]. In the same way, M to N interaction helps in the stabilisation of nucleocapsid proteins so overall completion of virion assembly [37,38]. E protein is the smallest one but mostly expressed in the infected cell, important for virus production and its maturation due its PDZ interaction to the C-terminus of target proteins such as the cellular adapter proteins involved in host-cell processes important for viral infection [39-44]. The first crystalline structure was first discovered for HCoV-NL63 S1-CTD complexed with human ACE2 followed by SARS-CoV S1-CTD complexed with ACE2, showing common receptors [45]. The crystal structures of MERS-CoV S1-CTD in complex with human DPP4 provided another view of coronavirus S1 and S1/receptor complex [45-47].

Replication and transcription of coronaviruses

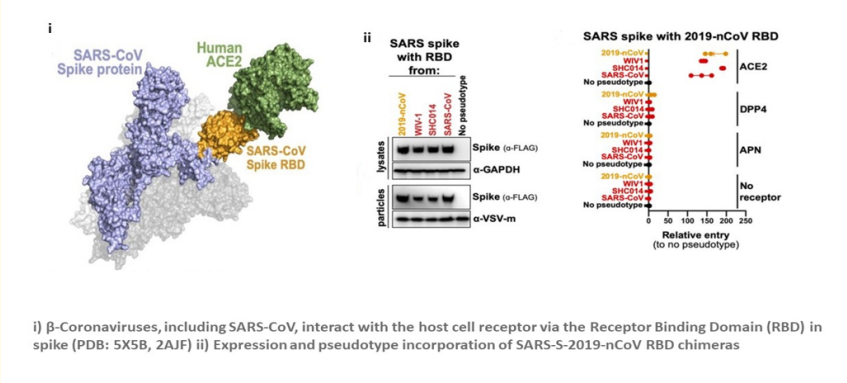

Figure 4: *Represents the interaction of 2019-nCoV virus with human ACE 2. Reproduced from reference 48.*

The newly discovered 2019-nCoV RBD shows interaction with ACE2 as shown 01-02-2020 as shown in figure 4 [48]. ACE2: a blood pressure regulator and a protector against severe acute lung damage: is a zinc-dependent carboxypeptidase [49-51]. Carbohydrates with proteins and fats on cell surfaces function in many biological processes such as immunity and cell-cell communication [52-54]. These cell-surface molecules are selected by viruses as their entry receptors has been a major puzzle in virology.

Generally, the transcription and replication of coronaviruses takes place in the host cell cytoplasm. As spike proteins of the virus binds with the host receptor, structural change occurs followed by endocytosis, which is pH dependent [55-58]. As soon the virus reaches the cytoplasm, it releases its whole RNA. RNA of coronavirus is polycistronic containing approximately seven genes: 5' region mainly contains large replicase gene for replication and transcription process and the 3' region contains non-essential accessory proteins expressed from sub genomic mRNAs (sgmRNAs) [59-61]. The large replicase gene at 5' end encodes replication-transcription complexes (RTCs) among Coronaviruses which comprises of two overlapping open reading frames (ORFs), ORF1a and ORF1b. Translation of these ORFs results in two very large polyproteins, pp1a and pp1ab, which further leads to formation of non-structural proteins by co and post translational modifications by various proteinases [62-66]. ORF1b encodes enzymes which are needed in RNA replication and its transcription [67-70]. Coronaviruses contain double-membrane vesicles (DMVs) which are attached with RTC's [71-73]. These DMVs are known to be derived from network of modified ER membranes, also referred to as convoluted membranes (CMs) [74]. The replication of coronaviruses is inhibited by addition of drugs in the early secretory phase or by addition of RNAi [75,76].

Conclusions and Future Directions

The recent outbreak of 2019-2020 Coronaviruses and over the past years is due to the ability of the viruses to recombine, mutate and infect different species. 2019 n-CoV belongs to the class of betacoronavirus possessing single stranded RNA as genome which can infect wild animals and humans too. Outbreak of this deadly virus took place in Wuhan region of China on 8th December 2019 and since then there are more than 300 deaths and 14000 infected cases till 2nd February 2020. This recently emerging virus is found to have quite resemblance to SARS virus and bat coronavirus HKU9-1. This virus is known to be transferred from bats to humans but the exact mechanism of its transference is yet to known. It is likely that these viruses will continue to emerge and to evolve and cause both human and veterinary outbreaks owing to their ability to recombine, mutate and infect multiple species and cell types. S-protein among corona viruses interacts with the human receptors like ACE2 in case of SARS -CoV and even 2019-nCov but the binding is weaker than SARS-ACE2 binding. The incubation period of the virus is about 14 days based on the current information from NHC. Disease is asymptomatic and may vary with conditions which are yet to know. Other Coronaviruses like SARS and MERS have longer incubation periods also so they evade immune responses during this period. 2019-nCoV is known to have multiple entry routes in the body and can cause mainly respiratory symptoms and mucosal surfaces. But the incubation period through different routes, effect on immune system, mechanism is yet a mystery. However, full genome sequencing of the virus and its interaction with human ACE2 receptor is discovered.

Future research on coronaviruses to investigate many aspects of their mode of transmission, replication and pathogenesis is required. How viruses move from one species to other, different reservoirs of the virus will help to reduce epidemics in future. Besides interaction and mechanism of action of various structural and accessory proteins would help in developing suitable therapeutic agents and vaccines. 2019-nCoV is known to target the mucosa of the respiratory tract, designing a vaccine that would compound the induction of strong immunity via the in route would be one of the best strategies to block 2019-nCoV infection. Which human receptors are involved in nCoV binding and how it provokes immune response would help in the development of vaccines and thus to reduce disease burden.

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