Review

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SARS-CoV-2: Literature Review Focusing on Structure, Diagnosis and Vaccine Development

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Abstract

SARS-CoV-2 is a highly pathogenic novel ongoing-pandemic virus. It causes COVID-19. Little is known about SARS-CoV-2 biology, countermeasure, and its origin. SARS-CoV-2 is characterized by high infectiousness and sever pathogenesis. COVID-19 crosses the bounders of all continents in a high spreading manner. Here, several aspects regarding the origin and the molecular structure of this novel virus as well as the production of effective vaccines have been addressed. This article illustrated that SARS-CoV-2 was not being recombined inside laboratory and it has a complicated genome that led to sophisticated pathogenesis. Additionally, an important structural protein known as spike S was demonstrated by researchers as an important protein used by the virus for host cell entry as well as for vaccine development. However, the efforts for viral diagnosis and genomic demonstration as well as vaccine production are promising to tackle COVID-19. These perspectives will help in COVID-19 control. However, further investigations are urgently needed to figure out which controlling tactic is more efficient not only in the case of SARS-CoV-2 but also for future pandemics.

Keywords: COVID-19; SARS-CoV-2; Vaccine development

Introduction

There are four coronaviruses that infect human including 229E, OC43, HKU1, and NL63. All are causing common cold manifestations [1]. The novel Severe Acute Respiratory Syndrome Coronavirus Disease 2019 (SARS-COVID-19) causes infection of the lower respiratory system with high ongoing infectiousness. This unprecedented disease has recently been reported as a worldwide health emergency pandemic at the end of January 2020 by the World Health Organization. The causative virus has renamed later soon as SARS-CoV-2 [2]. It belongs to β-coronavirus, subgenus sarbecovirus, and Orthocoronavirinae subfamily [3]. SARS-COVID-19 is the third epidemic coronavirus outbreaks within the last twenty years including Severe Acute Respiratory Syndrome Coronaviruses (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [4]. The latter two viruses causing fatal infections with a lower transmission rate [4–6]. However, SARS-CoV-2 has a relatively lower fatality rate but high human-to-human transmission.

Mostly, the clinical signs appear as a mild to moderate symptoms within young patients while sever systemic manifestations are noticed in old-aged patients [7, 8]. Numerous perspectives concerning the viral biology have not been clarified yet as the

virus is novel. Controlling the SARS-CoV-2 needs deep knowledge of its biology and behaviour. In this review, several questions will be discussed concerning the origin and molecular structure of this novel virus. This may help to determine whether this novel virus is intentionally recombined or wild type originated. Also, it demonstrates the recent techniques in its diagnosis. Furthermore, it speculates on the most recent trends to develop a suitable vaccine. Highlighting these perspectives will help researchers in tackling the widespread of this unprecedented disease.

Molecular Structure

Coronaviruses have a crown-spiky-enveloped. Its diameter is about 60−140 nm [1]. Like other coronaviruses, SARS-CoV-2 has a non-segmented positive-sense single stranded RNA [3]. SARS-CoV-2 belongs to β-coronavirus with high genetic similarity to two previously identified coronaviruses of bat origin (RaTG13 and β-coronaviruses). It looks genetically divergent from SARS-CoVs but shares a similar binding receptor domain within spike S glycoprotein, suggesting that bat is possibly the natural host for this novel virus [9–11]. In this section, the argument whether this novel virus has been intentionally recombined inside laboratory or has appeared naturally will be reviewed based on numerous scientific reports in which the whole genomic sequence of SARS-CoV-2 has been compared and analyzed with other SARS-CoVs.

SARS-CoV-2 contains a genome about 29.9 kB that arranged and annotated in [6–11] open reading frames (ORFs). Most of the genomic contents are located within the first ORF (a/b) that encodes for two proteins known as pp1a and pp1ab as well as 16 non-structural proteins. The viral structural proteins are encoded by the rest ORFs and the remaining codons translate four important structural proteins involving nucleocapsid, matrix, small envelop, and spike glycoproteins [3].

The similarity percentage of SARS-CoV-2 genome to the other two bat coronaviruses (RaTG13 and β-coronaviruses) has been demonstrated as 96.2% and 90% respectively [10, 12, 13]. This demonstrates that a possible genetic recombination has occurred between these viruses of bat and pangolin origins in the presence of unknown yet intermediate host [14]. This may refer to the way by which the SARS-CoV-2 crossed species to human.

To the best of our knowledge, there is no any evidence for genetic recombination processing inside laboratory. Therefore, the novel virus likely appeared as a result of SARS-CoV-2 crossing the reservoir hosts to human or recombined with another coronavirus. SARS-CoV-2 has been proposed to be transmitted from bat to human through unknown intermediate host. However, recently, numerous researchers have reported that pangolin (*Manis javanica*) likely involved in this scenario [1, 9, 13, 15]. In this aspect, addressing a logical question for the researchers including is recombination occurring in SARS-CoV-2 and will this lead to the emergence of new isolates or strains? Finding out a proofed answer is important for the researchers.

The whole genomic divergence of SARS-CoV-2 complicates the efforts to explain the immediate ancestor of this novel virus with RaTG13 and β-coronavirus. Therefore, numerous hypothesises, to demonstrate the evolutionary origin of SARS-CoV-2, have been reported including a possible viral adaptation, convergence, and recombination. However, there has not been any scientific indicator to explain the current situation yet [13].

One of the most important structural protein is the spike S glycoprotein. The gene that encodes for this protein has been compared among SARS-CoV-2 and other SARS-CoVs of bat and pangolin origins and it looks highly similar [3, 11, 14].

Another interesting finding has been achieved by Ref. [16] as a significant mutation in the gene encoding for S glycoprotein of SARS-CoV-2 (24 bp). This has led to cleave this glycoprotein for efficient entry and egress of the virus. This likely occurs via de-glycosylation of furin-cleavage site within the S glycoprotein. This could explain how SARS-CoV-2 crossed to infect human meanwhile the possibility of targeting this protein for viral prevention. Moreover, it has been found that the genetic analysis of SARS-COV-2 isolating from different patients revealed few mutation discrepancies. This has recently been categorized into two strains of SARS-CoV-2 including L and S with a population rate of 70% and 30% respectively. Importantly, the L-strain seems to be more pathogenic and is evolutionarily gained from the S-strain [3]. Thus, further investigation must be carried out to clarify this perspective and the outcomes possibly lead to produce attenuated vaccine from the S-strain.

Importantly, it has been thought that crossing

SARS-CoV-2 from animal to human and then human to human possibly has an effect on the transmission rate and pathogenicity of the virus. If this is a case, it means that the novel virus either disappears from the globe in the future or sustains like other corona viruses causing common cold. Nevertheless, it is likely to cause high global fatality [13]. Our current concern is that the novel virus may undergo a genetic mutation in the future or adapt to be harboured in unknown reservoir host.

In terms of COVID-19 pathogenesis, SARS-CoV-2 invades human pulmonary cells via angiotensin-converting enzyme 2 (ACE2) receptor which is the same binding receptor for the other SARS-CoVs [17]. Another important aspect is that finding a mutation within two genes that encode for two non-structural proteins known as (NSP3 and NSP2) of SARS-CoV-2 genome. These likely play a pivotal role in the pathogenesis of COVID-19 according to Ref. [18]. Moreover, Like other Bat-SARS-like coronaviruses, SARS-CoV-2 likely encodes for two highly conserved non-structural proteins known as NS7b and NS8 by which SARS-CoV-2 evades the host immunity [19]. Our suggestion includes that deletion of these genes possibly leads to attenuate SARS-CoV-2 for vaccine production.

Molecular Diagnosis

Currently, the real time quantitative polymerase chain reaction (RT-qPCR) has been recruited as a precisely molecular diagnostic technique to detect SARS-CoV-2. For this purpose, specific oligonucleotides are used to amplify conserved sequences within E and N genes (see Table 1) in the presence of specialised probes to increase the specificity of the assay [20]. Briefly, the protocol involved genomic RNA extraction. This process should be conducted in high precautions and possibly using suitable nucleic acid purification instruments with commercial extraction kits to avoid contaminations. However, there is a noticeable shortage of these kits globally due to the massive consumptions. This issue could be tackled by manual extraction of RNA. Nevertheless, all these procedures must be performed in a well-equipped laboratory as a Biosafety level 3 or 4 (BSL-3 or 4).

Nowadays, there are numerous commercial kits to transcribe the viral RNA into cDNA followed by amplification the targeted viral gene in one step. Thermal conditions are performed in a suitable instrument with 10 min at 55 °C followed by one cycle of 95 °C for 3 min then 45 cycles of 95 °C for 15 s and 58 °C for 30 s [20]. However, the drawbacks of this approach are that the diagnosticians need to deal with a seriously infectious agent and mainly detect the acute cases, which is also relatively laborious. Therefore, numerous commercial companies such as Qiagen provide an easier method for viral RNA extraction procedures. Furthermore, the RT-qPCR has been developed to detect SARS-CoV-2 directly from patent's sample without using RNA extraction step through physical disruption of sample material [21]. On the other hand, the advancement of molecular technique has led to develop a highly specific and sensitive serological assay based on recombinant protein (spike-antigen) [22]. Urgently, an efficient molecular approach should be developed to detect the lower SARS-CoV-2 load in asymptomatic patients in a lower cost and laborious. For instance, developing a specific Loop-mediated isothermal amplification (LAMP) assay or Polymerase Spiral Reaction (PSR) would be helpful in this aspect. Recent approach has been recruited by Shen et al. depending on magnetic nanoparticle dependant Immuno-chromatography assay [23]. Additionally, Li et al. developed an isothermal amplification detection kit depending on enzymatic and chromogenic chemicals, making the kits highly effective, sensitive, rapid and less consumable [24].

Table1 The sequences of the primers and probes used for COVID19 diagnosis by Taqman Real time PCR

Targeted gene	Oligos	Sequence 5-3
	E-Sarbeco-Forward	ACAGGTACGTTAATAGTTAATAGCGT
E	E-Sarbeco-Probe 1	FAM-ACACTAGCCATCCTTACTGCGCTTCG-BBQ
	E-Sarbeco-Reverse	ATATTGCAGCAGTACGCACACA
	N-Sarbeco-Forward	CACATTGGCACCCGCAATC
N	N-Sarbeco-Probe	FAM-ACTTCCTCAAGGAACAACATTGCCA-BBQ
	N-Sarbeco-Reverse	GAGGAACGAGAAGAGGCTTG

Vaccine Development

From early time of COVID-19 outbreak, producing an effective vaccine has become a priority by the researchers. Importantly, the current advancements in molecular and immune-informatics sciences will help in producing an effective vaccine soon.

Although the members of SARS-CoVs belong to the same family, their biological features seem to be discrepant in terms of infectiousness and pathogenesis. Thus, in order to prevent the pandemic COVID-19, it is necessary to understand the biological and genetic features of this novel virus. Actually, the global efforts for vaccine production have mostly speculated on two perspectives. These are an old platform including killed or attenuated vaccines and next generation vaccines involving recombinant viral particle subunits and nucleic acid vaccines (DNA or mRNA).

Whole virus vaccine is an old-platform in vaccinology which has a merit of leading fast production with effective immune response such as Toll-like Receptors (TLRs) whereas the drawbacks include short-term protection and risk of viral mutation [25]. Thus, many researchers around the globe are carrying out variable approaches to achieve the current target depending on the next generation vaccine platforms.

Bioinformaticians have suggested promising motifs that consist of highly conserved amino acids of many SARS-CoVs sequences including SARS-CoV-2 known as KRSFIEDLLFNKV. This represents a specific cleavage site for viral entrance into the host cell [26]. Others have also analyzed more viral spike epitopes to clarify which one is more immune-reactive based on Immuno-informatics platform [27, 28].

According to Ref. [29], certain immunological-targeted epitopes have been preliminarily proposed as promising vaccine candidates including the spike (S) and nucleocapsid (N) protein; apparently, both are highly conserved. The initial attempt for whole recombinant virus vaccines has been carried out in the UK using Adenovirus-vectored vaccine [30, 31]. Currently, numerous companies have announced to produce effective vaccines soon such as Live-attenuated vaccine, protein-based, recombinant nanoparticle, S-trimer recombinant, coronavirus (RBD) protein-based, oral recombinant protein, DNA, and mRNA vaccines [31].

Similarly, many researchers have reported that the receptor binding domain (RBD) of S glycoprotein is likely appropriate to countermeasure against SARS-CoV-2 in the globe as a target vaccine and significant epitopes have also been predicted to be effective candidates related to B-cells and cytotoxic T-cells as well as their correspondent MHC class-I [31, 32].

Some researchers hypothesized that SARS-CoV-2 mutations might be expected. This notion was excluded in case the glycoprotein S is targeted as a vaccine. Here, a bioinformatics analysis of the gene that encodes for the surface protein S was carried out in this review depending on sequence of various SARS-CoV-2 strains of infected patients originated from different countries including USA, Pakistan, Iran, Japan, Israel, Vietnam, Brazil, Italy, Nebal, Korea, India, Sweden, China, Peru, and Australia. The current result revealed high conservancy, hence targeting this protein for vaccine production could be helpful for SARS-CoV-2 eradication in the world. However, many mutations have been recorded within this target gene but all of them resulted in more infectiousness with less pathogenesis and luckily all of them have not resulted in vaccine abrogating. Similar to the native SARS-CoV-2 glycoprotein S, a recombinant subunit consisting of trimeric fusion proteins of MERS-CoV-S1, SARS-CoV-2-S1, and foldon domain originated from the C terminus of bacteriophage T4 fibritin. This has delivered by dissolving microneedle arrays (MNAs) and resulted in potential immunogenicity in mice model [33]. Recently, a successful vaccine has been produced at the University of Oxford [34] which passed the phases 1 and 2 of the clinical trial, which is promising to prevent COVID-19. However, development of vaccine depending on nano-technology approach has been designed by Gao et al. [35].

Since SARS-CoV-2 can be propagated with available permissive cell lines, producing an effective vaccine platform of old design would not be difficult. However, it needs laboratory with BSL4. On the other hand, there are many hurdles for manufacturers to produce a licensed effective vaccine such as safety concerns, challenging assessments, time, and cost.

However, a logical question must be answered which is does the virus change in patients? If so, whether the change increases or decreases mortality and infectivity rate?

Prediction of an Efficient Therapeutic at Early Time

An efficient therapeutic to mitigate the COVID-19 has been carried out at early stages of the outbreak. Thus, angiotensin receptor 1 (AT1R) blockers (Losartan) has been reported to mitigate the disease [36]. Others have cloned and expressed 26 SARS-CoV-2 proteins in human cell line. These were analyzed by mass-proteomic approach which revealed an interaction between SARS-CoV-2 and human proteins. Literally, 66 targets are possibly interacted with 69 existing drugs already approved by FDA in clinical or preclinical phases [37]. This finding will appropriately aid the researchers to choose durable therapeutics for COVID-19. However, it is interesting to note that a considerable number of these targets are not specifically expressed by epithelial cells, meanwhile more questions should be addressed to demonstrate the key events of COVID-CoV-2.

Conclusion

Global emerging novel-pandemic viruses are still expected since there are many predisposing factors such as climate changes which increase the human interference with the nature. Thus, efficient countermeasures are required around the world to tackle this issue. To some extent, COVID-19 has been underestimated by numerus countries. Also, the initial control strategy of COVID-19 has misconducted in others, especially during the early COVID-19 spreading. This has led to a considerable global crisis. For instance, in Iraq and Iran, the influx of travellers from infected countries (from China–Iran and from Iran–Iraq) has continued until late stage of COVID-19 spreading. In the later, suffering from trade sanction has deteriorated the situation. Tourism is another factor and it is one of the major causes of disease-spreading in many European countries such as Italy, Spain, Germany, and France. Moreover, In the UK, the government has initially followed a controversial strategy known as herd-immunity for disease-tackling. In the later stage, this strategy has been replaced by a community lock-down. Eventually, in last century, three coronaviruses have been emerged globally because of the unusual interference between human and wild animals in China. To avoid this culture, an effective action should be considered by the Chinese government in order to prevent the emerging of such pandemics. A global control, risk assessment and health safety countermeasures should be considered. This should be achieved with excluding the global political controversial issues. In the future, efficient global rules should be considered, allowing a leader role for the World Health Organization to tackle such a global pandemic.

Regarding COVID-19 pathogenesis, a vague question involved that whether co-infection plays a role in the outcome of COVID-19. If so, a suitable treatment must be clarified. Ironically, there is an urgent and unmet need to develop effective vaccine to reduce the Iraqi burden of infectious diseases in both animals and humans. Additionally, developing a robust and sensitive method of detecting SARS-CoV-2 is needed. This would better to be achieved in a local platform rather than importing vaccines which might not be effective enough.

Conflict of interest

The author declares that there is no any conflict of interest in writing this article.

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