Chapter

COVID-19 Researches: Where India Stands So Far?

Nikhil Srivastava and Gyaneshwer Chaubey

Abstract

By the end of the year 2019, in the month of November first pneumonia-like case of COVID-19 was detected in an individual aged 55 years in the Hubei Province of Central China. However the 'patient zero' or the first patient contracted with the disease is still unknown, but it is speculated that first contraction with virus occurred in Wuhan province of China. The rate by which the number of cases of the disease surged in China was remarkable and by the mid of January 2020 cases begin to appear in different parts of the world. WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern by the end of January 2020. Researchers from different parts of the world continue to study the pathogenesis and spread pattern of this disease. This chapter emphasizes upon some of the prominent studies in the field of COVID-19 researches from India. It also focuses upon the *ACE2* gene polymorphism which has decreased the susceptibility against the virus amongst human population, and explains how at the molecular level ACE2 receptor concentration may affect the entry of the virus into the host cell. It also highlights the impact of the viral RNA on mitochondrial machinery of the host cell and how it instigates a pro-inflammatory response by declining the efficiency of immune system in whole. We also aim to highlight two potential drug candidates of COVID-19 and how these are performing against the virus according to several studies.

Keywords: COVID-19, India, ACE2, hydroxychloroquine, mitochondria

1. Introduction

India reported its first COVID-19 case on January 30th, 2020 which was about the same day when World Health Organization (WHO) declared this outbreak "a public health emergency of international concern" [1, 2]. Today, when India is reporting ~100,000 cases every day, an extreme load on healthcare system is proving to be a challenging situation for the middle-income nation [3]. World Health Organization (WHO) accounted first severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 to 2003, which spread through 26 countries across the world and was considered 'the first serious emergent disease of 21st century' [4]. The Coronavirus disease (COVID-19) spread in 2019–2020 is caused by a novel coronavirus designated as SARS-CoV-2 [5]. Coronaviruses belong to Coronaviridae family of the order Nidovirales whose members are large and enveloped containing a single-stranded (+) RNA as genetic material, these are considered the largest known RNA viruses with genome size of 25 to 32 kb and virions of 118–140 nm in diameter [6]. Within the family Coronaviridae there are

two sub-families- Coronavirinae and Torovirinae further divided into six genera out of which members of the genus Betacoronavirus infects mostly mammals and genus Deltacoronavirus infect mammalian as well as avian hosts [7]. The COVID-19 causing SARS-CoV-2 belongs to genus Betacoronavirus [8].

As the surge in the number of cases started to be reported all across the world, major disparities on the basis of ethnicity, gender and populations were also noticed in different regions. The advancing age, and pre-existing medical conditions like diabetes, high blood pressure (BP), renal-associated diseases etc. increase the vulnerability of a person towards the severity in consequences of the disease [9, 10]. However, a surprising observation emanating from the pandemic is the rate of hospitalization of younger, ostensibly healthy individuals; which reflects that differences in the vulnerability of individuals to infection in the spectrum of COVID-19 symptoms remain to be understood [11]. This review will focus upon some of the studies leading to understanding the genomics of Indian populations and their vulnerabilities towards the SARS-CoV-2 infection, the studies relating to the mitochondrial impacts of the SARS-CoV-2 infection, molecular mechanisms through which ACE2 expression affects the viral pathogenesis and about two potential drug candidates of COVID-19.

This chapter provides an account on some of the major contributions towards the understanding the COVID-19 disease by Indian scientists and researchers.

2. ACE2 rs2285666 association with spatial distribution of COVID-19 in India

Host-pathogen interaction studies have revealed that ACE2 receptor present on the host cell works as a receptor for the spike glycoprotein of SARS-CoV-2 [12]. ACE2 is present on X-chromosome in humans, in which a polymorphism rs2285666 is shown to have significant disparity amongst Europeans and Asians

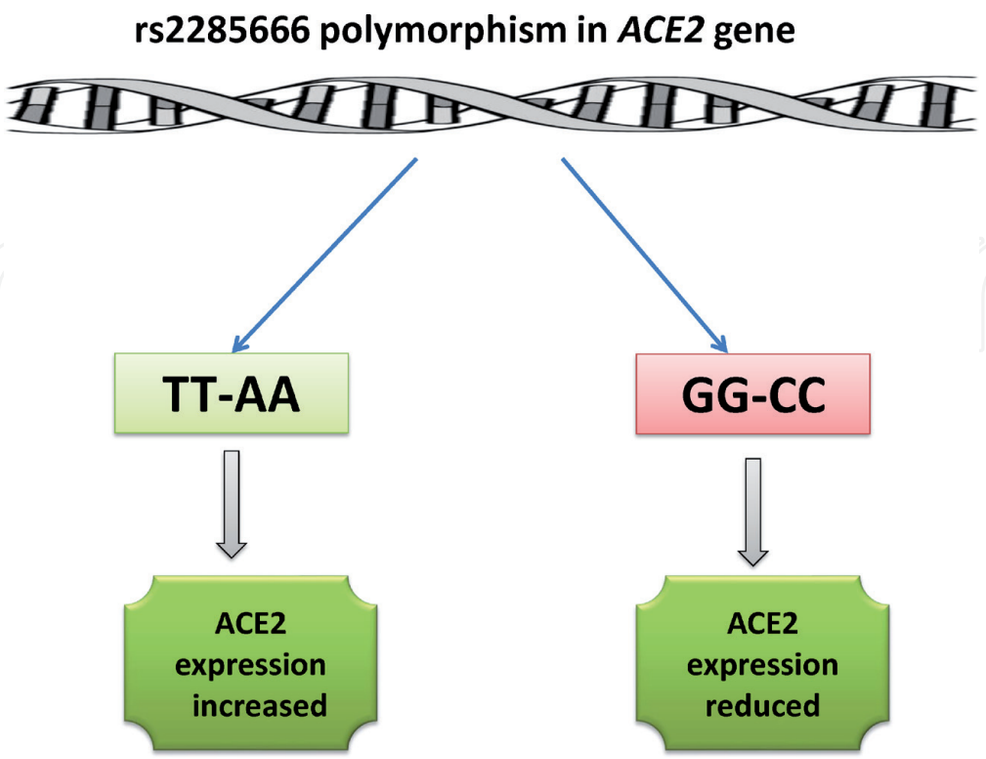

Figure 1.
Srivastava et al. have shown a direct correlation between the rs2285666 polymorphism and ACE2 gene expression.

[13, 14]. The decreased expression of ACE2 is frequently associated with increased susceptibility towards the severity of COVID-19 disease. Shrivastava et al. used this information as the principle of their study to find out the frequency of alternate allele (allele T on plus strand or allele A on minus strand) of this single nucleotide variation (SNV) in Indian populations and predict the cause of low infection rate as well as low Case Fatality Rate (CFR) in western states of India (**Figure 1**) [15].

In yet another study they showed that the overall genome of South Asians share greater genetic affinity with West Eurasians, however the ACE2 gene has greater genetic affinity with East Eurasians. The phylogenetic analysis of haplotypes distinctly classifies three types of haplotypes in order to identify the SNP which reveals greater affinity between South Asians and East Eurasians. Out of these three haplotypes- haplotype 3 (ht3) is shown to be harbored by East Eurasians and South Asians and derived from rs2285666 [16]. The ACE2 gene rs2285666 polymorphism is also shown to have association with type 2 diabetes mellitus (T2DM) in which A allele is associated with higher risk of T2DM [17]. The protective role of ACE2 in nephric tubules is shown in several studies, and its reduced expression contributes to the development and progression of kidney injury and diabetic nephropathy is explored by Reich et al. [18]. These studies strengthen the hypothesis of the association of rs2285666 (TT-plus strand or AA-minus strand), which increases the expression of ACE2 receptor protein with lower case fatality rate.

3. Molecular mechanisms of ACE2 expression during COVID-19

Angiotensin converting enzyme-2 (ACE2) receptors serve as medium for entry of SARS-CoV-2, the receptor is found attached in the plasma membrane of the cells in the heart, vessels, gut, lung, kidney, testis and brain and very rarely found solubilized in the circulation [19]. The function of ACE2 is to break down Ang II and form Ang 1-7, therefore ACE2 helps in checking the levels of Ang II and plays an important role in renin-angiotensin system (RAS) [20]. It is an established fact now that ACE2 expression is significantly down-regulated during COVID-19 which

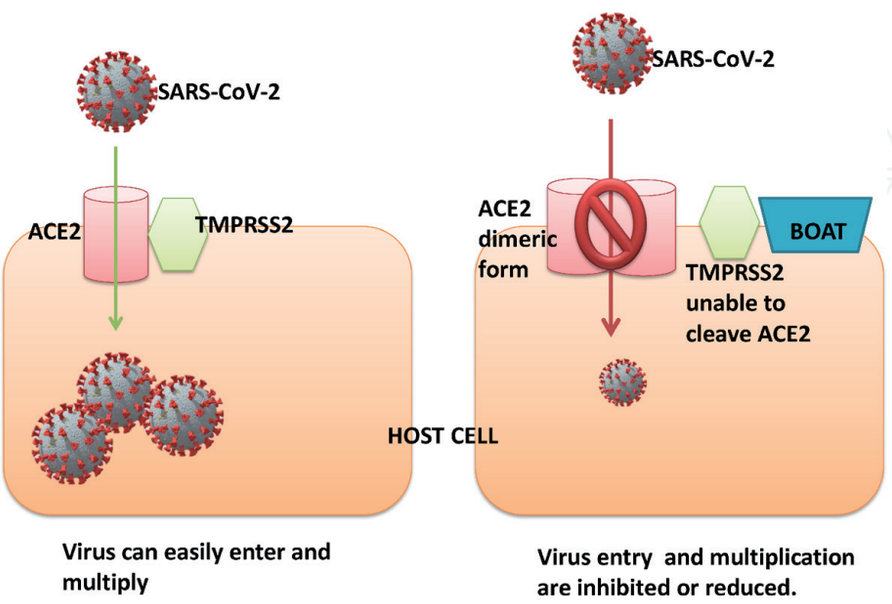

Figure 2.
Homo-dimerization of ACE2 receptor in case of higher expression levels of ACE2 gene results into decreased interaction and entry of virus into the host cell. BOAT transporter protein makes this process even more difficult, thereby decreasing the levels of viral multiplication.

results into abnormally increased levels of Ang II, which leaves critical organ systems susceptible to hyper-inflammation and failure [21, 22]. In an unpublished but important paper, it is significantly shown that the homo-dimerization of ACE2 as a result of its higher expression levels prevents binding of Spike protein (S-protein) complex of SARS-CoV-2 virus [23]. This study supports the hypothesis that ACE2 in its monomeric form, can bind to S-protein of the virus with greater preference. ACE2 acting as e-QTLs (Expression quantitative trait loci) due to natural genetic variations it results into homo-dimerized forms which lead to lowered cleavage by TMPRSS2 (**Figure 2**). The presence of broad neutral amino acid transporter, B0AT1 make the completion of this step even more difficult implied by the virus to get into the host cell. It is identified that natural variations in host genes like ADAM17, RPS6, HNRNPA1, SUMO1, NACA, BTF3 might help in bringing such homo-dimerizing structural variations in ACE2.

4. SARS-CoV-2, the highjacker of host mitochondria

A very interesting study focuses on yet another important aspect of COVID-19, that how 'the powerhouse of the cell' i.e. mitochondria are affected by the SARS-CoV-2 infection. The non-structural proteins of the virus are translated from two open reading frames (ORFs), ORF1a ORF3a, ORF6a, ORFF7a, ORF8a and ORF1b present in the genomic RNA of the virus. ORF1ab is responsible for the production of spike (S) protein, the envelope proteins (E), the membrane proteins (M), and the nucleocapsid proteins (N) of the viral structure [24–26]. Host mitochondria play a crucial role in the host immunity against the viral infection. The viral RNA genome portions and proteins localization into the mitochondria results into its dysfunction and production of mitochondria derived double-membranous vesicles (MDV) which work as a site of viral safe-house for unchecked replication (**Figure 3**). The viral pathogenesis is amplified as the hijacked mitochondria induce inflammatory responses and decrease the effectiveness of innate and adaptive immune responses [25].

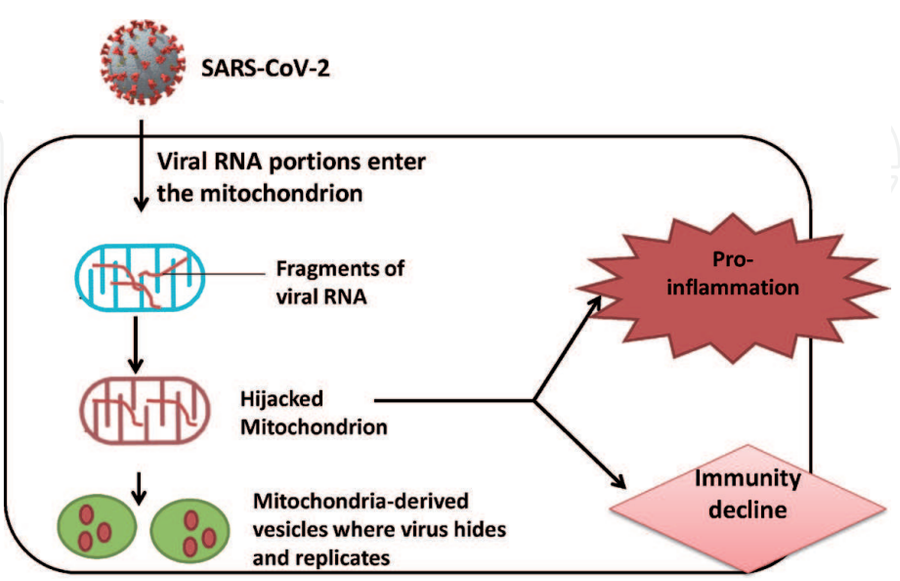

Figure 3.
There is an important role played by the host mitochondria in the host immunity against the viral infection. The MDV's (mitochondria derived double-membranous vesicles) formed from the hijacked mitochondria are the sites of unchecked viral replication.

5. Rapamycin and hydroxychloroquine: story of two repurposed drugs against the virus

SARS-CoV-2 spreads rapidly in comparison to its two cousins- SARS-CoV and MERS-CoV [27]. Therefore an effective drug development strategy is needed to control the faster spread of the disease, which is a time-consuming process. Repurposing or repositioning the already existing and approved drugs can help to shorten this time span and cost expenses. Rapamycin, which is an mTOR-inhibitor, is proposed to be a potential drug candidate against COVID-19 [28]. Rapamycin can play significant roles as a potential antibiotic in case of COVID-19, it can check the packaging of viral particles, prevent cytokine storms and also through its anti-aging and anti-obesity effects can be useful in this viral infection [28–30].

Hydroxychloroquine (HCQ), which is a much hyped candidate drug against COVID-19, has received a very straight forward judgment - it has no benefit in treatment of Covid-19 [31]. A group of medical doctors studied a population consisting of a total of 4984 patients with COVID-19, out of which 35.5% were provided with HCQ or its congeners and 62.01% were provided standard of care or had included antiviral medication. However, the estimated success of the treatment of both the groups was similar (77.45% and 77.87% respectively). This study shows that HCQ does not show any significant benefit in patients affected by COVID-19. Apart from many limitations in this study which includes patient cohort selection, variations in HCQ dosage etc. this study aligns with many studies regarding the ineffectiveness of the drug [32, 33].

6. Conclusion

COVID-19 is one of the most infectious diseases of 21st century which has already claimed to take lives of millions. The disease caused by the SARS-CoV-2 virus may affect a person symptomatically or asymptomatically. The range of symptoms may vary from mild to very high complications which may even lead to death. The people with already declined immunity with pre-occurring comorbidities like diabetes, cardiac-related ailments, and kidney-related problems are highly vulnerable towards the extreme effects of the disease. Strict actions like frequent hand-wash, use of face-masks and face-covers, use of hand sanitizers, at the community level are important to defeat this disease. Preventions and precautions are necessary to protect vulnerable and comorbid people from this viral infection along with normal people. The ICMR and Ministry of Health of the Government of India have provided several recommendations against the spread of COVID-19. India being one of the fastest growing nations amongst the South Asian countries needs to invest and believe more into research and development field, home to some prominent institutions of the region those are performing with their expanded capabilities towards the good cause of the nation. As of now, when every day approximately 100,000 cases of the disease are being observed in India, it is a need of time that people and government put more faith in science and medicine.

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Conflict of interest

The authors declare no conflict of interest.

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