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COVID-19 PANDEMIC-AN OVERVIEW AND FUTURE PERSPECTIVE

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Abstract

This paper aims to highlight and address topics on structure of virus, treatment protocols and success rates, development of diagnostic kits, vaccine trials, India's research and development progress and control and preventive measures of COVID- 19 . Systematic literature review was carried out and experimental studies , research findings and contributions , reports of scientists from across the world , knowledge and data from credible sources are collected and incorporated in the paper.

Key words-covid 19, pandemic, corona viruses

Introduction

Coronaviruses (CoVs) are a diverse family of viruses. They cause a variety of diseases in mammals and birds ranging from enteritis in cows and pigs and upper respiratory disease in chickens to potentially lethal human respiratory infections.[1] Severe acute respiratory syndrome (SARS), the first identified in 2002 and diagnosed in Southern China, occurred from a human CoV [2]. Then, exactly 10 years after the SARS-CoV emergence, a new emerging Coronavirus named Middle East Respiratory Syndrome (MERS-CoV) has infected people with a high mortality rate of nearly 50% in the Middle East. 10 March 2016, the World Health Organization (WHO) global case count for MERS was 1,651 laboratory-confirmed cases, including at least 590 deaths (case fatality rate 36%) since the first cases were reported in September 2012 [3].

Structure of Virus and its diversity

Coronavirus virions are spherical with diameters of approximately 125 nm as depicted in recent studies by cryo-electron tomography and cryo-electron microscopy [4]. The most prominent feature of coronaviruses is the club-shaped spike projections emanating from the surface of the virion. These spikes are a defining feature of the virion and give them the appearance of a solar corona, prompting the name, coronaviruses. Within the envelope of the virion is the nucleocapsid. Coronaviruses have helically symmetrical nucleocapsids, which is uncommon among positive-sense RNA viruses, but far more common for negative-sense RNA viruses. Coronavirus particles contain four main structural proteins. These are the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, all of which are encoded within the 3' end of the viral genome. The S protein (~150 kDa), utilizes an N-terminal signal sequence to gain access to the ER, and is heavily N-linked glycosylated. Homotrimers of the virus encoded S protein make up the distinctive spike structure on the

surface of the virus [5]. The trimeric S glycoprotein is a class I fusion protein [5] and mediates attachment to the host receptor [6]. In most, coronaviruses, S is cleaved by a host cell furin-like protease into two separate polypeptides noted S1 and S2 [7,8]. S1 makes up the large receptor-binding domain of the S protein, while S2 forms the stalk of the spike molecule [9].

The M protein is the most abundant structural protein in the virion. It is a small (~25–30 kDa) protein with three transmembrane domains [10] and is thought to give the virion its shape. It has a small N-terminal glycosylated ectodomain and a much larger C-terminal endodomain that extends 6–8 nm into the viral particle [11]. Despite being co-translationally inserted in the ER membrane, most M proteins do not contain a signal sequence. Recent studies suggest the M protein exists as a dimer in the virion, and may adopt two different conformations, allowing it to promote membrane curvature as well as to bind to the nucleocapsid [12].

The E protein (~8–12 kDa) is found in small quantities within the virion. The coronavirus E proteins are highly divergent but have a common architecture [13]. The membrane topology of E protein is not completely resolved but most data suggest that it is a transmembrane protein. The E protein has an N-terminal ectodomain and a C-terminal endodomain and has ion channel activity. As opposed to other structural proteins, recombinant viruses lacking the E protein are not always lethal, although this is virus type dependent [14]. The E protein facilitates assembly and release of the virus but also has other functions. For instance, the ion channel activity in SARS-CoV E protein is not required for viral replication but is required for pathogenesis [15].

The N protein constitutes the only protein present in the nucleocapsid. It is composed of two separate domains, an N-terminal domain (NTD) and a C-terminal domain (CTD), both capable of binding RNA in vitro, but each domain uses different mechanisms to bind RNA. It has been suggested that optimal RNA binding requires contributions from both domains [16, 17]. N protein is also heavily phosphorylated [18], and phosphorylation has been suggested to trigger a structural change enhancing the affinity for viral versus nonviral RNA. N protein binds the viral genome in a beads-on-a-string type conformation. Two specific RNA substrates have been identified for N protein; the TRSs [19] and the genomic packaging signal [20]. The genomic packaging signal has been found to bind specifically to the second, or C-terminal RNA binding domain [21]. N protein also binds nsp3 [22, 23], a key component of the replicase complex, and the M protein [24]. These protein interactions likely help tether the viral genome to the replicase–transcriptase complex (RTC), and subsequently package the encapsidated genome into viral particles.

A fifth structural protein, the hemagglutinin-esterase (HE), is present in a subset of β-coronaviruses. The protein acts as a hemagglutinin, binds sialic acids on surface glycoproteins, and contains acetyl-esterase activity [25]. These activities are thought to enhance S protein-mediated cell entry and virus spread through the mucosa [26].

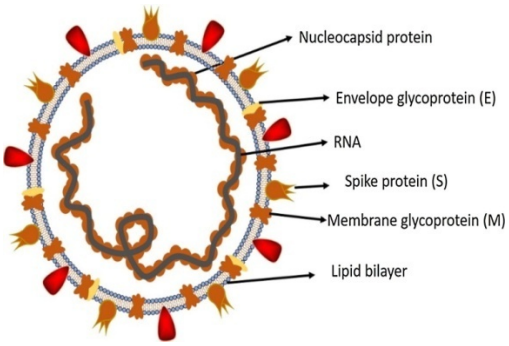

Fig. 1. Structure of respiratory syndrome causing human coronavirus. [27]

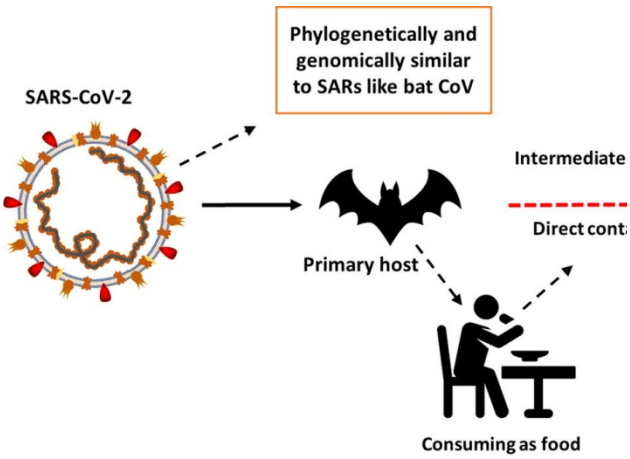

Fig 2 : Transmission modes. [27]

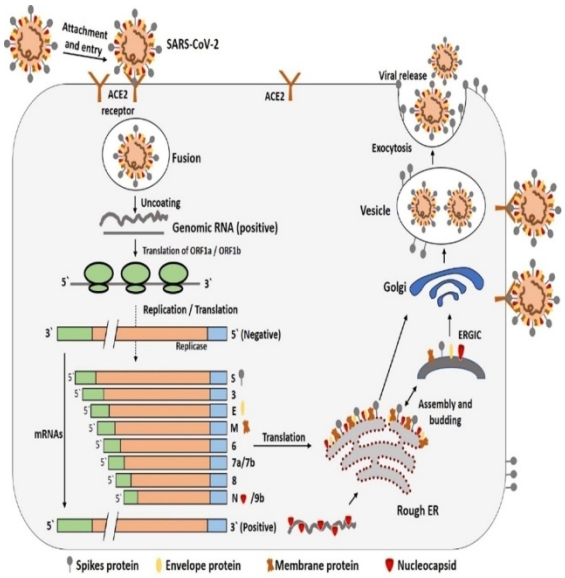

Fig. 3. The life cycle of SARS-CoV-2 in host cells; begins its life cycle when S protein binds to the cellular receptor ACE2. After receptor binding, the conformation change in the S protein facilitates viral envelope fusion with the cell membrane through the endosomal pathway. Then SARS-CoV-2 releases RNA into the host cell. Genome RNA is translated into viral replicase polyproteins pp1a and 1ab, which are then cleaved into small products by viral proteinases. The polymerase produces a series of subgenomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins. Viral proteins and genome RNA are subsequently assembled into virions in the ER and Golgi and then transported via vesicles and released out of the cell. ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment. [27]

Treatment protocols - Potential therapeutic strategies against COVID-19

Initially, interferons-α nebulization, broad -spectrum antibiotics, and anti-viral drugs were used to reduce the viral load [28], however, only remdesivir has shown promising impact against the virus [29]. Remdesivir only and in combination with chloroquine or interferon beta significantly blocked the SARS-CoV-2 replication and patients were declared as clinically recovered [30]. Various other anti-virals are currently being evaluated against infection. Nafamostat, Nitazoxanide, Ribavirin, Penciclovir, Favipiravir, Ritonavir, AAK1, Baricitinib, and Arbidol exhibited moderate results when tested against infection in patients and *in-vitro* clinical isolates [31]. Several other combinations, such as combining the antiviral or antibiotics with traditional Chinese medicines were also evaluated against SARS-CoV-2 induced infection in humans and mice [30]. Recently in Shanghai, doctors isolated the blood plasma from clinically recovered patients of COVID-19 and injected it in the infected patients who showed positive results with rapid recovery [32]. In a recent study, it was identified that monoclonal antibody (CR3022) binds with the spike RBD of SARS-CoV-2. This is likely due to the antibody's epitope not overlapping with the divergent ACE2 receptor-binding motif. CR3022 has the potential to be developed as a therapeutic candidate, alone or in combination with other neutralizing antibodies for the prevention and treatment of COVID-19 infection [33].

Vaccine trials for SARS-CoV-2

There is no available vaccine against COVID-19, while previous vaccines or strategies used to develop a vaccine against SARS-CoV can be effective. Recombinant protein from the Urbani (AY278741) strain of SARS-CoV was administered to mice and hamsters, resulted in the production of neutralizing antibodies and protection against SARS-CoV [34].

Antibodies from llamas have been engineered to block coronavirus. They are called single domain antibodies or nano antibodies. They bind to spike protein and prevents virus from invading human cells. TB vaccine offers hope for treatment of COVID- 19. Scientists are currently testing TB vaccine believed to sensitise immune system. A new inactivated COVID- 19 vaccine called PiCoVacc, shows promising results in neutralizing 10 different SARS –CoV2 strains that are circulating worldwide. The vaccine was tested on mice, rats and non human primates. It induced the production of antibodies that can target multiple strains of coronavirus SARS-CoV -2. Clinical trials are expected to begin later this year. [35].

A randomized, controlled trial involving 1063 patients funded by the U.S. NIH shows Remdesivir accelerates recovery from advanced covid – 19. Preliminary results indicate that patients who received Remdesivir had a 31% faster time to recovery than those who received placebo. The median time to recovery was 11 days for patients treated with Remdesivir compared with 15 days for those who received placebo. [36].

92 vaccines, 45 antibodies, 20 anti virals, 12 cell based therapies, 5 RNA based treatments and 52 other solutions are currently being explored to fight corona

virus SARS-CoV 2. Milken institute launched a website that tracks each one of these treatments and its progress, whether in preclinical or clinical stage. [37]

Development of Diagnostic kits

In response to Coronavirus disease 2019 (COVID-19), governments have instigated rules that constrain personal freedoms and hamstring their own economies, placing approximately 3 billion people under lockdown.Some have rolled out widespread testing for current infections, while others limited these tests to people who were hospitalised, atleast during the early stages of their responses. As new controls begin to bite, the race to develop and approve a test with a different purpose—to assess not current viral infection,but immunity to severe acute respiratory syndrome coronavirus 2(SARS-CoV-2)—has heated up. Medical diagnostic companies are scrambling,and governments are looking to order these antibody tests by the millions.The task now facing governments and national regulators is to balance urgency against the everyday sensitivity and specificity concerns that apply to any new medical diagnostic. A few technical questions still exist around optimizing test design, primarily hinging on understanding how the viral coating triggers a healthy immune system's recognition and neutralization of the virus. Antibody testing is multipurpose: it can verify that vaccines are working as intended during clinical trials, or be used in contact tracing weeks or longer after a suspected infection in an individual. Antibodies reveal evidence of a previous infection any time from about a week after the infection occurred. [38].

There are two tests for COVID – 19. Viral tests and antibody tests. Viral tests detects presence of current infection. Antibody tests detects presence of previous infection.

In the RT – PCR test for detection of SARS- CoV 2, two primers in the SARS –CoV 2 nucleocapsid (N) gene (N1 and N2), One primer for the universal detection of SARS – like coronavirus (N3) and one primer and probe set to detect human RNase P (RP) in a clinical sample. A no template control (NTC) is used to check for contamination of extraction and assay reagents. COVID-19 rapid test detects antibodies . Positive samples of RT – PCR are showing too much variation when tested by rapid kits in the range of 6 to 71% said Dr Raman Gangakhedkar, a top scientist at the Indian Council of Medical Research. FDA authorizes CRISPR- based test for COVID-19. It's the first authorization of CRISPR for patient use. CRISPR means clustered regularly interspersed short palindromic repeat region.

India's Science and technology research work against Covid 19

India's Science and technology Department , DST has been implementing several measures to fight COVID 19. It is seeking proposals from industries, academias, potential start ups with focus on affordable diagnostics, novel therapeutics and vaccines for the control of COVID - 19. As per DST secretary Ashutosh Sharma, there are 25 projects to study the pathology of the virus, 800 startups are

mapped for COVID specific products and 50 of these are selected for financial support. One of the most significant projects DST is working on is to create a national COVID 19 predictive model which will help guide policy decisions. Twenty research groups are working together to ensure a credible and scientific model comes by June. DST is supporting research by a team of scientists from IIT Kanpur to develop a protective coating that would help in making medicated masks to fight COVID- 19. The coating would include combination of common polymers containing anti microbial properties and re purposable anti viral molecules and materials used would make it a cost effective solution. Doctors and nurses, treating COVID 19 patients will benefit from this as it would add a layer of security for them while treating COVID 19 patients.
Sree Chitra Thirunal Institute for medical sciences and technology has developed as an innovative technology, magnetic nanoparticle based RNA extraction kit , called Chitra Magna to isolate RNA from swabs for PCR and LAMP tests for COVID 19 and has also applied for a patent.

Silver is known to possess strong antimicrobial activity. Professor Agrawal developed N9 blue nanosilver at SMITA Research Lab, IIT Delhi. As part of Nano mission programme, The Department of Science and technology (DST) has approved support for upscaling antiviral nano coating as appropriate material to produce anti COVID 19 triple layer medical masks and N -95 respirator. 3D Printed face shields manufactured through innovative open source design were distributed to 2500 police personnel and frontline healthcare workers in Maharashtra. [39]

Researchers and scientists at the S N Bose national Centre for basic sciences (SNNBNCBS) in Kolkata developed a nanomedicine, the nanoparticle technology which will specifically target the respiratory system of the Corona patients and therefore, provide better therapeutic efficacy against COVID 19 that causes pneumonia – induced death. The medicine has been tested successfully on animals and now awaits human trials. “ It may take two years to finally roll out the nanomedicine as some formalities are still involved in the process. We have applied to the Drugs Controller General Of India (DCGI) for its permission to begin human trials for the nanomedicine. We are also looking for the Food and Drug Administration (FDA) approval from the USA to get international market. We are the first institute in the world to conduct research and develop nanomedicine with respect to COVID – 19 “ , said Prof Samir Kumar Pal, a senior professor at the department of Chemical, Biological and Macromolecular Sciences under SNBNCBS.

Conclusions - Control and preventive measures

Covid 19 has drawn attention to the need for problem solving in a collaborative approach . It is important to think about real priorities in terms of social and economic aspects. Although finding vaccine is the long term permanent solution to end transmission of corona virus, our collective commitment and responsibility as citizens following strict protocol such as social distancing, containment measures will dictate control of spread

of virus. To tide over current crisis of COVID 19 pandemic, let us follow scientific principles of right precaution guidelines and stay healthy and safe. It is also important to keep ourselves updated with information on scientific progress, R and D innovation from credible sources and stop spreading or following fake news.

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