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REVIEW ON TARGETING ACE2 RECEPTORS TO PREVENT SARS COV-2 (COVID-19)

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ABSTRACT

The coronavirus disease (COVID-19) pandemic is sweeping the globe. Even with a number of effective vaccines being approved and available to the public, new cases and escalating mortality are climbing every day. ACE2 (angiotensin-converting enzyme 2) is the primary receptor for the COVID-19 causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its complexation with spike proteins plays a crucial role in viral entry into host cells and the subsequent infection. Blocking this binding event or reducing the accessibility of the virus to the ACE2 receptor, represents an alternative strategy to prevent COVID-19. In addition, the biological significance of ACE2 in modulating the innate immune system and tissue repair cascades and anchors its therapeutic potential for treating the infected patients. **Keywords:** COVID-19; ACE, Angiotensin, Enzyme, Receptors.

1. INTRODUCTION

The current COVID-19 pandemic is caused by a coronavirus named SARS-CoV-2. Coronaviruses (CoVs) are a large family of viruses, several of which cause respiratory diseases in humans, from the common cold to more rare and serious diseases such as the Severe Acute Respiratory Syndrome (SARS) and the Middle East respiratory syndrome (MERS), both of which have high mortality rates and were detected for the first time in 2003 and 2012, respectively. CoVs are divided into four genera: alpha- , beta-, gamma- and delta-CoV. All CoVs currently known to cause disease in humans belong to the alpha- or the beta-CoV. Many of these CoVs can infect several animal species as well. SARS-CoV infected civet cats and infected humans in 2002 and MERS- CoV is found in dromedary camels and infected humans in 2012. A virus that is regularly transmitted from an animal to a human is called a zoonotic virus. When a virus passes from animals to humans for the first time it is called a spillover event in March 2020, weeks before the corona-virus disease 2019 (COVID-19) pandemic surge was predicted to arrive in Massachusetts, two of us (J.N.J., L.E.H.) designed an ambulatory clinic specifically to care for patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). None of the hundreds of research reports published to date addressed caring for patients infected with SARS-CoV-2 in the ambulatory setting, and it became clear that one of the first challenges we faced was to gain an understanding of the typical presentation and early natural history of mild and moderate COVID-19 to guide our care during the pandemic. While we had access to state laboratory real-time reverse transcription polymerase chain reaction diagnostic testing for SARS-CoV-2, concerns regarding false-negative results and delays of up to 5 days made the results impractical for clinical management. Routine laboratory studies, likewise, did not appear to be clinically useful. We focused, instead, on trying to discern pat-terns from a detailed history and limited physical exam that might distinguish COVID-19 from other similar illnesses.

2. METHODOLOGY

RECENT RESEARCHS ABOUT SARS COV-2:

TRANSMISSION CYCLE:

A coronavirus (SARS-CoV) is considered as the etiological agent of SARS. Furtherinvestigation proved that the first transmission of the virus to human hosts occurredprobably in southern China in Guangdong province, from zoonotic reservoirs, including bats, Himalayan palm civets (Paguma larvata), and raccoon dogs (Nyctereutesprocyonoides), the latter two of which are sold in exotic animal markets (Graham and Baric 2010). Studies from the past suggest that SARS-CoV may also have a broad host range besides humans. SARS-CoV was transmitted directly to humans from market civets and is thought to have originated in bats (Cui et al. 2019). Earlier, genetically similar CoVs were isolated from civet cats and raccoon dogs (Guan et al. 2003). Studies show that SARS-CoV has the ability to infect and produce disease in macaques and ferrets too, while did not produce any readily observable symptoms in cats (Fouchier et al. 2003; Martina et al. 2003). A recent study reports about 80% gene similarity between SARS-CoV-2 and SARS-CoV (Gralinski and Menachery 2020; Xu et al. 2020). Correspondingly, one more study reports a 96% sequence similarity between SARSCoV-2 and the CoV isolated from Rhinolophus affinis indicating bats as virus source (Zhou et al. 2020). To date, there is not much clarity about SARS-CoV-2 host and it is reported to be snakes,

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minks, or other animals (Ji et al. 2020). Represents the tentative transmission path from a natural host to a human. The natural host of the CoV is considered as a bat (Li et al. 2020). While the species differ, CoV can still manage to migrate from its natural host to humans via intermediate host depending on its ability to access the host cell (Rodriguez-Morales et al. 2020). Since the last few decades, CoV has evolved to adapt to bind the receptors to enter inside the host's cells through its surface glycoproteins. These surface glycoproteins show significant variations that allow the virus to bind to varied mammalian host species (Rothan and Byrareddy 2020)and analysis which is performed in your research work should be written in this section. A simple strategy to follow is to use keywords from your title in first few sentences.

3. MODELING AND ANALYSIS

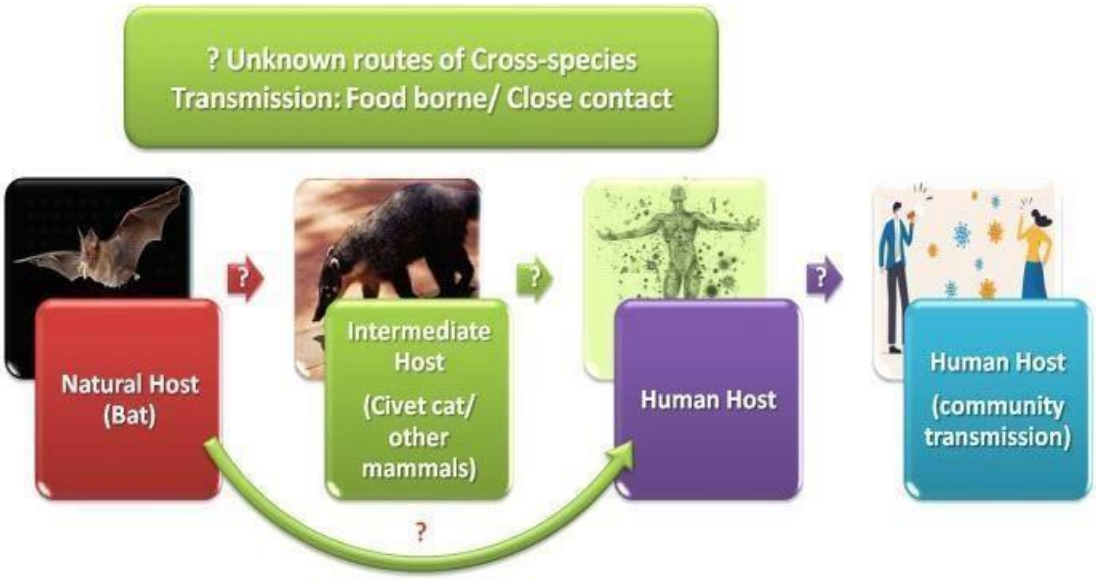

Figure 1: The probable transmission path of SARS-CoV and SARS- CoV- 2 from natural hosts to various host.

4. RESULTS AND DISCUSSION

Main applications of AI (artificial intelligence) in COVID-19 pandemic

1. Early detection and diagnosis of the infection

AI can quickly analyze irregular symptom and other 'red flags' and thus alarm the patients and the healthcare authorities. It helps to provide faster decision making, which is cost-effective. It helps to develop a new diagnosis and management system for the COVID 19 cases, through useful algorithms. AI is helpful in the diagnosis of the infected cases with the help of medical imaging technologies like Computed tomography (CT), Magnetic resonance imaging (MRI) scan of human body parts.

2. Monitoring the treatment

AI can build an intelligent platform for automatic monitoring and prediction of the spread of this virus. A neural network can also be developed to extract the visual features of this disease, and this would help in proper monitoring and treatment of the affected individuals. It has the capability of providing day-to-day updates of the patients and also to provide solutions to be followed in COVID-19 pandemic.

3. Contact tracing of the individuals

AI can help analyze the level of infection by this virus identifying the clusters and 'hot spots' and can successfully do the contact tracing of the individuals and also to monitor them. It can predict the future course of this disease and likely reappearance.

4. Projection of cases and mortality

This technology can track and forecast the nature of the virus from the available data, social media and media platforms, about the risks of the infection and its likely spread. Further, it can predict the number of positivecases and death in any region. AI can help identify the most vulnerable regions, people and countries and take measures accordingly.

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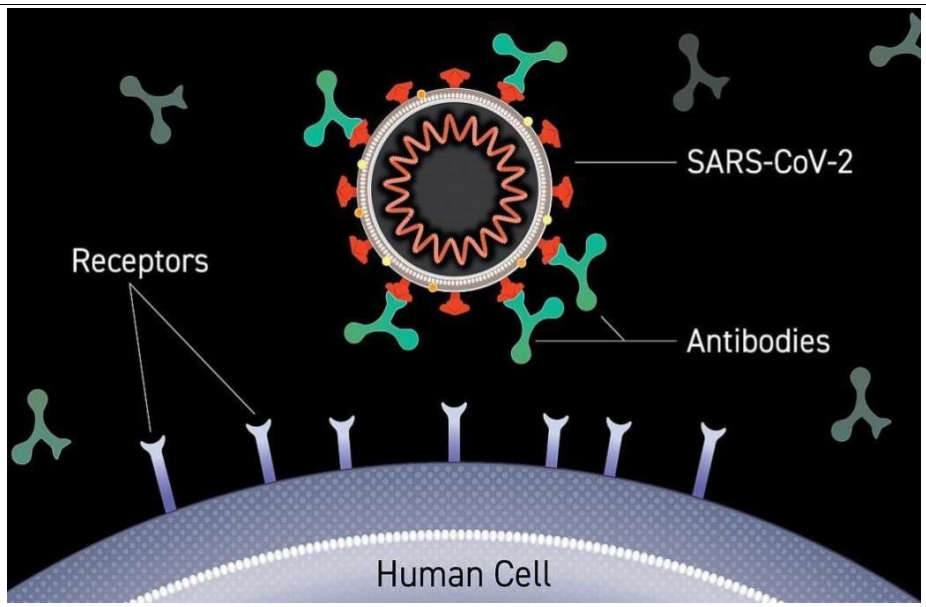

Figure 2: Image of an antibody binding to the surface of the virus blocking entry into a human

5. CONCLUSION

As mentioned in the Introduction, a deep knowledge of the life cycle of SARS- CoV-2 is essential to identify druggable targets that will allow the development of effective therapeutics against this coronavirus. Through the journey across the life cycle of the virus presented in this Perspective, we have considered several virus-based and host-based targets as objectives for pharmacological intervention as well as the host immune response. Among the virus-based targets, the importance of the structural spike (S) protein is remarkable due to its key role in SARS-CoV-2 entry through the interaction with the host receptor ACE2. We have also reviewed structural druggable sites and determinants of antibodies' efficacy against S protein. This coronavirus has 16 nsps Of special relevance for virus replication, and thus relevant as drug targets, are the two proteases (3CLpro and PLpro), the RNA-dependent RNA polymerase (RdRp), and the helicase. Those are highly conserved proteins and represent suitable targets for the development of pan-coronavirus antivirals. Study of the molecular basis of virus entry pointed to key cellular proteins involved in this process. This is the case of the already mentioned host receptor ACE2, host proteases like TMPRSS2 furin, or cathepsin L, or kinases that are implicated in the regulation of intracellular viral trafficking during endocytic entry, such AAK1, GAK, or PIKfyve. TPC2 is also an important host channel involved in the regulation of endolysosomal trafficking. Host immune modulation has proven to be a useful alternative for the clinical management of viral diseases lacking specific treatment. Moreover, targeting human proteins is an excellent alternative to avoid viral scape by mutation. Another promising alternative could be the combination of antiviral drugs acting through different targets in a multi-target strategy that has proven to increase efficacy and overall prevent viral resistance. Given the urgency of the COVID-19 pandemic, the repurposing of approved drugs is the only alternative to find a timely effective treatment. In fact, drugs currently under clinical trials were initially approved for other indications. However, the past and present coronavirus outbreaks require our preparednessnot only for the current situation but also for a future potential re-emergence of novel coronaviruses. In this sense, it is of utmost importance to design drugs acting as pan-coronavirus antivirals or through a multi-target approach to avoid a lack of effectiveness by viral mutation escape..

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