European Review for Medical and Pharmacological Sciences 2020; 24: 4554-4557

Could host cell receptor alteration prevent SARS-CoV-2 viral entry? – Hype or hope

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Abstract. – Cell-surface receptors are the inviters of many potent pathogens that can adjust to any kind of circumstance for their existence. Many of these organisms are highly resistant to the currently existing drugs and mutate to new strains with high levels of pathogenesis, posing life-threatening consequences. Owing to such concerns, antiviral strategies are being assessed based on host cell receptor targeting. Many natural compounds with a tendency to strip off the cell surface receptors are under evaluation. Compounds that are non-toxic, patient friendly, and yield a quick output are essential for the current scenario. Drugs targeting the cell surface receptors should, therefore, be developed and standardized for the effective management of SARS-CoV-2 viral infection.

Key Words:
SARS-CoV-2, Receptor modulation, Corona viral control strategy, Antivirals, Upper respiratory tract viruses.

Introduction

Cells of the respiratory tract are lined with several glycan-containing conjugates, many of which characterized with the sialic acid receptors that are expressed by the upper respiratory tract cells[1]. Viruses should penetrate the host cells to multiply and cause a disease. Most of the enveloped viruses, including the coronavirus, adopt receptor binding and fusion as the principal mode of entry. Coronavirus infections in humans involve the binding of the viral spike protein (S) to the respiratory tract receptors. SARS CoV-2 binds to the target cells through angiotensin converting enzyme 2 (ACE2), which is expressed by the epithelial cells of the lung, intestine, kidney, and blood vessels[2]. Consequently, the increased expression of ACE2 would facilitate SARS CoV-2 infection[3]. Herein, we speculate a compound which inhibits the host cell surface receptor and avoids direct fusion with the cell to prevent host-viral interactions[4]. The current hypothesis provides a strong basis for new strategies or therapeutic principles for effective antivirals. Compounds such as sodium metaperiodate could eliminate ACE2 overexpression without significant harmful effects and efficiently inhibit the viral binding to the host cell[5]. As prevention is better than cure, avoidance of entry is an attractive anti-viral approach. It can minimize the chances of viral evolution and the subsequent development of drug resistant strains causing SARS-CoV-2.

The current emergence of Coronavirus (2019-nCoV) has led to a global emergency alert. 2019-CoV is evocative of the previous SARS-CoV-2 outbreak in 2000. Host receptor recognition by the virus mainly involves interactions between SARS-CoV-2 zinc-dependent carboxypeptidase ACE2 and the cell surface moieties regulating both cross-species and human-to-human transmissions of the virus. Cellular immigration of the enveloped viruses is also frequently dependent on the attachment proteins expressed on the host cell surface. Only a small fraction of viral receptors has been identified so far as potential antiviral targets. Studies have established that

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ACE2 is the functionally active receptor for viral infection. Identification of ACE2 as a receptor for SARS-CoV-2 has possibly contributed to the development of new antiviral drugs and vaccines for the treatment of SARS-CoV-2[6]. The objective of the current communication is to initiate an effective framework of virus-host receptor interactions to inhibit the COVID viral entry and further pathogenesis. Figure 1 provides useful methodologies for the framework by focusing on the basic, translational and public health research communities with new predictive insights that may help in tackling the current corona viral infection scenario.

In the recent years, numerous life-threatening viral strains have emerged because of climate change and lifestyle. Among them, the SARS-CoV-2 has proven to be especially challenging around the world. Coronaviridae include coronaviruses (CoV), the large family of viruses that are zoonotic, i.e., transmitted from animals to humans and cause serious diseases such as the Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV). The MERS-Coronavirus was transmitted from camels to humans and the SARS-Coronavirus from civet cats to humans[7]. The most recently witnessed coronavirus disease of 2019 (COVID-19) has not been previously identified in humans. The illness has originated from the Wuhan City of China on December 28, 2019. As of 27 March 2020, according to WHO, totally 556,134 people have been infected and among them, 19,786 have died worldwide. Initially, SARS-CoV-2 was viewed as an epidemic in China. However, in the middle of January 2020, the World Health Organization (WHO) declared "Public Health Emergency of International Concern (PHEIC)" because of the possibility of the infection becoming pandemic, which means prevalent over a whole country or the world. The common symptoms of SARS-CoV-2 are fever, dry cough, dyspnea, pneumonia in lungs, difficult to breathing, hypertension, alveolar damage, diarrhea, aches, pains, runny nose, nasal congestion, and sore throat. In severe cases, the condition could even result in death. Bats, camels, and chimpanzees are the major animals that are responsible for the transmission of SARS-CoV-2, and it could also be transmitted directly from humans to humans through close contact with infected patients. The illness results in an accelerated rate of morbidity and mortality, thereby raising public health concerns worldwide. Until now, no specific treatment or antiviral vaccine has been identified.

Corona viral spike protein (S) contains an N-terminal receptor-binding (S1) and a C-terminal membrane fusion (S2) domain. The amphipathic heptad repeats, which have been predicted to

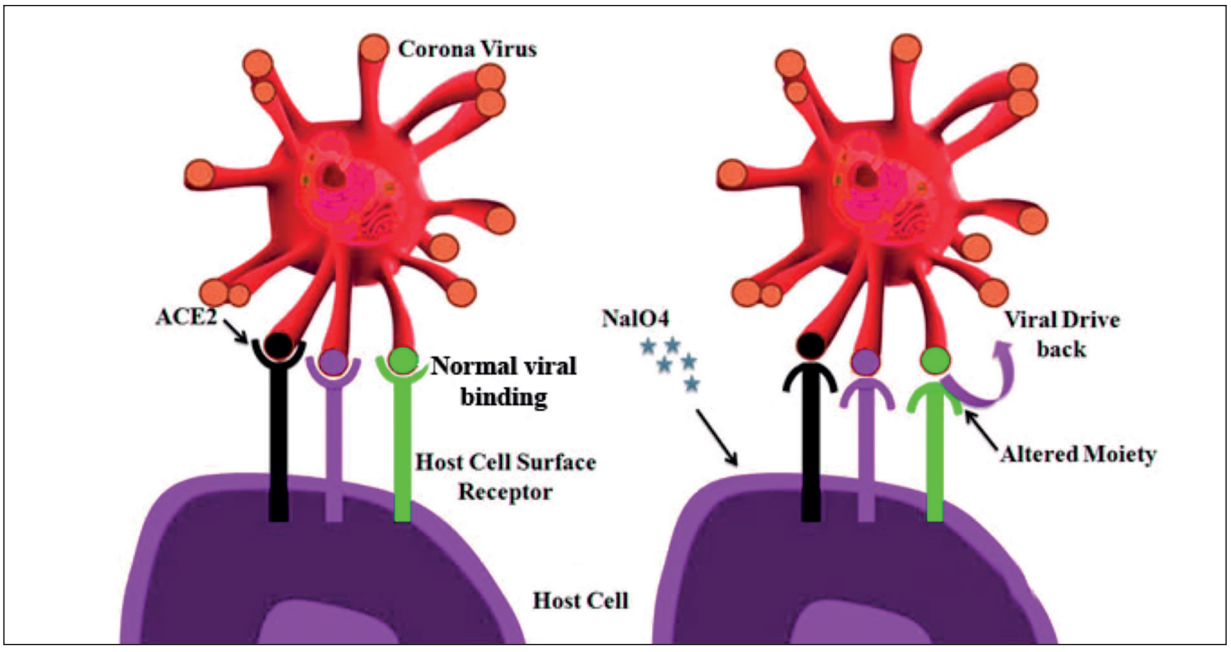

Figure 1. Schematic representation of COVID-19 viral binding with its host cell receptor. After modulation with NaIO4, the receptor becomes incompatible for viral binding.

engage in coiled-coil formation during cell-virus fusion[8]. The coronavirus consists of structural, non-structural and accessory proteins. Among them, the structural proteins compose the virion, including the Spike (S) glycoprotein, Envelope (E) protein, Membrane (M) protein, and the Nucleocapsid (N) protein. These proteins perform significant functions in the viral life cycle. Spike protein is the key determinant of cell tropism, host range, and viral entry[9]. The envelope protein facilitates viral assembly and virion release. Membrane protein maintains the membrane integrity of the virion, and finally, the nucleocapsid encapsulates the viral genome. Although most of these functions are essential for infection, the virus remains replication competent after the deletion of the envelop protein even though its strength is impaired[10]. However, unlike the non-structural and structural proteins, considerable variations in the function and number of accessory proteins between closely related viruses makes the latter poor targets for therapeutic approaches.

An antiviral drug such as Ribavirin is a guanosine analog with *in vitro* activity against a wide variety of highly lethal emerging viruses. The compound inhibits RNA synthesis by viral RdRp and further prevents the mRNA capping process. Moreover, findings demonstrated that while SARS-CoV is sensitive to ribavirin *in vitro*, the conditions and doses that significantly inhibit SARS-CoV-2 replication exceed the ribavirin concentrations achievable by typical human regimens. Recently, it was confirmed that the elimination of ribavirin nucleoside analogs by conserved coronavirus proofreading mechanisms likely accounted for the decreased *in vitro* efficacy of the drug. Additional *in vivo* testing of ribavirin in mouse models found restricted activity against SARS-CoV-2 by ribavirin alone and suggested that treatment with the drug improved SARS disease signs too. Likewise, combination treatment of ribavirin and type I interferons in primate models improved MERS disease signs. Nonetheless, studies still found only limited efficacy of ribavirin in treating patients infected with the highly pathogenic coronavirus[11].

In the last two decades, three outbreaks of previously unknown highly pathogenic coronaviruses, SARS-CoV and MERS-CoV, have been documented, indicating that CoVs will continue to spread among the human populations. Currently, public health measures have been adequate to confine the initial spread of SARS-CoV-2 owing to disease surveillance coupled with limiting the person-to-person transmission. However, biological factors that increase cross-species transmission and facilitate person-to-person spread may lead to future coronavirus strains that could not be controlled by timely quarantine of the infected individuals. Any increase in the virulence potential, pathogenesis, or transmission of SARS-CoV-2 would probably require a targeted medical countermeasure. With adequate investment in the development of drug discovery channels, coronaviral targets could be devised based on *in vitro* and *in vivo* evidence for the effective management of current and future SARS-CoV-2 outbreaks.

We suggest that the ACE2 receptor found in the upper respiratory tract of human beings could be transformed using non-toxic oxidizing agents such as sodium metaperiodate. Figure 2 gives a hypothetical illustration of host cell receptor knock down, which could lead to a drastic reduction in viral-host interactions during SARS-CoV-2 viral outbreaks. In the 21st century, inhaled drugs for the treatment of chronic obstructive pulmonary disease are needed. Besides, receptor modulators can be used in the form of inhalers to ensure consistent drug delivery to the respiratory tract to prevent host-virus interactions. From this step, further viral pathogenesis could be effectively avoided.

Conclusions

The recent emergence of coronavirus (2019-nCoV/ SARS-CoV-2) has put the world on high alert. Decade-long structural studies on receptor recognition by coronavirus have identified the key interactions between SARS-CoV-2 spike protein and its host receptor ACE2, which regulate human-to-human transmissions of the virus. One of the main goals of SARS-CoV-2 research was to identify patient-friendly methods for rapid recovery based on the virus-receptor interactions. Such a process would facilitate epidemic surveillance, predict species-specific receptor usage, and identify potential receptor modulators. In accordance with the ACE2 configurational change, we have proposed a framework to provide novel insights into receptor usage and likely host range of SARS-CoV-2. Presently, there are only limited references on receptor transformation. With patient-friendly active principles, the current novel approach could serve as a suitable alternative treatment for patients in the near future.

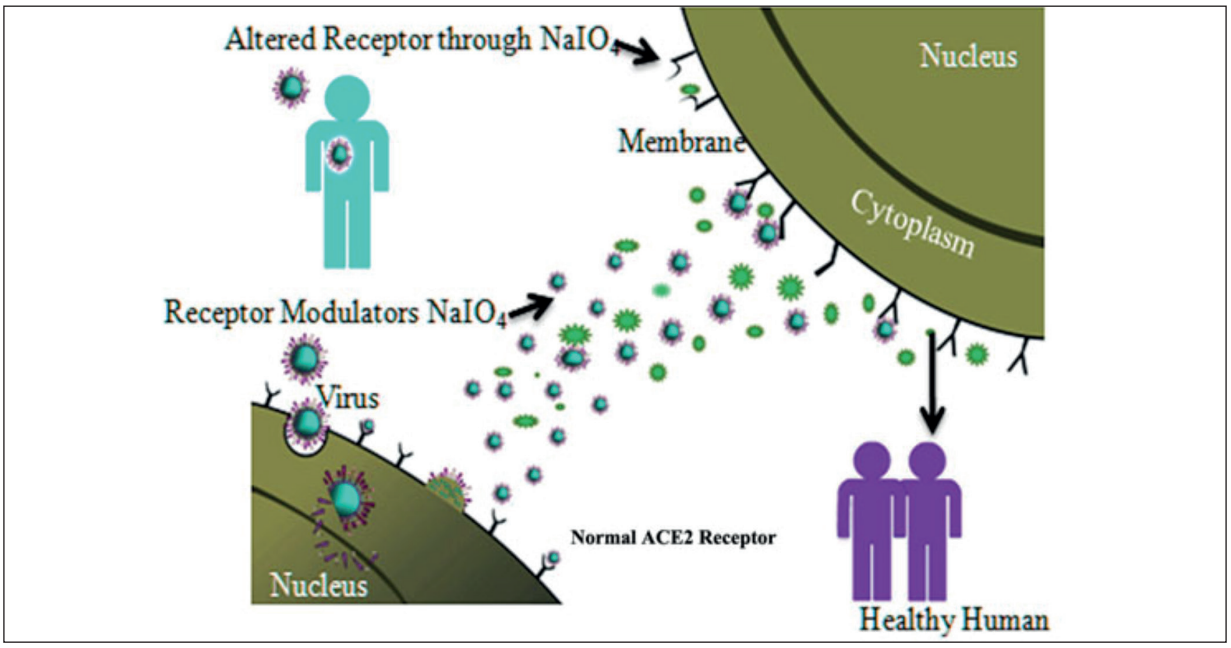

Figure 2. Schematic representation of the possible mechanism for future antivirals based on receptor misconfiguration to control COVID epidemics.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

We would like to acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi, for its assistance in the preparation of this work under the name of CSIR-POOL Scientist Scheme-9062. Besides, we are grateful to Bharathiar University, Coimbatore, for the administrative support rendered.

The authors thank European Review for Medical and Pharmacological Sciences for allowing the quick publication of this article without a fee.

References

1) Matrosovich M, Klenk HD. Natural and synthetic sialic acid-containing inhibitors of influenza virus receptor binding. Rev Med Virol 2003; 13: 85-97.
2) Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano D, Dononvan, AN, Woolf B, Robinson K, Jeyaseelan R, Breitbart RE, Acton S. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin. Circ Res 2000; 87: 1-9.
3) Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol 2020; 94. pii: e00127-20.
4) Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, Wang YY, Xiao GF, Yan B, Shi ZL, Zhou P. Molecular and serological investigation of 2019nCoV infected patients: implication of multiple shedding routes. Emerg Microb Infect 2020; 9: 386-389.
5) Paulpandi M, ThangamR, Gunasekaran P, Kannan S. Sodium periodate inhibits the binding efficiency of influenza A virus (H3N2) with mammalian cell lines. J Cell Anim Biol 2011; 5: 1-5.
6) Stadler K, Masignani V, Eickmann M, Becker S, Abrignani S, Klenk HD, Rappuoli R. SARS-beginning to understand a new virus. Nat Rev Microbiol 2003; 1: 209-218.
7) Guan Y, Peiris JS, Zheng B, Poon LL, Chan KH, Zeng FY, Chan CW, Chan MN, Chen JD, Chow KY, Hon CC, Hui KH, Li J, Li VY, Wang Y, Leung SW, Yuen KY, Leung FC. Molecular epidemiology of the novel coronavirus that causes severe acute respiratory syndrome. Lancet 2014; 363: 99-104.
8) Kuo L, Godeke GJ, Raamsman MJ, Masters PS, Rottier PJ. Retargeting of coronavirus by substitution of the spike glycoprotein ectodomain: crossing the host cell species barrier. J Virol 2000; 74: 1393-1406.
9) Chang A, Masante C, Buchholz UJ, Dutch RE. Human metapneumovirus (HMPV) binding and infection are mediated by interactions between the HMPV fusion protein and heparan sulfate. J Virol 2012; 86: 3230-3243.
10) Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol 2009; 7: 439-450.
11) Wang M. Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao Z. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269-271.