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Mini Review

Characterization of the Host Receptor Binding by the Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2), SARS-CoV and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

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Abstract

Current global COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is of the emergency public health concern. Prior to SARS-CoV-2 infection, the epidemics caused by the acute respiratory syndrome coronavirus (SARS-CoV) and by the Middle East respiratory syndrome coronavirus (MERS-CoV) were noticed. Therefore, unravelling the pathogenesis scheme of these β-coronaviruses is of major clinical significance of which the mechanism of viral entry demands the foremost focus. The first and foremost strategy of the viral pathogenicity into the host mostly relies on its entry into the host cell as revealed by the identification of the angiotensin-converting enzyme 2 (ACE2) in case of the ongoing COVID-19 disease caused by the SARS-CoV-2 and by the previous etiological agent SARS-CoV. In case of the initiation of the MERS-CoV infection, the dipeptidyl peptidase 4 (DPP4) was discovered as the host receptor. Since all these receptors play important biochemical and immunological roles on triggering the viral infectivity, current review highlighted on these receptor proteins in a comparative way between these three viruses.

Keywords: *Severe acute respiratory coronavirus-2 (SARS-CoV-2); SARS-CoV; The Middle East Respiratory Syndrome (MERS); Angiotensin-Converting Enzyme 2 (ACE 2) Receptor; Dipeptidyl Peptidase 4 (DPP4) Receptor*

Introduction

The ongoing COVID-19 pandemic caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), the ~30 RNA virus from *Nidovirales* order of the family *Flaviviridae* of β-Coronaviruses, which originated in Wuhan, Hubei province of China in the last of December, 2019 is continually exposing the global public health to its highest risk serious health threat, already causing 871,166 deaths out of 26,468,031 confirmed cases all over the world [1,2]. It's known that SARS-CoV-2 enters the nasopharyngeal tract from the respiratory droplets and move along the bronchial tubes to the lungs, making its mucous membrane inflamed and hard resulting in oxygen supply deficiency to the blood with the onset of the shortness of breathing ultimately causing the acute respiratory syndrome (ARDS) [3-5]. Another β-Coronavirus, the Middle East respiratory syndrome coronavirus (MERS-CoV) caused an epidemic in two dozens of countries which originated in the Saudi Arabia in 2012 and before that the severe acute respiratory syndrome coronavirus (SARS-CoV) epidemic was reported in 2003 which originated in the Guangdong province in China [5]. The invading viruses launch pathogenesis through the employment of several activities suppressing the innate immune cells (like the alveolar macrophages, airway epithelial cells, innate lymphoid cells, dendritic cells, etc.) engaged in the host defensive responses and thus accelerates viral entry into the host followed by replication and subsequent infection [6].

Prior to pathogenesis, the entry of virus into the is essential; and so far three host membrane receptors for the b-coronaviruses have been identified: the angiotensin-converting enzyme 2 (ACE2), the dipeptidyl peptidase 4 (DPP4) and the aminopeptidase N (APN) [7]. Therefore, these receptors play important roles directly to prime the viral pathogenesis. Current review thus emphasized very briefly on these receptor proteins in a bit comparative aspects between SARS-CoV-2, SARS-CoV and MERS-CoV, based on the previous and recent literature published. The basic genomic structure in relation to the encoded proteins required for viral entry and infectivity as well as the mode of transmission has also been discussed.

Mode of transmission and genomic characterization in relation to the β-coronavirus pathogenesis

Previous literatures reported that SARS-CoV and MERS-CoV had originated from bats; and afterwards SARS-CoV were noticed to bear the trait of being transmitted to humans from market civets; whereas while the MERS-CoV from the dromedary camels [8-11]. SARS-CoV-2 transmits nearly in similar way to SARS-CoV; and most emphasis is given to the circulation of SARS-CoV-2 within human-to-human via the respiratory droplets [10]. Global travelling of humans has also brought the significant threat of SARS-CoV-2 transmission [11]. In general, the coronavirus genome is arranged in a sequence starting from the 5′ cap-leader-UTR (untranslated region) followed by the large fraction of replicase after which the genes encoding the S (Spike) protein, E (Envelope) protein, M (Membrane) protein and N protein (Nucleocapsid) exist, ending at the 3′ UTR-poly (A) tail, together with the accessory genes (whose products are required for viral pathogenesis) interspersed within the structural genes at the 3′ end of the RNA [1]. The transcriptional regulatory sequences (TRSs) reside at the start point of each structural (or accessory) genes needed for the expression of the corresponding genes [1]. The 3′ UTR comprises the specialized RNA structures needed for the viral replication and synthesis of viral RNA [1].

Binding of spike (S) proteins to the host receptors to prime the viral entry and subsequent pathogenesis

The principal factor for the coronavirus disease manifestations depends on the angiotensin-converting enzyme 2 (ACE2) receptor both in SARS-CoV-2 and in SARS-CoV [1,12]. Studies showed that the SARS-CoV S spike protein (interacting with ACE2) and its RNA could only be detected in the ACE2-positive cells [13]. Also, the binding of SARS-CoV S protein to ACE2 was shown to down-regulate the expression of ACE2, that is actually confirmative of the importance of viral spike proteins in initiating the pathogenesis [13].

S protein of SARS-CoV-2 and the host angiotensin-converting enzyme 2 (ACE 2) receptor

The N-linked glycosylated S protein utilizes an N-terminal signal sequence to gain access to the ER; and the homotrimers of the S protein (class I fusion protein) form the distinctive spike structure which actually mediates attachment to the host receptor [1]. S is cleaved by a host cell furin-like protease into two separate polypeptides: S1, making up the large receptor-binding domain (RBD); and the S2, forming the stalk of the spike molecule [11,13,14]. Therefore, the spike protein mediates the viral entry into the host by binding to host cell surface receptor angiotensin-converting enzyme 2 (ACE 2) receptor (a typical zinc metallopeptidase) resulting in the fusion into the host membranes of the human host [1,7,9-11]. After the ACE 2 is attached with the S1 domain, the cellular surface serine protease TMPRSS2 (a plasma membrane-associated type II transmembrane serine protease) plays an important role mediate the membrane fusion, resulting in the release of the viral contents into the host [14]. Afterwards, the translation of the replicase gene starts and the viral multiplication takes place within the host.

This is to be mentioned that the human ACE2 protein plays an important role in the renin-angiotensin-aldosterone system (RAAS), cardinal in renal and cardiovascular physiology and pathophysiology [7]. The main effector of the RAAS is the angiotensin II, which possesses the trait of being vasoconstrictive as well pro-inflammatory, which in turn follows up the viral pathogenesis probably by the cytokine storm [6,7]. As stated earlier, binding of the SARS-CoV-2 or the SARS-CoV spike protein to ACE2 triggers the internalization of the viral particles and thus such interaction triggers the viral pathogenesis even leading to the ARDS ultimately [7].

S protein of SARS-CoV and the host ACE 2 receptor

Both SARS-CoV-2 and SARS-CoV can use human ACE2 the host cell entry receptor; the spike protein S1 subunits of SARS-CoV-2 and SARS-CoV have been found to share only 70% amino acid identity; and the external subdomain of the S1 head showed only 40% similarity with its counterparts in the bat- and human SARS-CoV-2 [14]. Such variability within the amino acids is thought evolve from the homologous recombinations between a bat CoV and another CoV from unknown origin. Besides, the binding affinity between the SARS-CoV-2 spike ectodomain and human ACE2 was calculated 10 - 20-fold higher than that of the SARS-CoV spike ectodomain and human ACE2 interaction [14,15]. Such higher receptor-binding ability of SARS-CoV-2 thus facilitates the entry of the SARS-CoV-2 into the host more efficiently compared to that of SARS-CoV and hence the person-to-person transmission speeds up through the respiratory droplets from another SARS-CoV-2 infected patient [15].

S protein of MERS-CoV and the host dipeptidyl peptidase 4 (DPP4) receptor

Although the genome structure of MERS-CoV closely resemblances the SARS-CoV and SARS-CoV-2; however, unlike these two, the MERS-CoV utilizes the host Dipeptidyl peptidase 4 (DPP4) as its receptor (instead of ACE-2 receptor) for its entry into the host [1]. The MERS-CoV spike receptor binding domain in complex with human DPP4 showed a significant structural overlap with the binding surface of the natural ligand, adenosine deaminase (ADA), whose primary function is to keep the homeostasis between the development and maintenance of the immune system [7,16]. The study by Bosch and colleagues (in 2014) revealed that 10 out of 14 residues on DPP4 interacting with ADA can also interact with the MERS-CoV RBD [7]. Indeed, DPP4 is considered as the multifunctional type II cell surface glycoprotein with an N-terminal b-propeller domain and a C-terminal hydrolase domain that and can form dimers; and though the necessary interactions with specific proteins, DPP4 has been shown to be engaged in cell adhesion, cell apoptosis and lymphocyte stimulation [16,17]. Like the ACE2 receptor, DPP4 also exhibits the dipeptidase activity, which in turn removes the N-terminal dipeptides of the regulatory hormones and the chemokines of the host immune system [7].

Conclusion

Entry of virus into the host is the prime step to initiate the viral pathogenesis. Current review accumulated the biochemical information on the corresponding receptor binding by the SARS-CoV-2, SARS-CoV, and MERS-CoV, using the reported information; and portrayed a comparative review on the ACE 2- and the DPP4 receptors. However, it is to be mentioned that the APN receptor has been excluded from the present discussion since this receptor is not utilized by any of the three coronaviruses mentioned here. Although a lot of detailed published papers have been found on such receptor binding activity by these viruses; however, the information provided in this review would be effective in terms of general understanding of the entry of this viruses into the hosts to initiate the viral pathogenesis. However, certain critical issues are also being investigated around the world concerning the viral evolution and transmission, the genomic influence on the viral pathogenesis and the pathophysiology; together with the diagnosis and the development of anti-viral therapies.

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Conflict of Interest

Authors have declared that they have no conflict of interest.

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