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Review Article

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SARS Cov-2 Pathogenicity-Dependent to Post-Transcription of GRP78, ASGR1 and KREMEN1

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Abstract

COVID-19 disease has drawn attention across the world pursuant to high morbidity and swift mortality. However, the death rate has declined the following generating different kinds of vaccines, there remain concerns about SARS-CoV-2. GRP78, ASGR1, and KREMEN1 are newly reported as alternative receptors for ACE2. In this study, we reviewed the role of these receptors in physiologic conditions as well as their linkage to COVID-19. We also viewed the genetic variants of these receptors. Our review revealed that these receptors are genetically modified, and thus it is better to consider these modifications on COVID-19 pathogenesis because it seems that these modifications heavily impact the interaction between SARS-CoV-2 and these receptors. However, there is no evidence to describe the exact mechanism and amount of contribution of individually each receptor with SARS CoV-2, these receptors may be responsible for COVID-19 severity apart from ACE2. Altogether, ACE2 alongside these receptors seems to drive the virus entry, replication, and severity. Hence, focusing on these four receptors simultaneously may give and identify new strategies against SARS-CoV-2.

Keywords: SARS CoV-2, GRP78 protein isoform/variant, ASGR1 protein isoform/variant, KREMEN1 protein isoform/variant, ACE2 alternative receptor

Introduction

GRP78

Folding and maturation of proteins are processes which are dominantly performed in endothelium reticulum (ER) [1]. Glucose regulated protein 78Ka (GRP78) is an ER chaperon which is characterized by cellular processes namely polypeptide synthesis and protein folding [2]. GRP78 has two main domains, a 44kDa N-terminal ATPase domain and a 20kDa C-terminal polypeptide-binding domain which polypeptide binding is mainly drive via ATPase domain [3]. GRP78 plays a role in protein folding via Unfold protein response (UPR) and deficiency in protein maturation [4]. It is well-established evidence that the GRP78- A chief regulator for unfold protein response (UPR) is elevated in response to ER-stress [5]. Nonetheless, stimuli containing environmental, physiological and pharmacological agents which can impact on protein folding and glycosylation are associated with GRP78 expression [3]. Detection of GRP78 in cell surface is considered as a co-receptor to bind different ligands [3].

GRP78 is also considered as transmembrane protein as it has hydrophobic domain that may constitute transmembrane helices [2]. Serving as a co-receptor to bind coxsackievirus A9 [6], and expression on the surface of many cancer cells have been reported for GRP78 [7]. The presence of GRP78 on the cell surface

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is relatively unclear, and specific mechanisms may be responsible for translocation GRP78 to the cell surface. Furthermore, the mechanism of expression GRP78 of its ER form and cell surface induced by ER stress is different and not fully clearly illustrated by Zhang et al. [8]. ER stress-induced GRP78 activation is mediated by elements which respond to ER stress consisting of transcriptional factors or may be driven by ER stress elements-responded pathways [9].

ATF6 is the main transcriptional factor for GRP78 activation [9]. Pathological and epigenetic events associated with viral infection is able to induce ER stress, and consequently upregulation of GRP78 [10,11]. The relation between clinical indication in patients with cancer as well as autoimmune diseases with GRP78 were confirmed by Banerjee et al. [12]. Nevertheless, they utilized an anti-body which was not able to detect all GRP78 protein isoform. Besides, in a PhD thesis were showed that three type of GRP78 isoforms at cell surface functionally differ from ER peers [13]. Hence, the role of GRP78 and its protein isoforms need further investigation.

GRP78 and SARS CoV-2

Sabirli et al. indicated that GRP78 expression increases in patients with SARS CoV-2 [14]. Moreover, GRP78 could be a therapeutic target for SARS CoV-2 showed by Palmeria et al. [15]. Patients with cancer, specifically lung cancer, are prone to COVID-19 disease because of higher expression level of GRP78 [16]. Taken together, it seems that GRP78 has a significant role in pathophysiology of SARS CoV-2 whereas a receptor it boosts the virus entry. Additionally, when the virus enters the cells, the maturation of its main protein, protein S is carried out in ER- Golgi where the GRP78 is placed and can affect the folding and maturation of protein of SARS CoV-2. [17,18]. Importantly, the SARS CoV-2 affinity to bind GRP78 at cell surface is variable due to mutation in SARS CoV-2 genome [19]. This interaction is more important where GRP78 affects glycosylation of SARS CoV-2 protein, suggesting the antigen of SARS CoV-2 proteins may change such as S protein which is significantly play role in SARS CoV-2 tropism.

This is also may influence vaccine effectiveness owing to change the antigen structure of S protein. Altogether, GRP78 has potential to modulate the virus entry, replication and effectivity of vaccines. In addition, its role has been expanded where its cytosolic variant, GRP78va approximately has potential ability of GRP78 [20]. In an in vitro study, a variant of GRP78 can be specific for tumours [21]. In this study were showed that the GRP78 identified can be therapeutic target via antibody approach. What is more, the intronic rs430397 polymorphism of GRP78 may impact on generating protein isoform, function and localization of GRP78 [22]. Thus, genetic modulation of GRP78 might affect the pathophysiology of COVID-19 disease.

ASGR1, KREMEN1 and SARS CoV-2

The asialoglycoprotein receptor (ASGPR) has two subunits which both are transmembrane protein. ASGRP potentially mediates the endocytosis and desialylation of glycoproteins; This receptor mainly expresses in liver [9]. The ASGR1 subunit is predominant isoform that is individually different [23,24]. It is also detectable in peripheral blood monocytes [23]. This receptor has high affinity glycoprotein-based ligands carrying out galactose [25]. Both subunits of ASGPR have role in binding virus showed by zhang et al. [26]. This study anti-ASGRP antibodies prevent the hepatitis E virus binding (HEV). Furthermore, using microarray for candidate genes which were responsible for HBV infection showed that ASGR1 was upregulated in HepG2 cell and may contributed to HBV infection [27].

In addition, ASGRP1 is considered as chief receptor for COVID-19 infection in liver cells where Yang et al depicted that ASGR1 antibodies decrease the infection [28]. The spike protein of SASR CoV-2 is highly glycosylated. This feature elevated its interaction with host cells because most of receptors in mammalian tissues have glycans such as sialic acid which this glycan considered as principal component to bind different ligands [9,29]. A study using STD-NMR method subtly revealed that interaction between spike protein of SARS CoV-2 and receptor in human [30]. In this study, they labelled sialic acids of receptors to determine the binding mechanism receptor containing sialic acid and binding site on spike protein where N-terminal domain of virus is identified with high affinity to bind sialic acids of receptor. They also show that spike glycoprotein carrying out galactose increases the ability of virus to bind receptor. This confirmed the results study of AA D'souza et al. mentioned above.

Alternative splicing is a process involving mRNA maturation [31]. Changes in spliceosome complex or factors participating in this process may lead to produce different variants of mRNA and consequently different protein isoform [31]. Although these variants and isoforms are functionally less activated, in some cases have potential to play identical role of original mRNA [31]. In some cases, they may have different structure and function compared to their primary mRNA and protein [32]. Different in structure and function of isoform may impact on gene and protein expression. A specific isoform of ASGR1 which carries a noncoding 12-base-pair (bp) deletion (del12) in intron 4 of ASGR1 is associated with the reduced risk of coronary artery disease [33]. Another isoform of ASGR1, p.W158X in the extended population of this study was related to low non-HDL cholesterol and coronary artery disease. Therefore, ASGRP has two isoforms which are functionally activated, and their pattern expression as well as epitope structure may differ from their original mRNA and protein respectively.

Kringle Containing Transmembrane Protein (KREMEN) is a transmembrane protein with an extracellular domain. This receptor has two subunits, KREMEN 1 and KREMEN2 which mainly express in liver, heart and lung [34]. Dickkopf (Dkk) protein which is an inhibitor for Wnt signalling is the main ligand for KREMEN1 [35]. Different ligands are identified to bind KREMEN1 [36]. KREMEN1 is considered as receptor which promotes Human type A Enteroviruses (EV-As) and coxsackievirus A10 (CV-A10) binding [37,38]. In patients with schizophrenia the rs713526, a SNP located in KREMEN1 promotor may impact on its gene function [39]. What is more, the KREMEN1 p.F209S mutation (c.626 T>C) on chromosome 22 differentially affect the regulation of Wnt signalling [40]. A RNAseq analysis-based study showed that KREMEN1 is highly susceptible to alternative splicing in patients with oral cancer of gingiva and tongue [41]. Another study showed that the mRNA of KREMEN1 is prone to alternative splicing by inhibition of histone deacetylases [42].

In some literatures reveal a strong interaction between ASGR1 and KREMEN1 receptor with COVID-19 disease [43,44]. Spike protein which has to subunit, S1 and S2. S1 protein is the main protein of SARS CoV-2 to bind host cells. The S1 subunit has a role in virus entry and S2 subunit plays role in virus fusion. Receptor binding domain (RBD) in S1 subunit is the main location to bind host cell receptors. By screening the 5054 human membrane proteins as target for spike protein of SARS CoV-2, ASGR1, KREMWN1 and ACE2 of host cells are used by COVID-19 to enter different cells and tissues. This study illustrated that virus susceptibility is highly correlated with utilizing of ASGR1/KREMWN1/ACE2 combination [43,44].

The three aforementioned receptors are targeted to bind RBD. Interestingly, ASGR1 and KREMEN1 can bind to different location of spike protein where the ACE2 which has been more studied just bind to RBD, while ASGR1 and KREMEN1 can interact with N-terminal domain (NTD) of S1 subunit, and KREMEN1 can bind exclusively interact with C-terminal domain (CTD) of S2 subunit [45]. To screen the ability of hepatocytes cells to bind S protein of SARS CoV-2 Collins et al. showed that ASGR1 is strongly targeted to bind S protein. In this study, they indicated that S protein could not bind to hepatocyte cells when they use antibodies against ASGR1 [46]. Using RNA seq analysis KREMEN1 was shown as primary receptor in cardiomyocytes to bind SAR CoV-2 [47].

Discussion

Genetic characteristics and clinical features of COVID-19 disease have been changing for a variety of reasons. Apart from background diseases, age, gender and ethnicity, the ability of virus to entry host cells has been at the center of attention. This feature has been expanded and more studied to combat SARS CoV-2, more specifically in producing vaccines. Accordingly, ACE2 is considered the chief receptor for cell entry. However, this is still a major receptor, owing to its different tissue and cell distribution, investigators have introduced new and potential receptors to bind viruses. In addition, the symptoms have differed from the initial incidence of SARS CoV-2 until now, which has convinced researchers to seek alternative receptors.

GRP78 has been reported as one of the alternative receptors for ACE2. It not only binds to virus at cell surface but also has role in protein maturation of virus in ER. However, the main role of GRP78 is reported to regulate the unfold protein response (UPR) in ER, it has protein isoforms which can bind to ligands such as virus antigens. Recently this receptor was identified as the receptor to bind S1 protein of SARS CoV-2. So, when the virus enters cells, its protein needs to be mature in ER of cell, where GRP78 can influence protein maturation of SARS CoV-2. Accordingly, GRP78 increases in patients with COVID19 infection because of virus-induced ER stress. So, it seems that there is a linear relation between GRP78 overexpression and virus load. Interestingly, GRP78 plays role in virus protein maturation which makes it a therapeutic target for COVID-19 disease.

In addition, it has cytosolic isoform which have approximately equal function of its ER form as Banerjii et al. not embedded cytosolic isoform of GRP78 in their study using antibodies against GRP78. Cytosolic isoform may have epitope site which is not detectable via antibodies for original form. In experimental study, positive reaction in western blot assay did not necessarily identify epitope on antigens showed by zhou et al. [48]. They showed that some protein may be eliminated before transferring to nitrocellulose membrane where antibodies detect the protein. Furthermore, Crèvecoeur et al. reported different functions for three cell surface isoforms of GRP78. Altogether, there is no literature covering GRP78 protein isoforms, and for scrutinizing its relationship with pathophysiology of SARS CoV-2 these aforementioned isoforms should be take into account. In other words, to determine the role of GRP78 on SARS CoV-2, its protein isoform is important, and investigators should consider these isoforms, if they use antibodies against GRP78 in their studies.

ASGR1 and KREMEN1 have potentially been selected as alternatives for ACE2 which differentially express in liver and heart respectively. However, ACE2/ASGR1/KREMEN1 combination increases the susceptibility of SARS CoV-2. There is few evidence between ASGR1/KREMEN1 with pathogenesis of COVID-19. Nonetheless it seems that these receptors are responsible for liver and heart involvement in COVID-19 disease. Moreover, previous studies showed that patients with liver and heart diseases prone to SARS CoV-2 infection [49-51]. Therefore, overexpression of these receptors may associate acute symptom or high death rate in patient with heart and liver diseases infecting with SARS CoV-2.

There is no study to elucidate the relation between genetic variations of ASGR1/KREMEN1 and SARS CoV-2, while previous studies reveal that genetic modification of these receptors has significant effect on their function as well as their target genes. More importantly, ASGR1 has the two protein isoforms which should be considered in antibody-based studies associated with SARS CoV-2, because Nioi et al. showed that low non-HDL cholesterol and coronary artery disease are associated with those patients carrying these isoforms. Therefore, ASGR1 may be responsible for severity COVID-19 diseases in patients with heart failure, as it potentially binds to viruses and increase virus tropism. In addition, Yang et al. demonstrated that antibodies against ASGR1 decline COVID-19 infection, while it seems that they ignored other ASG1 isoforms which may have different epitope structure. So, like the description about GRP78, using antibodies against original ASGR1 protein may not be effective, and needs further investigation.

As for KREMEN1, previous studies reveal that it is a Wnt signalling antagonize, a master pathway involving in the COVID-19 pathogenesis. A SNP, rs713526 located in the promotor of KREMEN1 and p.F209S mutation (c.626 T>C) of KREMEN1 has impact on Wnt signalling [40]. Hence, KREMEN1/Wnt signalling axis may be applicable target for treating strategies for COVID-19. Taken together, our review revealed that GRP78/ASGR1/KREMEN1 potentially associated with COVID-19 disease. However, we explain that GRP78 and ASGR1 have their own protein isoform which may have the same epitope sites, there need to experimental confirmation this issue. Moreover, genetic modifications of these receptors may deliver new insight into COVID-19 pathophysiology.

Suggestions

We recommend that SNP, variants, and protein isoforms of these receptors be studied because of their significant association with COVID-19.

Author Contribution

Mohammad Moradzad led the project including early proposal, organizing the evidence collection and write the paper, Hassan Soltani prepare information about ASGR1 and KREMEN1 and contributed to writing the paper, Dariush Khateri prepare information about GRP78.

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Conflict of Interests and Disclosure

The authors declare that they have no competing financial into interest Ethics.

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Consent statement/Ethical approval

Not required.

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