Management protocols for COVID-19: Will it include targeting ADAM 17.

Nagwa Ali Sabri[1*], Mohamed Ahmed Raslan[1,2], Mona Alshahawey[1], Eslam Mansour Shehata[2]

[1]Department of Clinical Pharmacy, Ain Shams University, Cairo, Egypt

[2]Department of Clinical Research and Bio analysis, Drug Research Centre, Cairo, Egypt

Abstract

Corona virus (SARS-CoV-2) infection or (COVID-19) that has emerged by the end of 2019 is leading to a global threat, which resulted in more than 11 million infections and 500 thousand deaths worldwide till July 2020.

Keywords: COVID-19, ADAM17, Targeting.

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Description

Recently, it has been found that angiotensin-converting enzyme 2 (ACE2) act as a receptor for SARS-CoV-2 despite amino acid variation at some key residues, which was identified by genome sequencing and homology modelling. ACE2 extracellular domain was demonstrated as a receptor for the spike (S) protein of SARS-CoV, predominant expression of ACE2 was found to be on the apical surface of well-differentiated airway epithelia especially ciliated cells [1-4].

ADAM17 (A disintegrin and metalloprotease 17), a transmembrane proteinase, can cleave the extracellular juxta-membrane region of ACE2; leading to ectodomain release (which is the catalytically active part of ACE2) into the extracellular milieu [5], resulting in what is called shedding. Some studies suggested that modulating high levels of shed ACE2 could be attained by up-regulation of ACE2 shedding, which can result in inhibition of SARS virus infectivity [6].

It becomes increasingly apparent that the proteolytic shedding of cell surface proteins is an important mechanism which regulate cell surface proteins expression and function. Ectodomain shedding event occurs for a variety of membrane proteins with distinct functions, including cytokines, enzymes, adhesion molecules, and proteins associated with neuropathological disorders [6].

Cellular level of ADAM17 was depleted by specific RNA interference in some experiments providing a direct evidence for ADAM17 involvement in the regulated shedding of ACE2. Moreover, ADAM17 transient overexpression showed a significant increase in stimulated ACE2 shedding in comparison with mock-transfected controls, which provide a strong evidence that ADAM17 is responsible for regulated shedding of ACE2 [6].

Besides, in a non-small cell lung cancer cell lines, estradiol showed to increase the expression levels and activity of ADAM17, which suggested a higher shedding of ACE2 in women which could partially explain the reduced incidence of COVID-19 in women compared to men [7].

Notch signalling pathway plays a major role in controlling cell fate during the development and in postnatal life. Four receptors (Notch 1–4) are found in humans, which are activated by binding with ligands (Jagged1,2 and Delta-like ligands (Dll)1,3,4) on the surface of adjacent cells [8], also, miRNA-145 which down regulates ADAM17 [9] is a target of Jagged1/Notch1 signalling in vascular smooth muscle cells [10]. Investigating whether antagomir to miRNA 145 would increase ADAM17 activity could be an interesting issue.

It is worthy to mention that ADAM17 act as regulator for IL-6 class switching as a mediator between pro- and anti-inflammatory responses to viral antigenic stimuli in Ebola virus, SARS-CoV and dengue infections in humans [11]. ADAM17 can be considered as a target molecule for antiviral drug investigations for COVID-19 infections.

Increased soluble ACE2 levels comes as a result of Angiotensin II type 1 receptor upregulation by ADAM17, implying a decrease in membrane-bound ACE2. There is an evidence from animal studies that ARBs may upregulate membrane-bound ACE2, whereas, ACE inhibitors may not, although ARBs may downregulate ADAM17 [12].

Increased release of EGFR ligands results from excess ADAM17 activity, which in turn can drive tumor progression, while decreased EGFR signalling as a result of low ADAM17 activity, can cause problems in cellular development and regeneration process. A full picture of ADAM17 regulation is still missing despite of many studies performed from different aspects. Phorbol-12- myristat-13-acetat (PMA), a non-physiological PKC activator are the strongest known and usually used stimulator of ADAM17-mediated shedding [13].

Other known physiological stimuli include thrombin, which stimulates ADAM17-mediated shedding through activation of the protease-activated receptor 1 (GPCR) although the intracellular pathways responsible for the physiological activation of ADAM17 is still not clear. Phosphorylation is a common way to regulate protein activity, where, p38 mitogen-activated protein kinases (p38 MAPK) is able to phosphorylate ADAM17 at T735 within the cytoplasmic region resulting in ADAM17 activation [13].

Severe (SARS-Cov-2) infections are more common in adults than in children, and in men than women, which may be related

to differences in membrane ACE2 (mACE2) expression and/or age- related alterations in the RAS (renin-angiotensin system), associated with increased angiotensin II/ADAM-17 activity and increased mACE2 shedding [14].

Conclusion

As a conclusion, the aforementioned data suggested the need for more studies to address the benefit of targeting ADAM17 in ACE2 shedding, and consequently the inhibition of SARS-CoV2 replication. It is recommended that more investigations have to focus on ADAM17 up-regulation. Activators or inducers for ADAM17 activity should be addressed too.

Conflict of Interest

All authors declares no conflict of interest

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*Correspondence to

Nagwa Ali Sabri, Ph.D.

Clinical Pharmacy

Faculty of Pharmacy

Ain Shams University

Cairo

Egypt

E-mail: nagwa.sabri@yahoo.com