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LETTER TO THE EDITOR

Hemagglutinin-esterase cannot be considered as a candidate for designing drug against COVID-19

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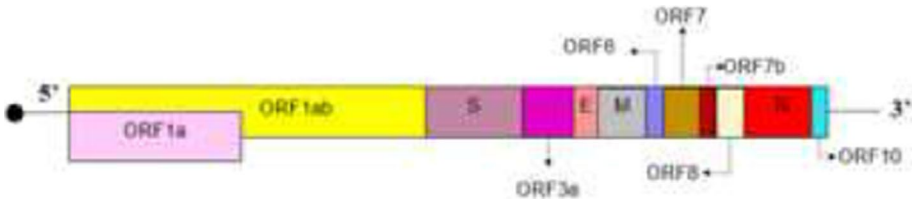
Abstract

We read with interest the article by Patel et al. on the identification of potential inhibitors of coronavirus hemagglutinin-esterase. The authors considered hemagglutinin-esterase as a glycoprotein of SARS-CoV-2 and selected hemagglutinin-esterase as a target to identify potential inhibitors using a combination of various computational approaches, and however, SARS-CoV-2 genome lacks hemagglutinin-esterase gene; thus, hemagglutinin-esterase does not exist in SARS-CoV-2 particle.

Graphic abstract



Keywords Hemagglutinin-esterase · SARS-CoV-2 · Genome · Betacoronavirus

In December 2019, a novel betacoronavirus "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) detected in China [1]. SARS-CoV-2 is a member of *Coronaviridae* family. There are four genera in coronaviruses apha-, beta-, gamma- and deltacoronavirus [2]. Betacoronavirus genera is classified into five subgenera or lineages (Table 1) [3]. SARS-CoV-2 is a positive-sense single-strand RNA virus, and the size of its genome is about 30 kb [4]. The 2/3 of genome of SARS-CoV-2 at 5′ end contains two overlapping open reading frames (ORF1a and ORF1b) which encode two polyprotein precursors including pp1a and pp1b, respectively. Two proteases cleave both pp1a and pp1b to produce non-structural proteins. The remaining 3′ third of the genome encodes four structural proteins including spike (S), envelope (E), matrix (M) and nucleocapsid (N), and also, accessory genes are distributed in among the structural genes[4, 5]. Novel coronavirus (n-CoV) as a betacoronavirus of lineage B does not contain hemagglutinin-esterase (HE) [6–10]. However, betacoronaviruses of lineage A (such as OC43-CoV, HKU1-CoV and Bovine-CoV) harbor HE gene which encodes HE that acts as a receptor-destroying enzyme [11]. Some studies mistakenly reported that SARS-CoV-2 contains HE. Duner et al. stated that some coronaviruses including SARS-COV-2 contain HE [12], and however, they cited a reference which is published in 1998 Aug [13], although SARS-CoV-2 is detected in 2019 Dec and lacks HE. In another article, authors reported that betacoronavirus mostly uses HE to link to sialic acid on the glycoprotein surface [14], and however, betacoronavirus is a genera (Table 1) and among betacoronaviruses, viruses which belong to *Embecovirus* subgenera can code HE as a glycoprotein surface [15]. Aktas A et al. examined the biological activity of Arbidol in the inhibition of HE and spike glycoproteins of SARS-CoV-2 in silico[16], but according to scientific evidences which are described above, SARS-CoV-2

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Table 1 Five subgenera and different species of betacoronavirus genus

Subgenera				
Embecovirus (Lineage A)	Sarbecovirus (Lineage B)	Merbecovirus (Lineage C)	Nobecovirus (Lineage D)	Hibecovirus
Species				
Bovine coronavirus	SARS-CoV	MERS-CoV	Eidolon bat coronavirus C704	Bat Hp-betacoronavirus Zhejiang2013
Human coronavirus OC43	SARS-CoV-2	Pipistrellus bat coronavirus HKU5	Rousettus bat coronavirus GCCDC1	
Human coronavirus HKU1	Bat SARS-like coronavirus WIV1	Hedgehog coronavirus 1	Rousettus bat coronavirus HKU9	
Mouse hepatitis virus	Bat coronavirus RaTG13	Tylonycteris bat coronavirus HKU4		

codes four structural proteins including spike, envelop, membrane and nucleoprotein [17], and therefore, Arbidol has no such interaction with HE in SARS-CoV-2 infection.

Recently in a published research article, authors presented that genome of SARS-CoV-2 harbors hemagglutinin-esterase gene and encodes HE glycoprotein, authors considered HE as a target for designing drug against SARS-CoV-2 infection [18], however, according to evidence SARS-CoV-2 genome lacks HE gene and cannot encode HE protein.

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Declaration

Conflicts of interest Authors declare no conflicts of interest.

References

1. Lai CC et al (2020) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents 55(3):105924
2. Li H et al (2020) Coronavirus disease 2019 (COVID-19): current status and future perspectives. Int J Antimicrob Agents 55(5):105951
3. Wong AC et al (2019) Global epidemiology of bat coronaviruses. Viruses 11(2):174
4. Rastogi M et al (2020) SARS coronavirus 2: from genome to infectome. Respir Res 21(1):1–15
5. Kelly JA et al (2020) Structural and functional conservation of the programmed−1 ribosomal frameshift signal of SARS coronavirus 2 (SARS-CoV-2). J Biol Chem 295(31):10741–10748
6. Shi C-S et al (2019) SARS-Coronavirus Open Reading Frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell Death Discov 5(1):1–12
7. Kumar S et al. (2020) *Morphology, genome organization, replication, and pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).* Coronavirus Disease 2019 (COVID-19), p. 23
8. Devasena T (2021) The nanotechnology-COVID-19 Interface. Nanotechnology-COVID-19 interface. Springer, Singapore, pp 31–58
9. Crawford KH et al (2020) Protocol and reagents for pseudotyping lentiviral particles with SARS-CoV-2 spike protein for neutralization assays. Viruses 12(5):513
10. Zandi M, Behboudi E, Soltani S (2021) Role of glycoprotein hemagglutinin-esterase in COVID-19 pathophysiology? Stem Cell Rev Reports 28:1–2
11. Lang Y et al (2020) Coronavirus hemagglutinin-esterase and spike proteins coevolve for functional balance and optimal virion avidity. Proc Natl Acad Sci 117(41):25759–25770
12. Duner P, Salehi A (2020) COVID-19 and possible pharmacological preventive options. J Clin Med Res 12(12):758
13. De Haan CA et al (1998) Coronavirus particle assembly: primary structure requirements of the membrane protein. J Virol 72(8):6838–6850
14. Frediansyah A et al (2020) Antivirals for COVID-19: a critical review. Clin Epidemiol Glob Health 9:90–98
15. Kim C-H (2020) SARS-CoV-2 evolutionary adaptation toward host entry and recognition of receptor O-Acetyl sialylation in virus–host interaction. Int J Mol Sci 21(12):4549
16. Aktas A et al (2020) How do arbidol and its analogs inhibit the SARS-CoV-2? Bratisl Lek Listy 121(10):705–711
17. Fani M et al (2021) The role of miRNAs in COVID-19 disease. Futur Virol 16(4):301–306
18. Patel CN et al (2021) Identification of potential inhibitors of coronavirus hemagglutinin-esterase using molecular docking, molecular dynamics simulation and binding free energy calculation. Mol Diversity 25(1):421–433