Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Discussion

Target genes used for biosensor development in COVID-19 diagnosis

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ABSTRACT

In a published review entitled "COVID-19 diagnosis —A review of current methods", the authors considered hemagglutinin esterase as one of the structural proteins of SARS-CoV-2 and also they did not represent ORF3b, ORF9b, and ORF9c in SARS-CoV-2 genome structure. However, according to the scientific evidence, among coronaviruses only some betacoronaviruses (*Embecovirus subgenera*) contain HE, and the genome of most of the coronaviruses such as SARS-CoV-2, SARS-CoV, and MERS-CoV lack the HE gene. In addition, the genome of SARS-CoV-2 contains several accessory proteins ORFs including ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c, and ORF10.

Severe acute syndrome coronavirus 2 (SARS-CoV-2) is an enveloped virus that contains a single-stranded, positive-sense RNA as genome (Pal et al., 2020). SARS-CoV-2 belongs to *Coronaviridae* family, this viral family is classified into four genera α-, β-, γ- and δ-coronavirus(2). Human coronaviruses belong to β-coronavirus and α-coronavirus genera (2). β-coronavirus genus has five subgenera including *Embecovirus* (HCoV-OC43, HCoV-HKU1), *Sarbecovirus* (SARS-CoV, SARS-CoV-2), *Merbecovirus* (MERS-CoV), *Nobecovirus*, and *Hibecovirus*(Decaro and Lorusso, 2020; Zandi and Soltani, 2021). The SARS-CoV-2 genome encodes four structural proteins (Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N), about 16 nonstructural proteins (nsp1-16), and several accessory protein ORFs (3a, 3b, 6, 7a, 7b, 8, 9b, 9c, and 10) (Michel et al., 2020; Gordon et al., 2020; Thomas, 2021; Pyke et al., 2021). Accessory proteins of SARS-CoV-2 such as ORF3b, ORF9b and ORF9c are essential as virulence factors during SARS-CoV-2 infection, although some of the accessory proteins are not important for replication.

All members of betacoronavirus from the *Embecovirus* subgenus have an additional HE gene which is located upstream of that encoding the S protein. HE is an integral membrane protein with a single TM domain and a relatively large ectodomain, which has the esterase core domain and a lectin subdomain acting as the RBD (Zeng et al., 2008). This gene is suspected to be transferred from the influenza C virus to the Embecovirus subgenus through heterologous recombination (Llanes et al., 2020).

There are three categories of diagnostic tests on the throat swab, nasopharyngeal swab, saliva, and blood samples have been commonly utilized to detect SARS-CoV-2 according to (a) virus detection via hybridization between sequence complementary to the target RNA genome, (b) antigen protein detection by the interaction of monoclonal antigen-specific antibody and virus antigen protein and (c) antibody detection by the interaction of recombinant antigen and target neutralizing antibody (Lim et al., 2021). However, the development of biosensors utilizes these approaches to target SARS-CoV-2. The RNA genome of SARS-CoV-2 (ORF1ab gene, RNA-dependent RNA polymerase gene, S gene, N gene), specific antigen protein (S protein (S1 subunit/RBD)), and also neutralizing antibody (IgM, IgG) are preferred to use in developing biosensors for COVID-19 diagnosis (Lim et al., 2021).

We read with great interest a review by Yuce et al., entitled COVID-19 diagnosis —A review of current methods (Yüce et al., 2020). In, the authors represented hemagglutinin esterase (HE) as one of the structural proteins of SARS-CoV-2, and stated hemagglutinin-esterase dimer, which acts as a potent mediator of attachment and destruction of sialic acid receptors on the host cell surface (Yüce et al., 2020). However, according to the scientific evidence, among β-coronavirus only (β-coronaviruses of *Embecovirus* subgenera) contain HE, and the genome of other β-coronaviruses such as SARS-CoV, MERS-CoV, and SARS-CoV-2 lack the HE gene and they have no hemagglutinin-esterase glycoprotein (Zandi and Soltani, 2021; Shi et al., 2019; Crawford et al., 2020; Kumar et al., 2020).

In addition, the authors did not represent ORF3b, ORF9b, and ORF9c in the SARS-CoV-2 genome structure in (Yüce et al., 2020). ORF3b

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protein with 22 aa in length as an interferon antagonist, can suppress the induction of type I interferon, studies have shown that SARS-CoV-2 ORF3b inhibits interferon more efficiently than its SARS-CoV ortholog (Konno et al., 2020). ORF9b, an alternative open reading frame within the N gene can suppress interferon type 1 production as a result of targeting mitochondria (Jiang et al., 2020), Kreimendahl et al. presented that ORF9b forms a complex with a mitochondrial import receptor (Tom70) which this complex may modulate the host immune response (Kreimendahl and Rassow, 2020).

ORF9c another accessory protein of SARS-CoV-2 can interfere with interferon signaling, antigen presentation and other immune and stress pathways (Lu, 2020; Andres et al., 2020). ORF9c also interacts with Sigma receptors that are implicated in lipid remodeling and ER stress response (Redondo et al., 2021). Thus, accessory proteins cannot use in developing biosensors for COVID-19 diagnosis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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