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A predicted receptor-binding and critical neutralizing domain in S protein of the novel human coronavirus HCoV-EMC

Dear Editor,

Most recently, Yuen and colleagues have prospected, in this journal, that the discovery of the novel human betacoronavirus 2c EMC/2012 (HCoV-EMC) may be the beginning of another SARS-like pandemic and the research preparedness against this potential pandemic is an important precautionary strategy.[1]

The rapid identification of HCoV-EMC that caused a SARS-like disease in Saudi Arabia[2] is attributed to the success in discovery of the SARS coronavirus (SARS-CoV).[3] Therefore, the knowledge gained from the research on SARS-CoV and the structures of its spike (S) protein may provide a useful template for identifying receptor for HCoV-EMC and developing vaccines against HCoV-EMC.[4]

SARS-CoV S protein consists of S1 and S2 subunits (Fig. 1a). The S1 subunit contains the receptor-binding domain (RBD, residues 318–510) responsible for its binding to the angiotensin-converting enzyme 2 (ACE2) receptor.[5] We previously demonstrated that the RBD is also a critical neutralizing domain (CND), which could induce highly potent neutralizing antibody responses in the immunized animals and protect against SARS-CoV challenge.[6,7] Therefore, the immunogen containing this CND is expected to be effective SARS vaccine candidates.[8]

Sequence alignment of the RBD/CND in SARS-CoV S with that of the corresponding region (residues 377–662) in HCoV-EMC S protein revealed that both fragments have low homology (14% identity and 38% similarity). However, the core domain consisting of β-sheets and α-helices in both fragments have higher homology (23% identity and 61% similarity). Strikingly, six cysteines are located at the same sites in both fragments (Fig. 1b), suggesting that they share conserved conformational structures.

Based on the X-ray crystal structure of the RBD/CND domain in the SARS-CoV S protein (PDB id: 2DD8),[9] the structure of the corresponding region in the HCoV-EMC S protein was predicted using the Swiss-Model Workplace homology modeling server.[10] The results indicate that like the RBD/CND domain in the SARS-CoV S protein,[9,11] the fragment of residues 377–662 in HCoV-EMC S protein also contains a core domain consisting of 5 β-sheets (β1–β4, β7) and 3 α-helices (αA–αC) and a long extended loop containing 2 anti-parallel β-sheets (β5–β6) (Fig. 1c). It has been demonstrated that the core in the RBD/CND domain of the SARS-CoV S protein is responsible for maintaining the overall conformation of the protein, while the extended loop is responsible for its binding with the receptor ACE2 or a neutralizing antibody.[9,11] These findings suggest that the region (residues 377–662) in HCoV-EMC S protein may also serve as a RBD/CND and can be used as a probe to identify HCoV-EMC's receptor and as an immunogen to design vaccines to prevent HCoV-EMC infection.

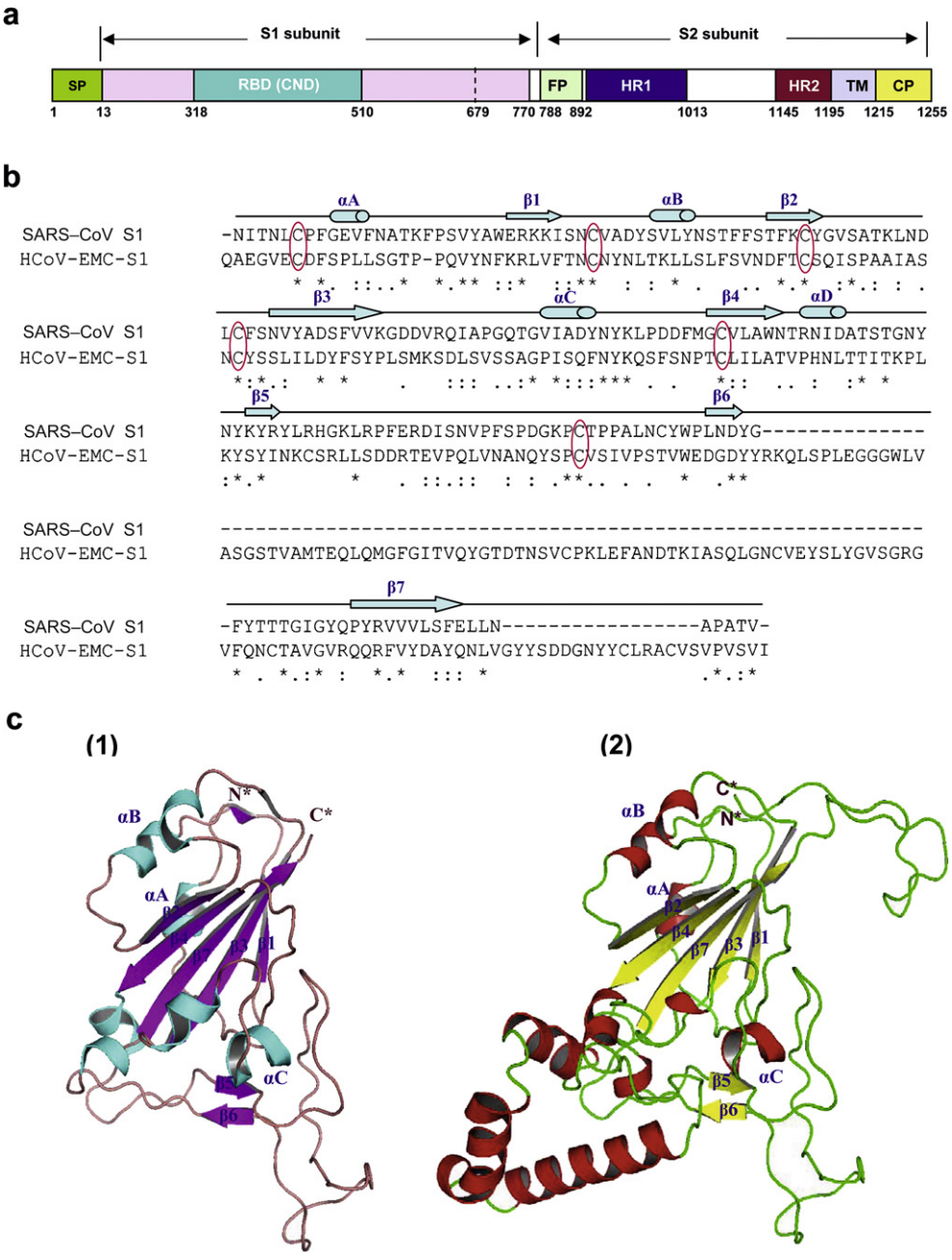

Figure 1 Prediction of the RBD/CND in the HCoV-EMC S protein S1 subunit based on the RBD in SARS-CoV S protein. (a) Schematic representation of the SARS-CoV S protein. SP, signal peptide; RBD, receptor-binding domain; CND, critical neutralizing domain; FP, fusion peptide; HR, heptad repeat; TM, transmembrane domain; and CP, cytoplasm domain. The residue numbers of each region represent their positions in the S protein of SARS-CoV. (b) Alignment analysis of the sequence of the RBD/CND (residues 321—508) in the SARS-CoV S protein[9] with the corresponding region (residues 377—662) in the HCoV-EMC S protein. The secondary structure assignments are listed above the primary sequence with β-sheets highlighted as arrows and α-helices highlighted by cylinders, respectively.[9] The conserved cysteines are highlighted with red circles. (c) Crystal structures of the RBD/CND in SARS-CoV S protein S1 subunit[9] (1) and predicted structure of RBD/CND in HCoV-EMC S protein S1 subunit (2). A core consists of a five-stranded anti-parallel β-sheet (β1—β4, β7) connecting with three short α-helices (αA—αC), and an extended loop contains two-stranded β-sheet (β5, β6). N* and C* stand for the N- and C-termini of RBD/CND, respectively.

Potential conflicts of interest

No reported conflicts.

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