LETTER

doi:10.1038/nature12328

Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26

Guangwen Lu[1]*, Yawei Hu[2]*, Qihui Wang[1]*, Jianxun Qi[1]*, Feng Gao[3,4]*, Yan Li[1], Yanfang Zhang[1,5], Wei Zhang[1], Yuan Yuan[1,6], Jinku Bao[4], Buchang Zhang[2], Yi Shi[7], Jinghua Yan[1] & George F. Gao[1,5,6,7,8]

The newly emergent Middle East respiratory syndrome coronavirus (MERS-CoV) can cause severe pulmonary disease in humans[1,2], representing the second example of a highly pathogenic coronavirus, the first being SARS-CoV[3]. CD26 (also known as dipeptidyl peptidase 4, DPP4) was recently identified as the cellular receptor for MERS-CoV[4]. The engagement of the MERS-CoV spike protein with CD26 mediates viral attachment to host cells and virus–cell fusion, thereby initiating infection. Here we delineate the molecular basis of this specific interaction by presenting the first crystal structures of both the free receptor binding domain (RBD) of the MERS-CoV spike protein and its complex with CD26. Furthermore, binding between the RBD and CD26 is measured using real-time surface plasmon resonance with a dissociation constant of 16.7 nM. The viral RBD is composed of a core subdomain homologous to that of the SARS-CoV spike protein, and a unique strand-dominated external receptor binding motif that recognizes blades IV and V of the CD26 β-propeller. The atomic details at the interface between the two binding entities reveal a surprising protein–protein contact mediated mainly by hydrophilic residues. Sequence alignment indicates, among beta-coronaviruses, a possible structural conservation for the region homologous to the MERS-CoV RBD core, but a high variation in the external receptor binding motif region for virus-specific pathogenesis such as receptor recognition.

[1]CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China. [2]School of Life Sciences, Anhui University, Hefei 230039, China. [3]Laboratory of Non-coding RNA, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China. [4]School of Life Sciences, Sichuan University, Chengdu 610064, Sichuan, China. [5]Laboratory of Protein Engineering and Vaccines, Tianjin Institute of Industrial Biotechnology, Tianjin 300308, China. [6]School of Life Sciences, University of Science and Technology of China, Hefei 230026, China. [7]Research Network of Immunity and Health (RNIH), Beijing Institutes of Life Science, Chinese Academy of Sciences, Beijing 100101, China. [8]Chinese Center for Disease Control and Prevention (China CDC), Beijing 102206, China.

*These authors contributed equally to this work.

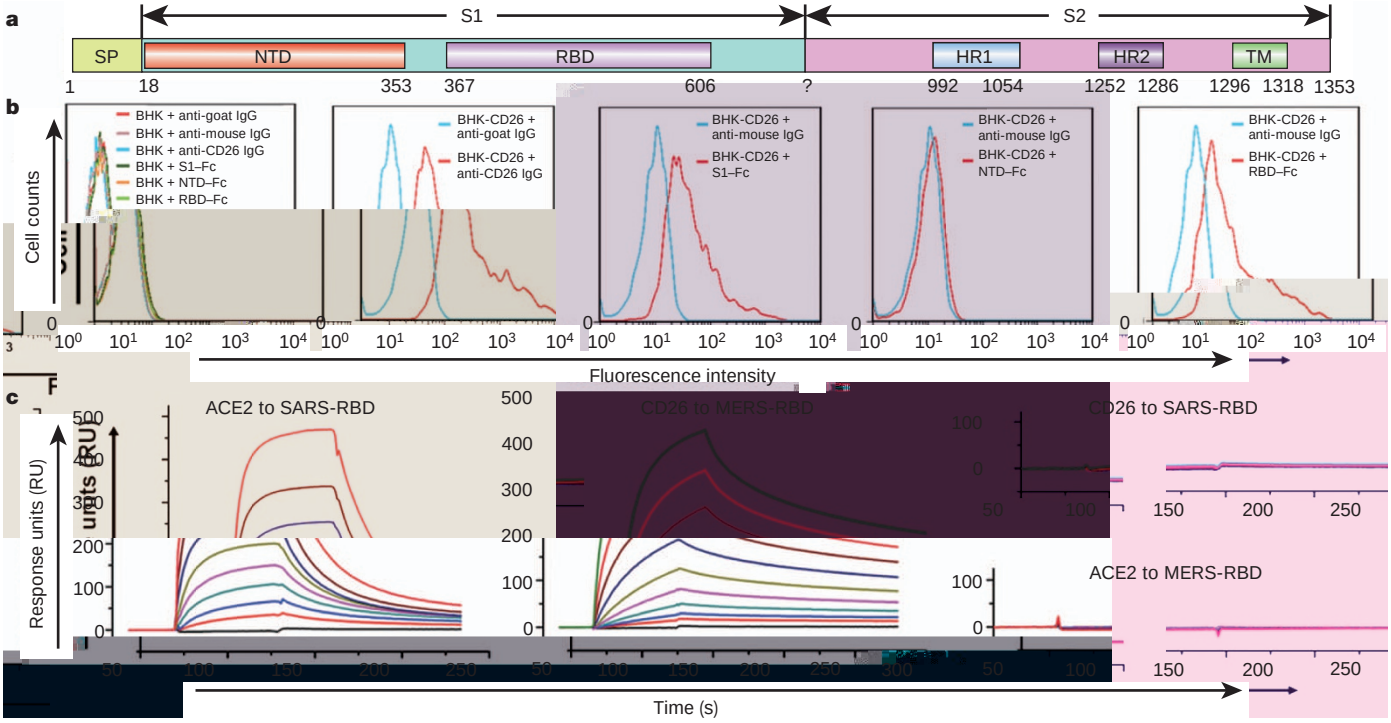


Figure 1 | Identification of the MERS-CoV RBD. a,

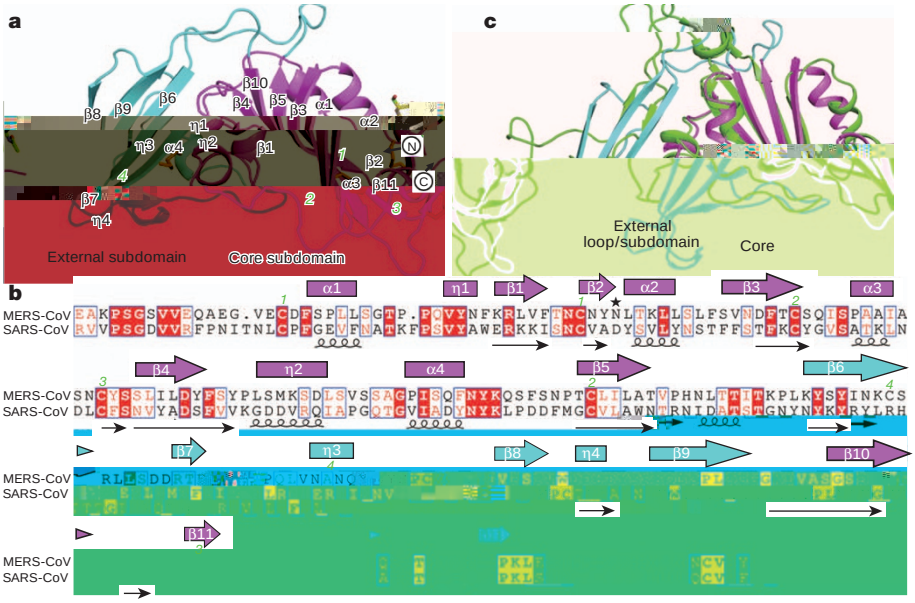
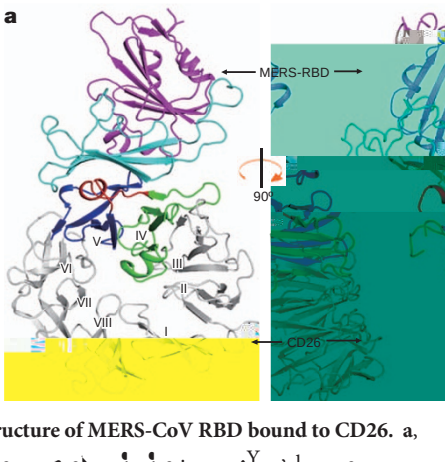


Figure 2 | The overall structure of MERS-CoV RBD. a,



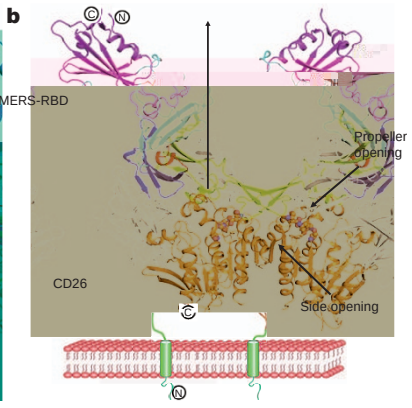
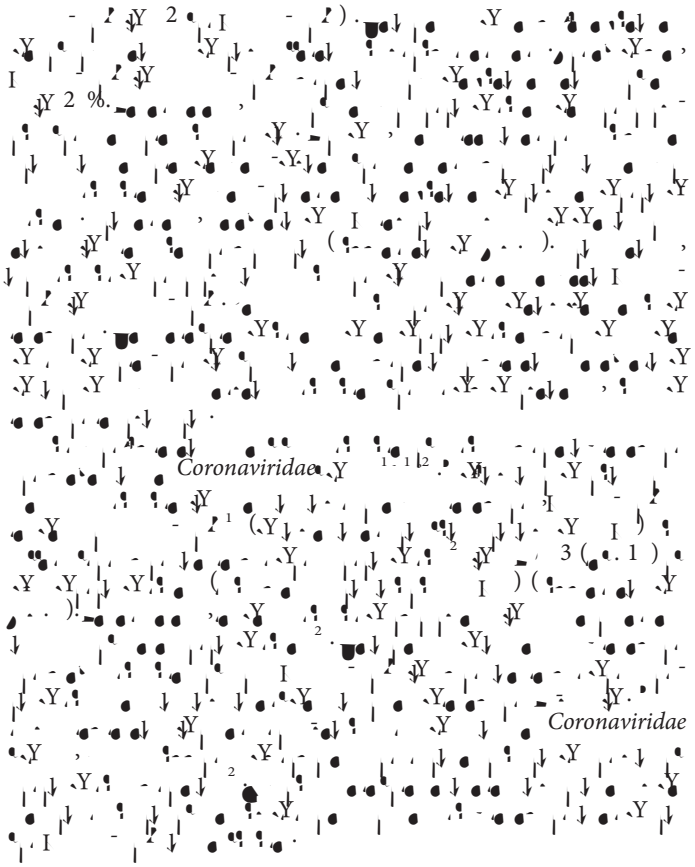


Figure 3 | The complex structure of MERS-CoV RBD bound to CD26. a,



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Supplementary Information is available in the online version of the paper.

Acknowledgements This work was supported by the Ministry of Science and Technology of China (MOST) 973 Project (Grant no. 2011CB504703) and the National Natural Science Foundation of China (NSFC, Grant no. 81290342). Assistance by the staff at the Shanghai Synchrotron Radiation Facility (SSRF) of China and the High Energy Accelerator Research Organization (KEK) of Japan is acknowledged. We thank Z. Fan and T. Zhao for their technical assistance. G.F.G. is a leading principal investigator of the NSFC Innovative Research Group (Grant no. 81021003). We thank M. Yang from Tsinghua University for his help with data collection.

Author Contributions G.F.G. designed and coordinated the study. G.L., Y.H., Q.W. and Y.S. conducted the experiments. J.Q. and F.G. collected the data sets and solved the structures. Y.L., Y.Z., W.Z., Y.Y. and J.Y. assisted with the cell maintenance and protein preparations. G.L. and G.F.G. wrote the manuscript and J.Y., J.B. and B.Z. participated in the manuscript editing and discussion.

Author Information The coordinates and related structure factors have been deposited into the Protein Data Bank PDB under accession numbers 4KQZ for the free MERS-CoV RBD structure and 4KR0 for the RBD–CD26 complex structure. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to G.F.G. (gaof@im.ac.cn).

METHODS

Protein expression and purification.

Crystallization.

Data collection, integration and structure determination.

Secondary-structure determination.

Analytical gel filtration.

Surface plasmon resonance assay.

Flow cytometric assay.

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