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REVIEW

The First Disease X is Caused by a Highly Transmissible Acute Respiratory Syndrome Coronavirus

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Abstract

Based on the announcement of the World Health Organization (WHO) in 2018, the Wuhan pneumonia caused by an unknown etiology should be recognized as the first Disease X. Later, the pathogen was identified to be a novel coronavirus denoted 2019-nCoV, which has 79.5% and 96% whole genome sequence identify to SARS-CoV and bat SARS-related coronavirus (SARSr-CoV-RaTG13), respectively, suggesting its potential bat origin. With high human-to-human transmission rate (R0), 2019-nCoV has quickly spread in China and other countries, resulting in 34,953 confirmed cases and 725 deaths as of 8 February 2020, thus calling for urgent development of therapeutics and prophylactics. Here we suggest renaming 2019-nCoV as "transmissible acute respiratory syndrome coronavirus (TARS-CoV)" and briefly review the advancement of research and development of neutralizing antibodies and vaccines targeting the receptor-binding domain (RBD) and viral fusion inhibitors targeting the heptad repeat 1 (HR1) domain in spike protein of 2019-nCoV.

Keywords Coronavirus · 2019-nCoV · SARS-CoV · Pneumonia · Acute respiratory syndrome · Disease X

On February 9, 2018, the World Health Organization (WHO) announced the Blueprint list of priority diseases, including Middle East respiratory syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), as well as Disease X, for research and development in emergency contexts. Disease X would be a new disease with an epidemic or pandemic potential caused by an unknown pathogen (www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-context). At that time, we believed that the first Disease X could be a transmissible infectious disease caused by a novel coronavirus originated from bats. This supposition was based on a live SARS-related coronavirus (SARSr-CoV), designated SARSr-CoV-WIV1, isolated from bat fecal samples in Vero E6 cells. It had 99.9% whole genome sequence identity to that of SARSr-CoV-Rs3367 identified from Chinese horseshoe bats and another novel strain, SARSr-CoV-RsSHC014, both of which could utilize human, civet and Chinese horseshoe bat angiotensin converting enzyme II (ACE2) as the host cell receptor for infecting human, civet and Chinese horseshoe bat target cells (Ge *et al*. 2013; Cui *et al*. 2019). This evidence prompted us to accelerate our efforts to develop viral fusion inhibitors and neutralizing antibodies with broad-spectrum inhibitory activity against divergent human coronaviruses and SARSr-CoVs (Zeng *et al*. 2017; Xia *et al*. 2019).

On 31 December 2019, the Wuhan Municipal Health Commission reported that 27 cases of unexplained pneumonia linked to the wholesale Huanan Seafood Market in Wuhan had been identified and hospitalized. By then, the investigation had not found significant human-to-human transmission and no medical personnel infected (www.sciencemag.org/news/2020/01/novel-human-virus-pneumonia-cases-linked-seafood-market-china-stir-concern). Based on the announcement of the World Health Organization, as noted above, the Wuhan pneumonia caused by an unknown etiology should be recognized as the first Disease X.

Soon after that, the pathogen causing Wuhan pneumonia was identified as a novel coronavirus, denoted 2019-nCoV

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by WHO (https://www.who.int/emergencies/diseases/novel-coronavirus-2019), with 79.5% and 96% whole genome sequence identity to SARS-CoV and bat coronavirus SARSr-CoV-RaTG13, respectively, suggesting 2019-nCoV's potential bat origin (Zhou *et al*. 2020). However, no name for the pneumonia caused by 2019-nCoV infection has been provided by WHO or by the International Committee on Taxonomy of Viruses (ICTV) so far. Accordingly, some researchers decided to denote this novel coronavirus as "novel coronavirus-infected pneumonia (NCIP)" in their publication (Li *et al*. 2020). However, in the generally accepted lexicon, one would then have to write "novel coronavirus-infected pneumonia coronavirus (NCIP-CoV)", which could be an awkward construct. Most reporters and media are still calling it "Wuhan pneumonia", but this terminology is detrimental to Wuhanese already facing lockdown and economic loss. The obvious dilemmas call for a renaming of the disease and virus causing the disease, one that is both lexicographically and taxonomically appropriate (news.ifeng.com/c/7tf2GFqwL4a).

Jiang and colleagues recently suggested renaming NCIP as "pneumonia-associated respiratory syndrome (PARS)" and 2019-nCoV as "PARS coronavirus (PARS-CoV)" (Jiang *et al.* 2020a, b) in order to retain terminology equivalent to that of SARS-CoV, which was based on the facts that (1) the novel coronavirus causing the pneumonia outbreak in Wuhan is rapidly becoming well known worldwide, (2) most patients suffer from pneumonia, (3) the pneumonia caused by 2019-nCoV is much less severe than that caused by SARS-CoV, and (4) the case-fatality rate (CFR) of patients with 2019-nCoV infection is much lower than that of individuals with SARS-CoV infection. However, several experts in the coronavirus field have expressed their concern that the term PARS seems to exclude associated respiratory syndrome arising from other etiologies of pneumonia. Therefore, we herein propose the following alternative terminology: "transmissible acute respiratory syndrome (TARS)" and "TARS-CoV" for the virus, similar to SARS-CoV, since 2019-nCoV is one of the most transmissible coronaviruses identified so far. Although the estimated R0 ($\sim$ 2.6) of 2019-nCoV (Zhao *et al.* 2020) is generally in line with that of SARS (R0: 2–5), it is much higher than that of MERS (R0: $<$ 1) (Chen *et al.* 2020). In addition, the number of 2019-nCoV-infected patients via human-to-human transmission is at least 3- and 10-fold higher than that of SARS-CoV- and MERS-CoV-infected patients, respectively. On 5 February 2020, the New Coronavirus Infection Pneumonia Diagnosis and Treatment Plan (trial version 5) published by the National Health Commission of the People's Republic of China indicated that the routes of transmission via aerosols and digestive tract were also possible, even though 2019-nCoV is, thus far, known to be primarily transmitted through respiratory droplets and contacts (m.chinanews.com/wap/detail/sp/sp/shipin/cns/2020/02-05/news9080314.shtml), rendering the virus even more transmissible or infectious. Please be aware that WHO may not take our suggestion and ICTV should make the final decision about renaming 2019-nCoV, as they did for naming MERS-CoV in 2013 (de Groot *et al*. 2013).

As of 8 February, 34,953 confirmed cases of 2019-nCoV infection and 725 deaths have been reported in China and 24 other countries (http://en.nhc.gov.cn/2020-02/08/c_76358.htm). This outbreak of 2019-nCoV infection has posed a serious threat to global public health, thus calling for the development of therapeutic and prophylactic strategies (Jiang *et al.* 2020a, b).

Based on the previous experience in the research and development of virus fusion inhibitors against HIV, SARS-CoV, and MERS-CoV (Jiang *et al.* 1993; Liu *et al*. 2004; Lu *et al*. 2014), Jiang and colleagues have recently developed a pan-CoV fusion inhibitor, EK1 peptide, with potent inhibitory activity against infection by 5 human coronaviruses tested, including SARS-CoV, MERS-CoV, and 3 bat-SARSr-CoVs (Xia *et al*. 2019). EK1 peptide could protect hDPP4-transgenic mice or regular mice treated with EK1 via intranasal application before or after challenge with MERS-CoV or hCoV-OC43, respectively. Most recently, Jiang and colleagues showed that EK1 peptide and the peptide derived from the HR2 domain in spike (S) protein of 2019-nCoV (2019-nCoV-HR2P) could effectively inhibit 2019-nCoV pseudovirus infection and S protein-mediated cell–cell fusion (Xia *et al*. 2020), indicating that either EK1 or 2019-nCoV-HR2P could be promising candidates to be developed for prevention and treatment of infection by 2019-nCoV, SARS-CoV, and possibly other emerging and reemerging coronaviruses in the future.

Jiang and colleagues have previously shown that the receptor-binding domain (RBD) in S protein of SARS-CoV contains at least 6 conformation-dependent neutralizing epitopes that can induce potent neutralizing antibody response and protection of immunized animals against SARS-CoV infection (Du *et al.* 2009, 2016). Interestingly, we have previously demonstrated that antibodies induced by SARS-CoV S-RBD could cross-neutralize infection by bat SARSr-CoVs, including bat-SARSr-CoV-W1V1 and bat-SARSr-CoV-SHC014 (Zeng *et al.* 2017). Most recently, we have shown that one SARS-CoV S-RBD-specific monoclonal antibody, CR3022, could potently bind with 2019-nCoV S-RBD, using different probative assays (Tian *et al.* 2020). These results suggest that the SARS-CoV S-RBD-based vaccine candidate should be tested for its in vitro and in vivo efficacy in inducing neutralizing antibody responses and protection of animals against

2019-nCoV infection. If it works, the already developed RBD-based anti-SARS vaccine candidate has sufficient potential to go to clinical studies for the prevention of 2019-nCoV infection.

Compliance with Ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal and Human Rights Statement This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Chen J (2020) Pathogenicity and transmissibility of 2019-nCoV—a quick overview and comparison with other emerging viruses. Microbes Infect. https://doi.org/10.1016/j.micinf.2020.01.004

Cui J, Li F, Shi ZL (2019) Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 17:181–192

de Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C, Enjuanes L, Fouchier RA, Galiano M, Gorbalenya AE, Memish ZA, Perlman S, Poon LL, Snijder EJ, Stephens GM, Woo PC, Zaki AM, Zambon M, Ziebuhr J (2013) Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Viro 87:7790–7792

Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S (2009) The spike protein of SARS-CoV–a target for vaccine and therapeutic development. Nat Rev Microbiol 7:226–236

Du L, Tai W, Yang Y, Zhao G, Zhu Q, Sun S, Liu C, Tao X, Tseng CK, Perlman S, Jiang S, Zhou Y, Li F (2016) Introduction of neutralizing immunogenicity index to the rational design of MERS coronavirus subunit vaccines. Nat Commun 7:13473

Ge XY, Li JL, Yang XL, Chmura AA, Zhu G, Epstein JH, Mazet JK, Hu B, Zhang W, Peng C, Zhang YJ, Luo CM, Tan B, Wang N, Zhu Y, Crameri G, Zhang SY, Wang LF, Daszak P, Shi ZL (2013) Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 503:535–538

Jiang S, Lin K, Strick N, Neurath AR (1993) HIV-1 inhibition by a peptide. Nature 365:113

Jiang S, Du L, Shi Z (2020a) An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. Emerg Microbes Infect 9:275–277

Jiang S, Xia S, Ying T, Lu L (2020b) Novel coronavirus 2019-nCoV causing pneumonia- associated respiratory syndrome. Cell Mol Immunol. https://doi.org/10.1038/s41423-020-0372-4

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Li M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JTK, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z (2020) Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. https://doi.org/10.1056/NEJMoa2001316

Liu S, Xiao G, Chen Y, He Y, Niu J, Escalante CR, Xiong H, Farmar J, Debnath AK, Tien P, Jiang S (2004) Interaction between the heptad repeat 1 and 2 regions in spike protein of SARS-associated coronavirus: implication for virus fusogenic mechanism and identification of fusion inhibitors. Lancet 363:938–947

Lu L, Liu Q, Zhu Y, Chan KH, Qin L, Li Y, Wang Q, Chan J, Du L, Yu F, Ma C, Ye S, Yuen KY, Zhang R, Jiang S (2014) Structure-based discovery of Middle East respiratory syndrome coronavirus (MERS-CoV) fusion inhibitor. Nat Commun 5:3067

Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, Lu L, Jiang S, Yang Z, Wu Y, Ying T (2020) Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect. https://doi.org/10.1080/22221751.2020.1729069

Xia S, Yan L, Xu W, Agrawal AS, Algaissi A, Tseng CK, Wang Q, Du L, Tan W, Wilson IA, Jiang S, Yang B, Lu L (2019) A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. Sci Adv 5:eaav4580

Xia S, Zhu Y, Liu M et al (2020) Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. Cell Mol Immunol. https://doi.org/10.1038/s41423-020-0374-2

Zeng LP, Ge XY, Peng C, Tai W, Jiang S, Du L, Shi ZL (2017) Cross-neutralization of SARS coronavirus-specific antibodies against bat SARS-like coronaviruses. Sci China Life Sci 60:1399–1402

Zhao S, Musa SS, Lin Q, Ran J, Yang G, Wang W, Lou Y, Yang L, Gao D, He D, Wang MH (2020) Estimating the unreported number of novel coronavirus (2019-nCoV) Cases in China in the First Half of January 2020: a data-driven modelling analysis of the early outbreak. J Clin Med 9(2):E388. https://doi.org/10.3390/jcm9020388

Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. https://doi.org/10.1038/s41586-020-2012-7