Commentary

A lethal mouse model using a mouse-adapted SARS-CoV-2 strain with enhanced binding to mouse ACE2 as an important platform for COVID-19 research

Hin Chu*, Jasper Fuk-Woo Chan a,b,c,*

*State Key Laboratory of Emerging Infectious Diseases, Carol Yu Centre for Infection, Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, China
bDepartment of Clinical Microbiology and Infection Control, The University of Hong Kong-Shenzhen Hospital, Shenzhen, Guangdong Province, China
cHainan Medical University-The University of Hong Kong Joint Laboratory of Tropical Infectious Diseases, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, China

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Since its discovery in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused over 146 million cases of Coronavirus Disease 2019 (COVID-19), including more than 3 million deaths worldwide as of 25 April 2021 [1,2]. In addition to in vitro and ex vivo culture systems, readily available animal models are essential to facilitate the investigation of the pathogenesis and transmission, as well as the evaluation of anti-virals and vaccine candidates for this major threat to global health [3–5]. In a recent study published in EBioMedicine, Huang et al. reports the generation of a lethal mouse model for COVID-19 by intranasally inoculating Balb/c mice with a mouse-adapted SARS-CoV-2 strain which is capable of utilizing mouse angiotensin-converting enzyme II (ACE2) for cell entry [6].

Currently, hamsters and mice are the two most commonly used small animal models for conducting basic and translational research on COVID-19 [5]. The golden Syrian hamster (Mesocricetus auratus) model closely resembles the virological, immunological, and pathological findings of the majority of mild to moderate human infection [7]. While being readily available and physiologically relevant, this non-lethal hamster model is not an optimal model for studying severe or lethal COVID-19 as the animals generally recover without treatment after 1 to 2 weeks of infection. Unlike hamsters that are susceptible to SARS-CoV-2, SARS-CoV-2 spike is unable to utilize mouse ACE2 (mACE2) for entry due to the different amino acid residues present on mACE2 compared with human ACE2 (hACE2) at the ACE2-spike interacting surface. Mouse models for COVID-19 require the expression of hACE2 through transgenic, knock-in, or vector-transduction strategies. Alternatively, residues at the receptor-binding domain of the SARS-CoV-2 spike can be modified with mouse adaptation or reverse genetics, which enables the virus to recognize mACE2 [5]. In hACE2-transgenic mouse models, the disease severity of the animals depends on the promoter used and may range from mild to lethal disease [5]. As demonstrated by Huang et al., another strategy for developing mouse model for COVID-19 is by adapting SARS-CoV-2 in mice. Through serial passages of wild-type SARS-CoV-2 in mouse lungs, the group generated a mouse-adapted virus strain (WBP-1) that consistently causes severe interstitial pneumonia and death in Balb/c mice intranasally challenged with 10^5 plaque-forming units of the virus [6]. The Q498H mutation emerged after only one passage, while the Q493K mutation started to appear in passage 5, which likely contributed to the high pathogenicity of WBP-1 in mice. These findings are timely and important because this novel mouse-adapted WBP-1 strain can be shared with laboratories that do not have access to the hamster and hACE2-transgenic mouse models for generating a readily available small animal model to conduct studies on COVID-19.

New SARS-CoV-2 variants continue to emerge as the COVID-19 pandemic expands. Some of these variants are considered to be “variants of concern” as they may be associated with enhanced transmission, pathogenicity, and/or immune evasion [1]. In the present study, Huang et al. characterized the adaptive mutations of the mouse-adapted WBP-1 strain and identified Q493K and Q498H in the SARS-CoV-2 spike receptor-binding domain as two key mutations associated with enhanced binding affinity towards mACE2 [6]. These results are particularly relevant to the control of the ongoing COVID-19 pandemic because the presence of these and other mutations that may facilitate binding with the ACE2 of mice and/or other animal species in clinical SARS-CoV-2 variants may suggest the need for tightened source control in order to minimize the contacts between humans and these...
potentially infected animal species leading to interspecies transmission.

Immunotherapies such as the interleukin-6 receptor antagonist tocilizumab and dexamethasone have demonstrated some benefits in critically ill COVID-19 patients [8,9]. To illustrate the translational value of the present study and to identify additional immunotherapies for COVID-19, Huang et al. employed the newly established lethal mouse model to evaluate the in vivo antiviral effect of the Toll-like receptor 7/8 agonist resiquimod (R848) against lethal SARS-CoV-2 infection, and showed that the mice treated with intraperitoneal R848 immediately after intranasal inoculation of WBP-1 had reduced clinical signs and survived. As a topically and systemically available drug compound, R848 has been evaluated in the treatment of dermatological conditions such as genital herpes and cutaneous T-cell lymphoma, and as an oral therapy for hepatitis C virus infection and adjuvant for vaccines [10]. These findings provide the basis for further clinical evaluations of R848 as a potential treatment option for severe COVID-19.

Declaration of Competing Interest

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