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SARS-CoV-2 infection of Chinese hamsters (*Cricetulus griseus*) reproduces COVID-19 pneumonia in a well-established small animal model

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Abstract

The SARS-CoV-2 pandemic has caused a yet unresolved global crisis. Effective medical intervention by vaccination or therapy seems to be the only possibility to control the pandemic. In this context, animal models are an indispensable tool for basic and applied research to combat SARS-CoV-2 infection. Here, we established a SARS-CoV-2 infection model in Chinese hamsters suitable for studying pathogenesis of the disease as well as pre-clinical testing of vaccines and therapies. This species of hamster is susceptible to SARS-CoV-2 infection as demonstrated by robust virus replication in the upper and lower respiratory tract accompanied by bronchitis and pneumonia as well as significant body weight loss following infection. The Chinese hamster features advantages compared to the Syrian hamster model, including more pronounced clinical symptoms, its small size, well-characterized genome, transcriptome and translome data and availability of molecular tools.

KEYWORDS

coronavirus, experimental animal models, histopathology

1 | INTRODUCTION

The rapid worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an unparalleled crisis and requires urgent testing of prophylactic and therapeutic measures. SARS-CoV-2 likely emerged from a yet unknown animal reservoir; its rapid spread can be attributed to efficient replication in the upper respiratory tract and robust human-to-human transmission. This characteristic clearly distinguishes this novel coronavirus from the related SARS-CoV-1 and MERS-CoV (Andersen et al., 2020). Interestingly, SARS-CoV-2 human-to-animal transmissions have also been reported

(Halfmann et al., 2020; Leroy et al., 2020). Currently, we find ourselves racing for efficacious therapies and protective vaccinations. In this context, small animal models are indispensable as pre-clinical studies in animals are of critical importance for basic and applied research on SARS-CoV-2 infection. Several SARS-CoV-2 animal models have been investigated, including non-human primates, ferrets, transgenic mice, cats and hamsters, (Chan et al., 2020; Dhama et al., 2020; Imai et al., 2020; Lakdawala & Menachery, 2020; Osterrieder et al., 2020; Sia et al., 2020; Trimpert et al., 2020; Yuan et al., 2020). However, in silico models with respect to potential usage of the entry receptor by the spike glycoprotein (S) of SARS-CoV-2 suggest susceptibility of Chinese

Bertzbach and Vladimirova equally contributed to this article.

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hamsters (*Cricetulus griseus*) (Luan et al., 2020; Luan et al., 2020) and a previous study in Chinese hamsters demonstrated susceptibility to SARS-CoV-1 (Luo et al., 2007). We here determined SARS-CoV-2 susceptibility of Chinese hamsters and established this species as novel small animal model for SARS-CoV-2 research.

2 | MATERIALS AND METHODS

2.1 | Viruses and cells

The SARS-CoV-2 München isolate (BetaCoV/Germany/BavPat1/2020) (Wölfel et al., 2020) was used for virus challenge. Stocks were propagated and titrated on Vero E6 cells (ATCC CRL-1586) in minimal essential medium (MEM; PAN Biotech, Aidenbach, Germany) supplemented with 10% foetal bovine serum (PAN Biotech), 100 IU/ml penicillin G and 100 µg/ml streptomycin (Carl Roth, Karlsruhe, Germany) and stored at -80°C prior to experimental infections.

2.2 | Experimental infection of Chinese hamsters

24 five- to seven-week-old female and male Chinese hamsters (*Cricetulus griseus*) were obtained via the German pet trade and kept in groups of six animals in enriched, individually ventilated cages. The hamsters had ad libitum access to food and water, and were allowed acclimatization to these conditions for seven days prior to SARS-CoV-2 infection. Cage temperatures and relative humidities were recorded daily and ranged from 23 to 24°C and from 50% to 65%, respectively. The animals were randomly distributed into two groups: SARS-CoV-2-infected ($n = 12$; 1×10^5 plaque-forming units (pfu) in a volume of 30 µl) and mock-infected ($n = 12$; 30 µl cell culture supernatant from uninfected Vero E6 cells). The infection was performed exactly as previously described (Osterrieder et al., 2020). Baseline body weights of all hamsters and body temperatures of at least three hamsters per group were measured before infection and then recorded daily throughout the 14-day experiment. Moreover, clinical signs of all animals were monitored twice daily throughout the experiment. On days 2, 3, 5 and 14 post-infection (dpi), three randomly assigned hamsters of each group were euthanized by exsanguination under general anaesthesia as described (Nakamura et al., 2017). For virus titrations and RT-qPCR and/or histopathological examinations, blood, bucco-laryngeal swabs and lungs (left and right) were collected.

2.3 | Histopathology and in situ hybridization

For histopathology, lungs were processed as previously described (Osterrieder et al., 2020). In brief, the left lung lobe was carefully removed and immersion fixed in buffered 4% formalin, pH 7.0, for 48 hr, embedded in paraffin and cut at 2 µm thickness. Sections were stained with haematoxylin and eosin (HE) followed by blinded microscopic

evaluation by board certified veterinary pathologists (K.D., A.D.G.). For in situ hybridization (ISH), the ViewRNA™ ISH Tissue Assay Kit (Invitrogen by Thermo Fisher Scientific, Darmstadt, Germany) was used following the manufacturer's instructions with minor adjustments. A probe for the detection of the N gene RNA of SARS-CoV-2 (NCBI database NC_045512.2, nucleotides 28,274–29,533, assay ID: VPNKRHM) was employed. Next, lung sections of 2 µm thickness were mounted on adhesive glass slides, dewaxed in xylol and dehydrated in graded ethanols. Tissues were incubated at 95°C for 10 min, and subsequently, protease digested for 20 min. Sections were fixed with 4% paraformaldehyde dissolved in phosphate-buffered saline (PBS) and hybridized with the probes. Amplifier and label probe hybridizations were performed according to the manufacturer's instructions using fast red as chromogen. Sections were counterstained with haematoxylin for 45 s, washed in tap water for 5 min and mounted with Roti®-Mount Fluor-Care DAPI (4, 6-diaminidino-2-phenylindole; Carl Roth). For negative and morphologically intact controls, lungs from uninfected hamsters were included. An irrelevant probe for the detection of streptococcal pneumolysin was used as a control for sequence-specific binding. HE-stained and ISH slides were analysed and photographs were taken using an Olympus BX41 microscope with a DP80 Microscope Digital Camera and the cellSens™ Imaging Software, Version 1.18 (Olympus Corporation, Münster, Germany). For overviews, slides were automatically digitized using the Aperio CS2 slide scanner (Leica Biosystems Imaging Inc., Vista, CA, USA) followed by image file generation using the Image Scope Software (Leica Biosystems Imaging Inc.).

2.4 | Virus titrations, RNA extractions and RT-qPCR

Virus titres from 50 mg lung tissue were assessed by serial dilution of tissue homogenates and subsequent titrations on Vero E6 cells. 3 dpi, cells were formalin-fixed, stained with crystal violet, and plaques were counted. RNA was extracted from tissue samples, blood and tracheal swabs using the innuPREP Virus RNA kit (Analytic Jena, Jena, Germany) and quantified with a one-step RT-qPCR reaction (NEB Luna Universal Probe One-Step RT-qPCR kit; New England Biolabs, Ipswich, MA, USA) and previously published TaqMan primers and probe (Corman et al., 2020).

2.5 | Statistical analyses

Data were analysed with GraphPad PRISM. We used Mann-Whitney U tests to compare body weights and body temperatures in mock-infected versus SARS-CoV-2 infected Chinese hamsters. Data were considered significant if $p < .05$ (* $p < .05$; ** $p < .01$).

3 | RESULTS AND DISCUSSION

The study, which was approved by the Landesamt für Gesundheit und Soziales in Berlin, Germany (permit # 0086/20), involved 24

female and male Chinese hamsters of 5–7 weeks of age. Hamsters were randomly assigned to two groups (SARS-CoV-2-infected, $n = 12$; mock-infected, $n = 12$) Upon intranasal infection with 1×10^5 plaque-forming units (pfu) of a human SARS-CoV-2 isolate, we observed clinical symptoms including transient but significant body weight loss and subtle drops in body temperatures at early time points after infection, a course of disease comparable to that in Syrian hamsters (Figure 1) (Chan et al., 2020; Imai et al., 2020; Kreye et al., 2020; Osterrieder et al., 2020; Sia et al., 2020). Differences in body weights between infected and mock-infected

animals were significant at 1–3 and at 5 days post-infection (dpi), infected hamsters did not reach pre-infection body weights before 14 dpi when the experiment was terminated (Figure 1a). However, the largest difference in mean body temperatures of infected compared to mock-infected animals was only -0.6°C at 3 dpi (Figure 1b), suggesting that this parameter may not be useful to assess the status of infection. We determined virus replication and virus spread by measuring RNA copy numbers in the lungs, bucco-laryngeal swabs and whole blood samples of all hamsters (Figure 1c–e).

FIGURE 1 Body weight changes, body temperatures and virus loads of mock-infected and SARS-CoV-2-infected Chinese hamsters. (a) Individual relative body weights of mock-infected (green) and SARS-CoV-2-infected (red) hamsters over the course of 14 days after infection. p -values indicate significant differences (Mann–Whitney U test). (b) Temperature changes (as means with SD). Virus loads were determined from total RNA in (c) 2.5 mg homogenized right cranial lung lobes, in (d) bucco-laryngeal swabs and (e) 2.5 μl of whole blood samples by RT-qPCR

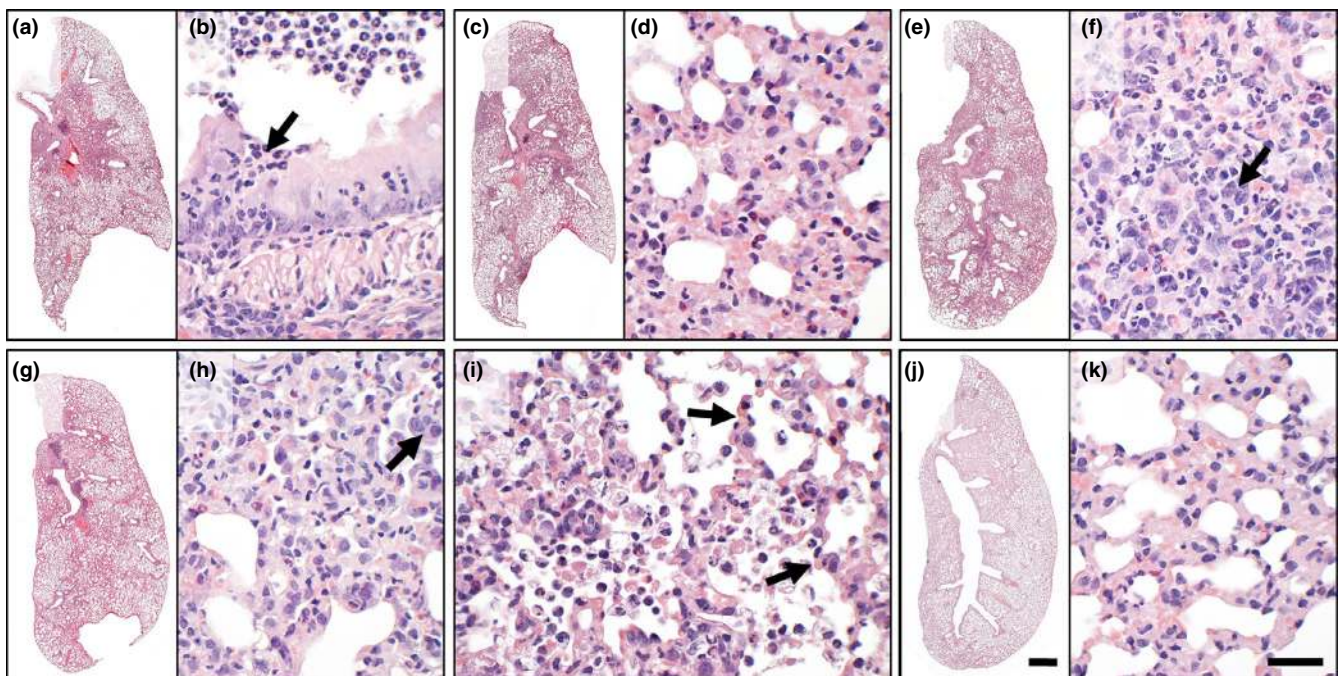
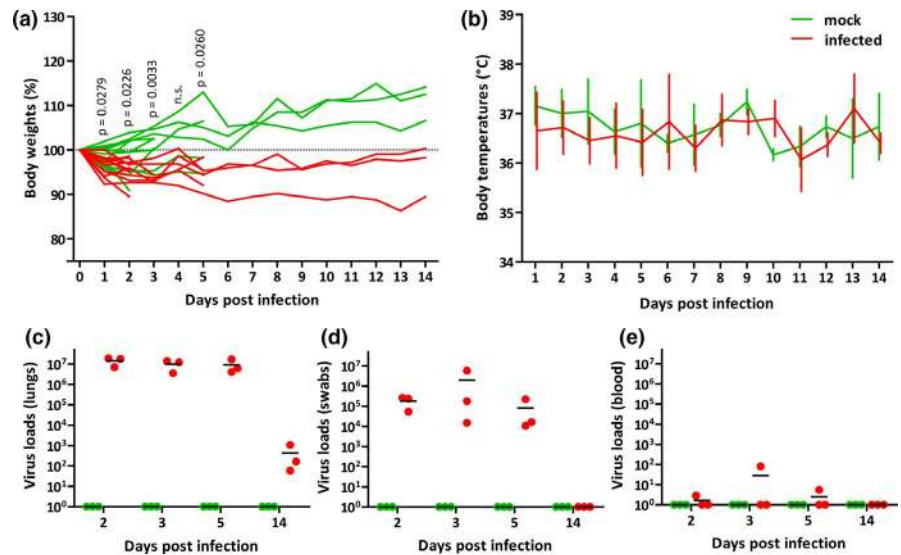


FIGURE 2 Histopathological assessment of mock-infected and SARS-CoV-2-infected Chinese hamsters. Histopathology of haematoxylin–eosin-stained lung sections from SARS-CoV-2-infected Chinese hamsters revealed suppurative bronchitis (a, b; arrow: neutrophils) and necrosuppurative pneumonia (c, d) at 2 and 3 dpi. At 5 dpi (e, f), additional hyperplasia of alveolar epithelial cells (AEC)-type II was salient (f, arrow). Tissue damage, cell influx and hyperplasia of AEC-II (h, arrow) were milder but still present at 14 dpi (g, h). Of note, acute alveolar damage (i, arrows) was multifocally distributed throughout the lungs across all time points investigated. None of these lesions was detected in mock-infected animals (j, k). Bars: 1 mm (a, c, e, g, j) or 50 μm (b, d, f, h, i, k)

In addition, we determined viral titres in the lungs of infected animals (Figure S1). Our assays confirmed high RNA copy numbers and corresponding viral titres at early time points after infection followed by a rapid but incomplete clearance of the virus infection until 14 dpi. With titres of up to 5×10^7 pfu per 50 mg lung tissue and viral RNA copies in the range of up to 1×10^7 per 2.5 mg lung tissue at early time points after infection, we concluded that Chinese hamsters are highly susceptible to SARS-CoV-2. On the other hand, virus loads in blood samples were below 1×10^2 RNA copies per 2.5 μ l of whole blood (15.6 ± 29.8 SD) at all time points, indicating lack of significant viremia and systemic infection (Figure 1e). These observations match findings from other animal models for emerging coronaviruses (Yuan et al., 2020).

Lung histopathology revealed tissue damage and inflammation principally similar to what has been described in Syrian hamsters (Figure 2) (Chan et al., 2020; Gruber et al., 2020; Imai et al., 2020; Kreye et al., 2020; Osterrieder et al., 2020; Sia et al., 2020). However, the course of bronchitis and pneumonia was in general milder than in Syrian hamsters, and pneumonia was more prolonged. Specifically, prominent acute alveolar damage was present until 14 dpi with persistence of viral RNA (Figures 1c, 2g-i and S2), indicating overall slower recovery than described for Syrian hamsters. Similarly, viral RNA was localized by in situ hybridization to bronchial epithelial cells, alveolar epithelial cells type-I and type-II and alveolar macrophages (Figure S2, arrows).

In agreement with the clinical course of disease, virological and histopathological results confirm that this animal model withstands the comparison with the Syrian hamster model with the advantage of a prolonged period of significantly reduced body weights following infection with SARS-CoV-2. Moreover, the considerably smaller size of the Chinese hamster offers an important practical advantage when compared to the rather large Syrian hamster and allows husbandry in smaller cages and larger groups. Additionally, the Chinese hamster genome, transcriptome and translome are well characterized and a variety of molecular tools is available for this species as Chinese hamster ovary (CHO) cells are widely used in biopharmaceutical research and industry (Matasci et al., 2008; Walsh, 2018). At the same time, the usefulness of any model depends on fundamental knowledge of species-specific similarities to and differences from the human disease, as well as other confounding factors, including age and comorbidities (Metersky & Waterer, 2020). Because of the heterogeneous disease phenotype in humans, there is a need for different SARS-CoV-2 animal models that allow evaluation of vaccines and antiviral therapies for different subsets of the human population.

Taken together, our results suggest the suitability of the Chinese hamster small animal model to study SARS-CoV-2 infections, with body weight losses as a robust clinical disease parameter. As an established model for SARS-CoV-1 infection, the Chinese hamster may also allow comparison between experimental coronavirus infections. Moreover, our findings highlight the possibility of comparing, in future studies, the effects of preventive as well as therapeutic measures to restrain infection and viral replication in different animal models.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

NO and JT were involved in conceptualization. LDB, DV, KD, AA, ADG and JT were involved in investigation. LDB, DV, KD, ADG, NO and JT were involved in writing. All authors were involved in editing and had the opportunity to comment on the draft manuscript.

ETHICAL APPROVAL

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to, and the appropriate ethical review committee approval has been received. Animal experimentations were approved by the Landesamt für Gesundheit und Soziales in Berlin, Germany (AUP number 0086/20) and performed in compliance with relevant national and international guidelines for care and humane use of animals. All in vitro and animal work was conducted under appropriate biosafety conditions in the BSL-3 facility at the Institute of Virology, Freie Universität Berlin, Germany.

DATA AVAILABILITY STATEMENT

All data relevant to this study are included in the manuscript and supplementary information.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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