Article

Pathogenicity of SARS-CoV-2 Omicron BA.5 and BE.1 variants in Syrian hamsters and hACE2-transgenic mice

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Abstract: A new variant of the SARS-CoV-2 Omicron BA.5 virus has displaced all previous variants of the virus around the world. Preliminary assessment of the effectiveness of drugs for the prevention and treatment of COVID-19 requires the availability of infection models in animals. In this study, we characterize the infection model SARS-CoV-2 Omicron BA.5 and its progeny sublineage BE.1 in hACE2-transgenic mice and in Syrian hamsters. Both sublineages turned out to be pathogenic for animals – the challenged animals showed weight loss, a high level of viral load and acute inflammation in the lungs. Part of BA.5-infected mice died after virus challenge, indicating that this virus variant is more pathogenic than the previous BA.1 variant but less pathogenic than Wuhan variant.

Keywords: SARS-CoV-2, Omicron BA.5, Omicron BE.1, animal model

1. Introduction

The SARS-CoV-2 virus actively mutates, which leads to the emergence of new variants of the virus. Today, a number of mutations in the glycoprotein are known to increase the binding affinity for the ACE2 receptor and reduce the neutralizing activity of antibodies. Until the beginning of March 2022, the Alpha, Beta, Gamma, Delta and Omicron variants were classified by WHO as VOC. On June 7, 2022, the list of VOCs was revised by the WHO Commission, and today only the Omicron variant is included in the VOC [1]. Phylogenetic analysis of genome-wide sequences, as well as amino acid sequences of the S-protein and RBD-domain, shows that the Omicron variant is genetically significantly removed both from the original SARS-CoV-2 variant and from all previous VOCs [2]. Moreover, a lot of studies confirm the weak cross-reactivity of the immune response formed to the variants of the virus from Alpha to Delta, in relation to the Omicron variant, as well as cross-reactivity in the opposite direction [3, 4]. The Omicron variant shows sufficient genetic and structural distance from other SARS-CoV-2 variants, that suggests the possibility of separating the Omicron variant and its sub-lineages into a separate SARS-CoV-2 serotype [5]. Today we are already seeing the second wave of COVID-19 associated with the Omicron variant. At the end of 2021 – beginning of 2022, the COVID-19 wave was associated with the Omicron variant of the BA.1 and BA.2 sublines. Novel wave is associated with the spread of the Omicron variant sublineage BA.5.

The emergence and spread of new variants require an assessment of the protective efficacy of vaccines and therapeutics in animal studies. Thus, COVID-19 models based on

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ACE2-transgenic mice and Syrian hamsters are used to evaluate the effectiveness of COVID-19 vaccines and therapeutics. Animals are challenged with the SARS-CoV-2 VOC against which the vaccine or therapeutics protection activity is planned to be evaluated. Previous studies showed that first sublineage of Omicron variant was significantly less pathogenic for animal models [6] that greatly complicates the assessment of protection activity of different drugs. Emergence of a new Omicron sublineage BA5, replacement of previous Omicron sublineages made it obvious that it is extremely important to evaluate BA.5 pathogenicity and lethality in animal models for the subsequent assessment of the vaccines and therapeutics effectiveness studies.

Here we report data of the Omicron BA.5 variant pathogenicity in Syrian hamsters and in ACE2 transgenic mice.

2. Materials and Methods

2.1. Viruses

The viruses SARS-CoV-2 Omicron BA.5 and BE.1 were isolated from a nasopharyngeal swab and sequenced (S hCoV-19/Russia/SPE-RII-25357S/2022 and hCoV-19/Russia/MOW-PMVL-LSCV-AC2906/2022). For comparison study of survival rate of transgenic mice challenged with Omicron BA.5, BA.1 and Wuhan variants we used SARS-CoV-2 virus B.1.1.1 (Wuhan D614G hCoV-19/Russia/Moscow_PMVL-1/2020) and B.1.1.529 BA.1 (hCoV-19/Russia/MOW-Moscow_PMVL-O16/2021). Isolation and production of the viruses was carried out on Vero E6 cells, the virus titer was determined by $TCID_{50}$ using the Reed–Muench method. All studies using the virus were conducted in BSL-3 facilities.

2.2. Studies in hamsters and mice

All studies were approved by the Biomedical Ethics Committee of the Gamaleya Center (Protocol No. 24, 21/04/22). The study used 12 Syrian hamsters (90-110 g) and 46 hACE2-transgenic mice (20-25 g). Hamsters were obtained from the Nursery for laboratory animals Pushchino, mice were obtained from crossing transgenic males B6.Cg-Tg(K18-ACE2)2Prlmn/J (Jackson Laboratory, SOPF) and non-transgenic C57BL/6 females (SPF). Animals were housed in the Tecniplast Isocage N system and had free access to food and water. Animals were infected intranasally under inhalation anesthesia: hamsters were challenged with $2x10^5$ $TCID_{50}$, mice - $5x10^4$ $TCID_{50}$. After challenge, the dynamics of the weight of animals was assessed for 21 days, as well as the viral load, macroscopic and histopathological analysis in the lungs of infected animals on the 4th day after infection. In comparison study of survival rates in transgenic mice challenged with BA.5, BA.1 and Wuhan variants, animals were infected intranasally under inhalation anesthesia with 10^5 $TCID_{50}$. After challenge, the dynamics of the weight and survival of animals was assessed for 21 days

2.3. Determination of viral load in the lungs of infected animals

Viral load was determined in 10% organ homogenates prepared using an MPbio homogenizer. To determine the titer of the infectious virus, the homogenates were titrated in 10-fold steps in Vero E6 cells, the development of the cytopathic effect in the cell monolayer was recorded visually after 96 hours. The virus titer was determined by the method of Reed and Mench. To determine the viral load by PCR, RNA was isolated from 10% organ homogenates using the QIAamp® Viral RNA Mini Kit. PCR was performed using the Polivir SARS-CoV-2 Express kit (Lyteh, Russia). Determination of the concentration of viral RNA in the samples was carried out using a calibration curve based on 10-fold dilutions of virus RNA with a known concentration in the same PCR. Primers for the mouse and hamster beta-actin gene were used to control RNA isolation (mice: F: CTATTGGCAACGAGCGGTTC, R: CGGATGTCAACGTCACACTTC, P: ROX-GCTCTTTTCCAGCCTTCCTTCTTG-BHQ2; hamsters: F: ACTGCCGCATCCTCTTCCT, R: TCGTTGCCAATGGTGATGAC, P: FAM-CCTGGAGAAGAGCTATGAGCTGCCTGATG-BHQ1 [7]).

2.4. Morphological study

Lungs from each mouse were fixed in 10% neutral buffered formalin (Soluformtm, JLSChemical, Russia) at +4°C, dehydrated in isoprepe (BioVitrum, Russia) using Microm

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STP 120 (Thermo Scientific, USA), and embedded in HISTOMIX (BioVitrum, Russia) using HistoStar workstation (Thermo Scientific, USA). 3-μm thick sections were cut using a Finesse ME+ microtome (Thermo Scientific, USA), stained with hematoxylin and eosin and mounted in Vitrogel (all BioVitrum, Russia). Pictures were obtained using Histoscan Leica Aperio CS2 and microscope Leica DM2000 with an camera (Leica, Germany) at 10x, 20x and 40x magnification.

2.5. Statistical analysis

Statistical analysis was performed in GraphPad Prism 9 software (v. 9.4.0, GraphPad, USA). The normality of data distribution was analyzed using the Shapiro-Wilks test. Depending on the normality, t-test or the Mann-Whitney test for unpaired samples. Differences were considered significant at $p < 0.05$.

3. Results

3.1. Challenge with Omicron BA.5 and BE.1 variants leads to weight loss and viral replication in infected hamsters and transgenic mice

hACE2-transgenic mice (8 animals per virus variant) and Syrian hamsters (6 animals per virus variant) were challenged intranasally with SARS-CoV-2 Omicron BA.5 and BE.1 at doses $5x10^4$ $TCID_{50}$ per mice and $2x10^5$ $TCID_{50}$ per hamster. Challenge with SARS-CoV-2 Omicron BA.5 led to weight loss in hACE2-transgenic mice and Syrian hamsters with maximum on days 10 and 6, respectively (fig.1AB). Notably, half of BA.5-challenged hACE2-transgenic mice died till day 11 after virus challenge. Challenge with SARS-CoV-2 Omicron BE.1 also led to weight loss of animals with maximum at day 6 after challenge, but the level of weight decrease was not such significant as in groups challenged with SARS-CoV-2 Omicron BA.5 ($p=0.0025$ at day 10). No lethal cases in BE.1-challenged hACE2-transgenic mice was detected.

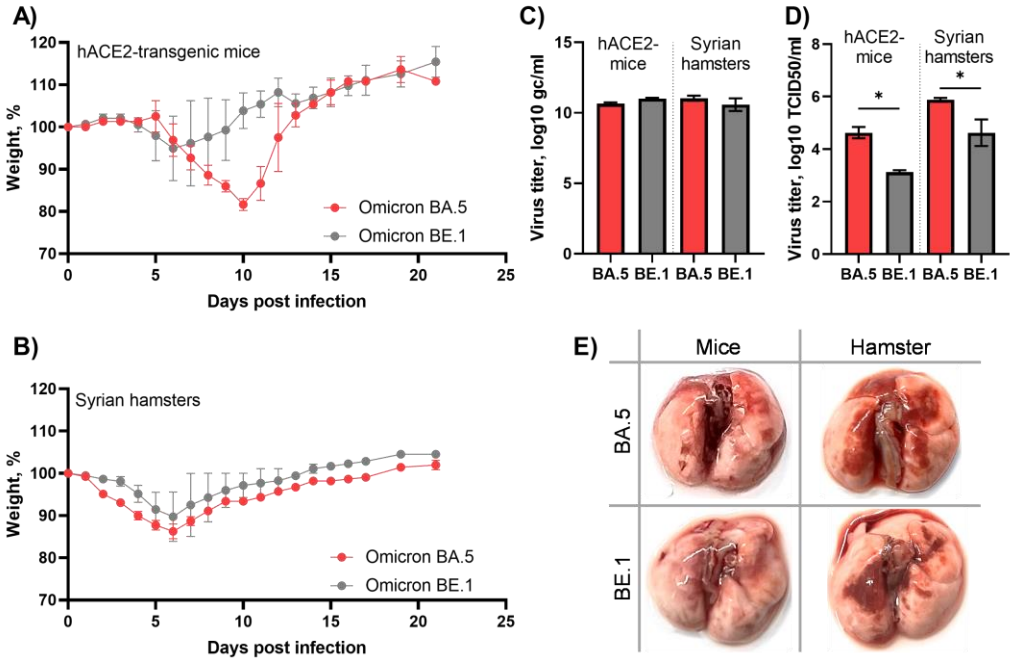

Figure 1. Weight dynamics of infected hACE2-transgenic mice (A) and Syrian hamsters (B) (mean±SEM), and viral load in lungs on day 4 (c – in genome copies, d – in TCID50), mean±SEM, *-$p<0.05$. E – photo of lungs of animals at day 4 after challenge with SARS-CoV-2 Omicron BA.5 and BE.1. Challenge doses: mice - $5x10^4$ $TCID_{50}$, hamsters - $2x10^5$ $TCID_{50}$.

Four days after the challenge, half of the animals were euthanized and macroscopic and histopathological analysis in the lungs and viral load were assessed. Viral load analysis showed that both animals were suspectable to SARS-CoV-2 Omicron BA.5 and BE.1 infection (fig.1CD). Despite the fact that no difference in viral load was detected between two Omicron sublineages by Real-Time PCR analysis, we found that infectious viral titer

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was higher in animals challenged with Omicron BA.5 (fig.1D). Infectious titer analysis appeared to be more indicative in viral load analysis than Real-Time PCR analysis. In the lungs of infected animals, multiple lesions in the form of hyperemia and hemorrhages were observed (fig.1E) especially in lungs of challenged hamsters.

We also performed comparison study of survival rates of Omicron BA.5, Omicron BA.1 and Wuhan variants. hACE2-transgenic mice (10 animals per virus variant) were challenged intranasally with SARS-CoV-2 Wuhan, Omicron BA.1 and BA.5 at doses 10^5 $TCID_{50}$ per mice We showed that after challenge with the Omicron BA.5 variant, weight loss of mice reached a maximum on the 10th day post infection, in contrast to the Wuhan variant, where the weight of animals began to decrease much earlier. It was also shown that intranasal challenge with Omicron BA.5 with a dose of 10^5 $TCID_{50}$ resulted in the death of 60% of infected animals (fig.2). Notably, 100% of animals challenged with Wuhan variant and none of animals challenged with Omicron BA.1 variant died. Thus, the Omicron BA.5 variant in terms of pathogenicity is in an intermediate position between the Wuhan and Omicron BA.1 variants: the animals demonstrate clinical signs of infection (weight loss), but the mortality rate is about 60%.

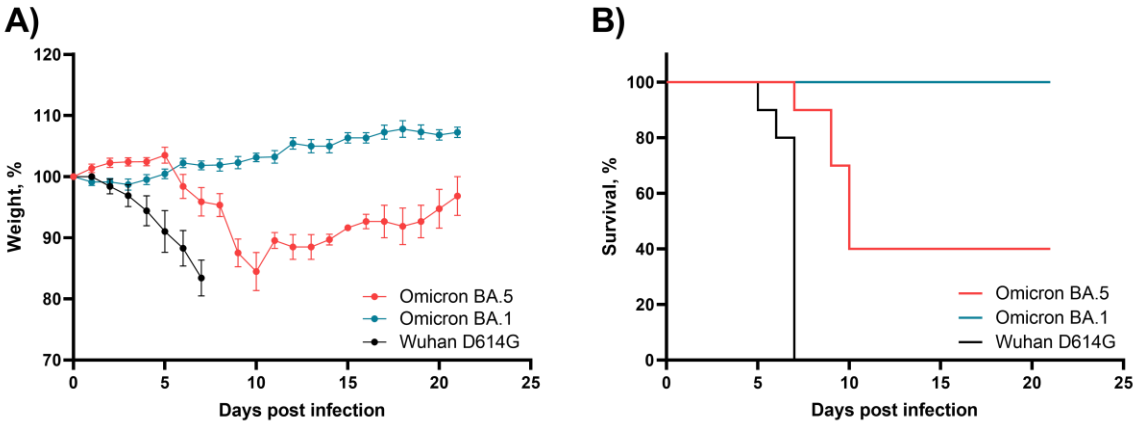

Figure 2. Weight dynamics (A, mean±SEM) and survival rates (B) of hACE2-transgenic mice challenged with 10^5 $TCID_{50}$ SARS-CoV-2 Omicron BA.5, Omicron BA.1 and Wuhan D614G variants.

3.2. Histopathological findings in the lungs of SARS-CoV-2 Omicron BA.5 and BE.1 challenged hACE2-transgenic mice and Syrian hamsters

In the lungs of hACE2-transgenic mice and Syrian hamsters after intranasal infection with SARS-CoV-2 Omicron BA.5 and BE.1, especially in hamsters, perihilar damage was noted, which was centrifugal in nature - from the bronchi to the respiratory section (lung periphery) and was accompanied by a heterogeneous bronchointerstitial lesion: from large bronchi to terminal bronchioles, weak (in mice) and moderate (in hamsters) intraluminal, intraalveolar and interstitial infiltration by neutrophils and macrophages, as well as perivascular lymphocytes (in the form of a "cuff") (fig.3).

In addition, in hamsters infected with SARS-CoV-2 Omicron BA.5, moderate regenerative hyperplasia and stratification of the single-layer bronchial epithelium (like squamous metaplasia) were found. Diffuse alveolar damage was less pronounced and was characterized by foci of desquamation of the alveolar epithelium, mild edema, and the presence of single neutrophils. The interalveolar septa wee narrowed. Moderate inflammatory infiltration, predominantly lymphocytic, was observed in the peribronchial space. The vascular component of the lungs demonstrated pathognomonic morphological signs of infection, such as: edema of the endothelium of medium-sized arteries and veins, vacuolization, necrosis and detachment with subendothelial and perivascular accumulations of monomorphonuclear cells and single neutrophils, transmural extravasation of immune cells.

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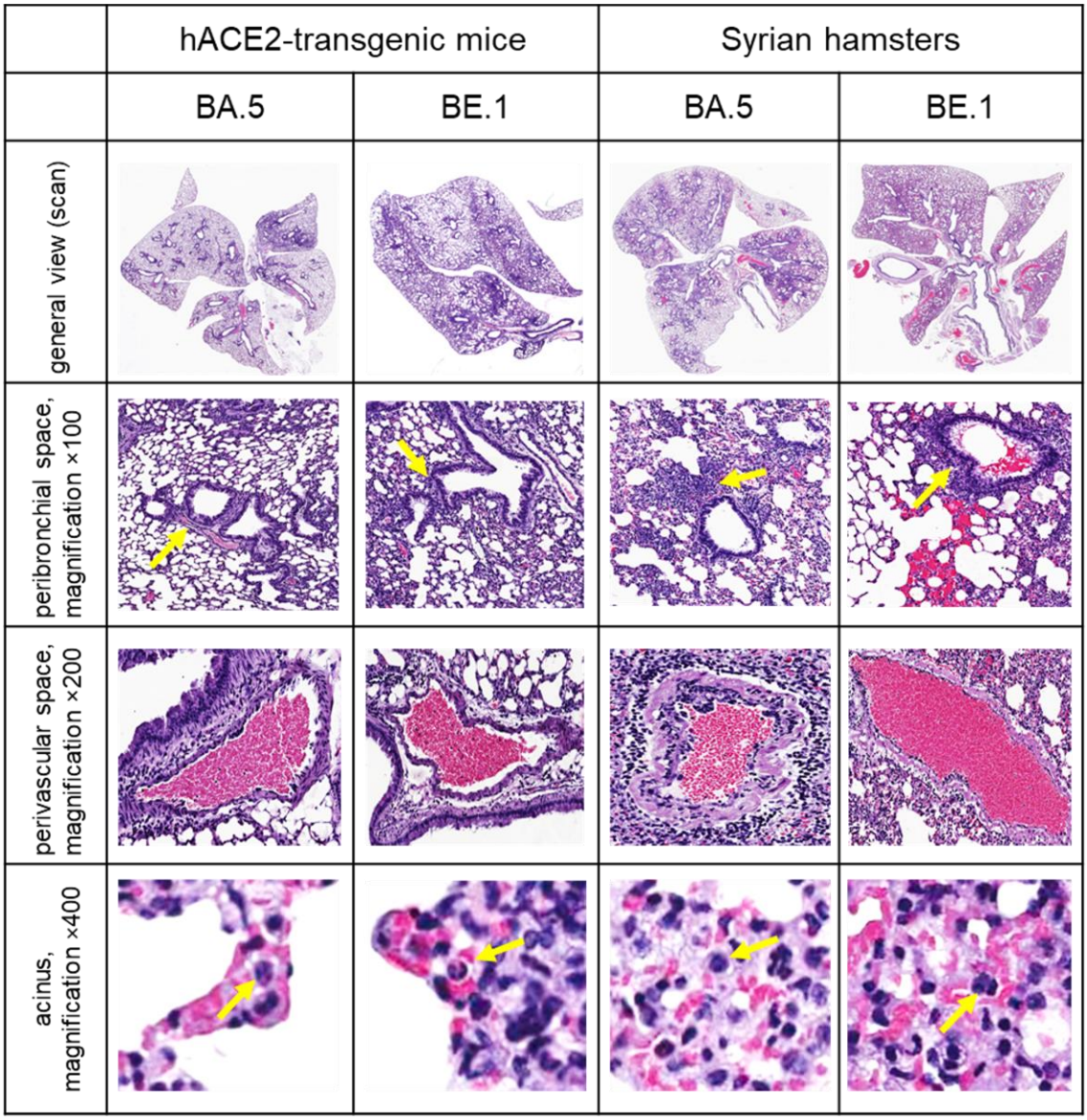

Figure 3. Histopathological changes in the lungs hACE2-transgenic mice and Syrian hamsters at day 4 after challenge with SARS-CoV-2 Omicron BA.5 and BE.1. Stain: hematoxylin and eosin (H&E). Lung parenchyma with signs of dystelectasis, airiness (aeration area) is reduced over a large area. Arrows indicate foci of peribronchial and perivascular inflammation ranging from mild (mice challenged with BE.1) to moderate (hamsters challenged with BA.5). Plethora of blood vessels and hemocapillaries.

Acute inflammation in the lungs and inflammation of the peribronchial and perivascular spaces were also assessed (Table 1). As part of the assessment of acute inflammation, the following indicators were analyzed: neutrophils in the alveolar space, neutrophils in the interstitial space, proteinaceous debris filling the airspaces and alveolar septal thickening. Inflammation analysis revealed that a similar level of inflammation was detected in the lungs of mice infected with the BA.5 and BE.1 sublineages, while analysis of hamster lungs revealed that the level of inflammation of the lung tissue was higher in the lungs with BA.5 than with BE.1.

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Table 1. Acute inflammation in the lungs and inflammation of the peribronchial and perivascular spaces

	Score			
	hACE2-transgenic mice		Syrian hamsters	
	BA.5	BE.1	BA.5	BE.1
Acute lung inflammation				
Neutrophils in the alveolar space	2	1	3	2
Neutrophils in the interstitial space	2	2	4	3
Proteinaceous debris filling the airspaces	0	0	1	0
Alveolar septal thickening	2	2	4	2
TOTAL:	6	5	12	7
Peribronchial and perivascular inflammation				
Peribronchial space	2	2	4	3
Perivascular space	2	2	4	3
TOTAL:	4	4	8	6

4. Discussion

Various studies have shown a decrease in the effectiveness of existing vaccines against new variants of the SARS-CoV-2 virus [8-10]. SARS-CoV-2 Omicron variant shows a decrease in the pathogenicity in animal models [11-12]. Variant Omicron sublineage BA.5 were first detected in South Africa in February 2022 [13]. A decrease in the pathogenicity of the virus for model animals may limit the possibility of studying the protective efficacy of drugs for the prevention and treatment of COVID-19.

Previous studies in hamsters have shown the pathogenicity of the BA.5 variant compared to Delta, BA.2 and BA.4 [14]. In the study, no significant weight loss was found after challenge with variants BA.2, BA.4 and BA.5. Also, there were no significant changes in the lung tissue of infected animals. At the same time, after infection with the Delta variant, there was a significant weight loss 7 days after infection (-7.6%) and significant damage in the lungs. The replicative activity of the virus has been shown by analysis of plaque-forming units in lung tissues and in turbinates. A decrease in the replicative activity of the BA.2, BA.4 and BA.5 variants was shown compared to the Delta variant [14]. In another study, the BA.4/5 variant was shown to be more pathogenic in hamsters than BA.2. [15].

This study demonstrated the course of the disease caused by the SARS-CoV-2 virus variant Omicron BA.5 and BE.1 in Syrian hamsters and in hACE-2 transgenic mice. Despite moderate damage in lung tissues, BA.5 cause partly lethal outcomes (up to 60% in transgenic mice challenged with 10^5 $TCID_{50}$) in hACE2-transgenic mice model and no lethal outcomes in Syrian hamster model. Peak weight decline was 14% at day 6 in Syrian hamsters and 18% at day 10 in hACE-2 transgenic mice after challenge with SARS-CoV-2 Omicron BA.5. Both Omicron sublineages demonstrated viral reproduction in lungs of challenged animals, but the level of BA.5 was higher than the level of BE.1. Analysis of the infectious virus titer showed that the viral load in BA.5-challenged animals was significantly higher than in BE.1-challenged animals. This observation can be compared with the lethality of these viruses for hACE2-transgenic mice: we detected lethality in BA.5-challenged mice and no lethality in BE.1-challenged mice. Apparently, the BA.5 virus was able to reproduce more efficiently in the cells of hACE2-transgenic mice, which led to a more severe course of the disease and death. The revealed pathomorphological changes in the lungs (early bronchointerstitial pneumonia, diffuse interstitial pneumonia, endotheliitis) indicated the pathogenicity of the SARS-CoV-2 Omicron BA.5 and BE.1 virus for hACE2-transgenic mice and Syrian hamsters. Comparative study of pathogenicity of Omicron BA.1 and Omicron BA.5 variants showed that Omicron BA.5 variant was more

pathogenic than the previous BA.1 variant: we detected significant weight loss and partial lethality in BA.5-challenged group in comparison to BA.1-challenged group where no weight loss or lethality was detected.

Interestingly, the Omicron BA.5 and BE.1 sublineages differ only in the substitutions of two amino acids at positions ORF1a:L3829F and ORF1b:M1156I, while we showed a significant difference in pathogenicity: challenge of mice with the Omicron BA.5 led to the partial lethality of animals, which was not observed after challenge with Omicron BE.1. Moreover, the Omicron BA.5 variant led to more severe damage in the lungs than BE.1. This may be due to the peculiarities of virus replication: despite comparable levels of viral load in the Real-Time PCR analysis, we showed a different viral load in the infectious titer analysis - in groups BE.1-challenged animals it was lower. This makes it obvious that there is a need for further study of SARS-CoV-2 non-structural proteins, the impact of mutations in these proteins on virus replication and spread. Understanding the fundamental principles of the SARS-CoV-2 pathogenesis will help in the future to develop and obtain highly effective drugs for the treatment and prevention of COVID-19 and other coronavirus infections.

In summary, our data shows that BA.5 can efficiently reproduce in the lungs of hACE2-transgenic mice and Syrian hamsters, leading to extensive damage to lung tissue, causing severe respiratory illness and death of animals (hACE2-transgenic mice). We found that lung damage and viral load were generally greater in hamsters than in hACE2-transgenic mice, despite the BA.5 variant being lethal in hACE2-transgenic mice. Based on this, we can assume that both animal models can be used in the study of the effectiveness of drugs for the prevention and treatment of COVID-19: Syrian hamsters can be used for lung damage and viral load analysis, and hACE2-transgenic mice - for weight dynamics and survival analysis.

Author Contributions: ID - performed research, coordination of study, statistical analysis, manuscript preparation. DG, IZ - animal challenge experiments. AK (Anna Kovyrshina), AI, AB - virus isolation, determination of virus titer and viral load in lungs. NK, AP, VG, AK (Andrei Komissarov), DD, DL (Dmitry Lioznov) - next generation sequencing. GD, AS, AN - histopathological analysis. AT, DS – manuscript preparation, editing. DL (Denis Logunov), AG - organization of the study, editing, final decision to submit for publication. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: All authors declare no competing interests.

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