

Laboratory Mouse & COVID-19 Research

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ABSTRACT

SARS-CoV-2 (COVID-19) rapidly spread and led to an outbreak in China and then became a global health emergency. The scientific community importance around the world is evident by investigation for new knowledge, treatments and a vaccine against COVID-19. An important biomodel in this intense research is mouse lab. However, standard murine models, currently available, are resilient to COVID-19 infection experimental. Thus, laboratory animal science researchers' mice transgenic (humanized) developed and enable this biomodel susceptible, therefore, able to collaborate in efforts to control this tragic pandemic. In this review, the objective was to summarize, mainly by the most important animal laboratories, specialized in breeding and genetic manipulation science and to demonstrate to the researchers the possibilities of developing in vivo assays using the mouse lab biomodel in pre-clinical trials against COVID-19.

INTRODUCTION

In late 2019, a novel coronavirus (first: 2019-nCov, then: SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases, which infected a lot of people in Wuhan, a city in the Hubei province of China [1]. SARS-CoV-2 (COVID-19) rapidly spread and led to an outbreak in China and then became a global health emergency. Although control measures and isolations have been applied for prevention, the infection has increased and caused a pandemic [2]. Although this virus belongs to a relatively well-known viral family, Coronaviridae and is similar to viruses that caused severe acute respiratory syndrome (SARS), which had an outbreak in 2002, and Middle East respiratory syndrome (MERS), which had an outbreak in 2012. The COVID-19 in some characteristics, there are a lot of uncertainties and unknown specifications about this virus such as its origin and source of infection, its emergence, and its mechanism of action and transmission [3-6].

PATHOLOGY

Human pathogenic coronaviruses COVID-19 bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is

express by epithelial cells of the lung, intestine, kidney, and blood vessels [7]. The expression of ACE2 is substantially increased, mainly, in hypertensive patients and with type 1 or type 2 diabetes, who are treated with ACE inhibitors and angiotensin II (ANG II) type-I receptor blockers (ARBs) [8,9]. Hypertension is also treated with ACE inhibitors and ARBs, which results in an upregulation of ACE2 [9]. These data suggest that ACE2 expression is increase in diabetes and treatment with ACE inhibitors and ARBs increases ACE2 expression. Consequently, the increase expression of ACE2 would facilitate infection with COVID-19. We therefore hypothesis that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19 [10].

REVIEW OBJECTIVE

The mouse (*Mus mus musculus*) is the most used species for scientific purposes. Its genetic homology of 97 to 99%, its short life cycle, ease of maintenance in research facilities, among other characteristics are factors that make this biomodel used in

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research on immunology, physiology, oncology and discoveries of new therapies and vaccines. However, in relation to COVID-19, this model, the strains generated and most common are resilient to coronavirus infection. In this review, we will demonstrate a compilation of the knowledge and development of transgenic mice available for use in the study of the experimental infection of COVID-19.

MOUSE BIOMODEL

COVID-19 uses the ACE2 protein to enter cells [11]. In vitro studies showed that ACE2 from many species facilitated entry into HeLa cells, but mouse ACE2 did not [12]. This poses a challenge for mouse studies of COVID-19, and there is one report that SARS-CoV-2 cannot replicate in the outbred ICR mouse stock following intranasal inoculation.

Standard Mouse Strains

Mouse-adapted COVID-19 lineages induce clinical illness in BALB/c mice, with similar disease characteristics as seen in humans. When mouse-adapted COVID-19 isolates become available, inbred mice may be useful for studies of vaccines, antiviral drugs and disease pathogenesis [13]. Inbred mice have been used extensively in SARS studies. Young inbred mice such as BALB/c, C57BL/6 and 129S6 support viral replication of SARS-CoV and may be useful for COVID-19 vaccine and antiviral studies even without supporting development of disease. They may also be useful in studying immune responses to infection [14]. In contrast to young mice, 12-14-month-old BALB/c mice develop clinical illness including patchy interstitial pneumonia following SARS infection and may be useful to model the age-related mortality increase seen in humans seen in COVID-19. Aged C57BL/6 and 129S6 mice may also be useful to study age-related mortality increases, but with lower viremia compared to BALB/c based on SARS research [14]. C57BL/6 mice have been used in various models of acute lung injury, and these models may be useful for studies directed at treating ARDS associated with COVID-19.

Genetically Engineered Models (GEMs)

Human ACE2 expression: Transgenic mice expressing human ACE2 are likely to be critical for animal studies of COVID-19. Bao et al. reported that transgenic hACE2 mice developed clinical illness following SARS-CoV-2 infection, including weight loss and interstitial pneumonia [15].

Ace2 knockout: Acute respiratory distress syndrome (ARDS) is a serious complication of COVID-19 and present in a large percentage of COVID-19 deaths. ACE2 is protective against ARDS. Binding of viral spike SARS protein to ACE2 in mice downregulates ACE2 expression. Loss of ACE2 expression is associated with severe lung failure. ACE2 knockout mice have been used in ARDS and SARS research and may be useful for study of COVID-19-related ARDS [16,17].

Tmprss2 knockout: TMPRSS2 is involved in SARS-CoV-2 entry into cells. Inhibition of this protein may constitute a treatment/prophylaxis mechanism. Tmprss2 knockout mice may be useful in studying COVID-19 disease pathogenesis [18].

Stat1 knockout: Stat1 knockout mice support SARS-CoV viral replication in the lungs and develop progressive lung disease including diffuse interstitial pneumonia with inflammation and systemic spread to other organs. These mice may be useful to study COVID-19 disease pathogenesis and antiviral treatments [19].

Perlman's mice: These mice, unlike normal mice, are susceptible to SARS. In humans, the virus' spike protein attaches to the ACE2 receptor on epithelial cells and enters the lungs. But coronaviruses like SARS-CoV and COVID-19 do not infect your normal laboratory mouse- or, if they do, it's at a very low rate of infection and the virus doesn't replicate readily. That is because the virus' spike protein does not recognize the regular lab mouse's ACE2 receptor. So, the mice are relatively protected.

Perlman made the mice susceptible by introducing into them the gene for the human ACE2 receptor. So now, in addition to the mouse ACE2 receptor, you have the human ACE2 receptor being made in these mice, making it possible for the coronavirus to enter the lungs. Perlman, in a 2007 paper about these mice, recognized that SARS was not the first coronavirus, and it was not going to be the last [20].

Humanized Immune System Mice

This biomodel offer a small animal model engrafted with human immune cells. Immunodeficient NOG mice engrafted with human peripheral blood mononuclear cells (model huPBMC-NOG) have been used to study SARS vaccine response. Humanized immune system mice may be useful for studies into human immune system response to infection and/or vaccine response.

CONCLUSION

During normal times, no profit biomedical research institution serves as a leading supplier of research mice to labs around the world. It breeds, maintains and distributes more than 11,000 strains of genetically defined mice for research on a huge array of disorders: common diseases such as diabetes and cancer through to rare blood disorders such as aplastic anaemia. But these are not normal times. The COVID-19 pandemic has skyrocketed the demand for new lineage of mice to help scientists understand the progression of the disease, test existing drugs, find new therapeutic targets and develop vaccines. At the same time, with many universities scaling back employees on campus, the coronavirus crisis forced labs studying a broad range of topics to cull their research animals, many of which took years to breed and can take equally long to recoup.

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