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COMMENTARY

Selection of animal models for COVID-19 research

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Abstract The researcher community across the globe is on a search for a promising animal model that closely mimics the clinical manifestation of SARS-CoV-2. Though some developments were seen such as serial adaptation in various animal species or the creation of genetically engineered models, a suitable animal model remains elusive. A model that could display the severity of human illness and can be used for the fast-track evaluation of potential drugs as well as for the clinical trials of vaccines is an urgent need of the hour. In the light of huge information generated on SARS-CoV-2 and daily updates received from the research community, we have chosen to review the current status of animal models of SARS-CoV-2 in encompassing the areas of viral replication, transmission, active/passive immunization, clinical disease, and pathology. The review is intended to help the researchers in the selection of appropriate animal models for SARS CoV-2 research in the fight against the current global pandemic.

Keywords Animal models · SARS-CoV2 · Macaques · Transgenic mice · Immunogenicity · Antiviral · Vaccines

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Introduction

Emerging and re-emerging coronavirus outbreaks and nonavailability of vaccines and antiviral therapy for the recent worldwide pandemic of SARS-CoV-2/COVID-19, across the world, has encouraged the interdisciplinary collaborative efforts based on the concept of a "One Health approach" between human health, veterinary medicine, and environmental sciences [27]. The unpredictable nature of these viruses in terms of host transmission [2, 35], interspecies shift [8], evasion from host responses [11], high adaptation and relapsing nature [1] have severely hampered the evaluation of therapeutic modalities against these agents directly in humans. To recognize the epidemiology of various factors that contribute to the diseases, the use of various animal models of disease is of paramount importance for vaccine or antiviral therapy. In this article, we explored the animal models that can be used to study SARS-CoV-2 pathogenesis with the primary aim of the evaluation of antiviral therapies and vaccines.

Requirements of an animal model against highly pathogenic viruses

Direct clinical trials on humans for highly pathogenic viruses are not feasible and also not ethically permitted without prior preclinical studies. Therefore, animal studies

play an essential role in characterizing the viral pathogenesis and evaluation of antiviral agents and vaccines for these viruses. The ideal animal models should be permissive to infection and must reproduce the clinical course and pathology observed in humans [30]. A disease animal model can truly replicate the type of human disease as closely as possible in immunocompetent animals with a challenge dose and with a suitable exposure route that can be administered in humans. The animal model should be customized to the goals of the study. The model should replicate the key aspects of the disease. The availability of immunological reagents and the demographic background of animals should be taken into consideration. In addition to assessing vaccine/antiviral efficacy, the studies must demonstrate meaningful differences between vaccinated and unvaccinated control groups followed by detectable immunological responses to animals from different demographic backgrounds to the vaccine/antiviral under investigation [16].

Different animal models used

Mouse models

One of the best mouse models used for COVID-19 is the K18-hACE2 transgenic mouse. A transgene of human ACE2 (hACE2) expression is driven into the mouse epithelial cells under the control of the human cytokeratin 18 (K18) promoter [24]. K18-hACE2 mice when treated with doses of SARS-CoV (2.3×10^4 PFU) that induced severe lung damage and neuronal damage of CNS in transgenic mice. But it did not induce CNS pathology in nontransgenic mice. The transgenic mice showed replication of the virus in the lungs, had weight loss, and developed pathological lung inflammation, and died at 4 days post-infection. However, a recent study showed that SARS-CoV-2 can infect K18- hACE2 mice in a transgene-dependent manner [4]. SARS-CoV-2 at 10^5 $TCID_{50}$ caused weight loss, evoked antibody responses, and developed histological evidence of lung inflammation in a K18-hACE2 transgene-dependent manner with interstitial congestion, inflammatory exudate, epithelial damage, etc. [4, 24]. Additional transgenic mouse strains have been developed to express hACE 2 using various promotors. HFH4-ACE2 transgenic mice developed using the human HFH4 promoter [19], AC70 transgenic mice developed using CAG promoter [36], and mouse ACE2 promoter-driven hACE2 Tg mice using mouse ACE2 promoter [34]. The above ACE2 transgenic mice models will be useful to study on SARS-CoV-2 replication in the lungs and its pathogenesis.

The limitation in these ACE2 transgenic mouse model is its lethal effects caused by neuroinvasion affecting CNS. The other limitations are its limited availability and the comparatively long breeding time.

An adeno-associated virus (AAV) delivery based mouse model that expresses the SARS-CoV-2 receptor in the mouse lungs [14, 15, 29] was developed to study SARS-CoV-2 pathogenesis. The model was a more efficient and rapid, and reproducible murine model for SARS-CoV-2. The limitations are that this model artificially expresses ACE2 in non-relevant cell types in the mouse respiratory system making pathology and immune response data hard to interpret in the situation of human SARS-CoV-2 infection. However, this model can be suitable for drug therapy and antibody testing.

SARS-CoV-2 cannot infect wild type and laboratory inbred mouse strains due to incompatible interactions between the viral spike (S) protein and the murine ortholog of the human receptor, ACE2. Standard inbred mouse strains such as BALB/c, C57BL/6 cannot be directly used for the studies. Nevertheless, these mouse strains by adaptation can be used to study the development of neutralizing antibodies against the spike protein, pseudo viral vaccine candidate, and antiviral drugs [32]. However, a mouse model was developed using a clinical isolate of SARS-CoV-2 by serial passaging in the respiratory tract of aged BALB/c mice [14]. The resulting mouse-adapted strain showed marked infection in mouse lung leading interstitial pneumonia and inflammatory responses after intranasal inoculation. In another study, reverse genetics was used to develop a mouse model using inbred BALB/c mice where the interaction between S and mACE2 was remodeled resulting in a recombinant virus (SARS-CoV-2 MA) that utilized mACE2 for entry in BALB/c mice. The SARS-CoV-2 MA replicated well in adult and aged BALB/c mice causing more severe infections in aged mice. It was concluded that this model is more clinically relevant phenotypes than HFH4-hACE2 transgenic mice [10].

Besides the above transgenics mouse, a few knock out mouse model has been developed to understand the pathology of SARS-CoV-2. Among them, $ACE^{-/-}$ knockout mice can be used to study the effects of Angiotensin conversion enzyme during acute lung injury study [17]. Using $TMPRSS2^{-/-}$knockout mice the role of TMPRSS2 during SARS-CoV entry into cells can be studied for new drugs against SARS-CoV-2 infections [18]. Humanized DPP4 mice and $STAT\text{-}1^{-/-}$knockout mice having susceptibility coronavirus infection and used as a model for MERS can help in SARS-CoV-2 also [12, 22].

Hamsters

Sia et al., 2020 opined that the Goldern syrian hamster is a good model for the study of COVID- 19. Golden Syrian hamsters after infection with the SARS-CoV-2 virus

showed weight loss, efficient viral replication in the nasal mucosa, and epithelial cells of the lower respiratory system. The virus was shown to be transmitted from the naive to co-housed animals either by aerosols or by fomites. The infected hamsters also generated neutralizing antibody responses in response to SARS-CoV-2 infection [28]. A significant drawback with hamster was that 14 days post-infection, the lung pathology had resolved to normalcy. Hamsters can be used to study mild SARS-CoV-2 infections in humans and host defense response to the virus [5].

Ferrets

Ferrets have previously been used as a good model for the study of viral diseases especially for respiratory pathogens like influenza. For studying SARS-CoV-2 the animals were inoculated with the virus and found to develop similar symptoms as in humans within 2 and 12 days post-infection [20]. Histologically, SARS-CoV-2 infected ferret lungs have exhibited severe pulmonary lymphoplasmacytic perivasculitis and vasculitis at 13 days post-infection [20]. However, in another study using ferrets it was found that SARS-CoV-2 was transmitted efficiently via direct contact and via the air (via respiratory droplets and/or aerosols) between ferrets [26]. Considering the above, it can be seen that ferret can be a suitable model for disease transmission studies.

Non-human primates

Nonhuman primates (NHP) in particular *M. mulatta* (Rhesus macaques) can be a good model to study COVID-19 pathogenesis. NHP models have been developed for SARS-CoV-2 to resemble the condition seen in human pathogenesis.

Three Non-human primates species, rhesus macaques (*Macaca mulatta*), crab-eating macaques (*Macaca fascicularis*), and common marmosets (*Callithrix jacchus*) were compared for SARS-CoV-2 infections and found that rhesus macaques and c rab-eating macaques had developed typical lung pathology lesions seen in humans. Additionally, the viral antigens were detected in alveolar epithelial cells and macrophages in these macaques [23]. Yu et al., 2020, compared the severity of interstitial pneumonia between young and aged rhesus macaques and concluded that severity is more pronounced in aged rhesus monkeys [38]. In another study by Munster et al., adult rhesus monkeys were challenged using a live virus and were found to have viral replication and shedding along with COVID-19 symptoms with pathological lesions [25].

Passive immunity studies on [6, 9] rhesus monkeys were done to evaluate whether re-exposure to the virus led to the reoccurrence of the virus and it was found that there was no recurrence of SARS-CoV-2 infection, suggestive of protective immunity [3]. Cynomolgus macaques were also evaluated for susceptibility to SARS-CoV-2, and pathological lesions including alveolar and bronchiolar epithelial necrosis, alveolar edema, hyaline membrane formation, and accumulation of immune cells could be demonstrated which can make them an additional model for COVID-19 research for the development of COVID-19 therapeutics and vaccines [21].

In addition to infection studies, the therapeutic efficacy of drugs such as Remdesivir has been studied in rhesus monkeys. Rhesus macaques were primarily used to evaluate many vaccine candidates before undergoing testing in humans in clinical trials [7, 31, 33, 37].

From the above studies, one could say that NHP models may be an appropriate model for SARS-CoV-2 for virus replication, mimicking mild human COVID-19. Besides, NHP models can be applied in drug evaluation and vaccine candidate efficacy testing before the initiation of various phases in human clinical trials.

Conclusion

Several models have been attempted thus far. However, there is no clear model that is preferred for studying SARS-CoV-2 infection as the clinical signs, recovery, and transmission vary between and within species. Each animal model seems to have its own merits and demerits, and careful consideration is required before the selection of animal models. In transgenic animal model selection, various transgenic mouse models developed for SARS-CoV are in use for COVID-19 research. However, before their application in SARS-CoV-2, they must be aptly validated and ascertained that these mouse models could replicate the same pathogenesis as seen in humans. The researchers using these mouse strains should be careful in interpreting the data obtained from these mouse models. Possibly the study on the transgenic mouse can provide a proof of concept for understanding pathogenesis.

Hamsters can be best used to study replicate mild SARS-CoV-2 infections seen in humans and host defense response to the virus and will also help to understand SARS-CoV-2 pathogenesis and for testing vaccines and antiviral drugs. Ferrets on the other hand can be appropriate for disease transmission and lung infections. Considering that the SARS-CoV-2 infection in Non-human primates, rhesus macaque most closely resembles that observed in humans, it could be a valuable model to evaluate vaccines and drug efficacy.

Given the above, it is understood that a comprehensive model for SARS- CoV-2 infection that would exactly replicate human disease remains elusive. Yet an

Table 1 Animal models used for study clinical manifestation/pathogenesis, drug and vaccine efficacy

Animal models	Strains	Dose and route used	Clinical/pathological Lesions	Uses/limitations
Mice [4, 24]	K18-hACE2 transgenic	Intranasal inoculation with SARS-CoV-2 stock virus at a dosage of 10^5 $TCID_{50}$ SARS-CoV-2	Bodyweight loss from 3-5 days, lethargic with laboured breathing, and all mice died within 7 days Interstitial pneumonia, neural damage of CNS was also seen	Animal model for COVID-19 pathogenesis for evaluating vaccines and therapeutics Limitation: Lethal encephalitis
Mice [19]	HFH4-hACE2 transgenic mice	Intranasal inoculation of 3×10^4 $TCID_{50}$ SARS-CoV-2	Bodyweight loss from day 4 to 6, respiratory distress and neurological symptoms Pathological changes include interstitial pneumonia	Animal model for COVID-19 pathogenesis for evaluating vaccines and therapeutics Limitation: Lethal encephalitis, HFH4-hACE2 mice showed different susceptibility with the infection of SARS-CoV-2 based on gender and age
Mice [14, 15, 20]	Ad5-hACE2-transduced mice using inbred mice	Intranasal inoculation with 1×10^5 PFU of SARS-CoV-2	Bodyweight loss at 4 to-6 days, labored breathing, interstitial pneumonia	Useful to study the efficacy of vaccines and therapies such as convalescent plasma therapy Limitation: Don't develop severe disease and no extrapulmonary manifestations of diseases
Mice [10]	SARS-CoV-2 MA model (Reverse genetics Using BALB/c mice)	Intranasal inoculation with 10^5 PFU SARS-CoV-2	Bodyweight loss at 3 -4 days, Pathological changes in lungs varies depending on mice age	Used for antiviral and vaccine development Inbred mice model, age-related COVID-19 infections studies
Mice [22]	C57BL/6 hDPP4	1×10^4 PFU mouse-adapted SARS-MA15 in 50 µl	The antiviral drug had improved pulmonary function and reduced virus titer and body weight loss in C57BL/6 hDPP4 mice	This model can be used to study antivirals drugs for COVID-19
Non-Human Primates [23, 25, 38]	*Macaca mulatta* (Rhesus monkey) *acaca fascicularis* (Cynomolgus monkey)	4.75 ml of 10^6 pfu/ml SARS-CoV-2 intratracheally (4 ml), intranasally (0.5 ml) and on the conjunctiva (0.25 ml)	*M. mulatta* showed a good response to SARS-CoV-2, with decreased bodyweight, pulmonary abnormality, viral replication, increased inflammatory cytokine expression and pathological changes in the lungs	Good animal model for COVID-19 pathogenesis for evaluating drugs and vaccines. A good model for mild to moderate illness studies Limitation: NHPs do not develop the acute lung injury that is observed in mouse models
Ferrets [30]	*Mustela putorius furo*	Intranasal inoculation with $10^{5.5}$ $TCID_{50}$ of NMC-nCoV02	Weight loss increased body temperatures	Useful for the studies related to disease transmission, antiviral, and new vaccine development
Hamsters [5, 28]	*Mesocricetus auratus*	Intranasal inoculation of 10^5 plaque-forming units in 100µl of SARS-CoV-2	Increased respiratory rate, decreasing activity, progressive weight loss with pathological lesions in the lower respiratory tract	Limitations: Mortality was not observed in hamsters
Animal models used for disease transmission and neutralization antibodies production studies				
Hamsters [5, 28]	*Mesocricetus auratus*	Intranasal inoculation with 8×10^4 $TCID_{50}$ SARS-CoV-2	Disease transmitted from donor to naive contact hamsters by direct contact or via aerosols	Model to study on mild COVID-19 cases that occur in humans and for disease transmission studies
Ferrets [26]	*Mustela putorius furo*	Intranasal dose with 6×10^5 $TCID_{50}$ of SARS-CoV-2 virus	Virus shedding was found during direct contact and indirect recipient ferrets	A good model for the study transmission between individuals
Mice and Rats [13]	BALB/c mice and Wistar rats	Inactivated Vaccine administered at a various dose to see whether neutralizing antibodies are produced	PicoVacc inactivated vaccine	An inactivated virus vaccine (PiCoVacc) generated neutralizing antibodies in this strain
Mice [12, 17, 18]	Knockout mice $ACE2^{-/-}$	Intranasal inoculation with SARS -CoV virus $10^{5.23}$ $TCID_{50}$	ACE2 receptor is needed for acute lung injury	Acute lung injury studies
	$STAT\text{-}1^{-/-}$	Intranasal inoculation with 10^5 pfu/50 µl rMA15 or the recombinant or biological epidemic virus, icSARS or Urbani,	Increased susceptibility, prolonged virus shedding, and mortality following infection with either virus	Useful in SARS CoV studies but not in SARS-CoV 2
	$TMPRSS2^{-/-}$	Intranasal inoculation with SARS-CoV10^5 TCID50	TMPRSS2 is needed for virus entry for pathogenesis	Use to understand virus entry and the development of inhibitors

appropriate animal model susceptible to SARS-CoV-2 virus with comorbidity conditions as seen in humans needs to be developed for complete understanding and treatment of the COVID-19 pandemic. Nevertheless, the models available so far suggest that it is possible to choose models depending on the scientific goals of the researchers (Table 1).

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