Biological Models Research and Technology
ISSN 9675-9225X (Online)

BMRT

REVIEW ARTICLE

Murine animal models for *in vivo* studies of Zika and Chikungunya viruses

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How to cite: Lins CRB, Curvêlo CS, Medeiros DBA, Aquino IRPUC, Dhalia R, Crovella S. Murine animal models for *in vivo* studies of Zika and Chikungunya viruses. Bio M Res Tech. 2022;2:e00022022. https://doi.org/10.4322/2675-9225.00022022

Abstract

Arboviruses are worldwide distributed arthropod-borne viruses representing a constant threat to public health. Among these arboviruses, the Chikungunya (CHIKV) and Zika (ZIKV) viruses have a high prevalence in Brazil being responsible for recent outbreaks resulting mainly in irreparable socioeconomic damages such as the high rate of cases of comorbidities and microcephaly in newborns, respectively. Therefore, it is necessary to understand the biology of these arboviruses and develop effective treatments against them; moreover, appropriate mice animal models are strongly encouraged. Here we reviewed the scientific literature aiming to improve the search for the best murine animal model, specific for the arboviruses, specifically, CHIKV and ZIKV. In this way, we performed a comparison between the various mice models currently available, among them: genetically modified immunosuppressed animals, as the A129 and AG129 which are knockout animals for the α/β and α/β/γ receptors, respectively, neonatal immunocompetent models C57BL/6 strains used between 6-8 days old for neuropathogenesis studies or 1 day old for vaccine safety studies and finally immunosuppressed induced by dexamethasone or interferon 1 blocker for pathogenesis studies. Mice models are the first option after in vitro analysis, as they are small animals, which facilitates handling and maintenance, in addition to being more inexpensive and abundantly available in different genetic strains, both wild and modified. If the results of this stage are promising, the studies move forward to the use of models with animals of greater complexity, such as rats, non-human primates and finally humans. For this review, we searched through articles in PubMed, Scopus and ScienceDirect databases using the criteria of date publications, titles, abstracts and complete manuscripts. The correct choice of these models during experimental planning is essential, since increases the confidence and the rational use of animals in experimentation in accordance to current bioethics guidelines.

Keywords: alphavirus, animal models, CHIKV, flavivirus, viral pathogenesis, ZIKV.

INTRODUCTION

Arboviruses are arthropod-borne viruses that have worldwide distribution and represent a constant threat to public health. Among the arboviruses, the Chikungunya virus (CHIKV), belongs to genus *Alphavirus*, family *Togaviridae*, is a positive-sense RNA virus transmitted by mosquitoes of the *Aedes* genus with a great impact on human health[1]. This virus causes the Chikungunya fever, mainly characterized by fever, intense arthralgia, headache, swelling and/or rash. These symptoms,

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Competing interests: The authors have declared that no competing interests exist.
Received: January 20, 2022. Accepted: April 06, 2022.

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despite being similar to other arboviruses, stands out in CHIKV infection, as they usually cause partial or severe disability for years, which can lead to a significant reduction in the quality of life of those infected[2,3] can also infect other species, such as non-human primates (NHP), and maintain a wild enzootic transmission cycle involving the Aedes mosquitoes that live in the forest. Mice animal models can be used to better understand the immunological and chronification mechanisms that influence CHIKV infection[4,5].

Another arbovirus of great relevance on human health is the Zika virus (ZIKV)[6]. ZIKV has been associated to neurological injure such as Guillain-Barré syndrome, neuropathy and myelitis, particularly in adults as well as pregnancy complications such as fetal loss, stillbirth, preterm birth and a distinct pattern of birth defects and disabilities, called congenital Zika syndrome (CZS)[7]. This virus belongs to the *Flavivirus* genus, family *Flaviviridae* and has a positive-sense single-stranded RNA genome[8].

ZIKV is mainly transmitted to humans through the bite of some species of infected mosquitoes. However, the virus can also be transmitted by blood transfusion, transplacentally, perinatally and sexually[7]. To study the clinical manifestations of ZIKV infection in humans, several *in vitro* and *in vivo* models have been designed with the aim of discovering the mechanisms of ZIKV pathogenesis and transmission, also contributing to stimulate the development of vaccines and antivirals[8].

When considering the desirable characteristics of the animal model to be chosen, for in example, for vaccine development studies, the model must present: robust and reproducible viremia, be immunocompetent and have pathological and clinical signs similar to those found in the human host. However, at present time, there is no model that meets all these criteria[4,9-12].

So, to understand the biology of arboviruses during infection and to develop an effective treatment against them, an appropriate animal model for these studies is needed. It is noteworthy that the use of these animals requires careful interpretation of results due to differences in the biology of mice and humans, in addition to differences in immune status when using wild and knockout mice[13]. Thus, this study aims to carry out a literature review in order to assist the scientific community in the search for the best animal model, specific for the purpose of each study, involving arboviruses, in particular, ZIKV and CHIKV.

MATERIALS AND METHODS

This work is a literature review based on the search, through the adoption of methodological criteria, of scientific articles available in the following databases: PubMed, Scopus and ScienceDirect. For this, the descriptors were selected as follows; "Descriptors in Health Science - DeHS", comprising the following terms: animal models, *in vivo*, ZIKV, CHIKV and viral pathogenesis crossed with each other through the Boolean operator "AND". A total of 775 articles were screened, according to the selection, of which 65 were selected according to the evaluation criteria (Figure 1).

As a first evaluation, articles published in English with dates between the years 2015-2021 were selected. However, a total of 26 studies outside this range were also cited for better support of some articles used. The works resulting from this selection were submitted to the second evaluation criterion: title readings, in which articles that did not involve murine animal models used in studies of the Chikungunya or Zika virus were excluded.

The selected articles were submitted to the third evaluative criterion, based on the reading of the abstracts. At this stage, the authors of the research based themselves more precisely on reading encyclopedias, book chapters, reviews and works carried out that associated the use of murine animal models in studies involving the arboviruses under study.

Finally, the articles that met the adopted inclusion criteria were submitted to the fourth evaluative criterion: full reading, and articles that were indexed in more than one database were excluded, and only one of them was selected (Figure 1).

LITERATURE REVIEW

Chikungunya virus

Chikungunya virus (CHIKV) is an alphavirus belonging to the *Togaviridae* family, firstly isolated from a human patient in Tanzania in 1952[14]. CHIKV is mainly transmitted by *Aedes aegypti* and *Aedes*

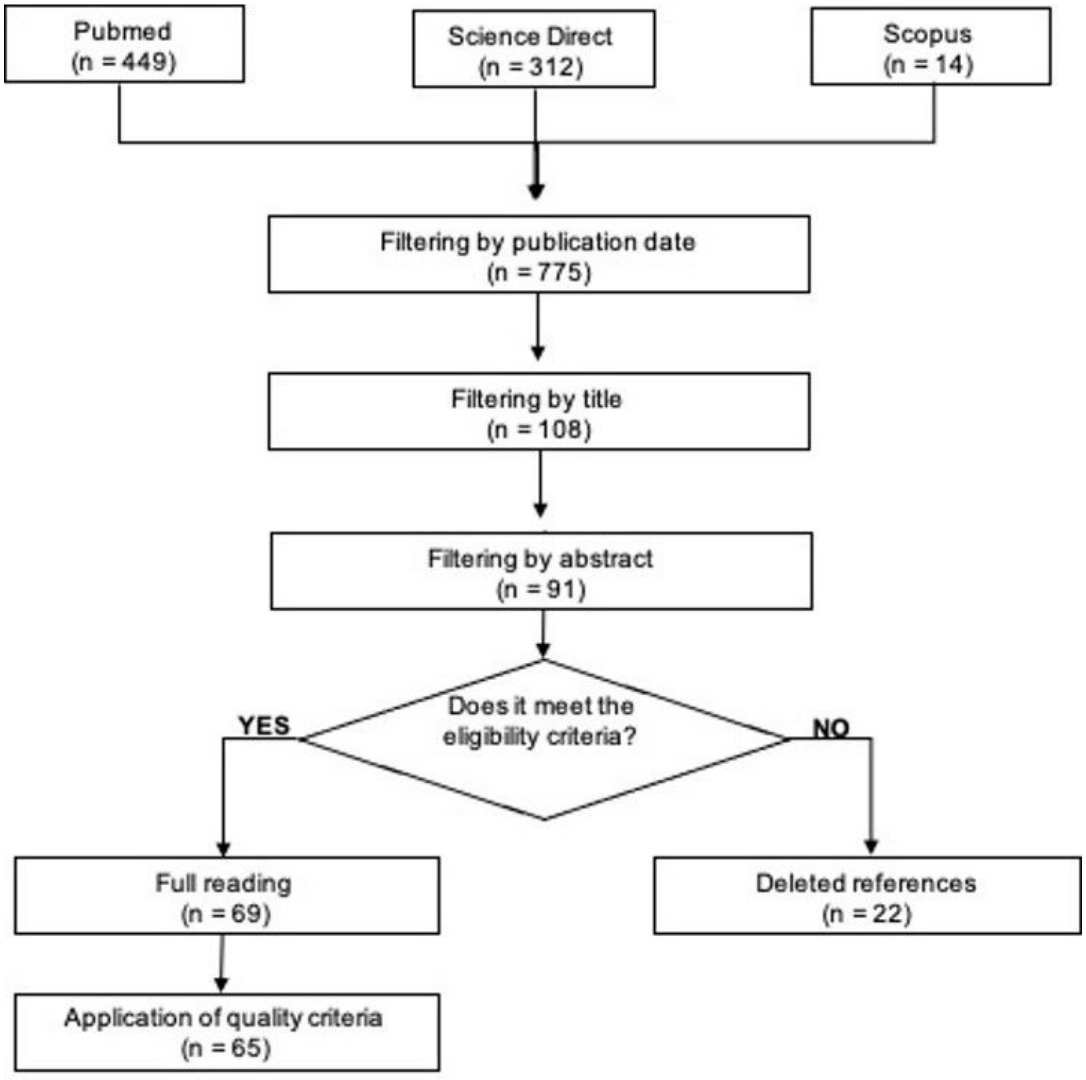

Figure 1. Total articles selected according to each criterion chosen for this study. Trials of the four determining criteria for the choice of articles using Pubmed, Science Direct and Scorpus databases: publication date between 2015-2021 (n=775), title (n=108), abstract (n=91) and complete reading (n=69). At the end, 65 references were selected according to the application of the quality criteria and 22 were deleted. Additional older articles were intentionally cited, in order to better support the choice of selected articles.

albopictus[15]. Genetic analysis identified four distinct strains of CHIKV: the West African (WAF) strain, the East-Central-South African (ECSA) strain, the Asian and Indian Ocean strain (IOL)[16].

In Brazil, Chikungunya fever was firstly detected in August 2010 and the number of cases of the disease has increased since then. According to data from the Ministry of Health (2016; 2020), in 2015, 38,499 thousand probable cases were distributed in 704 municipalities. Compared to 2016, of the 271,824 thousand probable cases in 2,829 Brazilian municipalities, 151,318 were confirmed. Of these, there were 196 deaths, with the highest number occurring in Pernambuco. In 2019, 132,205 probable cases were reported in the country. The Southeast and Northeast regions had the highest incidence rates, 104.6 cases/100 thousand inhabitants and 59.4 cases/100 thousand inhabitants, respectively. The states of Rio de Janeiro and Rio Grande do Norte concentrate 75.6% of probable cases[17,18].

One goal of vaccine and therapeutic efforts against viruses is the development of broadly neutralizing antibodies that inhibit most strains within a genetically diverse virus family[19]. Although there are currently no licensed vaccines or therapies available for CHIKV or any other Alphavirus,

studies have demonstrated the importance of protection mediated by neutralizing antibodies that bind to conserved epitopes of domain B, glycoprotein E2, and inhibit the entry or exit of the virus in the cell[20].

Zika virus

ZIKV was first isolated from a Rhesus monkey (*Macaca mulatta*), as sentinel, in the Zika forest of Uganda in 1947. Historically, human cases have rarely been reported, being misdiagnosed as dengue virus infections, however, as of 2007 in the Yap Islands in Micronesia[21] and later in 2013 in French Polynesia the epidemiology of ZIKV has changed, with higher rates of symptomatic disease, including an association with Guillain-Barré syndrome in adults, and evidence of epidemic transmission[22].

ZIKV emerged in the Western Hemisphere in 2015 and caused epidemics in Central and South America as well as in the Caribbean islands[23]. During its spread throughout the Americas, ZIKV became a public health problem due to its ability to cross the placental barrier and infect neuroprogenitor cells in the fetal brain, leading to microcephaly, congenital abnormalities, premature birth and death[24].

In response to the ZIKV pandemic and congenital disease outbreak, animal models were developed to study the pathogenesis of ZIKV and evaluate countermeasures, including new vaccines and targeted therapies. Thus, researchers were allowed to confirm the teratogenic effects of ZIKV infection[25]. So, animal models could provide a mean to evaluate new interventions, such as the pathogenicity of different strains and the effects of their mutations[26].

Murine models

Mice are the animals most used as models for viral infections in humans. Its low cost, short breeding time, large and easy-to-handle litters make it easy to use on a large scale. They reproduce important aspects of human diseases, including viral and bacterial infections[27]. They also contributed to elucidating several aspects of ZIKV pathogenesis, including the link between ZIKV infection in pregnant women and birth defects[28].

Mice have also been a valuable model for the evaluation of vaccine and antiviral candidates[8]. In addition, they have the ability to be genetically manipulated (transgenes, CRISPR-Cas9 mutations, homologous recombination and conditional deletions) to examine how specific genes influence infection and in immunity, this makes them a preferred model for many *in vivo* studies[25].

However, there are still cases in which these animals do not reproduce specific aspects of human ZIKV and CHIKV infection, due to the lack of functional conservation between mouse and human genes[4]. Therefore, several mice animal models, both immunocompetent and immunodeficient, have been used to better elucidate the pathogenesis and other biological aspects involving these arboviruses (Tables 1 and 2).

Immunocompetent mouse models for the study of CHIKV

Initial evidence of neural tropism was demonstrated in newborn mice after CHIKV intracerebral inoculation, which leads to lethality, severe necrosis and leptomeningeal infiltration[29]. In newborn mice, CHIKV spreads to the brain after initial virus replication and is usually cleared from this site by day 10 post infection (dpi)[58,59], suggesting that young age is a factor of high susceptibility to infection in this model of CHIKV infection[60].

In addition to their usefulness as models of pathogenesis, newborn mice are sensitive tools for testing the efficacy of polyclonal and monoclonal antibodies specific for CHIKV (mAbs). However, because of their immature immune system, they cannot be used to directly test vaccine efficacy, although they are useful for testing the safety of live attenuated vaccines[61].

Subcutaneous inoculation by CHIKV in the plantar region of the paw of wild-type C57BL/6 mice resulted in a bilateral edematous response in the inoculated paw, with peaks occurring at approximately 3 and 7 dpi[62]. These animals cleared the infection with undetectable serum viral titers at all time intervals tested[13].

Table 1. Animal models of immunocompetent mice used for studies of Zika and Chikugunya viruses

Mice strains	Clinical Signs	References
SWISS	Necrosis of the cerebrum, lethargy, loss of balance and difficulty walking, dragging of the hind limbs, hair loss around the inoculation site, microcephaly and other neurodevelopmental disorders.	29-34
C57BL/6J	Weight loss, swelling of the inoculated limb, severe malformations, severe CNS damage and high viremia, with or without immunosuppression.	35-40
BALB/c	High viral load and development of various inflammations in organic tissues with immunosuppression.	41
Humanized mouse (hSTAT2 KI)	Spread of virus to placenta, spleen and fetal brain.	42
129 Sv/Ev	No develop clinical symptoms or histological changes, despite the viral RNA being detectable in the blood, spleen and ovaries.	43

Table 2. Animal models of immunodeficient mice used for studies of Zika and Chikugunya viruses

Mice strains	Clinical Signs	References
A129 (IFNα and β receptors)	High levels of viremia in the spleen, signs of neurological disease, including tremors, weight loss and death.	43-45
AG129 (IFNα / β and γ0 receptors)	Viremic spread observed in visceral organs and brain with associated serious pathologies only in the brain and muscles.	8,46-48
Irf3 $^{-}$ / $^{-}$ Irf5 $^{-}$ / $^{-}$ Irf7 $^{-}$ / $^{-}$ (Transcription factors - interferon pathway)	Signs of neurological disease, including hind limb weakness and paralysis.	49,50
IFNAR1 $^{-}$ / $^{-}$ (IFNα and β receptors)	High viral load in the central nervous system (CNS), transplacental transmission, neuroinvasion, consequences of neurological diseases and death.	13,51-56
Rag1 -/- (T and B cell responses)	Dramatic weight loss, infection in the brain and testes.	57

Immunocompetent mice for study of ZIKV

ZIKV infection in immunocompetent C57BL/6, BALB/c, CD-1 mice, pregnant or not, subcutaneously, intraperitoneally or intravenously, did not result in a clinical sign of the disease and there was little viral replication[63]. One of the reasons for this phenotype is the ability of ZIKV to degrade STAT2, an IFN-regulated transcriptional activator in humans, but not in mice[64]. However, on deeper analysis it was revealed that some viral replication occurs in these mice and that under certain circumstances, vertical transmission and associated fetal abnormalities may occur[65].

In order to optimize ZIKV infection in these animals, it is known that they are sensitive to the action of IFN types I, II and III, and the blockade of IFN receptors has been used to develop models of susceptible mice[49,66]. Lazear and colleagues used an IFNAR1 blocking monoclonal antibody (MAR1-5A3) in C57BL/6 mice to make them susceptible to ZIKV infection. Although these animals did not develop neurological manifestations, they had a milder disease phenotype than the one observed in IFNAR1-/-mice[49].

This model was used for vertical transmission studies in which females and wild males of the C57BL/6 lineage were mated, and the mothers were treated with the anti-IFNAR1 antibody immediately before ZIKV infection. Moreover, the vertical transmission of the virus reaching the fetal brain was demonstrated[67]. The use of this model is suggested to define the transplacental transmission mechanisms of ZIKV to the fetus[51].

This model also allowed further investigation on the pathogenesis and persistence of ZIKV in the male reproductive tract[51]. ZIKV has been detected in several cells, including spermatogonia, spermatocytes, mature sperm and Sertoli cells, in addition to testes and epididymis[68].

Five-week-old C57BL/6 mice previously treated with anti-IFNAR1 antibodies and later infected with the DAKAR 41519 strain showed a survival rate of almost 20%[69]. In routine use, they cannot completely deplete the IFN response[70]. Alternative ways to develop immunocompromised models should be explored[8].

Infection of 7- to 8-day-old C57BL/6 with this strain or ZIKV H/PF/2013 by subcutaneous or intraperitoneal injection resulted in central nervous system pathology and partial lethality[49]. The use of newborn animals may be useful, as the main processes of brain development in rodents occur after birth[71]. Animals inoculated with the DAKAR strain, either subcutaneously or intraperitoneally, had mortality rates of 40 and 100%, respectively[35].

One or three-day-old neonatal Swiss mice inoculated subcutaneously or intracranially with strain of ZIKV[72], also exhibited lethargy, ataxia, paralysis, microcephaly and other neurodevelopmental disorders with evidence of ZIKV infection in the brain[30,65]. The use of this model whose portion survives may allow the assessment of long-term neurological and behavioral sequelae associated with ZIKV infection in the maturing brain[51].

In the context of pregnancy, there are advantages and disadvantages to using mice to study human infections and diseases, for example, in mice the gestation period is shorter compared to humans, only 20 days, in addition the placental structure is different[49,73]. Interestingly, pregnant SJL mice, when inoculated intravenously with a high dose of 1010 to 1012 PFU of ZIKV, generated offspring that presented neurological and ophthalmologic malformations similar to those observed in humans, in addition to intrauterine growth retardation[65]. When CD1 mice were challenged. intracranially with the MR766 ZIKV strain, they exhibited an 80-100% mortality rate regardless of age. Intraperitoneal inoculation with the same strain generated signs of morbidity, but no dose-dependent mortality[74].

The use of a humanized mouse model in which gene manipulation techniques are used to produce knock-in animals (KI) with modification of human STAT2 at the mouse STAT2 locus (hSTAT2 KI) generated a fully immunocompetent animal model. The infection of these pregnant animals, performed by a highly virulent adapted strain, resulted in viral dissemination to the placenta and fetal brain[75].

A hematogenous infection model was designed to assess the effects of this ZIKV infection on embryonic and fetal development using FBV/NJ and C57BL/6J mice. These early infections caused growth restriction and severe malformations in infected embryos[36].

In a recent study with intravaginally infected C57BL/6 females, high rates of long-term viral replication were observed. Furthermore, fetuses of pregnant females inoculated by this route developed brain infection and intrauterine growth retardation[76]. Thus, this model will likely have additional usefulness to test whether candidate countermeasures can prevent congenital malformations or fetal injury in the context of sexual transmission of ZIKV[51].

Immunocompetent mice have been used to assess the immunogenicity of candidate vaccines, as well as their protective efficacy against viremia[51]. Thus, one study used BALB/c and SJL mice to test a DNA vaccine encoding the ZIKV M and E proteins with immunization intramuscularly and prevented viremia after intravenous inoculation of Brazilian or Puerto Rican strains of ZIKV[77]. In analogous studies, immunization with a purified and inactivated ZIKV vaccine intramuscularly or subcutaneously in BALB/c mice also prevented viremia. In both cases, protection was mediated by specific antibodies to ZIKV[77].

The technique of intracranial inoculation via the post-glenoid foramen used by Iwami et. al., in the implant of intracerebral cancer cells, with the advantage of not compromising the cranial vault of adult mice[78]. It was used, in another study, for the infection of mice with a relatively low dose of ZIKV MR766, in which animals of the C57BL/6 lineage were used between 8 and 20 weeks immunocompetent resulting in lethal encephalitis[79].

Immunodeficient strains for the study of CHIKV and ZIKV

In the early 1990s, Muller and collaborators generated interferon receptor (IFNARs) type I, IFN-α/β and IFNAR-/-, deficient mice by homologous recombination in embryonic stem cells. Although

these transgenic mice showed no obvious abnormalities at six months of age and were fertile, the animals were totally devoid of the effects of type I IFNs[80].

The role of INF against viral diseases has been widely studied, as well as the strategies developed by the viruses to antagonize the effects of these IFNs. Both type I and II IFNs were correlated in host antiviral defense and immunomodulatory functions during infection[81]. The IFNAR-/- receptor knockout mouse model was used to study infection, disease, pathogenesis and vaccine testing against several arbovirus families, such as *Togaviridae*, *Bunyaviridae*, *Flaviviridae*, *Rhabdoviridae*, *Orthomyxoviridae* and *Reoviridae*[13].

The susceptibility of IFNAR-/- mice, as well as the role of IFNAR receptors in the control and elimination of CHIKV were studied. A dose of 10^2 PFU injected intradermally (id) was sufficient to kill the IFNAR-/- mice and the injection of 10^6 PFU resulted in even faster death[82]. The maternal-fetal transmission of CHIKV in IFNAR-/- pregnant mice was also analyzed. However, CHIKV has been shown to be unable to cross the placental barrier from mother to fetus in mice[83].

The main disadvantage of immunocompromised mice is the lack of essential components of the immune response, which may underestimate the efficacy of some vaccine candidates, in addition to not expressing the pathogenesis of the disease accurately in these hosts. However, these models have been successfully used for preclinical evaluation of vaccines and antivirals against these arboviruses[84-87]. Although they are deficient in the innate interferon response, they retain their adaptive immunity[26].

In a study using SCID mice (deficient in T and B lymphocytes), it was observed that the animals developed the disease severely, but were more resistant to infection than the AG129 model, reinforcing the thesis that ZIKV infection in mice is mainly controlled by the innate immune response mediated by IFNs and not by the adaptive response mediated by T cells[88].

Mice of the A129 strain were one of the first models used to characterize ZIKV infection, although already been used in studies of other viruses, such as CHIKV and the yellow fever virus (YFV)[26,89]. Younger (3 weeks) mice they are good models for testing antiviral compounds in preventing weight loss, neurological disease, viremia and death. This strain can also be used in vaccine trials aged 3-4 weeks approximately to measure its protection and challenged at 7-8 weeks or more. In this model, vaccine efficacy evaluations can include protection against weight loss and clinical signs of the disease, as well as reduction or not of viremia[12,63].

AG129 mice have double knockout for IFNα/β/γ receptors and are more susceptible to ZIKV-induced disease than A129 mice. Although the kinetics of ZIKV infection in AG129 mice are similar to that of A129, disease signs are more severe in AG129, especially due to the severity of neurological manifestations, probably because of the immune-protective role of IFNγ[46,63]. These observations suggest the relevance of these strains for the study of the pathogenesis of human diseases, including Guillain-Barré syndrome and microcephaly[8]. Studies with CHIKV were also carried out using this animal model[47].

IFNAR1-/- mice infected with ZIKV strains from French Polynesia or Brazilian developed conjunctivitis and panuveitis, these disease manifestations were associated with ZIKV RNA in the cornea, iris, optic nerve and retinal ganglion and bipolar cells[90]. Thus, IFNAR1-/- mice may be useful to investigate the pathogenesis of ocular disease associated with ZIKV infection[51].

Irf3-/-, Irf5-/- and Irf7-/- mice represent a relevant model since that have the C57BL/6 genetic background and are triple knockout (TKO) for interferon transcription regulatory factors 3, 5 and 7, respectively[91]. This strain has been used to study the impact of ZIKV on the CNS, where high levels of viral RNA were detected in tissues after infection and severe signs of neurological disease could be observed[49].

Another strategy for infection in immunocompetent animals would be the administration of immunosuppressive drugs. As described in a study using BALB/c mice immunocompromised with dexamethasone. In which high viral replication was obtained in several organs, inflammation and slight weight loss after ZIKV infection, intraperitoneally[41]. By using this model, the authors showed that administration of exogenous type I IFN can improve clinical outcome[51].

Several evidences of immunological pathology come from animal models[92]. CHIKV causes inflammatory arthritis and myositis in both mice and non-human primates[93]. Components of the innate and adaptive immune system contribute to alphavirus-induced arthritis and myositis[92]. Both

monocytes and macrophages participate in arthritis or myositis caused by CHIKV in mouse models, and the reduction of these cells results in reduced signs of disease[94].

Given the importance of monocytes and macrophages in the pathogenesis of CHIKV, studies have evaluated the potential of monocyte inhibitors as therapies for alphavirus-induced arthritis[92]. When genetically deficient mice were used for an inhibitor of monocyte chemotactic proteins (CCL2) that acts as a receptor for several chemokines, including CCL2, showed a more severe picture of arthritis characterized by neutrophil infiltration in joint tissues[95].

CONCLUSION

We can conclude that there is a wide variety of mice animal models for studying CHIKV and ZIKV. Among these models, the most used are the knockouts of alpha and beta interferon receptors, but controversial findings have been reported for these models, leading to eventually underestimate vaccine efficacy tests, in addition to having a higher cost and little availability. In this way, there is a gap for new immunocompetent models to be developed in the future. However, it is worth emphasizing the importance of choosing these models correctly during experimental planning, in order to avoid economic losses and unnecessary use of animals.

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