REVIEW

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Recent Advances in Animal Models of Zika Virus Infection

Shupeng Dong[1] · Qiming Liang[1]

Abstract

An infection by Zika virus (ZIKV), a mosquito-borne flavivirus, broke out in South American regions in 2015, and recently showed a tendency of spreading to North America and even worldwide. ZIKV was first detected in 1947 and only 14 human infection cases were reported until 2007. This virus was previously observed to cause only mild flu-like symptoms. However, recent ZIKV infections might be responsible for the increasing cases of neurological disorders such as Guillain-Barré syndrome and congenital defects, including newborn microcephaly. Therefore, researchers have established several animal models to study ZIKV transmission and pathogenesis, and test therapeutic candidates. This review mainly summarizes the reported animal models of ZIKV infection, including mice and non-human primates.

Keywords Zika virus · *Flavivirus* · Rodent models · Non-human primate models

Introduction

Zika virus (ZIKV) is a mosquito-borne flavivirus first isolated from a febrile sentinel rhesus macaque in the Zika forest of Uganda in 1947 (Dick *et al*. 1952). In the same forest, ZIKV was isolated from *Aedes africanus* mosquitoes in 1948. Although the first case of human infection was documented in 1954 (Macnamara 1954), until the outbreak on Yap Island in 2007 (Duffy *et al*. 2009), only 14 cases of human infection had been reported. However, in the past 2 years, this virus re-emerged in South American regions, especially in Brazil, and showed a tendency of spreading to North America and even worldwide. ZIKV infection was previously observed to cause only mild symptoms, such as skin rashes, conjunctivitis, muscle and joint pain, or headache, in a part of patients. In contrast, the 2013–2014 ZIKV outbreak was associated with Guillain–Barré syndrome (GBS) in French Polynesia (Bautista and Sethi 2016; Cao-Lormeau *et al*. 2016). In 2015, ZIKV swept over South and Central America, and infected thousands of people in Brazil and Colombia, where it was

responsible for an obvious increase in severe fetal abnormalities, including spontaneous abortion, stillbirth, microcephaly, hydrocephaly, and placental insufficiency (Paploski *et al*. 2016; Sejvar *et al*. 2011). Therefore, the World Health Organization (WHO) declared that ZIKV is a global health emergency in February 2016. This sudden challenge urged scientists to establish a series of animal models to explore the transmission and pathogenesis of ZIKV, and to evaluate the vaccines and therapeutics.

Part One: Rodent Models of ZIKV Infection

Immunocompetent Mouse Model

As the most common laboratory animals, mice were first used to establish an animal model of ZIKV infection. Wild-type (WT) C57BL/6 mice (5–6-week-old) exhibited no weight loss, morbidity, or mortality after ZIKV infection. However, 1-day-old C57BL/6 mice subcutaneously inoculated with ZIKV (strain PRVABC59) developed unsteady gait with widening stance, hyperactivity, and ataxia within 2 weeks post-infection. This was followed by reduced mobility, intermittent alternating collapse of the hind limbs, loss of balance, and seizures. Moreover, these mice showed detectable levels of viral RNA in the central nervous system (CNS), especially in the cerebellar white matter and granular layers, as well as in the hippocampal

✉ Qiming Liang
liangqiming@shsmu.edu.cn

1   Shanghai Institute of Immunology, Department of
    Immunology and Microbiology, Shanghai Jiao Tong
    University School of Medicine, Shanghai 200025, China

region. However, there is no evidence of viral infection in the spleen or liver, indicating selective infection in the CNS (Manangeeswaran *et al.* 2016). In the CNS, ZIKV infection profoundly upregulated the genes involved in the recruitment and activation of neutrophils as well as monocytes/macrophages. After virgin female C57BL/6 mice were intravaginally inoculated with ZIKV (strain FSS13025), ZIKV RNA and infectious virus were persistently detectable in the vaginal mucosa (Yockey *et al.* 2016). In mice, embryonic day 4.5 (E4.5) corresponds to the initiation of embryonic development at the late blastocyst stage, whereas E8.5 corresponds to the late gastrulation and beginning of organogenesis (Ko 2001). ZIKV replicated substantially in the vaginal tract of pregnant C57BL/6 mice that were infected at the two early phases of pregnancy, E4.5 and E8.5. Although ZIKV RNA became undetectable in the placenta at E18.5 (just prior to birth), significant intrauterine growth retardation (IUGR) was observed in fetuses of pregnant mice infected on E4.5, and the presence of ZIKV in the fetal brains was detected by immune-electron microscopy using an antibody specific to flavivirus NS1, suggesting that the sexual transmission of ZIKV probably occurs in mice and leads to more severe effects than those by other transmission routes (Yockey *et al.* 2016).

Mouse Models with Interferon Pathway Deficiency

An immunocompromised mouse is majorly used to study ZIKV infection (Fig. 1). The innate immune system detects viral infections through the recognition of pathogen-associated molecular patterns (PAMPs) by the host pattern recognition receptors (PRRs) (Medzhitov 2001). Interaction between PRRs and PAMPs turns on signaling cascades, leading to the production of cytokines, including type I interferon (IFN), by the transcription factors NF-κB and interferon regulatory factors (IRFs) (Honda and Taniguchi 2006). Engagement of type I IFNs to their receptor IFNAR1 finally induces a group of IFN-stimulated genes (ISGs) that work in combination to repress viral replication and prime adaptive immune responses to eliminate the virus (Schoggins and Rice 2011). A129 mice ($Ifnar1^{-/-}$) subcutaneously challenged with ZIKV exhibited weight reduction and abnormal fluctuations in body temperature. ZIKV viral RNA was detected in multiple organs with the highest level in the spleen (Dowall *et al.* 2016). Additionally, ZIKV persistently infected the testis and epididymis of male mice, resulting in diminished testosterone and inhibin B levels. ZIKV can infect spermatogonia, primary spermatocytes, and Sertoli cells, leading to cell death and destruction of the seminiferous tubules (Govero *et al.* 2016; Ma *et al.* 2016). When pregnant $Ifnar1^{-/-}$ mice, which mated with WT mice, were inoculated with ZIKV on E6.5 and E7.5 and sacrificed on E13.5 and E15.5, respectively, most $Ifnar1^{+/-}$ heterozygous fetuses demised and were resorbed on E13.5, leaving only a placental remnant. ZIKV RNA were present in different trophoblast cells in the placenta, including glycogen trophoblasts, spongiotrophoblasts, mononuclear trophoblasts, and syncytiotrophoblasts (Miner *et al.* 2016). These results are consistent with the cell culture studies that demonstrated that ZIKV could infect human trophoblast cell lines (Bayer *et al.* 2016). Additionally, ZIKV-infected placentas exhibited severe vascular injury, such as irregularly shaped, reduced fetal capillaries, and destruction of the placental microvasculature (Miner *et al.* 2016). These results demonstrated that ZIKV could pass the mother fetal blood barrier during pregnancy to cause the potential fetal defects in mice.
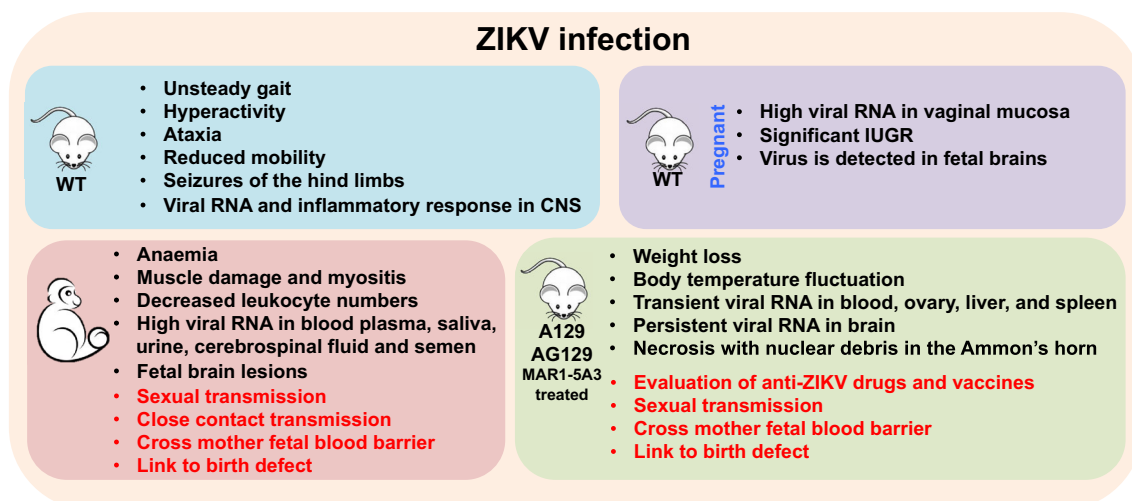

ZIKV infection

WT
- Unsteady gait
- Hyperactivity
- Ataxia
- Reduced mobility
- Seizures of the hind limbs
- Viral RNA and inflammatory response in CNS

WT Pregnant
- High viral RNA in vaginal mucosa
- Significant IUGR
- Virus is detected in fetal brains

- Anaemia
- Muscle damage and myositis
- Decreased leukocyte numbers
- High viral RNA in blood plasma, saliva, urine, cerebrospinal fluid and semen
- Fetal brain lesions
- Sexual transmission
- Close contact transmission
- Cross mother fetal blood barrier
- Link to birth defect

A129 AG129 MAR1-5A3 treated
- Weight loss
- Body temperature fluctuation
- Transient viral RNA in blood, ovary, liver, and spleen
- Persistent viral RNA in brain
- Necrosis with nuclear debris in the Ammon's horn
- Evaluation of anti-ZIKV drugs and vaccines
- Sexual transmission
- Cross mother fetal blood barrier
- Link to birth defect

Fig. 1 Animal models of ZIKV infection.

Similar to the A129 mice, MAR1-5A3 (anti-IFNAR1 monoclonal antibody) pre-treated C57BL/6 mice could support ZIKV infection *in vivo*. ZIKV mRNA was present in multiple organs and caused fatality in these mice (Sheehan *et al*. 2006). In pregnant mice, MAR1-5A3 treatment did not lead to fetus demise after ZIKV infection, but these fetuses exhibited more significant IUGR (Miner *et al*. 2016). However, MAR1-5A3-treated mice exhibited no evidence of lesions in the placentas or fetuses, as well as IUGR after DENV serotype 3 (DENV-3) infection (Pinto *et al*. 2015; Sarathy *et al*. 2015), suggesting that ZIKV, rather than DENV-3, has a greater tropism for the placental cells. The levels of ZIKV RNA in the fetuses were dependent on the dose of MAR1-5A3 administered in the maternal mice. MAR1-5A3 treatment at a concentration of 1–2 mg led to high viral loads in fetuses (Lazear *et al*. 2016) and ZIKV RNA persisted in the fetal heads and bodies on E16.5, a crucial period in the early development of the fetus brain (Miner *et al*. 2016). In another study, MAR1-5A3 treatment resulted in 40% mortality of mice with subcutaneous inoculation of ZIKV, but 100% mortality of mice with intraperitoneal inoculation. Both the exposure routes led to weight loss, high viremia, and severe neuropathological changes in ZIKV-infected mice. More importantly, acute encephalitis and encephalomyelitis were observed in MAR1-5A3 pre-treated mice, suggesting the crucial role of type I IFN in controlling ZIKV pathogenesis (Smith *et al*. 2017).

AG129 is another immunocompromised mouse model lacking both type I and II IFN receptors, which have been successfully used to imitate infection with flaviviruses such as DENV (Shresta *et al*. 2004) and yellow fever virus (Thibodeaux *et al*. 2012). Although both A129 and AG129 mice support ZIKV replication *in vivo*, the neurological symptoms are much severe in AG129 mice. A129 mice became lethargic and unresponsive to stimuli before death or euthanasia, but AG129 mice were still active and interested in food before death, but remained uncoordinated (Dowall *et al*. 2016). Therefore, the potential neuroprotective role of IFNγ against ZIKV infection cannot be neglected. In addition, under the same infection conditions, SCID mice (deficient in both T and B lymphocytes) succumbed to infection approximately 26 days later than AG129 did, indicating the vital protective roles of innate immune response against ZIKV infection. Elevated levels of inflammatory cytokines (IFNγ, IL-18, IL-6, and TNF-α) and chemokines (CCL2, CCL5, CCL7, CXCL1, and CXCL10) were detectable in the sera of ZIKV-infected AG129 mice. Among these cytokines, IFNγ and IL-18 levels continuously increased during the course of infection, suggesting their possible roles in evaluation of the disease progression and severity in mouse model. Since ZIKV infection leads to the production of IL-18, it is

possible that the inflammasome is activated during the course of infection (Zmurko *et al*. 2016).

The engagement of PRRs with PAMPs turns on the type I IFN production through the activation of the transcription factors, such as IRF3 and IRF7. $Irf3^{-/-}$ mice exhibited no overt illness during ZIKV infection; however, similar to $Ifnar1^{-/-}$ mice, 4–6-week-old $Irf3/Irf5/Irf7$ triple knockout (TKO) mice developed neurological disease signs including hindlimb weakness and paralysis. Additionally, the exhibition of clinical signs in TKO mice is much quicker than that in $Ifnar1^{-/-}$ mice, suggesting a possible IFNα/β-independent role of IRFs after ZIKV infection (Miner *et al*. 2016). Mice deficient in both IRF3 and IRF7 ($Irf3^{-/-}Irf7^{-/-}$) harbored high titers of ZIKV in the vaginal tract after vaginal infection and continued to persist until 7 days post-infection (dpi). Interestingly, ZIKV RNA level was much higher in the placentas of $Irf3^{-/-}Irf7^{-/-}$ pregnant mice than in those of $Ifnar1^{-/-}$ mice upon infection. Therefore, PRR-signal-induced ISGs are more critical in controlling ZIKV replication in the vagina and placenta, while IFNAR-induced ISGs are more important in blocking systemic spread of the virus from the vagina to the blood stream (Yockey *et al*. 2016).

Other Rodent Models

Other rodents, such as hamster and guinea pigs, are also used to evaluate ZIKV infection. Subcutaneous ZIKV infection of hamsters caused morbidity and mortality. ZIKV RNA was detectable in multiple organs, including the uterus, placenta, brain, spinal cord, and testicles. Similar to those in ZIKV-infected A129 mice, morphological changes in Sertoli cells and spermatogonia were observed in the testes of male hamsters. Additionally, STAT-2 knockout resulted in a more severe infection in adult and fetal hamsters, suggesting the protective role of STAT-2 against ZIKV infection (Siddharthan *et al*. 2017). Upon subcutaneous inoculation with ZIKV, guinea pigs demonstrated clinical signs of infection, such as fever, lethargy, hunched back, ruffled fur, and decrease in mobility. ZIKV RNA was also detectable in the whole blood and ZIKV replication was observed in the brain and spleen (Kumar *et al*. 2017). Intranasal inoculation of ZIKV can also establish the infection in guinea pigs, the viral E antigen is detected in the brain and parotid glands after infection, raising the possibility of close contact transmission of ZIKV in humans (Deng *et al*. 2017).

Part Two: Non-human Primate Models of ZIKV Infection

Though mouse models are easily accessible, non-human primates (NHPs) are more clinically relevant in ZIKV research. WT mice do not exhibit clinical signs after ZIKV

infection; therefore, NHP models could provide more valuable information such as virus pathogenesis, the efficacy and safety of therapeutics, and optimized dose and route for drug administration.

When rhesus macaques were subcutaneously inoculated with ZIKV, five of the six non-pregnant monkeys exhibited mild-to-moderate inappetence as well as mild regenerative anemia. Two of these also developed mild rash around the inoculation site at 1 dpi, which persisted for 4–5 days. In addition, all the six monkeys exhibited elevated serum creatine kinase, which peaked at 5 dpi and was strongly associated with muscle damage and myositis (skeletal, smooth, and cardiac) (Lugo-Roman et al. 2010). Total leukocyte numbers decreased in all the infected monkeys, and then increased almost to pre-infection levels at 10 dpi. Innate and adaptive immunocytes, such as natural killer (NK) cells, CD8$^+$ T cells, and CD4$^+$ T cells, expanded above baseline levels at 6 dpi, followed by the exhibition of high neutralizing antibody (nAb) titers at 14 dpi (Dudley et al. 2016). High ZIKV RNA was detected in the blood plasma, saliva, urine, cerebrospinal fluid, and semen of the cynomolgus macaques after subcutaneous infection, but was only transiently present in the vaginal secretion. Interestingly, viral RNA was cleared from the blood plasma and urine within 10 dpi; however, it was still detectable in the saliva and semen until 4 weeks pi (Osuna et al. 2016). Rechallenge at 10 weeks after the initial ZIKV infection resulted in undetectable viral replication, suggesting the effective immune defense through nAb and ZIKV-specific T-cells (Dudley et al. 2016). In addition, ZIKV infection of pregnant pigtail macaques led to fetal brain lesions, including periventricular white matter gliosis, significant cerebral white matter hypoplasia, axonal and ependymal injury, and asymmetry in the occipital-parietal lobes (Adams Waldorf et al. 2016). High infection rates of adult macaques after intravaginal or intrarectal inoculation with ZIKV have been reported. After intravaginal infection by ZIKV, no clinical signs, such as pyrexia, joint swelling, weight loss, or decreased appetite, were observed in the infected macaques. The body temperature increased, and virus RNA and viremia were detectable in both ZIKV-infected rhesus and cynomolgus macaques. The magnitude and duration of detectable viremia suggested that these infected NHPs could potentially infect mosquito vector species (Haddow et al. 2017). Collectively, these studies demonstrated that ZIKV can pass through the mother fetal blood barrier and damage the fetal brain during pregnancy, and sexual transmission plays potential roles in ZIKV spread in NHPs.

Part Three: Atypical Models of ZIKV Infection

Historically, chick embryos have been extensively used as models in developmental biology, teratology, and virology (Drake et al. 2006; Woodruff and Goodpasture 1931). Embryonated broiler eggs, amniotic infected with ZIKV (strain MEX1-44) on E2.5 or E5, exhibited more than 100-fold increase in viral loads and showed dramatic mortality within 3 dpi. High viral loads were consistently identified within the brain and eyes of chick embryos. Magnetic resonance imaging (MRI) showed a decreased growth of total brain volume (-18%), telencephalon (-18%), and brain stem (-32%). Interestingly, ZIKV-infected chick embryos exhibited enlarged ventricular space ($+30\%$), suggesting that ZIKV-infected embryos had less cortical tissue compared to that in sham-infected controls (Goodfellow et al. 2016).

Fission yeast has also been used to analyze the global functions of the ZIKV genome, which encodes 14 proteins or small peptides including capsid protein (C), membrane-anchored capsid (anaC), premembrane protein (prM), membrane protein (M), protein pr (Pr), envelope protein (E), and NS1, NS2A, NS2B, NS3, NS4A, NS4B, 2K, and NS5. Fission yeast strains individually expressing seven ZIKV proteins (anaC, C, prM, M, E, NS2B, and NS4A) exhibited various inhibitory effects on yeast colony formations. Expressions of prM or NS2B almost abolished yeast growth, whereas expressions of anaC, C, M, E, or NS4A attenuated yeast growth. Interestingly, these ZIKV proteins also led to abnormal yeast cell morphology such as cell elongation and hypertrophy. Yeasts expressing NS4A exhibit balloon-like morphology, and NS4A-induced hypertrophy and growth delay are likely mediated by the target of rapamycin (mTOR) cellular stress-response pathway, specifically via Tor1 and Tip41. Expression of prM resulted in cell cycle G1 accumulation, whereas expressions of anaC, M, E, and NS4A caused cell cycle G2/M accumulation, indicating that ZIKV infection leads to cell cycle dysregulation (Li et al. 2017).

Human neural progenitor cells (hNPCs) derived from induced pluripotent stem cells (iPSCs) were utilized for ZIKV infection model in 2D cell culture. ZIKV infection leads to dysregulation of genes associated with cell cycle and apoptotic cell death (Tang et al. 2016). iPSC-derived brain-region-specific organoids have also been used as mini-bioreactors for modeling ZIKV exposure. Among different cell types in the 3D organoid, ZIKV exhibits specific tropism toward NPCs. In addition, the forebrain organoids exhibit many features of microcephaly upon ZIKV exposure, including decreased neuronal layer thickness and overall brain size as well as enlarged lateral ventricles (Qian et al. 2016).

Conclusion

In the past year, ZIKV has attracted attention toward the fields of virology, immunology, and neurology worldwide. Although several animal infection models have been established, the molecular mechanisms underlying ZIKV immune evasion and pathogenesis are still largely unknown. Most of these animal model studies focus only on the changes in phenotype after ZIKV infection, without including another closely related virus, such as DENV or West Nile virus, as a control. The key question, why ZIKV causes newborn microcephaly, but other close flavivirus family members do not, remains unanswered. The unique molecular mechanisms of ZIKV pathogenesis still need to be further explored by molecular and biochemistry approaches. Additionally, these animal models will not only play a key role in understanding the pathological mechanism of ZIKV infection, but also be useful for evaluation of therapies and candidate vaccines.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal and Human Rights Statement This article does not contain any studies with human or animal subjects performed by any of the authors.

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