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Abstract

Flaviviruses are arthropod-borne viruses, several of which represent emerging or re-emerging pathogens responsible for widespread infections with consequences ranging from asymptomatic seroconversion to severe clinical diseases and congenital developmental deficits. This variability is due to multiple factors including host genetic determinants the role of which has been investigated in mouse models and human genetic studies. In this review, we provide an overview of the host genes and variants which modify susceptibility or resistance to major mosquito-borne flaviviruses infections in mice and humans.

Introduction

Flaviviruses constitute a large genus of arthropod-borne viruses, several of which represent emerging or re-emerging pathogens. Important members of this genus include West Nile (WNV), dengue (DENV), Zika (ZIKV), Japanese encephalitis (JEV) and yellow fever (YFV) viruses, all of which are transmitted by mosquitoes. In humans, flaviviruses infections can remain asymptomatic, trigger flu-like symptoms, or progress towards severe complications such as encephalitis, hemorrhagic fever or, in the case of ZIKV, Guillain-Barré syndrome and congenital brain developmental deficits. Because of the rapid progression of these infections, the innate immune response plays a key role in the quick control of viral multiplication and dissemination (Suthar et al. 2013). Flaviviruses cell entry and genome replication trigger multiple sensing events, activation of antiviral effectors through the type I interferon (IFN) pathway, cellular stress reaction and inflammation (Valadao et al. 2016). Like other viruses, they have evolved a variety of mechanisms to block the IFN pathway at different steps through interactions between their non-structural proteins (Cedillo-Barrón et al. 2018), in particular NS5 (Best 2017; Laurent-Rolle et al. 2010), and molecular components of this pathway (Cumberworth et al. 2017; Wu et al. 2017).

Mouse models have been developed to study the pathophysiology of mosquito-borne flavivirus infections, to model the complications observed in humans (in particular encephalitis and neuroinvasive disease, but also intrauterine growth restriction and fetal demise caused by ZIKV infection during pregnancy) and to test novel preventive and therapeutic countermeasures (Julander and Siddharthan 2017). However, while most laboratory strains of mice are naturally susceptible to WNV (Mashimo et al. 2002) and JEV (Wang and Deubel 2011), their infection with DENV fails to elicit overt signs of disease (Zellweger and Shresta 2014) and they are somewhat refractory to ZIKV with the exception of very young mice or genetically manipulated strains with immune deficit (Julander and Siddharthan 2017). In humans, DENV and ZIKV inhibit type I IFN response by STING cleavage (Aguirre et al. 2012; Ding et al. 2018) and by NS5-induced STAT2 degradation (Best 2017; Grant et al. 2016), but these restriction mechanisms are inefficient in mice (Best 2017; Ding et al. 2018; Miorin et al. 2017). Efficient infection is obtained in mice genetically deficient in the receptors for type I (encoded by the *Ifnar1* and *Ifnar2* genes) and/or type II (*Ifngr1* and *Ifngr2* genes) IFNs. Alternatively, the type I IFN receptor can be blocked pharmacologically by anti-IFNAR antibody injection prior to infection (Sheehan et al. 2006; Sheehan et al. 2015). Recently, an immunocompetent mouse model for ZIKV infection has been produced by infecting with a mouse-adapted ZIKV strain mice in which the *Stat2* gene had been replaced with its human version (Gorman et al. 2018).

The mechanisms underlying the variable severity of symptoms in human patients and between mouse inbred strains remain poorly understood, although the viral strain and inoculum are obvious contributing factors. Host microbiota can also influence susceptibility to flaviviruses, as shown in mice by oral antibiotic treatment (Thackray et al. 2018). Host genetic determinants affect the susceptibility of humans or animal species to infections. In this review, we will summarize the evidence demonstrating the role of host genes in the susceptibility or resistance to flaviviruses in mice and humans, with emphasis on innate immunity. We will focus on infections caused by WNV, DENV, ZIKV, JEV and YFV. While many host genes have been shown to interfere with virus biology in cultured cells, we will consider only genes for which variants have been associated with differential clinical severity. Many mouse studies have focused on WNV, while human studies investigated mostly susceptibility to highly prevalent DENV, thus limiting comparisons between the two species.

Mouse models

In mice, the effect of specific genetic variants has been identified either through a genome-wide, forward genetic approach (from phenotypic variation to underlying gene variants), or by testing the consequences of genetic ablation of specific genes chosen from their function (reverse genetic approach). Table 1 presents a cross-compilation of all mouse genes which have been shown to influence clinical severity and/or lethality after infection with WNV, DENV, ZIKV, YFV or JEV. The corresponding experimental details, results and references are provided in Table 2.

Genome-wide search for genetic association

The forward genetic approach to identify flavivrus-resistance genes has been successfully applied so far only to WNV infection, taking advantage of the contrast between the high susceptibility of several laboratory inbred strains and the strong resistance of wild-derived inbred strains, one of the first examples of inherited resistance to a pathogen to be described in mice (Webster 1937; Webster and Clow 1936). Flavivirus resistance was found to be inherited in a monogenic, autosomal dominant manner (Darnell et al. 1974; Sangster et al. 1993) and was mapped to chromosome 5 (Urosevic et al. 1995). Two groups simultaneously identified a loss-of-function mutation in the 2'-5' oligoadenylate synthetase 1b (*Oas1b*) mouse gene (Mashimo et al. 2002; Perelygin et al. 2002) and experimentally confirmed its causative role in knocked-in (Scherbik et al. 2007) and transgenic mice (Simon-Chazottes et al. 2011). As pointed out by Mashimo et al., the susceptibility to WNV of almost all laboratory strains most likely results from the shared inheritance of a haplotype carrying the *Oas1b* mutation from one of the very few progenitors at the origin of laboratory mice (Mashimo et al. 2002).

Oas1b is one of the hundreds of IFN-stimulated genes (ISG) which have antiviral and immune modulatory activity to limit viral replication and spread. The mouse *Oas* gene cluster includes *Oas1*, *Oas2*, *Oas3*, and *OasL* genes. The *Oas1* gene has eight copies (*Oas1a* to *Oas1h*), compared to one copy (OAS1) in humans (Mashimo et al. 2003). Most *Oas* genes encode 2'-5' oligoadenylate synthetases (OAS) which bind to double-stranded RNA (dsRNA) and polymerize ATP into 2'-5'-linked oligoadenylates (2-5A). 2-5A bind and activate ribonuclease L (RNase L), a latent endoribonuclease. Upon activation during viral infection, RNase L cleaves viral and cellular single-stranded RNAs (ssRNAs). RNase L contributes to host resistance to WNV since RNAse L-deficient mice showed increased mortality (Samuel et al. 2006). RNase L products of RNA degradation can also bind and activate RIG-I-like receptors (RLR), resulting in enhanced innate immune signaling (Choi et al. 2015). However, *Oas1b* lacks 2-5A activity (Elbahesh et al. 2011). Moreover, RNase L has an antiviral effect against WNV infection in mouse embryonic fibroblasts carrying either functional or deficient *Oas1b* alleles, indicating that *Oas1b* controls WNV infection through another, RNase L-independent, mechanism (Elbahesh et al. 2011; Scherbik et al. 2006). Further insight into this mechanism may come from the identification of molecular partners of *Oas1b* (Courtney et al. 2012) and from the analysis of innate immune gene signatures that correlate with variations in *Oas1b* gene dosage, in genetically diverse mouse populations such as the Collaborative Cross (Green et al. 2017). This collection of recombinant inbred strains with large genetic diversity (Churchill et al. 2004) is an ideal platform for modelling a large range of phenotypes and has led to the development of several new models for human WNV disease where *Oas1b* is not the sole determinant (Graham et al. 2016; Graham et al. 2015).

Despite differences in the genomic organization of the members of this gene family across mammals, the conservation of the OAS pathway and of its role in host response to WNV allowed to successfully identify a variant of the equine OAS1 gene associated with symptomatic forms of WNV disease in horses (Rios et al. 2010).

An amino-acid substitution in the *Stat1* gene, resulting in partial inactivation of the IFN pathway, was recently identified in a backcross involving an MHC-II knockout mouse strain, through genome-wide

SNP genotyping followed by sequence capture and sequencing of the candidate interval (Larena and Lobigs 2017).

Similar genetic association studies have not yet been reported with other flaviviruses. In the case of Dengue and Zika viruses, they are more difficult to perform due to the necessity to analyze mice with an abrogated type I IFN response.

Functional analysis of candidate genes

Host genetic factors involved in mouse susceptibility to flavivirus infections have also been identified through reverse genetic approaches, by evaluating the phenotype resulting from a specific genetic modification. Most candidate genes have been tested based on their role in immune responses and validated through functional analysis using mice carrying loss-of-function mutations. In particular, the IFN signaling pathways are crucial in the innate immune response against flaviviruses (Miorin et al. 2017), although adaptive immunity also plays a significant role, as illustrated by the enhanced susceptibility to DENV or ZIKV of mice lacking *Rag1* or *Rag2* (Shresta et al. 2004; Winkler et al. 2017), two genes critical for B and T cell development (Table 2). The importance of several mechanisms in the host susceptibility to these infections has been confirmed *in vivo* by reverse genetics (Figure 1). These host genetic determinants are reviewed hereafter according to their function in the immune responses to viral infection.

Interferon responses

Type I IFNs are secreted by infected cells, induce an antiviral state and promote immune responses against viral pathogens in an autocrine and paracrine manner. These signaling pathways are finely regulated by host factors at multiple levels starting from viral sensing and recognition to transduction and regulation of transcription.

A variety of pattern recognition receptors (PRRs) are involved in the recognition of the virus, including Toll-like receptors (TLRs) and RLRs. Among the RLRs, *Ddx58* and *Ifih1* (which encode viral nucleic acid sensors known as RIG-I and MDA5, respectively), are essential PRR genes : mice deficient for either of them showed increased lethality after WNV infection, and mice lacking both genes were extremely susceptible (Errett et al. 2013; Lazear et al. 2013). Likewise, mice deficient for *Mavs*, the downstream adaptor molecule of these PRRs which coordinates pathways leading to the activation of NFκB, IFN regulatory factors (IRFs) 3 and 7, showed enhanced WNV replication and dissemination, with high mortality (Suthar et al. 2010). LGP2, another member of the RLR family, is not essential for induction of innate immune response but promotes antigen-specific CD8$^+$ T cell survival, proliferation, and anti-viral effector functions (Suthar et al. 2012). It was recently demonstrated that LGP2 associates with DICER and blocks the cleavage of viral dsRNAs, therefore inhibiting antiviral RNA interference (van der Veen et al. 2018). TLR7, a sensor for ssRNA, is another critical host sensor of WNV. *Tlr7* inactivation in mice led to an ineffective viral clearance and resulted in increased susceptibility to lethal WNV encephalitis (Town et al. 2009). MYD88 is considered the exclusive adaptor molecule for TLR7 and is required for signal transduction after viral RNA sensing and for an effective IFN response against WNV (Wang et al. 2004). Accordingly, *Myd88* KO mice displayed the same highly susceptible phenotype as *Tlr7* KO mice following WNV infection (Szretter et al. 2010; Town et al. 2009). By contrast, the analysis of *Tlr3*-deficient mice has led to contradictory results. A first study found that *Tlr3* KO mice were more resistant to WNV infection than controls, with decreased viral load in the brain and reduced blood-brain barrier permeability (Wang et al. 2004), while another study reported higher mortality and increased viral burden in the central nervous system (CNS) (Daffis et al. 2008a). Discrepancies were attributed to differences in passage history of the virus, and to dose or route of inoculation. Finally, MB21D1, also known as cGAS, is a cytosolic sensor of dsDNA and a cGMP-AMP synthase which plays a

key role in restriction of DNA viruses (Ma and Damania 2016). Interestingly, it is also important for innate immunity against RNA viruses with no DNA intermediates in their life cycle, as demonstrated by the increased susceptibility of *Mb21d1* KO mice to WNV (Schoggins et al. 2014). cGMP activates TMEM173, better known as STING (also MITA or MYPS). DENV protein NS2B3 is able to cleave human, but not mouse STING (Aguirre et al. 2012; Ma and Damania 2016; Stabell et al. 2018; Yu et al. 2012), a phenomenon which contributes to the natural resistance of mice to DENV. NS2B3 protein from WNV, ZIKV and JEV, but not YFV, showed the same property (Ding et al. 2018). However, *Tmem173*-deficient mice did not exhibit increased susceptibility to ZIKV (Ding et al. 2018).

Viral recognition by TLRs or RLRs activates multiple transcription factors including NF-κB and IRFs, directly or through TBK1. *Irf3*, *Irf5* and *Irf7* seem to have redundant functions since these three genes need to be inactivated to induce susceptibility to DENV or ZIKV (Carlin et al. 2017; Lazear et al. 2016). Although signaling through the same pathway, IRFs can influence host susceptibility through cell and tissue-specific processes. Mice deficient for either *Irf1*, *Irf3*, *Irf5* or *Irf7* showed increased mortality upon WNV infection with intact IFN-β production (Brien et al. 2011; Daffis et al. 2007; Daffis et al. 2008b; Thackray et al. 2014). IRFs stimulate in turn the transcription of type I IFNs. Mice deficient for the *Ifnb* gene, or injected with an antibody directed against IFN-α or/and IFN-β before and during WNV infection displayed increased lethality, highlighting the critical contribution of type I IFNs in antiviral responses against WNV (Lazear et al. 2011; Sheehan et al. 2015). Likewise, mice deficient for the type II IFN *Ifng* gene showed enhanced mortality with higher viremia and replication in lymphoid tissue (Shrestha et al. 2006).

IFN receptors are the central players of the IFN system and are activated upon binding of their subtype-specific IFN. Noteworthy, mice deficient in *Ifnar1* and in both *Ifnar1* and *Ifngr1* genes (often referred to as A129 and AG129, respectively, when bred on the 129S2/SvPas background) are currently the most widely used models in YFV, DENV and ZIKV studies. *Ifnar1* KO mice were more susceptible than WT controls to WNV (Samuel and Diamond 2005), ZIKV (Dowall et al. 2017; Lazear et al. 2016; Rossi et al. 2016; Tripathi et al. 2017), DENV (Orozco et al. 2012; Prestwood et al. 2012; Shresta et al. 2004), and YFV (Meier et al. 2009) infections, with high levels of viral replication and disease manifestations allowing for pathogenesis and mechanistic studies *in vivo.* Morbidity and lethality were very high with WNV, ZIKV and YFV, and were dose-dependent with DENV. By contrast, *Ifngr1* KO mice were resistant to YFV (Meier et al. 2009), moderately susceptible to DENV (Shresta et al. 2004) but highly susceptible to WNV (Shrestha et al. 2006). Mice lacking the receptor for type III IFN (*Ifnlr1* gene) were resistant to YFV but exhibited enhanced WNV neuroinvasion with increased blood-brain barrier permeability (Lazear et al. 2015) and enhanced ZIKV transplacental transmission (Jagger et al. 2017). For all the above viruses, *Ifnar1/Ifngr1* double KO mice displayed very high susceptibility with 100% mortality (Aliota et al. 2016; Meier et al. 2009; Prestwood et al. 2012; Shresta et al. 2004; Thibodeaux et al. 2012). Likewise, *Ifnar1/Ifnlr1* double KO mice were highly susceptible to YFV (Douam et al. 2017). These mouse models have allowed to decipher the roles of the different IFNs and IFN-receptors subtypes in response to flaviviruses. For example, in DENV infection, IFNAR signaling limits initial viral replication and controls its subsequent dissemination. By contrast, IFNGR-mediated responses appear to act at later stages of dengue disease by restricting viral replication in the periphery and eliminating virus from the CNS (Shresta et al. 2004).

IFN-receptors signal through different tyrosine kinases which recruit signal transducers and activators of transcription (STAT). STAT proteins are key mediators of the IFN response. IFNAR and IFNLR signal through both STAT1 and STAT2 whereas only STAT1 is activated after IFNGR stimulation. STAT2 is one of the targets of the NS5 protein of flaviviruses, a potent and specific antagonist of IFN signaling which acts through virus-specific mechanisms (Grant et al. 2016). ZIKV NS5 binds to and targets human

(Kumar et al. 2016), but not mouse, STAT2 for proteasomal degradation, which provides the mechanism underlying the natural resistance of mice to ZIKV and DENV (Best 2017; Grant et al. 2016; Miorin et al. 2017). The difference between human and mouse STAT2 for the binding of DENV NS5 was mapped to the coiled-coil domain (Ashour et al. 2010). To bind STAT2, DENV and YFV require E3 ubiquitin ligases UBR4 (Best 2017; Grant et al. 2016) and TRIM23 (Laurent-Rolle et al. 2014), respectively. WNV NS5 binds to prolidase, a cellular peptidase, to suppress IFNAR maturation and cell surface expression (Laurent-Rolle et al. 2010; Lubick et al. 2015). By analyzing multiple crosses between mice inactivated for either *Ifnar1*, *Ifngr1*, *Stat1* or *Stat2* genes, Perry *et al.* have demonstrated the importance of STAT proteins in the host immune response against DENV. They have shown that the combined loss of STAT1 and STAT2 resulted in severe disease and death in mice challenged with DENV. They also showed, using high virus doses, that *Stat1* KO mice succumbed to dengue disease unlike *Stat2* KO mice, and concluded that STAT1 plays a more prominent role than STAT2 in anti-DENV responses (Perry et al. 2011). *Stat1* KO mice were also highly susceptible to ZIKV and YFV infections although morbidity and mortality rates varied according to viral strains (Kamiyama et al. 2017; Meier et al. 2009). After ZIKV infection, *Stat2* KO mice displayed neurological symptoms and viral dissemination to the brain and gonads. Interestingly, clinical signs of Zika fever were delayed and milder in *Ifnar1* KO mice compared with *Stat2* KO mice, pointing to a possible protective role of INF-λ response (Tripathi et al. 2017).

Once activated, STAT proteins stimulate the transcription of hundreds of ISGs. In addition to *Oas1b*, several ISGs have been shown to influence mouse susceptibility to WNV infection. Mice lacking *Rsad2* (also known as viperin), *Ifi27l2a, Ifitm3* or *Ifit2* were all more vulnerable to lethal WNV challenge and allowed higher viral replication mainly in the CNS (Cho et al. 2013; Gorman et al. 2016; Lucas et al. 2015; Szretter et al. 2011). *Rsad2* inhibits ZIKV replication by inducing proteasome-dependent degradation of ZIKV NS3 (Panayiotou et al. 2018) and the synthesis of a replication-chain terminator (Gizzi et al. 2018), and has cell-type specific activity in the CNS (Lindqvist et al. 2018). *Ifitm* proteins alter the properties of cell and viral membranes and can inhibit the replication of a wide range of pathogenic viruses (Perreira et al. 2013). They induce similar restriction of primary and antibody-dependent enhancement secondary DENV infections in human leukemia cells (Chan et al. 2012). *Ifitm3* inhibits the early stages of Zika virus replication and can prevent Zika virus-induced cell death (Savidis et al. 2016). In a model of direct inoculation of ZIKV in the eye, *Isg15* KO mice showed increased ocular tissue pathology, characterized by a severe chorioretinitis with enhanced retinal cell death (Singh et al. 2017).

Overall, many studies have emphasized the crucial role of IFN responses, and especially the type I IFN pathway, which constitute an essential line of defense for the host after infection by flaviviruses.

Cytokines and chemokines regulating the immune response

The role of cytokines and chemokines as important regulators of immune responses has also been investigated in flaviviral infections using mice deficient for cytokines, chemokines or chemokine receptors.

After WNV infection, *Il10* KO mice had a decreased mortality rate, suggesting that IL-10, which has immunosuppressive properties, promotes WNV pathogenesis (Bai et al. 2009). Mice lacking IL-12b or IL-23a were more susceptible to WNV induced encephalitis, but not mice deficient for IL-12a, indicating that survival required intact IL-23 as opposed to IL-12 responses (Town et al. 2009).

Chemokines and chemokine receptors, which modulate leukocytes trafficking, play an important role in the regulation of immune responses. Several of them have been implicated in host susceptibility to flaviviruses, sometimes with opposing effects depending on the virus and its cell tropism. Deficiency

in *Cxcr3*, the receptor for chemokines CXCL9, CXCL10 and CXCL11, resulted in increased lethality in mice infected by DENV or WNV, with a decrease in T lymphocytes in the brain, CD8^{+} T cells in particular (Hsieh et al. 2006; Zhang et al. 2008). Mice lacking CXCL10 also showed enhanced susceptibility to DENV infection with higher viral loads in the brain but unchanged number of infiltrating T cells, suggesting that CXCL10 protective effect in dengue might be due to its direct antiviral activity rather than its role in lymphocyte recruitment (Hsieh et al. 2006; Ip and Liao 2010). *Cxcl10* KO mice showed enhanced susceptibility to WNV with increased viral burden in the brain and a decrease in CXCR3^{+} CD8^{+} T-cell trafficking, supporting a neuroprotective role for *Cxcl10* in the brain (Klein et al. 2005). *Ccr2* KO mice displayed increased survival time associated with decreased liver damage following DENV infection, whereas they showed a higher mortality rate combined with a reduction of monocyte accumulation in the brain after WNV infection (Guabiraba et al. 2010; Lim et al. 2011). Upon WNV infection, *Ccr7*-deficient mice exhibited enhanced mortality and CNS viral load, associated with marked leukocyte accumulation in the brain. These results indicate that CCR7 contributes to viral clearance and effectively modulates neuroinflammation in a model of WNV encephalitis (Bardina et al. 2017).

Other stimulatory molecules of immune cells have crucial functions in promoting or restricting flaviviral infections. CLEC5a is a C-type lectin which regulates cell adhesion and cell-cell signaling during the immune response. CLEC5a has been shown to act as a susceptibility factor in DENV infection. *Stat1* KO mice treated with an anti-CLEC5a antibody showed increased survival associated with a reduction of plasma leakage and TNF-α serum level (Chen et al. 2008). Mice deficient in *Tnfrsf9*, a T cell co-stimulatory factor, displayed reduced mortality rate in a model of Japanese encephalitis, highlighting a detrimental role of this molecule in the immune response against JEV (Kim et al. 2015).

Other Mechanisms

Autophagy is an essential mechanism which targets cellular components for lysosomal degradation. In the immune system, autophagy has many functions in both innate and adaptive responses, such as intracellular pathogen detection, modulation of the inflammatory processes as well as regulation of lymphocytes homeostasis. Mice carrying a hypomorphic variant of *Atg16l1*, a key autophagy gene, and treated with an anti-IFNAR antibody showed reduced ZIKV vertical transmission and placental damage. This phenotype was shown to result from a placental cell-autonomous effect of autophagy activity indicating that autophagy promotes ZIKV pathogenesis during gestation (Cao et al. 2017).

Semaphorins constitute a group of proteins that are involved in connecting the neuronal and immune systems. Following WNV infection, *Sema7A* KO mice exhibited increased survival, correlated with a reduction of blood-brain barrier permeability. SEMA7A thus appears to play a deleterious role during WNV infection *in vivo* (Sultana et al. 2012).

Human vs mouse genetics

While mouse genetics studies improve our understanding of the function of genes and identify new susceptibility genes in genome wide screens, the main obstacle in studying flaviviruses using mouse models is the inherent resistance of mice to most mosquito-borne flaviviruses (such as DENV and ZIKV). Several mouse models frequently used in flaviviral research are constitutively deficient for the IFN type I and/or type II responses, and therefore do not reflect an intact functioning human immune system. Moreover, these models are generally more susceptible to mouse adapted viral strains, which are genetically different from human pathogens Therefore, human cohorts are important to understand the role of the genes in protection or pathogenesis of human diseases, although human genetic studies are highly dependent on patient numbers.

Human genetic studies

Multiple approaches have been taken to identify genetic variants in human populations associated with susceptibility or resistance to flaviviruses, in particular case-control studies to test candidate genes, genome-wide association studies, association with specific HLA alleles, and allelic selection in exposed populations or ethnicities. Many studies have focused on favorable or disadvantageous immunological mechanisms involved in the pathogeny of infection but few have identified underlying genetic variants.

West Nile virus

WNV is a neurotropic virus and is transmitted to humans, who are a dead end host, by *Culex* mosquitoes. WNV causes a self-limiting febrile illness in most individuals that occasionally progresses to severe neurological disease including meningitis and encephalitis (Colpitts et al. 2012). Currently, there is no vaccine licensed in humans. Although there were a few human genetic studies on WNV, the most significant data resulted from the confirmation of the findings of the mouse model. Two polymorphisms of human OAS1, a splicing variant (rs10774671) (Lim et al. 2009), and an intron 2 variant (rs34137742) (Bigham et al. 2011), were associated with symptomatic WNV seroconversion. Another study found a polymorphism of human OASL (rs3213545) associated with hospitalized WNV fever, meningitis and/or WNV encephalitis (Yakub et al. 2005). Two studies have identified associations between the clinical severity of WNV infection and HLA Class I and II alleles (Lanteri et al. 2011; Sarri et al. 2016).

Dengue virus

Classification of Dengue cases

DENV, which is the most common mosquito borne viral infection, is spreading worldwide. There is one dengue vaccine licensed. The strategic Advisory Group of Experts on Immunisation (SAGE) recommended limited usage of the vaccine in only seropositive individuals since April 2018 (http://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/). There are four serotypes of DENV co-circulating (DENV-1 to DENV-4). Infection by one of the four can result in a spectrum of clinical outcomes ranging from asymptomatic to inapparent infection (patients developed mild disease but not enough to seek medical advice) to undifferentiated fever, classical dengue fever (DF) with or without hemorrhage, dengue hemorrhagic fever (DHF) with plasma leakage leading to shock (dengue shock syndrome (DSS)) and other organ involvement (such as hepatitis, encephalitis).

There are several difficulties in performing genetic studies of dengue even though there are a high number of cases. First, clinical case definition can be based on either WHO 1997 (WHO 1997) or WHO 2009 criteria (WHO 2009), that define severity of dengue in different ways. The WHO 1997 utilizes well defined criteria focused on plasma leakage to differentiate DF, DHF and DSS. The WHO 2009 criteria are designed for patient management and rely on more subjective criteria including several signs and symptoms of multiple organ involvement, hence complicating our understanding of disease pathogenesis. Therefore, most human genetic studies used WHO 1997 criteria, which is specific for plasma leakage.

Secondly, previous infection history and infecting dengue serotypes are the two most important confounding factors for genetic studies but are expensive, time consuming and not always possible to determine. Most studies, which are designed to distinguish primary from secondary infection and can identify the infecting dengue serotype indeed showed interaction of these variables and genetic factors (Simon-Loriere et al. 2015; Stephens et al. 2002).

There were more human genetics studies of DENV compared to mouse genetic studies, which were more focused on candidate genes related to IFN pathways. There are several excellent recent reviews on human genetic susceptibility to dengue, including a meta-analysis (Xavier-Carvalho et al. 2017a). Associations could be replicated in at least two populations for only one locus and six genes (Xavier-Carvalho et al. 2017a). The region which was replicated in many populations is the HLA locus on chromosome 6 including HLA-A*24 (Loke et al. 2001; Malavige et al. 2011; Nguyen et al. 2008), MHC class I polypeptide-related sequence B MICB (rs3132468) (Dang et al. 2014; Khor et al. 2011; Whitehorn et al. 2013) and tumor necrosis factor TNF (-308, rs1800629) (Fernandez-Mestre et al. 2004; Fernando et al. 2015; Sam et al. 2015; Santos et al. 2017). The other six genes are C-type lectin, CD209 (rs4804803) (Sakuntabhai et al. 2005; Wang et al. 2011; Xavier-Carvalho et al. 2013), C-type lectin domain containing 5A CLEC5A (rs1285933) (Xavier-Carvalho et al. 2017b; Xavier-Carvalho et al. 2013), immunoglobulin heavy chain receptor FcgR IIA (Arg131His-rs1801274) (Garcia et al. 2010; Mohsin et al. 2015; Noecker et al. 2014), cytokine IL-10 (-1082/-819/-592) (Fernando et al. 2015; Perez et al. 2010), alpha tryptase 1 TPSAB1 (Velasquez et al. 2015) and phospholipase C epsilon 1 PLCE1 (rs3765524, and rs3740360) (Dang et al. 2014; Khor et al. 2011; Whitehorn et al. 2013). Among these genes, how CLEC5A contributes to pathology has been investigated in a mouse model for DENV (Chen et al. 2008).

Although there was a bias of patient selection among the studies (more studies on DHF/DSS than DF), there was evidence that different sets of genes are associated with DF (mild clinical dengue) and/or DHF/DSS (severe dengue). While the more severe form of dengue is associated with HLA class I, and genes associated with inflammation and immune response (CLEC5A) (Xavier-Carvalho et al. 2017b; Xavier-Carvalho et al. 2013), cytokine response (IL-10), NK cell (MICB), mast cell activity (TPSAB1) (Velasquez et al. 2015) and lipid metabolism (PLCE1, PLCB4, OSBPL10, RXRA) (Sierra et al. 2017), DF is associated with genes in xenobiotic pathway (CHST10, AHRR, PPP2R5E and GRIP1) (Oliveira et al. 2018) and HLA class II (LaFleur et al. 2002; Sierra et al. 2007; Stephens et al. 2002; Weiskopf et al. 2015). Genes involved in viral entry (CD209, FcgRII) and TNFα pathway were associated with both forms of diseases. In addition, a non-synonymous variant of OAS3 was associated with severe dengue caused by DENV serotype 2 (Simon-Loriere et al. 2015). Adaptive immunity could play a more important role in eliminating the virus and in the development of clinical and severe dengue disease. More human genetic studies with well-characterized patients are needed in order to understand protection and pathogenesis of mild clinical and severe dengue in humans.

An association between HLA class I alleles and DHF susceptibility was shown in a large cohort of Vietnamese patients. More specifically, it was found that children with HLA-A*33 were less likely to develop DHF, whereas children with HLA-A*24 were at increased risk of developing DHF (Loke et al. 2001). Analyses of NS3- and NS5-specific CD8 T cell responses in different donors suggest opposing roles for T cells in both protection and development of DHF. Likewise, a more recent study in Vietnam confirmed the HLA association between HLA-A*24 and DHF or DSS and showed that HLA-A*24 with histidine at codon 70 is a susceptible allele, whereas the HLA-DRB1*0901 class II allele is protective against development of DSS, in patients with DENV-2 infection (Nguyen et al. 2008).

A second and larger case-control study in ethnic Thai patients revealed a variety of HLA class I association with the severity of clinical disease during secondary DENV infections (Stephens et al. 2002). The HLA-A*0203 allele was in particular associated with less severe DF, regardless of the secondary infecting virus serotype. By contrast, HLA-A*0207 was associated with susceptibility to the

more severe DHF in patients with secondary DENV-1 and DENV-2 infections. Conversely, HLA-B*51 was associated with the development of DHF in patients with secondary infections, and HLA-B*52 was associated with DF in patients with secondary DENV-1 and DENV-2 infections. Moreover, HLA-B44, B62, B76 and B77 also appeared to be protective against developing clinical disease after secondary dengue virus infection. Interestingly, at least for the HLA-A*02 class I alleles, the strong binding potential to viral peptides was suggested to enable T cell activation and protection observed in these patients with secondary DENV infections.

Another study of HLA polymorphism in the Cuban population revealed an increased frequency of HLA-A*31 and -B*15 class I alleles in symptomatic dengue virus infection compared with controls, and conversely, an elevated frequency of HLA-DRB1*07 and DRB1*04 class II alleles in control subjects compared with dengue case patients (Sierra et al. 2007). In a Mexican population, HLA-B*35 was negatively associated with symptomatic disease, whereas HLA-DQB1*0302 was positively associated with DHF, and HLA-DQB1*0202 was positively associated with DF only (Falcon-Lezama et al. 2009). Finally, in a Sri Lankan population, it was found that HLA-A*31 and HLA-DRB1*08 were associated with susceptibility to DSS, during secondary infection, and HLA-A*24 and HLA-DRB1*12 were strongly associated with DHF during primary dengue infection (Malavige et al. 2011).

One of the reasons for the association observed between certain HLA alleles and dengue disease severity is linked to the ability of these class I or class II alleles to induce a strong CD8+ or CD4+ T cell response against dengue epitopes. In that respect, it was found that T cell responses that were weak in magnitude, for example those observed against dengue epitopes restricted by HLA-A*0101 and HLA-A*2401, correlated with disease susceptibility, whereas strong and polyfunctional CD8+ T cell responses were observed in HLA-B*3501 individuals and were negatively associated with symptomatic disease (Weiskopf et al. 2013). Likewise, a higher resistance and susceptibility to severe dengue clinical outcome were shown to be associated with a more vigorous CD4+ T cell response in the context of DRB1*0401 and DRB1*0802, respectively (Weiskopf et al. 2015).

Protective or enhancing Killer immunoglobulin-like receptors (KIRs) in DENV infection

An association between KIR-ligands pairs and susceptibility to dengue in Southern Brazil was also detected, in the context of DENV3 infection (Beltrame et al. 2013). Although the exact role of NK cells expressing either activating or inhibitory KIRs has yet to be determined during DENV infection in humans, several studies strongly support the ability of DENV- or Flavivirus-derived conserved peptides, to stimulate or to inhibit KIR2DS2 or RIR3DL1 NK cells *in vitro* against NS1 or NS3 peptides, and in the context of HLA-C*0102 or HLA-B*57, respectively (Naiyer et al. 2017; Townsley et al. 2016).

The HLA transgenic mice as models to study the immune protection against DENV infection

To allow the identification of HLA-restricted peptides derived from the viral proteins, several HLA class I and class II transgenic mice have been developed to study the T cell response against the whole virus or the peptides derived from the viral proteins (Boucherma et al. 2013; Pascolo et al. 1997). Strikingly, most DENV-derived T cell epitopes inducing a T cell response in HLA class I mice correspond to the peptides identified from human individuals after DENV infection (Duan et al. 2015; Elong Ngono et al. 2017; Rivino et al. 2013a; Rivino et al. 2013b; Weiskopf et al. 2013; Weiskopf et al. 2011). Importantly, as the magnitude of the T cell response reflects the binding affinity of the different peptides to an HLA allele, analysis of the magnitude of T cell response in these transgenic mice against the different peptides covering the whole sequence should allow the identification of the most immunogenic peptides inducing a long lasting immunity.

An improvement of this mouse model involves a transient blockade of type I interferon signaling, after treatment with anti-IFNAR antibody. Commonly used in wild type mice to study the cellular effectors of the immune response to different viruses, such as the WNV or ZIKV (Lazear et al. 2016; Ng et al. 2015; Pinto et al. 2011; Sheehan et al. 2015; Zhao et al. 2016), this procedure is currently adapted to the HLA transgenic mice, with the objective to study the role of peptide-specific T cells in the induction of long lasting immunity against DENV and ZIKV infection.

Perspectives

A number of studies on flaviviruses have focused on the influence of viral virulence factors on viral multiplication, on the inhibition of immune responses of the infected host, and on disease severity. By contrast, the role of host genetic determinants on clinical severity of flavivirus infections remains elusive, with the notable exception of type I IFN responses. The few examples of genes identified which are not directly related to the type I IFN responses demonstrate that genome-wide, unbiased approaches will be essential in identifying novel actors. Despite differences in host-virus interactions, the mouse can successfully serve as an experimental model to assess the role of specific genes and to query the genome for host genetic determinants in genetic reference populations with vast genetic polymorphism, such as the Collaborative Cross (Aylor et al. 2011) and the Diversity Outbred mice (Recla et al. 2014). Their IFN response could be abrogated by antibodies directed against the type I IFN receptor (Lazear et al. 2016). These resources will be highly valuable to address the complex host-virus interactions through systems biology approaches.

Along with these innovative mouse model, well-characterized human cohorts of flaviviral infections should be collected. More DENV cohorts with well-characterized virological, immunological and clinical parameters from different countries are needed to understand human genetic basis of susceptibility to severe dengue, host-viral interaction and genetic susceptibility to ADE phenomenon. In addition, cohorts of asymptomatic DENV infected patients will help us understand protective immunity and will serve as the best control for symptomatic and severe dengue. Beyond DENV and WNV, ZIKV infection represents an ongoing public health challenge because of its complications. Collecting a sufficient number of samples from ZIKV-infected donors living in different endemic regions is a necessary step forward to be able to identify host genetic factors influencing persistent infection, susceptibility to neurological complications, mother-to-child transmission, and susceptibility to brain pathology.

Conflict of interest statement

On behalf of all authors, the corresponding authors state that there is no conflict of interest.

Figure legends

Figure 1 : Innate immune response triggered by flavivirus infection, highlighting mouse genes involved in susceptibility or resistance.

Following infection by a flavivirus, viral RNA is detected by TLRs and RLRs which induce activation of several transcription factors such as NF-κB and IRFs which, in turn, promote the transcription of type I, type II and type III IFNs. Once secreted, each IFN subtype (α/β, γ, λ) binds to its specific receptor (IFNAR, IFNGR, IFNLR) which leads to the activation of the JAK/STAT transduction pathways. IFNAR and IFNLR both signal through STAT1, STAT2 and IRF9 whereas only STAT1 is activated by IFNGR. STAT proteins activate the transcription of hundreds of ISGs, including *Oas* genes, some of which sense viral

dsRNA and further promote viral ssRNA cleavage by activating RNase L. Genes of the IFN signaling pathway identified in the mouse as host genetic factors of susceptibility to flaviviral infections are depicted in red.

Abbreviations: TLR, Toll-like receptor; RLR, RIG-I-like receptor; IFN, interferon; IRF, IFN regulatory factor; ISG, IFN stimulated gene; ssRNA, single-stranded RNA; dsRNA, double-stranded RNA.

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Figure 1
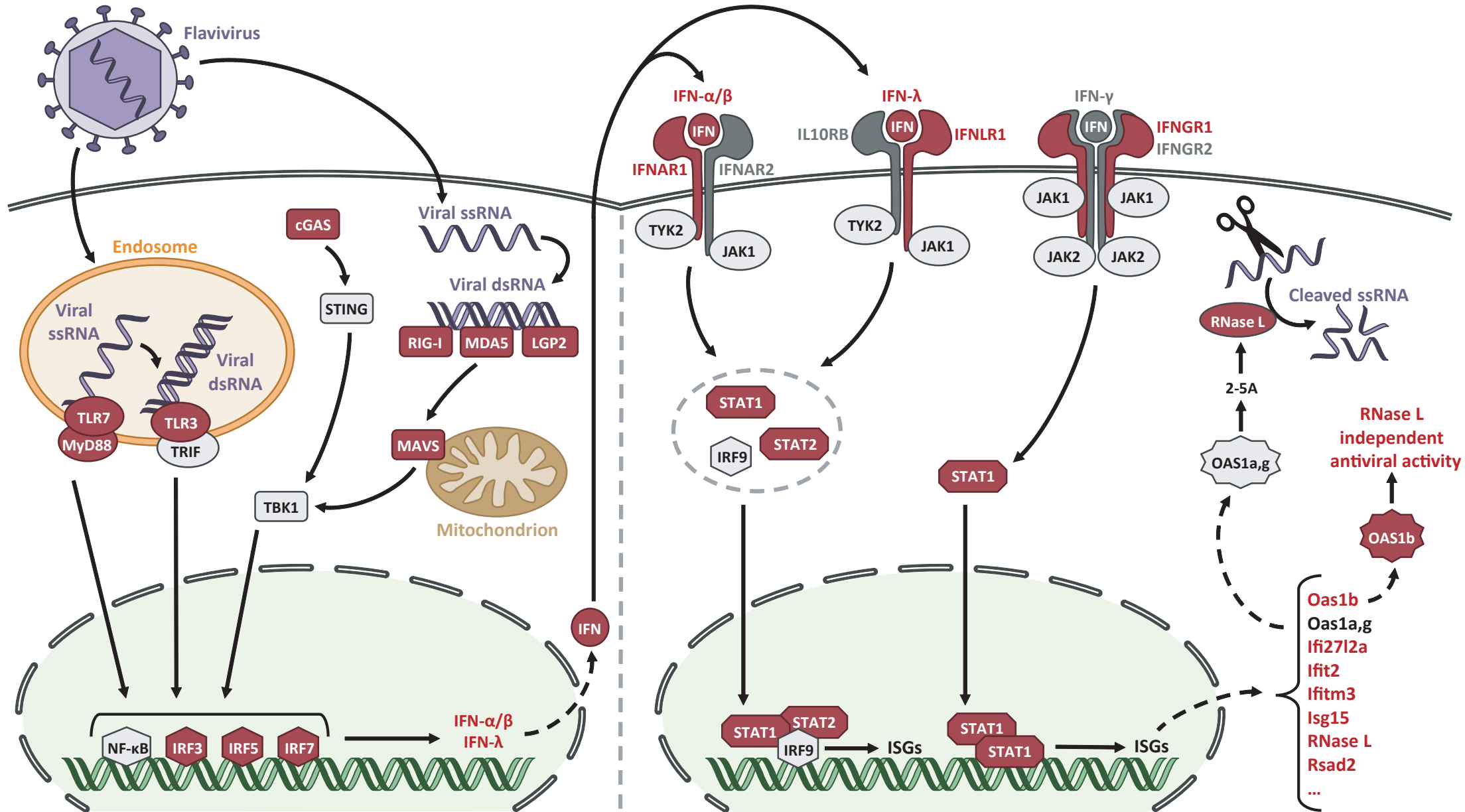
Gene *(synonym)*	WNV	DENV	ZIKV	YFV	JEV
Atg16l1			X		
Ccr2	X	X			
Ccr4		X			
Ccr7	X				
Clec5a		X			
Cxcl10	X	X			
Cxcr3	X	X			
Ddx58 (RIG-I)	X				
Dhx58 (LGP2)	X				
Ifih1 (MDA5)	X				
Ifi27l2a	X				
Ifit2	X				
Ifitm3	X				
Ifna	X				
Ifnb	X				
Ifng	X				
Ifnar1	X	X	X	X	
Ifngr1	X	X	X	X	
Ifnlr1	X		X	X	
Il10	X				
Il12a	X				
Il12b	X				
Il23a	X				
Irf1	X	X			
Irf3	X	X	X		
Irf5	X	X	X		
Irf7	X	X	X		
Isg15			X		
Mavs (IPS-1)	X				
Mb21d1 (cGas)		X			
Myd88	X				
Oas1b	X				
Rag1		X	X		
Rag2		X			
Rnasel	X				
Rsad2	X				
Sema7a	X				
Stat1	X	X	X	X	
Stat2		X	X		
Tlr3	X				
Tlr7	X				
Tnfrsf9					X

Table 1 : List of mouse genes which have been shown to affect clinical outcome and/or mortality following infection with WNV, DENV, ZIKV, YFV and JEV. Details of supporting studies are given in Table 2.

Gene symbol (synonym)	Function / pathway	Virus	Mouse strains / cell type	Experimental conditions	Phenotype, observations	References
			Genes identified by forward genetics approaches			
Oas1b	Activation of RNA decay pathway by dsRNA recognition	WNV	Susceptible BALB/cByJ, C57BL/6J vs resistant MAI/Pas and MBT/Pas, backcrosses and congenic strains	WNV strain IS-98-ST1, 1000 ffu ip, 6-wk-old mice	Most laboratory inbred mouse strains carry a non-sense, loss of function mutation making them highly susceptible.	Mashimo et al. 2002
		WNV	MEFs from susceptible C3H/He and resistant C3H.PRI-*Flv^r* congenic strain	WNV strain Eg101. In vitro infection of MEFs transfected with cDNAs of candidate genes	C3H.PRI-*Flv^r* congenic strain carries a non-sense mutation resulting in higher viral replication in MEFs.	Perelygin et al. 2002
		WNV	Collaborative Cross (CC) and F1 crosses of CC mice	WNV strain TX-2002-HC, 10^2 pfu footpad, 8-10-wk-old mice	*Oas1b* plays a role in susceptibility to WNV but a wide range of WNV-associated phenotypes are observed for a given *Oas1b* allele.	Graham et al. 2015
Stat1	Promotes transcription of ISG and IFN subtypes	WNV	Backcross between C57BL/6-*MHCII-Aα/β-/-* and C3H	WNV strain Kunjin, 10^3 pfu footpad, 8-wk-old mice	Highly susceptible *MHCII-Aα/β-/-* mice have acquired a spontaneous amino-acid substitution mutation.	Larena et al. 2017
			Genes identified by their function in host immune responses			
Ccr2	Chemokine receptor expressed on Ly6c^{hi} inflammatory monocytes and other leukocyte subtypes	WNV	C57BL/6J WT and *Ccr2* KO	WNV strain NY99-35262, 100 pfu sc, 8-12-wk-old mice	Increased mortality, large and selective reduction of Ly6c^{hi} monocyte accumulation in the brain, sustained monocytopenia.	Lim et al. 2011
Ccr7	Chemokine receptor expressed by numerous cell types, which regulates the homing of T cells into lymphoid organs	WNV	C57BL/6J WT and *Ccr7* KO	WNV strain NY99, 10^4 pfu footpad, 8-12-wk-old mice	Increased mortality and CNS viral loads, leukocyte accumulation in the CNS with neuroinflammation and reduced viral clearance.	Bardina et al. 2017
Cxcl10	Chemokine of the CXC subfamily which binds to CXCR3 receptor	WNV	C57BL/6J WT and *Cxcl10* KO	WNV strain NY99, 10^4 pfu footpad, 5-9-wk-old mice	Enhanced morbidity and mortality, increased viral burden in the brain, decreased CXCR3$^+$ CD8$^+$ T-cell trafficking	Klein et al. 2005

Gene	Description	Virus	Mouse model	Infection	Phenotype	Reference
Cxcr3	Receptor for chemokines CXCL9, CXCL10 and CXCL11 which stimulates leukocyte trafficking	WNV	C57BL/6J WT and *Cxcr3* KO	WNV strain 3000.0259, 10^2 pfu footpad, 5-8-wk-old mice	Enhanced mortality with increased viral burden and reduced CD8+ T cell trafficking specifically in the cerebellum.	Zhang et al. 2008
Ddx58 (RIG-I)	Cytoplasmic sensor of viral ssRNA and dsRNA	WNV	WT and *Ddx58* KO (mixed genetic background)	WNV isolate TX 2002-HC, 100 pfu footpad, 6-12-wk-old mice	Increased mortality. Decreased innate immune signaling and virus control in MEFs. *Ddx58-Ifih1* double KO are extremely susceptible.	Errett et al. 2013
Dhx58 (LGP2)	Cytoplasmic sensor of viral RNA and inhibitor of antiviral RNAi by association with Dicer	WNV	C57BL/6J WT and *Dhx58* KO	WNV isolate TX 2002-HC, 100 pfu footpad, 6-12-wk-old mice	Increased mortality despite activation of innate immune response. LGP2 regulates CD8+ T cell survival and effector functions.	Suthar et al. 2012
Ifih1 (MDA5)	Cytoplasmic sensor of viral dsRNA	WNV	C57BL/6J WT and *Ifih1* KO	WNV isolate TX 2002-HC, 100 pfu footpad, 6-12-wk-old mice	Increased mortality. Decreased innate immune signaling and virus control in MEFs. *Ddx58-Ifih1* double KO are extremely susceptible.	Errett et al. 2013
			C57BL/6J WT and *Ifih1* KO	WNV strain 3000.0259, 10^2-10^4 pfu footpad, 9-12-wk-old mice	Reduced survival. Increased viral burden primarily in the CNS.	Lazear et al. 2013
Ifi27l2a	ISG expressed at higher levels in granule cell neurons than in cortical neurons	WNV	C57BL/6J WT and *Ifi27l2a* KO	WNV strain 3000.0259, 100 pfu footpad, 8-12-wk-old mice	Increased susceptibility. Viral burden higher only in the CNS, associated with reduced cell death.	Lucas et al. 2016
Ifit2	Aka ISG54, member of the IFN-induced proteins with tetratricopeptide repeats	WNV	C57BL/6J WT and *Ifit2* KO	WNV strain 3000.0259, 100 pfu footpad or 10 pfu ic, 8-10-wk-old mice	Increased susceptibility with higher replication in the brain.	Cho et al. 2013
Ifitm3	ISG inhibiting virus entry and preventing viral fusion and release of viral contents into the cytosol	WNV	C57BL/6J WT and *Ifitm3* KO	WNV NY1999, 100 pfu sc, 8-9-wk-old mice	Increased susceptibility with higher viral burden in peripheral organs and CNS. Decreased B-cells, CD4+ T cells and Ag-specific CD8+ T cells.	Gorman et al. 2016
Ifna	Interferon-α (type I) with multiple members	WNV	C57BL/6J treated with anti-IFN-α mAb	WNV strain 3000.0259, 100 pfu footpad or 10 pfu ic, 8-12-wk-old mice	Increased lethality when mAb injected one day prior and two days following WNV infection.	Sheehan et al. 2015
Ifnb	Interferon-β (type I)	WNV	C57BL/6J WT and *Ifnb* KO	WNV strain 3000.0259, 100 pfu footpad or 10 pfu ic, 8-12-wk-old mice	Increased mortality with enhanced viral replication in peripheral tissues and the CNS.	Lazear et al. 2011
Ifng	Interferon-γ (type II)	WNV	C57BL/6J WT and *Ifng* KO	WNV strain 3000.0259, 100 pfu footpad or 10 pfu ic, 8-12-wk-old mice	Increased mortality with enhanced viremia and viral replication in lymphoid tissues, earlier detection of WNV the CNS.	Shrestha et al. 2006

Gene	Description	Virus	Mouse strain	Infection conditions	Phenotype	Reference
Ifnar1	Receptor of type I (α and β) interferons	WNV	C57BL/6J WT and *Ifnar1* KO 129Sv/Ev WT and *Ifnar1* KO	WNV strain 3000.0259, 100 pfu footpad or 10 pfu ic, 8-10-wk-old mice	High susceptibility with death in 4 days and increased infection in macrophages, B cells, and T cells in the spleen.	Samuel and Diamond 2005
Ifngr1	Receptor of type II (γ) interferon	WNV	C57BL/6J WT and *Ifng* KO	WNV strain 3000.0259, 100 pfu footpad or 10 pfu ic, 8-12-wk-old mice	Increased mortality with enhanced viremia and viral replication in lymphoid tissues, earlier detection of WNV the CNS.	Shrestha et al. 2006
Ifnlr1	Receptor of type III (λ) interferon	WNV	C57BL/6J WT and *Ifnlr1* KO	WNV strain 3000.0259, 100 pfu footpad, 5-12-wk-old mice	Increased viral load in the brain due to enhanced blood-brain barrier permeability.	Lazear et al. 2015
Il10	Pleiotropic cytokine with immunosuppressive properties	WNV	C57BL/6J WT and *Il10* KO	WNV strain 2741, 2000 pfu ip, 7-8wk-old mice	Markedly reduced infection with increased production of antiviral cytokines.	Bai et al. 2009
Il12a	p35 subunit of IL12 which activates NK cells and induces differentiation of CD4+ T-cells into IFN-γ producing Th1 cells.	WNV	C57BL/6J WT and *Il12a* KO	WNV strain 2741, 2000 pfu ip, 8-12wk-old mice	No difference in susceptibility with wildtype controls.	Town et al. 2009
Il12b	p40 subunit of IL12	WNV	C57BL/6J WT and *Il12b* KO	WNV strain 2741, 2000 pfu ip, 8-12wk-old mice	Increased mortality.	Town et al. 2009
Il23a	Associates with IL12B to form IL23, which can activate STAT4 and stimulate the production of IFN-γ	WNV	C57BL/6J WT and *Il23a* KO	WNV strain 2741, 2000 pfu ip, 8-12wk-old mice	Increased mortality.	Town et al. 2009
Irf1	Transcriptional regulator of interferon stimulated genes	WNV	C57BL/6J WT and *Irf1* KO	WNV strain 3000.0259, 100 pfu footpad, 8-12-wk-old mice	Increased mortality, elevated viral burdens in peripheral tissues and the CNS.	Brien et al. 2011
Irf3	Transcriptional regulator of interferon stimulated genes	WNV	C57BL/6J WT and *Irf3* KO	WNV strain 3000.0259, 100 pfu footpad, 8-12-wk-old mice	Increased mortality, elevated viral burdens in peripheral tissues and the CNS.	Daffis et al. 2007
Irf5	Transcriptional regulator of interferon stimulated genes	WNV	C57BL/6J WT and *Irf5* KO	WNV strain 3000.0259, 100 pfu footpad, 9-10-wk-old mice	Increased lethality with elevated infection in peripheral organs and the CNS.	Thackray et al. 2014
Irf7	Transcriptional regulator of interferon stimulated genes	WNV	C57BL/6J WT and *Irf7* KO	WNV strain 3000.0259, 100 pfu footpad, 8-12-wk-old mice	Increased lethality with blunted systemic type I IFN response. Increased viral titers in primary macrophages, fibroblasts, dendritic cells, and cortical neurons.	Daffis et al. 2008b
Mavs (IPS-1)	Adaptor molecule of RIG-I and MDA5	WNV	C57BL/6J WT and *Mavs* KO	WNV isolate TX 2002-HC, 100 pfu footpad, 6-12-wk-old mice	High susceptibility in 8 days with enhanced viral replication and dissemination (similar to *Ddx58-Ifih1* double KO).	Suthar et al. 2010 Errett et al. 2013

Mb21d1 *(cGas)*	Cytosolic DNA sensor, cGMP-AMP synthase, activator of *Tmem173* (STING)	WNV	C57BL/6J WT and *Mb21d1* KO	WNV NY1999, 100 pfu sc, 8-9-wk-old mice	Increased mortality but no increase in brain viral load	Schoggins et al. 2014
Myd88	Adaptor molecule of TLR7	WNV	C57BL/6J WT and *Myd88* KO	WNV strain 2741, 2000 pfu ip, 8-12wk-old mice	Increased mortality. Increased viral burden systemically and in the CNS.	Town et al. 2009
			C57BL/6J WT and *Myd88* KO	WNV strain 3000.0259, 100 pfu footpad, 8-10-wk-old mice	Increased mortality. Increased viral burden primarily in the CNS.	Szretter et al. 2010
Rnasel	Ribonuclease L (2',5'-OAS-dependent)	WNV	C57BL/6J WT and *Rnasel* KO	WNV strain 3000.0259, 100 pfu footpad or 10 pfu ic, 8-10-wk-old mice	Increased mortality (even higher if combined with *Eif2ak2* (PKR) knockout). Increased viral burden in tissues and CNS.	Samuel et al. 2006
Rsad2	Aka viperin : ISG expressed in response to type I and II interferons. Modulates cholesterol and isoprenoid biosynthesis, and lipid raft formation.	WNV	C57BL/6J WT and *Rsad2* KO	WNV strain 3000.0259, 100 pfu footpad or 10 pfu ic, 8-10-wk-old mice	Increased lethality. Modest increase of viral replication in macrophages. No difference in cortical neurons.	Szretter et al. 2011
Sema7a	A membrane-associated/secreted protein involved in connecting the neuronal and immune systems.	WNV	C57BL/6J WT and *Sema7a* KO	WNV strain 2741, 1000 pfu ip, 6-8wk-old mice	Increased survival, reduced viral burden and blood–brain barrier permeability.	Sultana et al. 2012
Tlr3	Recognition of dsRNA	WNV	C57BL/6J WT and *Tlr3* KO	WNV strain 2741, 1000 pfu ip, 6-10-wk-old mice	Reduced mortality, reduced viral load, inflammatory responses and neuropathology in the brain.	Wang et al. 2004
				WNV strain 3000.0259, 100 pfu footpad, 8-12-wk-old mice	Increased mortality with higher viral burden in the CNS.	Daffis et al. 2008a
Tlr7	Recognition of ssRNA	WNV	C57BL/6J WT and *Tlr7* KO	WNV strain 2741, 2000 pfu ip, 8-12wk-old mice	Increased mortality. Increased viral burden systemically and in the CNS.	Town et al. 2009
Ccr2	Chemokine receptor expressed on Ly6c^{hi} inflammatory monocytes and other leukocyte subtypes	DENV	C57BL/6J WT and *Ccr2* KO	Mouse-adapted DENV-2 strain P23085, 20 pfu ip, 8-10-wk-old male mice	Enhanced survival associated with decreased liver damage, decreased cell activation and decreased cytokine storm.	Guabiraba et al. 2010
Ccr4	Chemokine receptor which regulates leukocytes trafficking	DENV	C57BL/6J WT and *Ccr4* KO	Mouse-adapted DENV-2 strain P23085, 20 pfu ip, 8-10-wk-old male mice	Enhanced survival associated with decreased hemoconcentration, thrombocytopenia, liver damage, systemic inflammation and leukocyte activation.	Guabiraba et al. 2010

Gene	Description	Virus	Mouse model	Virus strain and infection	Phenotype	Reference
Clec5a	C-type lectin which regulates cell adhesion, cell-cell signaling during immune response	DENV	*Stat1* KO (unspecified genetic background) treated with anti-CLEC5A mAb	Mouse-adapted DENV-2 strain New Guinea C-N, 10^5 pfu ip and ic simultaneously, unspecified mouse age	Decreased plasma leakage and TNF-α serum level without suppression of viral replication and overall reduced lethality.	Chen et al. 2008
Cxcl10	Chemokine of the CXC subfamily which binds to CXCR3 receptor	DENV	C57BL/6J WT and *Cxcl10* KO (unspecified genetic background)	Mouse-adapted DENV-2 strain New Guinea C-N, 2.10^5 pfu ic, 6-8-wk-old mice	Increased mortality rate but unchanged number of infiltrating T cells in the brain. *Cxcl10* KO mice tend to be more susceptible than *Cxcr3* KO mice.	Hsieh et al. 2006 Ip and Liao 2010
Cxcr3	Receptor for chemokines CXCL9, CXCL10 and CXCL11 which stimulates leukocyte trafficking	DENV	C57BL/6J WT and *Cxcr3* KO (unspecified genetic background)	Mouse-adapted DENV-2 strain New Guinea C-N, 2.10^5 pfu ic, 6-8-wk-old mice	Increased mortality rate with high viral load associated with a decrease in CD8^{+} T cells in the brain.	Hsieh et al. 2006
Ifnar1	Receptor of type I (α and β) IFNs	DENV	C57BL/6J WT and *Ifnar1* KO	Mouse-adapted DENV-2 strain D220 or DENV-2 strain D2S10, 10^{5-6-7} pfu iv, 6-8-wk-old mice	Susceptible to both viral strains with 100% morbidity. Mortality rate varies between 15% and 100% according to the viral strain and dose. Viral replication is observed in blood, liver and blood marrow. Increased serum levels of TNF-α and IL-10.	Shresta et al. 2004 Orozco et al. 2012
			129Sv/Ev WT and *Ifnar1* KO (also called A129 mice)	DENV-2 S221 strain, 10^{11-12} genomic equivalents (GE) iv, 5-6-wk-old mice	100% morbidity with observation of systemic disease but no sign of limb paralysis. Mortality rate varies between 0% and 100% according to the inoculum dose. Viral replication is observed in blood, spleen and blood marrow.	Prestwood et al. 2012
Ifnar1 / Ifngr1	Receptors of type I (α and β) and type II (γ) IFNs	DENV	129Sv/Ev WT and *Ifnar1-Ifngr1* double KO (also called AG129 mice)	DENV-2 strain PL046, $10^{5-6-7-8}$ pfu iv or mouse adapted DENV-1 strain Mochizuki, 4.10^4 pfu iv, 5-6-wk-old mice	Highly susceptible to both viral strains. Mortality rate varies between 0 and 100% depending on DENV-2 infectious dose. Clinical signs include limb paralysis. Viral replication is observed in blood, spleen, lymph nodes and CNS.	Shresta et al. 2004 Prestwood et al. 2012
Irf1 / Irf3 / Irf5 / Irf7	Transcriptional regulators of IFN stimulated genes	DENV	C57BL/6J WT and *Irf3-Irf5-Irf7* triple KO (TKO) C57BL/6J WT and *Irf1-Irf3-Irf5-Irf7* quadruple KO (QKO)	DENV-2 S221 strain, 5.10^6 ffu iv, under ADE conditions, 5-6-wk-old male and female mice	Both TKO and QKO mice sustain viral replication but only QKO mice succumb to infection. DENV infection of TKO mice results in minimal type I IFN production but a robust type II IFN response.	Carlin et al. 2017
Rag1	Protein involved in activation of immunoglobulin V(D)J recombination during B and T cell development	DENV	C57BL/6J WT and *Rag1* KO (deficient in B and T lymphocytes)	DENV-2 strain PL046, $10^{5-6-7-8}$ pfu iv or mouse adapted DENV-1 strain Mochizuki, 4.10^4 pfu iv, 5-6-wk-old mice	Increased mortality rate with mouse-adapted DENV-1 strain but no detection of viral replication in peripheral organs.	Shresta et al. 2004

Gene	Function	Virus	Mouse model	Virus/infection conditions	Main findings	References
Rag2	Protein involved in the initiation of V(D)J recombination during B and T cell development	DENV	129Sv/Ev WT and *Rag2* KO (deficient in B and T lymphocytes)	DENV-2 strain PL046, $10^{5\text{-}6\text{-}7\text{-}8}$ pfu iv or mouse adapted DENV-1 strain Mochizuki, 4.10^4 pfu iv, 5-6-wk-old mice	Increased mortality rate with mouse-adapted DENV-1 strain but no detection of viral replication in peripheral organs.	Shresta et al. 2004
Stat1	Promotes transcription of ISG and IFN subtypes	DENV	129Sv/Ev WT and *Stat1* KO	DENV-2 strain PL046, $10^{7\text{-}8}$ pfu iv or mouse adapted DENV-1 strain Mochizuki, 4.10^4 pfu iv, 5-6-wk-old mice	Increased mortality rate with both DENV strains but viral replication is only transient (DENV is undetected at day 3 p.i. in various tissues).	Shresta et al. 2005 Perry et al. 2011
Stat2	Promotes transcription of ISG and IFN subtypes	DENV	C57BL/6J WT and *Stat2* KO	Mouse adapted DENV-2 D2S10 strain, 106 ffu iv, under ADE conditions, unspecified mouse age	Extended viral detection in spleen and lymph nodes but no mortality.	Perry et al. 2011
Stat1 / Stat2	Promotes transcription of ISG and IFN subtypes	DENV	129Sv/Ev WT and *Stat1-Stat2* double KO	DENV-2 S221 strain, 2.10^5 pfu iv, 5-6-wk-old mice	Highly susceptible, 100% morbidity and lethality contrary to single-deficient mice.	Perry et al. 2011
Atg16l1	Part of a protein complex necessary for autophagy	ZIKV	C57BL/6J WT and *Atg16l1^{Hm}* (hypomorphic) treated with anti-IFNAR mAb	ZIKV strain Paraiba 2015 (Asian), 10^3 ffu sc, 8-10-wk-old pregnant female mice	Restricted ZIKV vertical transmission and placental/fetal damage. Overall improved placental and fetal outcomes.	Cao et al. 2017
Ifnar1	Receptor of type I (α and β) IFNs	ZIKV	C57BL/6J WT and *Ifnar1* KO	Several ZIKV strains (African and Asian), 10^3 ffu sc, 5-6-wk-old male mice ZIKV strain MR766 (African) or PF13 (Asian), 10^2 ffu sc, 5-6-wk-old male mice	Highly susceptible to the African strains, 100% morbidity and lethality. Depending on the Asian strains, mortality rate varies between 0 and 100%. Viral replication is observed in all cases in blood, brain, spleen, liver and testis.	Lazear et al. 2016 Tripathi et al. 2017 Other results reviewed in Winkler and Peterson 2017 Dowall et al. 2017 Rossi et al. 2016
			129Sv/Ev WT and *Ifnar1* KO (also called A129 mice)	ZIKV strain MP1751 (African) or PRVABC59 (Asian), 10 or 10^6 ffu sc, 6-8-wk-old male mice ZIKV strain FSS13025 (Asian), 10^5 ffu ip, 3-5-11-wk-old mice	Highly susceptible to the African strain, 100% morbidity and lethality. Viral dissemination to the brain, spleen, liver and testis. Susceptibility to Asian strain is age-dependent, only mice under 6 weeks of age display morbidity and lethality. Viral replication is observed in all cases in blood, brain, spleen, liver and testis.	

Gene	Function	Virus	Mouse model	Virus strain and inoculation	Phenotype	Reference
Ifnar1 / Ifngr1	Receptors of type I (α and β) and type II (γ) IFNs	ZIKV	129Sv/Ev WT and *Ifnar1-Ifngr1* double KO (also called AG129 mice)	ZIKV strain PF13 (Asian), 10^5 pfu sc, 3-4-8-wk-old mice	Highly susceptible regardless of mouse age or infectious dose. 100% morbidity and mortality. Viral replication is observed in blood and organs including spleen, liver and CNS but is associated with severe pathological findings only in the brain and muscle.	Aliota et al. 2016 Other results reviewed in Winkler and Peterson 2017
Ifnlr1	Receptor of type III (λ) interferon	ZIKV	C57BL/6J WT and *Ifnlr1* KO	ZIKV strain Paraiba 2015 (Asian), 10^3 pfu footpad	Increased ZIKV replication in the placenta and fetus	Jagger et al. 2017
Irf3 / Irf5 / Irf7	Transcriptional regulators of IFN stimulated genes	ZIKV	C57BL/6J WT and *Irf3-Irf5-Irf7* triple KO (TKO)	ZIKV strain MR766 (African) or PF13 (Asian), 10^2 ffu sc, 5-6-wk-old mice	Highly susceptible to both ZIKV strains, 100% morbidity and lethality.	Lazear et al. 2016
Isg15	Ubiquitin-like protein activated by type I IFNs	ZIKV	C57BL/6J WT and *Isg15* KO	ZIKV strain PRVABC59 (Asian), 10^4 pfu intravitreally in the right eye, 4-6-wk-old male and female mice	Severe chorioretinitis associated with increased retinal cell death and higher ZIKV RNA and protein levels.	Singh et al. 2017
Rag1	Protein involved in activation of immunoglobulin V(D)J recombination during B and T cell development	ZIKV	C57BL/6J WT and *Rag1* KO (deficient in B and T lymphocytes) treated with anti-IFNAR mAb	Mouse-adapted ZIKV strain Dakar 41519 (African), 10^6 ffu sc, 7-wk-old male mice ZIKV strain Paraiba (Asian), 10^4 pfu ip, 8-10-wk-old male mice	ZIKV replication is observed in male reproductive organs. Enhanced morbidity with signs of severe disease. Viral replication is observed at high level in the brain and testes.	Govero et al. 2016 Winkler et al. 2017
Stat1	Promotes transcription of ISG and IFN subtypes	ZIKV	129Sv/Ev WT and *Stat1* KO (unspecified genetic background)	ZIKV strain MR766 (African), 10^4 pfu sc, 7-8-wk-old male mice	Highly susceptible, 100% morbidity and lethality. High viral load in the blood and in the brain.	Kamiyama et al. 2017
Stat2	Promotes transcription of ISG and IFN subtypes	ZIKV	C57BL/6J WT and *Stat2* KO	ZIKV strain MR766 (African), 10^3 ffu sc, 5-6-wk-old female mice	Highly susceptible, 100% morbidity with neurological symptoms and 100% lethality. High viral loads in the CNS, gonads, spleen and liver.	Tripathi et al. 2017
Ifnar1	Receptor of type I (α and β) interferons	YFV	129 and *Ifnar1* KO	YFV Asibi and Angola wildtype strains, 10^4 pfu footpad and YFV 17D-204 vaccine strain, 10^6 pfu footpad, 3-4wk-old mice	Highly susceptible to viscerotropic YFV strain but subclinical infection with 17D vaccine strain.	Meier et al. 2009
			C57BL/6J and *Ifnar1* KO	YFV 17D vaccine strain, 10^4 pfu ip, 3-4wk-old mice	Viscerotropic disease with mortality by ip but not by im, footpad or sc routes.	Erickson and Pfeiffer 2015

Ifngr1	Receptor of type III (γ) interferon	YFV	129 and *Ifngr1* KO	YFV Asibi and Angola wildtype strains, 10^4 pfu footpad and YFV 17D-204 vaccine strain, 10^6 pfu footpad, 3-4wk-old mice	Resistant to YFV wildtype and 17D vaccine strains.	Meier et al. 2009
Ifnar1 / Ifngr1	Receptors of type I (α and β) and type II (γ) interferons	YFV	129 and *Ifnar1-Ifngr1* double KO	17D-204 vaccine strain, 10^6 pfu footpad, 3-4wk-old 17D-204 vaccine strain, 2.105 pfu ip, 7-8-wk-old mice	Highly susceptible to 17D-204 vaccine strain. Highly susceptible to 17D-204 vaccine strain, with neurotropic and viscerotropic infection (high viral titers in brain and liver).	Meier et al. 2009 Thibodeaux et al. 2012
Ifnlr1	Receptor of type III (λ) interferon	YFV	C57BL/6J WT and *Ifnlr1* KO	17D vaccine strain, 10^{6-7} pfu iv, 2-6mo-old	KO resistant to vaccinal strain 17D like *Ifnar1/2* mice, but mice with double *Ifnar1/2* and *Inflr1* KO highly susceptible.	Douam et al. 2017
Stat1	Promotes transcription of ISG and IFN-α subtypes	YFV	129 and *Stat1* KO	YFV Asibi and Angola wildtype strains, 10^4 pfu footpad and YFV 17D-204 vaccine strain, 10^6 pfu footpad, 3-4wk-old mice	Highly susceptible to viscerotropic YFV strain but subclinical infection with 17D vaccine strain.	Meier et al. 2009
Tnfrsf9	Aka CD137, T cell costimulatory molecule	JEV	C57BL/6 WT and *Tnfrsf9* KO	JEV Beijing-1 strain, 1.5-3.10^5 pfu ip, 4-5wk-old mice	Reduced mortality rate and reduced viral burden in extraneural tissues and the CNS.	Kim et al. 2015

Table 2 : Detailed information on mouse genetic studies supporting the role of specific genes on susceptibility or resistance to flaviviruses.