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Running interference: Interplay between Zika virus and the host interferon response

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ABSTRACT

The interferon (IFN) family of cytokines is a crucial part of the host's ability to mount an effective immune response against viral infections. In addition to establishing an antiviral state within cells, IFNs also support the optimal activation of other key immune cell types. The ability of members of the *Flaviviridae* family to suppress type I IFN responses has been well-described. Of these viruses, Zika virus (ZIKV) has recently attracted international attention due to a series of major outbreaks that featured the novel association of neurological symptoms with infection. Researchers have begun to investigate the strategies ZIKV uses to evade type I IFNs, and the impact this has on the host. However, a unique feature of ZIKV infection compared to other *flaviviruses* is its capacity to be transmitted sexually, as well as its ability to infect and persist within reproductive tissues. As such, this raises the question of a potential role for type III IFN during ZIKV infection. In this review, we will discuss the interplay between these two classes of IFN with ZIKV, models that have been used to interrogate these interactions, and the effect this interplay has on infection and infection outcomes. We will also consider the intriguing possibility of whether ZIKV has evolved improved evasion mechanisms to suppress the IFN response in recent outbreaks.

1. Introduction

Zika virus (ZIKV) is a mosquito-borne virus (family *Flaviviridae*, genus *flavivirus*) that has emerged as a significant global health threat after causing several major outbreaks since 2007 [1]. Although it was initially isolated in the Zika forest region of Uganda in 1947, the first undisputed human infection was not described until 1964 [2–4]. Throughout the remainder of the 20th century, this was followed by only a small number of isolated reports of ZIKV infection [1,5]. However, between April and July 2007 ZIKV caused a major outbreak on Yap Island, Federated States of Micronesia, during which 73% of the island's population (approximately 5,000 people) is estimated to have been infected [6]. This was followed by major ZIKV outbreaks in French Polynesia (2013) [7], and South and Central America (2015) [8]. Most recently, western India reported an outbreak that began in September 2018 with 135 confirmed cases, and ZIKV detected in 75,000 of 200,000 mosquito breeding sites tested in this region [9–10].

Infection with ZIKV is usually asymptomatic, however in up to 20% of cases it may cause symptoms characteristic of a mild, febrile illness, including fever, maculopapular rash, headaches, joint and muscle pain, fatigue, and conjunctivitis [1]. In recent outbreaks, this list has been expanded to include retro-orbital pain, edema and vomiting [1,6]. However, the most striking aspect of recent outbreaks has been the novel association of ZIKV infection and severe neurological symptoms, such as Guillain-Barré syndrome (GBS; an autoimmune ascending paralysis) and fetal microcephaly (a neurodevelopmental disorder due to ZIKV infection during pregnancy) [1]. Phylogenetic analyses of isolates from recent outbreaks have found that all contemporary ZIKV isolates fall within the Asian lineage, as opposed to the originally identified African lineage [11]. Furthermore, several amino acid polymorphisms have been identified that are common to Asian lineage ZIKV isolates with known clinical outcomes [1,12–13]. Understanding how ZIKV has shifted from causing sporadic, innocuous infections, to becoming a widespread health concern has been a significant focus of recent ZIKV research. Although there are a number of factors that may be involved in this shift, one intriguing possibility is that viral evolution has led to an improved capacity to evade host immunity.

A critical aspect of the antiviral immune response is the production of interferons (IFNs). The IFN superfamily is subdivided into three classes: type I, II, and III IFN. The type I IFN family is mainly composed

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of IFN-α and IFN-β. These signal through the type I IFN receptor (IFN-α/β receptor; IFNAR), which is expressed on all cell types, consequently leading to a diverse range of effects on many different cell types during infection [14]. Type II IFN, or IFN-γ, is mainly produced by T cells and natural killer (NK) cells, and functions to support immune responses against certain pathogens [14]. Lastly, the most recently discovered class of IFN, type III IFNs, are expressed at mucosal sites and function similarly to type I IFNs despite using a different receptor [14]. Since much of the work relating to IFN and ZIKV infection has focused on the role of type I and type III IFNs, this review will be centered on these two families.

The interplay between the host IFN response and evasion or suppression of this response by members of the *flavivirus* genus is well established. In particular, the non-structural (NS) 5 protein of many *flaviviruses* suppresses type I IFN signaling through a number of different strategies. These include proteasomal degradation of signal transducer and activator of transcription (STAT) 2, a protein in the type I IFN signaling pathway (ZIKV, Dengue virus [DENV]); suppressing IFN-stimulated gene (ISG) translation (Spondweni virus, yellow fever virus [YFV]), or suppression of IFNAR maturation and expression (West Nile virus [WNV]) [15]. However, there are many additional viral strategies for evading the IFN response, as well as ways in which the host attempts to counter these strategies. Less is known about the interplay between ZIKV and type III IFNs, although it is recognized that they play an important role in ZIKV immunity [16–19]. In this review, we will discuss type I and III IFNs, their role in ZIKV immunity, and how ZIKV counters these key host defenses. Further, we consider whether ZIKV has evolved enhanced capacity to evade the host's antiviral IFN response.

2. Type I and type III IFN

2.1. Production

Viral interference, the ability of an infected cell to become resistant to re-infection, is a concept that has been described for decades. However, it was in 1957 that Isaacs and Lindenmann first identified a secreted molecule capable of decreasing virus production following re-challenge. They hypothesized that this protein was capable of aborting (or interfering with) viral replication and it was therefore coined as IFN [20]. Since this discovery, the IFNs have been expanded to a superfamily of cytokines with three distinct classes (types I, II and III) which were categorized based on their structure, receptor utilization and biological function. The type I IFN class consists of 13 or 14 IFN-α subtypes, in humans and mice respectively, and a single subtype for IFN-β, as well as other, less studied subtypes such as IFN-ε, IFN-τ, IFN-κ, IFN-ω, IFN-δ and IFN-ζ. The type II IFN family consists of just one subtype, IFN-γ [14]. In 2003, three new IFN-like cytokines IFN-λ1, -λ2, and -λ3 (IL-29, IL-28A and IL-28B respectively) were identified and together with a more recently discovered cytokine, IFN-λ4, constitute the type III IFN class [21–23]. The IFN response is initiated following the detection of broadly conserved microbial molecular domains, termed pathogen-associated molecular patterns (PAMPs), by three groups of cellular sensors: Toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and DNA sensors (Fig. 1A). Once a sensor has been triggered, this initiates a signaling cascade that leads to the production of IFNs and activation of the innate immune system [24].

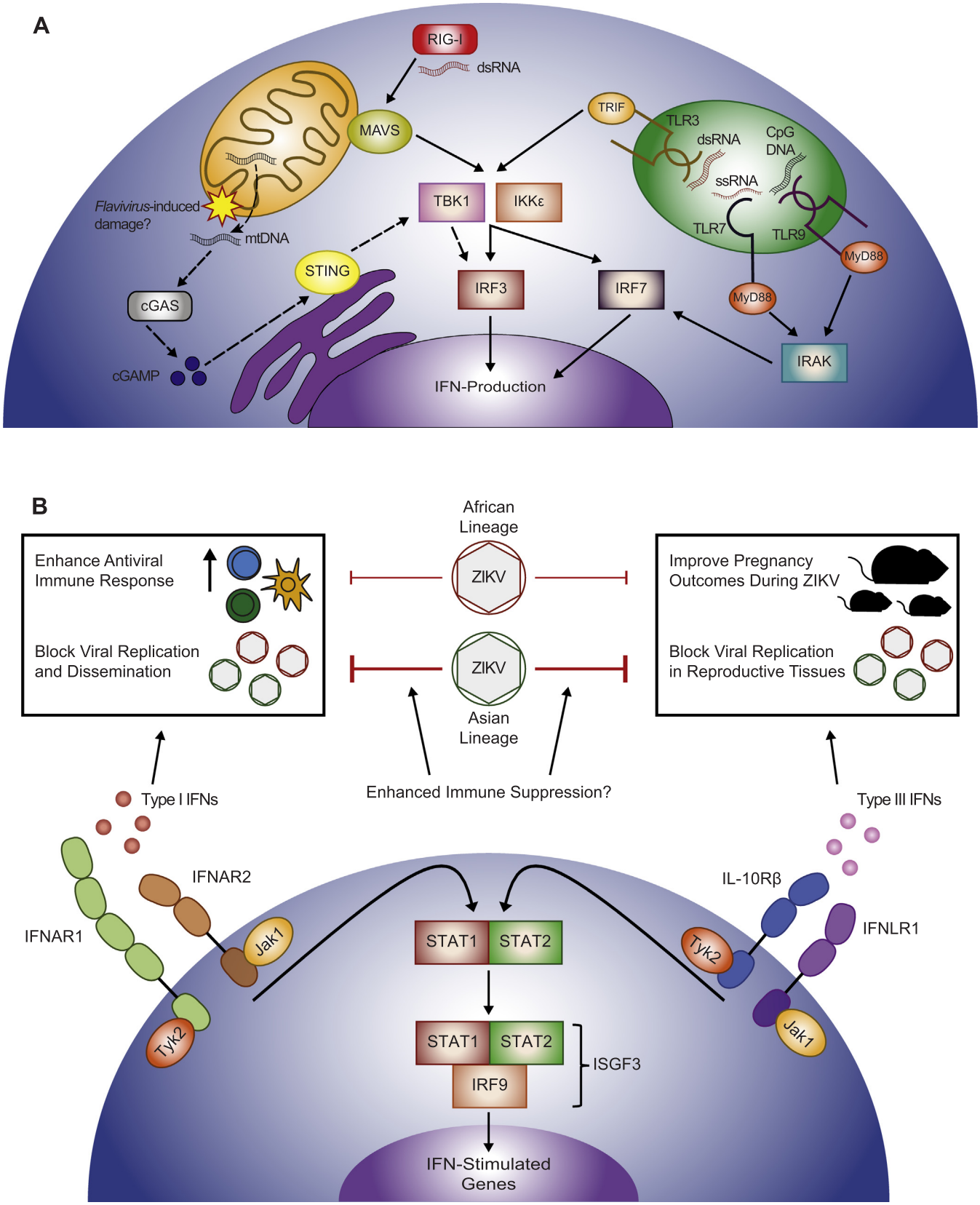
TLRs are transmembrane proteins whose locations (extracellular or endosomal) are dictated by the ligand for which they are specific. They can function as viral sensors and are expressed in key sentinel cell types, such as epithelial cells and cells from the innate and adaptive immune systems. Due to the broad range of ligands that may be recognized, TLRs are able to induce IFN production in response to most types of viruses, ensuring the establishment of an antiviral state [25]. Plasmacytoid dendritic cells (pDCs) express TLR7 and TLR9 that trigger a signaling cascade through the myeloid differentiation factor 88 (MyD88) pathway following recognition of single-stranded (ss)RNA or unmethylated CpG sequences in DNA, respectively. MyD88 activates interleukin (IL)-1 receptor associated kinase (IRAK) family kinases, ultimately leading to phosphorylation of IFN regulatory factor (IRF)7, which is essential for IFN production [24]. Conversely, double-stranded (ds)RNA activates TLR3, which is expressed in myeloid DCs and epithelial cells. Following activation, TLR3 utilizes the TIR-domain-containing adapter inducing IFN-β (TRIF) protein pathway for IFN production (Fig. 1A) [26]. The RLR family is composed of three cytosolic sensors of virus replication, which are broadly expressed in most cell types: retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated protein 5 (MDA5), and Laboratory of Genetics and Physiology 2 (LGP2) [27]. Following dsRNA binding, both RIG-I and MDA5 undergo conformational changes exposing their caspase activation and recruitment domain (CARD) which binds to a CARD domain in the mitochondrial antiviral-signaling (MAVS) adapter molecule. This interaction leads to the formation of MAVS aggregate structures on the mitochondrial membrane, recruitment and activation of noncanonical IκB kinases (IKK) TANK-binding kinase 1 (TBK1) or IKKε, and phosphorylation of IRF3 and IRF7, which are necessary for IFN expression (Fig. 1A) [24]. Although LGP2 lacks the CARD domain and is unable to signal through this process, it is thought to be important for regulation of the two other members of the RLR family [28]. DNA sensors are less characterized, however the cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase-stimulator of IFN genes (cGAS-STING) pathway has been shown to be important in IFN production [29]. Recognition of cytoplasmic DNA (either self or foreign) by cGAS triggers the synthesis of cyclic GMP-AMP (cGAMP) [30]. This secondary messenger binds to STING, an endoplasmic reticulum membrane protein, thereby triggering a conformational change that enables it to recruit TBK1. The latter activates IRF3, leading to IFN production (Fig. 1A) [30]. Combined, these pathways enable cells to induce IFN synthesis by recognizing a broad range of PAMPs, ensuring the establishment of an antiviral state within the cell.

ZIKV is speculated to induce type I IFN production by activating TLR3, TLR7, RIG-I and MDA5. The virus' ssRNA genome could serve as an activating ligand for TLR7, while a dsRNA intermediate formed during replication of the genome could activate TLR3, RIG-I or MDA5. It has also been shown that mitochondrial damage induced by infection with DENV (and potentially other *flaviviruses*) can cause release of mitochondrial DNA (mtDNA) into the cytoplasm, leading to activation of the cGAS-STING pathway and IFN production [31–32]. However, one study demonstrated significantly higher viral RNA accumulation only after small interfering (si)RNA silencing of TLR3, not TLR7, RIG-I or MDA5 [33]. Similarly, mice lacking MAVS (which is crucial for RIG-I and MDA5 signaling) or IRF3 (which is involved in IFN induction through the cGAS-STING, RIG-I, MDA5 and TLR3 pathways; Fig. 1A) did not succumb to ZIKV infection, in contrast to IFNAR KO mice [34]. Together, this suggests a key role for TLR7 in IFN induction during ZIKV infection, but does not rule out a contribution from other PRRs.

2.2. Signaling

In the absence of stimuli, IFN gene expression is virtually silent, although it has been shown that a low level of IFN production is important for maintaining an adequate level of critical signaling proteins (such as STAT1) in the cell [35]. This silencing is accomplished through a number of transcriptional repressors localized in the promoter regions of IFN proteins. However, following triggering by PAMPs, transcriptional repressors are replaced by activating IRF proteins (such as IRF3 and IRF7), thereby allowing IFN gene transcription. While IRF3 is constitutively expressed, IRF7 expression must be induced. As such, IRF3 is crucial during the early stages of viral infection, while signaling through IRF7 may result in delayed IFN induction [24].

Following expression, IFNs bind to their cognate receptors, which triggers a signaling cascade that induces changes in gene expression and



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provides an early line of defense against viral infections. IFN receptors are class II helical cytokine receptors, however each family utilizes a different receptor dimer [36]. Type I IFNs signal through a heterodimeric receptor composed of IFNAR1 and IFNAR2, which are low and high affinity, respectively. IFNAR2 exists in three different isoforms, however only IFNAR2c is able to signal through the Janus Kinase (JAK)-STAT pathway leading to an antiviral response. IFNAR2c possesses a long transmembrane domain and the full intracellular domain

Fig. 1. Interplay between ZIKV and the type I and type III IFN responses. (A) IFN production may be induced by a variety of stimuli, including CpG DNA (TLR9), ssRNA (TLR7), dsRNA (TLR3 and RIG-I) or mitochondrial (mt)DNA (cGAS-STING). Solid arrows indicate canonical signaling pathways for RIG-I and TLRs. Dashed arrows indicate proposed pathway by which *flavivirus* infection could cause mtDNA release into the cytoplasm, leading to activation of cGAS-STING, which uniquely activates TBK1 and IRF3. (B) Type I and type III IFNs signal through their cognate receptors, activating downstream signaling via STAT1-STAT2 heterodimers, which bind to IRF9 to form the IFN-stimulated gene factor 3 (ISGF3) complex. ISGF3 then translocates to the nucleus to activate IFN-stimulated gene transcription. During ZIKV infection, type I IFNs have been shown to block virus replication and dissemination, at least in part by enhancing the antiviral immune response. During ZIKV infection in the context of pregnancy, type III IFNs block virus replication in reproductive tissues which contributes to improving pregnancy outcomes. Although ZIKV has many strategies to suppress IFN response, the question remains whether contemporary, Asian lineage isolates have enhanced capacity to evade host immunity.

which is required for adapter binding and correct signal transduction [36]. Type III IFNs are different from the other two families since they use a heterodimeric receptor composed of one unique subunit (IFN-λ receptor 1 [IFNLR1]) and IL-10 receptor β (IL-10Rβ). The latter is also involved in signal transduction for IL-10, IL-22 and IL-26 [36]. During the canonical pathway, cytokine engagement and receptor dimerization allows the transphosphorylation and activation of receptor-associated kinases JAK1 (associated with IFNAR2 and IFNLR1) and tyrosine kinase 2 (TYK2; associated with IFNAR1 and IL-10Rβ; Fig. 1B). After activation, the receptor-associated kinases phosphorylate several tyrosine residues on both receptor subunits, creating a docking site. STAT2 then translocates to this docking site on the receptor and is phosphorylated by TYK2, allowing for the recruitment and binding of STAT1. Phosphorylated STAT1 and STAT2 dimerize, dissociate from the receptor, and associate with IRF9 (forming the IFN-stimulated gene factor 3 [ISGF3] complex) as they translocate to the nucleus. This complex is able to bind to ISG promoters and induce the activation of several hundred ISGs, ultimately ensuring the establishment of an antiviral state in the cell [37].

The signaling cascades induced by both type I and III IFNs are similar, yet these two cytokine families have different physiological outcomes, which may be explained by receptor distribution. Although all nucleated cells express IFNAR, the IFNLR1 chain of the IFNLR is restricted to epithelial cells (e.g. gastrointestinal and reproductive tracts) and to some immune cells [38–39]. For example, pDCs express IFNLR1 at high levels, leading to robust STAT phosphorylation and ISG induction in response to IFN-λ stimulation [39]. Due to the functional tissue specificity, type III IFNs are unable to protect the host against systemic infections but can provide protection from certain local infections. For example, rotavirus infects intestinal epithelial cells, and this infection is controlled in IFNAR-deficient, but not IFNLR-deficient mice. Moreover, systemic treatment with IFN-λ, but not IFN-β, results in the repression of rotavirus replication, further demonstrating the differential roles of type I and III IFNs in epithelial antiviral host defense [40].

2.3. Function

Once bound to the ISG promoters, each class of IFN induces the expression of a unique and partially overlapping set of genes. This gene expression pattern can be further modulated depending on the cell type, IFN dose and timing. ISGs can target different steps of the viral life cycle such as entry, uncoating, transcription, translation, assembly and egress, and may have broad or restricted activity against different virus groups [41]. Some ISGs, such as *MX1*, *OAS1*, *EIF2AK2* (which encodes protein kinase R [PKR]), *TRIM5*, *ZC3HAV1* (which encodes zinc finger antiviral protein [ZAP]), *APOBEC3G*, and *IFITM3* are considered to be individually very potent at blocking viral infection. However, it is hypothesized that the expression of multiple modest ISGs may be more advantageous, since high expression of a single, highly potent ISG could result in immunopathology [41]. ISGs exert their antiviral effects via a broad range of mechanisms. For example, the activation of 2′-5′-oligoadenylate synthetase 1 (OAS1) occurs following binding of viral dsRNA and leads to the synthesis of 2′-5′-oligoadenylates. This substrate activates latent ribonuclease (RNase L) which indiscriminately degrades all RNA (host or viral) in the infected cell [42]. Another well-studied ISG is PKR, which is activated by autophosphorylation following binding of dsRNA. Once activated, PKR phosphorylates eukaryotic initiation factor 2α (eIF2α), which inhibits viral RNA and most host mRNA translation [42]. Several other IGSs have been identified and further analysis of their antiviral activity was conducted via overexpression screen studies, in which the activity of 380 genes were compared between several viruses, such as hepatitis C virus, YFV, WNV, chikungunya virus, Venezuelan equine encephalitis virus and human immunodeficiency virus type-1 [43]. There are also several ISGs that are not able to directly induce an antiviral response, but instead act to enhance pattern recognition receptor (PRR) pathways. These ISGs support post-translational modifications of genes downstream of PAMP recognition, which ultimately enhances the IFN response [44]. Together, the global change in gene expression allows the cell to create an environment where viral replication is abrogated, decreasing the chances of virus dissemination.

3. IFNs during ZIKV infection

3.1. In vitro and ex vivo studies

Since the 2015 ZIKV outbreak in the Americas, a number of models of ZIKV infection have been established to interrogate how ZIKV interacts with its host and counters the type I IFN response. Systems using immortal cell lines allow for more precise analysis of interactions between specific viral and host proteins, and the impact of these interactions. Similarly, a small number of studies using primary human cells have provided some insight into the normal course of infection in humans. Mouse models have also been an important method to improve our understanding of the impact of IFN on ZIKV pathogenesis and the immune response to infection.

Disruption of the type I IFN response by the NS5 protein during infection has been well-described for a number of *flaviviruses*, including DENV, YFV, WNV and Japanese encephalitis virus (reviewed in [15]). Similarly, two independent groups have demonstrated that the ZIKV NS5 protein targets STAT2 for proteasomal degradation, thereby disrupting type I IFN signaling [45–46]. This effect was observed in A549 lung carcinoma cells [46], Vero (African green monkey kidney epithelial) cells and primary human fibroblasts [45], but not mouse embryonic fibroblasts (MEFs) [45–46], which has had significant implications for *in vivo* models of ZIKV infection (discussed below). Intriguingly, a separate study demonstrated that STAT2 degradation by NS5 promoted STAT1 homodimerization, which increased transcription of the IFN-γ-inducible gene *CXCL10* and supported virus replication [47]. A similar “pro-inflammatory” effect of ZIKV infection was observed in THP-1 cells (a human monocyte cell line), in which ZIKV infection induced inflammasome activation [31]. Mechanistically, it was shown that NS1 promoted the stability of caspase-1, which cleaves cGAS and prevents cGAS-STING-mediated IFN production [31]. Whether IFN-γ or the inflammasome have pro-viral functions beyond suppressing the type I IFN response remains unknown, but each represents an intriguing example of differential regulation of inflammatory cytokines by ZIKV.

In addition to disrupting type I IFN signaling and cGAS-STING activation, a number of ZIKV’s NS proteins are capable of blocking detection of viral RNA by RIG-I or TLR3. In one study, transfection of

Table 1
ZIKV Strains Used in Cited Studies.

Name in text	Isolate name	Source	Lineage	Location	Year of isolation	Accession number	References
MP1751	MP1751	Mosquito (*Aedes africanus*)	African	Uganda	1962	KY288905.1	
$ZIKV^{PBR}$	Paraiba_01	Human	Asian	Paraiba, Brazil	2015	KX280026.1	[82]
$ZIKV^{CBD}$	FSS13025	Human	Asian	Cambodia	2010	KU955593.1	[83]
$ZIKV^{CDN}$	PLCal_ZV	Human	Asian	Canada via Thailand	2013	KF993678.1	[84]
$ZIKV^{FP}$	H/PF/2013	Human	Asian	French Polynesia	2013	KJ776791.2	[85]
$ZIKV^{MYS}$	P6-740	Mosquito (*Aedes aegypti*)	Asian	Malaysia	1966	KX694533.2	[83]
$ZIKV^{NIC}$	Nica 2–16	Human	Asian	Nicaragua	2016	N/A	[86]
$ZIKV^{RBR}$	PE243	Human	Asian	Recife, Brazil	2015	KX197192	[70]
$ZIKV^{PR}$	PRVABC-59	Human	Asian	Puerto Rico	2015	KX377337.1	
$ZIKV^{SEN}$	DakAr41525	Mosquito (*Aedes africanus*)	African	Senegal	1984	KX601166.2	[83]
$ZIKV^{UG}$	MR766	Rhesus Macaque	African	Uganda	1947	KX421193.1	[2,83]

individual NS proteins from $ZIKV^{CBD}$ (Cambodia 2010; Table 1) into 293 T cells demonstrated that NS2A, NS2B, NS4A, NS4B and NS5 all suppressed IFN promoter activation by polyinosinic:polycytidylic acid (polyI:C) or RIG-I agonist treatment [48]. When these experiments were repeated using the NS proteins from a more recent isolate, $ZIKV^{PR}$ (Puerto Rico 2015; Table 1), an A188V mutation in the NS1 protein was found to have conferred the capacity to block phosphorylation of TBK1 downstream of RIG-I activation [48]. Similar studies using 293 T cells transfected with individual $ZIKV^{UG}$ (Uganda 1947; Table 1) proteins showed inhibition of type I IFN production by NS1, NS2B-NS3 and NS4B [49]. Recently, Chatel-Chaix et al. identified a mechanistic role for NS4B in evasion of type I IFN production [50]. They showed that ZIKV infection of Huh7 hepatocarcinoma cells caused NS4B-dependent mitochondrial elongation, which supports ZIKV replication by blocking recruitment of RIG-I or MDA5 to MAVS on the mitochondrial membrane [50]. Together, these studies have helped improve our understanding of some of the diverse strategies ZIKV uses to antagonize type I IFN production and signaling.

A small number of studies using primary human cells have been informative on cell tropism and infection dynamics in humans. A longitudinal study from Singapore tracked the cytokines present in serum from 55 patients infected with ZIKV at acute, early convalescent, late convalescent and recovery phases. They detected a small but significant difference in IFN-α in the serum during the early and late convalescent phases, with less IFN-α detected in the ZIKV-infected group than the healthy controls [51]. However, IFN-α is more likely to be involved during the acute, viremic phase of the response, so the authors are warranted in not drawing conclusions from this result. Primary human blood samples and *ex vivo* infections using $ZIKV^{NIC}$ (Nicaragua 2016; Table 1) in primary peripheral blood mononuclear cells (PBMCs) from a pediatric cohort were used to identify $CD14^+CD16^+$ monocytes as the primary target of ZIKV infection in the blood. This study also identified a significant increase in the frequency of pDCs, a cell type known to be a major source of type I IFN during infection [52], in the blood of ZIKV-infected patients [53]. Similarly, lower viral load and increased frequency of $CD14^+$ non-classical monocytes were found in PBMCs infected with the Asian lineage isolate $ZIKV^{FP}$ (French Polynesia 2013; Table 1), compared to the African lineage isolate $ZIKV^{UG}$ [54]. This was associated with a virtually undetectable IFN response, and upregulation of the anti-inflammatory cytokine IL-10 during $ZIKV^{FP}$ infection [54]. Activated monocytes are known to produce large amounts of cytokines to direct their own differentiation, and their skewing towards a less inflammatory, "non-classical" phenotype may indicate an additional method of host immune evasion by ZIKV. It is of particular interest that this effect was only observed during infection with the more contemporary $ZIKV^{FP}$, which raises the possibility that recent ZIKV isolates have an improved ability to dampen inflammatory immune responses.

More specific information on the impact of ZIKV on particular cell types has come from studies using human monocyte-derived dendritic cells (MDCs) [55] and primary human brain microvascular endothelial cells (hBMECs) [56]. Bowen et al. found that $ZIKV^{UG}$, $ZIKV^{SEN}$ (Senegal 1984; Table 1), $ZIKV^{MYS}$ (Malaysia 1966; Table 1), and $ZIKV^{PR}$ all induced transcription of type I IFN genes, but not translation in MDCs [55]. However, $ZIKV^{UG}$ and $ZIKV^{SEN}$ (African lineage) replicated to much higher titers, and were more cytotoxic than their Asian lineage counterparts, suggesting that contemporary isolates may have evolved to be less inflammatory [55]. In line with this finding, $ZIKV^{PR}$ was found to persistently infect hBMECs, which rendered the cells unable to respond to IFN-α [56]. ZIKV was continuously released from the basolateral membrane of the hBMECs [56]. Since these cells help form the blood-brain barrier, it was proposed that basolateral release of the virus would provide a means by which ZIKV could enter the central nervous system, for example in the context of fetal infection, although this remains to be demonstrated experimentally [56]. Together, this suggests that contemporary ZIKV isolates may have an enhanced ability to suppress the type I IFN response to reach immune-privileged sites such as the brain.

3.2. Mouse studies

The 2015–2016 Brazilian outbreak was unprecedented for ZIKV, both in terms of the magnitude of the outbreak, as well as the novel association of GBS and fetal microcephaly with infection. In response to the outbreak, several research groups proposed mouse models of ZIKV infection, to attempt to recapitulate the severe symptoms rarely associated with infection. Such models include mice genetically deficient for IFNAR or IFNAR and the IFN-γ receptor [34,57–59], mice deficient in IFNAR in a subset of myeloid cells [60], mice that produce little to no IFN (*Irf3*$^{-/-}$*Irf5*$^{-/-}$*Irf7*$^{-/-}$ "triple knockout" [TKO] mice) [34,61], STAT2 KO mice [62], or mice that have human *STAT2* introduced into the murine *Stat2* locus [63]. Some studies also opted to use a less disruptive approach, by treating mice with an IFNAR-blocking antibody prior to infection. In addition to these models, there are several papers in which the mice remain unmanipulated with regards to the IFN response, which have proven valuable for improving our understanding of the immune response to ZIKV infection [64–66].

Models in which IFNAR has been deleted or blocked have enabled dissection of tissues in which ZIKV can replicate, and how it causes pathogenesis. Virus has been detected in virtually all tissues examined, including the spleen, kidneys, liver, and immune privileged sites such as the brain, testes, ovaries, and eyes [34,57–59,67]. Virus replication and destruction of neural progenitor cells in the forebrain of TKO mice may also provide clues for how ZIKV induces fetal microcephaly in the developing brain [61]. These models provide useful tools for testing novel therapeutic or vaccination approaches, since the pathogenesis ZIKV induces enables researchers to measure the therapeutic effect of treatment. However, the impact of these modifications on the immune response, and thus how relevant some findings are to typical human infections, remains unclear.

Common features of ZIKV infection in mice that lack IFNAR or both IFNAR and the IFN-γ receptor include systemic viremia, severe illness

and symptoms ranging from ruffled fur, to paralysis, to death [34,57–59]. In one particular model, infection with as little as one plaque-forming unit (PFU) proved lethal [57]. These studies highlight the importance of an intact IFN response in protecting hosts from ZIKV infection. However, they are not representative of the normal course of infection in humans, of which 80% are asymptomatic, and the majority of symptomatic infections are characterized by self-limiting, flu-like symptoms and are rarely, if ever, associated with mortality [1]. The widespread use of these models likely stems from the aforementioned papers in which the ZIKV NS5 protein antagonized IFN signaling by targeting STAT2 for degradation in human, but not mouse cells [45–46], as well as the lack of obvious pathogenesis present in wild-type (WT) mice. However, it is clear that ZIKV can establish an active and detectable infection in WT mice [34,58,64], which much more closely resembles the normal course of human ZIKV infection.

ZIKV infection in immunocompetent mice has enabled characterization and tracking of the immune response to infection. In particular, our group has demonstrated that infection of WT C57BL/6 mice with $ZIKV^{CDN}$ (Canada via Thailand 2013; Table 1) induces type I IFN production, DC and NK cell activation, and a robust, prototypical Th1 CD4 and effector CD8 T cell response [64]. These responses required active viral replication, as they were only observed in mice infected with live ZIKV and not mice inoculated with UV-inactivated virus [64]. Optimal activation of many immune cell types, including CD8 T cells, is one of many important functions of type I IFNs during viral infections, in addition to establishing an antiviral state [68]. The robust, polyfunctional CD8 T cell response described by our group and later by Huang et al. would not be present in immunodeficient mouse models which lack IFNAR signaling [64–65]. As such, fully immunocompetent mouse models (with no anti-IFNAR antibody blockade) represent an important tool to interrogate the immune response to infection, and whether ZIKV has evolved to modulate the immune response.

The importance of the adaptive immune responses present in WT mice has been highlighted by the spread of ZIKV to the brain and testes of Rag1 KO mice pre-treated with anti-IFNAR blocking antibody, which was not observed in WT mice [69]. Similarly, another group infected A129 mice (which lack IFNAR) with $ZIKV^{RBR}$ (Recife, Brazil 2015; Table 1), and adoptively transferred purified CD4 T cells 7 days post-infection to naïve A129 mice. The same day as the adoptive transfer, mice were infected with $ZIKV^{UG}$, which is lethal in A129 mice. They found that mice that received CD4 T cells from $ZIKV^{RBR}$-infected mice were protected against lethal $ZIKV^{UG}$ infection, in contrast to mice that received naïve CD4 T cells [70]. Although each of these studies took place in the context of immunodeficient mice, they outline an important role of adaptive immune responses in controlling ZIKV infection and protecting from pathogenesis.

The type I and type III IFN responses in the lower female reproductive tract (LFRT) have been closely analyzed in a WT model that used intravaginal infection with $ZIKV^{PR}$. Although $ZIKV^{PR}$ was found to productively infect the LFRT, it induced minimal type I and type III IFN transcription [66]. However, both systemic induction of the IFN response by intraperitoneal infection with lymphocytic choriomeningitis virus (LCMV) and local induction by intravaginal acitretin treatment (a retinoic acid derivative that enhances RIG-I signaling) were found to inhibit ZIKV replication in the LFRT [66]. This emphasizes the importance of an intact IFN response in host protection and suggests that this contemporary ZIKV isolate induces minimal inflammation. Whether this would also be true for an African lineage isolate would be of great interest for understanding whether ZIKV has recently acquired this capacity to counter host defenses.

Our understanding of how ZIKV modulates the IFN response, and the impact this has on the immune response to infection has been significantly advanced by the above studies. As a whole, research into the relationship between IFNs and ZIKV underscores the important role these key antiviral cytokines play in protecting from ZIKV infection. One notable exception was observed when IFNAR KO bone marrow was transferred to IFNAR KO and WT mice. The IFNAR KO mice reconstituted with IFNAR KO bone marrow had high systemic viral loads, leading to paralysis [71]. However, WT mice reconstituted with IFNAR KO bone marrow maintained this high viremia, in the absence of any neurological symptoms [71]. Depleting CD8 T cells in IFNAR KO mice was also found to prevent paralysis in spite of high viral load, suggesting a pathogenic role for IFNs and CD8 T cells during infection [71]. Nonetheless, in systems in which the IFN response is intact, virus is rapidly controlled by the immune response, much like what is observed during human ZIKV infections.

4. IFNs and ZIKV infection during pregnancy

By far the most dramatic development during recent outbreaks was the novel association of ZIKV infection with fetal microcephaly [1,72]. During the Brazilian outbreak, the prevalence of fetal microcephaly among ZIKV-infected pregnant women was 2.3%, significantly higher than the baseline prevalence of 0.02% in Brazil [73–74]. Microcephaly results from a defect in fetal brain development, resulting in a head size that is smaller than normal. This is often associated with both cognitive and developmental delays. Given the severe short- and long-term health threat this poses, significant research has been undertaken to understand how ZIKV causes these defects, and the role type I and III IFNs play in this process.

Type III IFNs are primarily produced at epithelial surfaces, and their important role in protecting against ZIKV in the context of pregnancy was clearly shown by the Coyne group in 2016 [16]. They demonstrated that primary human trophoblasts constitutively release IFN-λ1, which acts in an autocrine and paracrine manner to render these cells resistant to infection with $ZIKV^{UG}$ or $ZIKV^{CBD}$ [16]. Similarly, they used the JEG-3 placental cell line to generate 3D organoids, which enable the cells to form syncytia and are therefore more representative of a full-term placenta. They found that the 3D organoids, in contrast to 2D cultured cells, basally expressed type III IFN, like the primary human trophoblasts, which was protective against infection with $ZIKV^{CBD}$ or $ZIKV^{PBR}$ (Paraiba, Brazil 2015; Table 1). Conditioned media from the 3D organoids was also able to inhibit ZIKV infection of hBMECs, demonstrating the important role of basal type III IFN secretion in protecting the placenta from infection [17]. This has also been documented in mouse models, in which administration of recombinant murine IFN-λ2 to ZIKV-infected IFNAR KO dams [18] or pegylated mouse IFN-λ2 to ZIKV-infected WT dams treated with IFNAR-blocking antibody [19] reduced viral loads in the fetus. Both of these studies only saw therapeutic effects when ZIKV infection and IFN-λ treatment occurred mid-gestation (infections occurred either 10.5 days post-conception [E10.5] [18] or on E12 [19]). This suggests that the cells that IFN-λ acts on in order to confer resistance to infection (e.g. trophoblast or fetal membrane epithelial cells) are not yet present at the earlier time points tested [18].

These studies outline the protective role of type III IFNs during ZIKV infection in the context of pregnancy. In addition, several mouse models have also sought to understand the viral and immune correlates of fetal pathogenesis during ZIKV infection. Such studies have found both a protective and pathogenic role for type I IFN with ZIKV infection during pregnancy. Infecting IFNAR KO dams early in pregnancy caused fetal demise [18], and when IFNAR KO dams were crossed with WT males to generate $IFNAR^{+/-}$ fetuses, significant intrauterine growth restriction (IUGR) and fetal resorption were observed [75]. Even in WT dams mated with WT sires, anti-IFNAR antibody treatment resulted in IUGR, although no fetal resorption was observed [75]. Intravaginal infection of WT pregnant dams led to productive infection of the LFRT and IUGR in fetuses, which was more severe when the fetuses were $IFNAR^{+/-}$ [76]. However, Yockey et al. took this approach a step further by crossing IFNAR KO females with $IFNAR^{+/-}$ males to generate a mix of $IFNAR^{+/-}$ and IFNAR KO fetuses [77]. They found that only the heterozygous fetuses were resorbed after intravaginal infection on E5.5, or

displayed IUGR after infection on E8.5, in spite of higher viral loads in the IFNAR KO fetuses, suggesting a pathogenic role for type I IFN. Mechanistically, they found that treating placental explants with IFN-β caused disruption of villous structures, while IFN-λ treatment had no impact [77]. Together, this presents a model in which ZIKV infection of the fetus can induce a robust type I IFN response, which restricts fetal growth.

Reconciling the protective and pathogenic roles of the type I IFN response to ZIKV during pregnancy may be dependent on the context of infection. The two Yockey et al. studies found IUGR was more severe in IFNAR$^{+/-}$ fetuses compared to both WT and IFNAR KO fetuses. In WT mice, the intact maternal IFN response is likely responsible for limiting virus infection of the fetus. In contrast, the IFNAR$^{+/-}$ fetuses contain the only cells capable of responding to type I IFN, in an environment in which high viral replication is supported and type I IFNs are still produced [48,78]. The protective role of type III IFNs appears to be clearer, providing robust antiviral protection without the damaging side effects induced by type I IFNs.

5. Has ZIKV evolved to suppress the IFN response?

Since its initial isolation ZIKV has progressed from a relatively innocuous pathogen, which caused only a handful of isolated infections, to a global health concern which has caused several severe outbreaks and is now associated with GBS and fetal microcephaly. A number of factors may explain this shift, including interactions with vector species, new host populations, and virus evolution. Interestingly, a recent paper has suggested that contemporary ZIKV isolates replicate more efficiently in a human astrocytoma cell line compared to their pre-epidemic counterparts, implying ZIKV may have evolved to have increased viral fitness [79]. Whether ZIKV has evolved to cause more severe pathogenesis was recently discussed in a review by Rossi et al., [80] but it merits consideration whether ZIKV has specifically mutated to suppress IFN responses.

Only two studies have compared infection with African and Asian lineage ZIKV isolates, both in the context of immunocompromised mice. Dowall et al. found that infecting A129 mice with as little as 10 PFU of the African lineage ZIKV isolate MP1751 (Uganda 1962; Table 1) caused lethal infection within 7 days [81]. In contrast, mice infected with ZIKV^{PR} (Asian lineage) survived regardless of the infectious dose (between 10 and 10^6 PFU) [81]. High viral loads were detected in all tissues assayed from both groups, yet ZIKV^{PR} caused no clinical disease in the mice [81]. Similarly, Tripathi et al. observed lethality in STAT2 KO mice only after subcutaneous infection with ZIKV^{UG} or ZIKV^{SEN} (African lineages), but not with ZIKV^{PR}, ZIKV^{CBD}, or ZIKV^{MYS} (Asian lineages) [62]. Mortality correlated with inflammatory cytokine induction [62]. Indeed, IFN-α and IFN-β mRNA levels were highest during ZIKV^{UG} infection, however IFN-α mRNA expression was higher during ZIKV^{PR} infection compared to ZIKV^{SEN}, and IFN-β induction was comparable between the two strains [62]. However, these two studies share in common a more inflammatory, more lethal infection in immunocompromised mice during African lineage ZIKV infection. This provides potential support for the hypothesis that ZIKV has evolved to suppress inflammatory immune responses, including the type I IFN response, which could contribute to the enhanced pathogenesis and severity of recent outbreaks.

6. Conclusion

The interplay between ZIKV and type I and III IFNs is complex and much remains to be understood. In its effort to suppress type I IFN, ZIKV may in fact promote other inflammatory responses. The benefit to or detraction from virus replication of these responses remains to be further investigated. Extensive work has recently been done in *in vivo* systems, however it is still unclear what impact conducting this work in various immunocompromised settings may have on infection outcomes. This is particularly true if it is shown that ZIKV has evolved to suppress the IFN response, as these effects would be lost in hosts unable to produce or respond to IFNs. Although recent outbreaks have been controlled, ZIKV remains a virus that has the capacity to cause severe neurological symptoms in naïve populations, which it may encounter as its mosquito vectors' geographical ranges expand. Future research efforts are therefore necessary to continue to improve our understanding of this pathogen, especially its pathogenicity and interplay with the IFN response.

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Declarations of interest.

The authors declare no competing interests.

References

[1] M.M. Rajah, R.D. Pardy, S.A. Condotta, M.J. Richer, S.M. Sagan, Zika virus: emergence, phylogenetics, challenges, and opportunities, ACS Infect. Dis. 2 (11) (2016) 763–772, https://doi.org/10.1021/acsinfecdis.6b00161 PubMed PMID: 27704772.
[2] G.W. Dick, S.F. Kitchen, A.J. Haddow, Zika virus. I. Isolations and serological specificity, Trans. R. Soc. Trop. Med. Hyg. 46 (5) (1952) 509–520 PubMed PMID: 12995440.
[3] D.I. Simpson, Zika virus infection in man, Trans. R. Soc. Trop. Med. Hyg. 58 (1964) 335–338 PubMed PMID: 14175744.
[4] N. Wikan, D.R. Smith, First published report of Zika virus infection in people: Simpson, not MacNamara, Lancet Infect. Dis. 17 (1) (2017) 15–17, https://doi.org/10.1016/S1473-3099(16)30525-4 PubMed PMID: 27998553.
[5] M.K. Kindhauser, T. Allen, V. Frank, R.S. Santhana, C. Dye, Zika: the origin and spread of a mosquito-borne virus, Bull. World Health Organ. 94 (9) (2016) 675–686, https://doi.org/10.2471/BLT.16.171082 PubMed PMID: 27708473.
[6] M.R. Duffy, T.H. Chen, W.T. Hancock, A.M. Powers, J.L. Kool, R.S. Lanciotti, et al., Zika virus outbreak on Yap Island, Federated States of Micronesia, N. Engl. J. Med. 360 (24) (2009) 2536–2543, https://doi.org/10.1056/NEJMoa0805715 PubMed PMID: 19516034.
[7] E. Oehler, L. Watrin, P. Larre, I. Leparc-Goffart, S. Lastere, F. Valour, et al., Zika virus infection complicated by Guillain-Barre syndrome–case report, French Polynesia, December 2013, Euro. Surveill. 19 (9) (2014) PubMed PMID: 24626205.
[8] The History of Zika Virus. World Health Organization. 2017. Available from: http://www.who.int/emergencies/zika-virus/history/en/.
[9] G. Swati, Zika spreads rapidly in India, with 94 cases confirmed. CNN.2018.
[10] J. Slater, India wrestles with first significant outbreak of Zika virus. The Washington Post. 2018.
[11] A.D. Haddow, A.J. Schuh, C.Y. Yasuda, M.R. Kasper, V. Heang, R. Huy, et al., Genetic characterization of Zika virus strains: geographic expansion of the Asian lineage, PLoS Negl. Trop Dis. 6 (2) (2012), https://doi.org/10.1371/journal.pntd.0001477 PubMed PMID: 22389730.
[12] L. Wang, S.G. Valderramos, A. Wu, S. Ouyang, C. Li, P. Brasil, et al., From mosquitos to humans: genetic evolution of Zika virus, Cell Host Microbe 19 (5) (2016) 561–565, https://doi.org/10.1016/j.chom.2016.04.006 PubMed PMID: 27091703.
[13] Q. Ye, Z.Y. Liu, J.F. Han, T. Jiang, X.F. Li, C.F. Qin, Genomic characterization and phylogenetic analysis of Zika virus circulating in the Americas, Infect Genet. Evol. 43 (2016) 43–49, https://doi.org/10.1016/j.meegid.2016.05.004 PubMed PMID: 27156653.
[14] F. McNab, K. Mayer-Barber, A. Sher, A. Wack, A. Ogarra, Type I interferons in infectious disease, Nat. Rev. Immunol. 15 (2) (2015) 87–103, https://doi.org/10.1038/nri3787 PubMed PMID: 25614319.
[15] S.M. Best, The many faces of the flavivirus NS5 protein in antagonism of Type I interferon signaling, J. Virol. 91 (3) (2017), https://doi.org/10.1128/JVI.01970-16 PubMed PMID: 27881649.
[16] A. Bayer, N.J. Lennemann, Y. Ouyang, J.C. Bramley, S. Morosky, E.T. Marques Jret al., Type III interferons produced by human placental trophoblasts confer protection against Zika virus infection, Cell Host Microbe 19 (5) (2016) 705–712, https://doi.org/10.1016/j.chom.2016.03.008 PubMed PMID: 27066743.
[17] J. Corry, N. Arora, C.A. Good, Y. Sadovsky, C.B. Coyne, Organotypic models of type III interferon-mediated protection from Zika virus infections at the maternal-fetal

interface, Proc. Natl. Acad. Sci. U S A 114 (2017) 9433–9438, https://doi.org/10.1073/pnas.1707513114 Epub 2017/08/09.
[18] J. Chen, Y. Liang, P. Yi, L. Xu, H.K. Hawkins, S.L. Rossi, et al., Outcomes of congenital Zika disease depend on timing of infection and maternal-fetal interferon action, Cell Rep. 21 (6) (2017) 1588–1599, https://doi.org/10.1016/j.celrep.2017.10.059 PubMed PMID: 29117563.
[19] B.W. Jagger, J.J. Miner, B. Cao, N. Arora, A.M. Smith, A. Kovacs, et al., Gestational stage and IFN-lambda signaling regulate ZIKV infection in utero, Cell Host Microbe 22 (3) (2017) 366–376 e3, https://doi.org/10.1016/j.chom.2017.08.012 PubMed PMID: 28910635.
[20] A. Isaacs, J. Lindenmann, Virus interference. I. The interferon, Proc. R. Soc. Lond. B Biol. Sci. 147 (927) (1957) 258–267 PubMed PMID: 13465720.
[21] P. Sheppard, W. Kindsvogel, W. Xu, K. Henderson, S. Schlutsmeyer, T.E. Whitmore, et al., IL-28, IL-29 and their class II cytokine receptor IL-28R, Nat. Immunol. 4 (1) (2003) 63–68, https://doi.org/10.1038/ni873 PubMed PMID: 12469119.
[22] L. Prokunina-Olsson, B. Muchmore, W. Tang, R.M. Pfeiffer, H. Park, H. Dickensheets, et al., A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus, Nat. Genet. 45 (2) (2013) 164–171, https://doi.org/10.1038/ng.2521 PubMed PMID: 23291588.
[23] S.V. Kotenko, G. Gallagher, V.V. Baurin, A. Lewis-Antes, M. Shen, N.K. Shah, et al., IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex, Nat. Immunol. 4 (1) (2003) 69–77, https://doi.org/10.1038/ni875 PubMed PMID: 12483210.
[24] D.E. Levy, I.J. Marie, J.E. Durbin, Induction and function of type I and III interferon in response to viral infection, Curr Opin Virol. 1 (6) (2011) 476–486, https://doi.org/10.1016/j.coviro.2011.11.001 PubMed PMID: 22323926.
[25] D.B. Stetson, R. Medzhitov, Type I interferons in host defense, Immunity 25 (3) (2006) 373–381, https://doi.org/10.1016/j.immuni.2006.08.007 PubMed PMID: 16979569.
[26] M. Matsumoto, T. Seya, TLR3: interferon induction by double-stranded RNA including poly(I:C), Adv. Drug Deliv. Rev. 60 (7) (2008) 805–812, https://doi.org/10.1016/j.addr.2007.11.005 PubMed PMID: 18262679.
[27] Y.M. Loo, M. Gale Jr., Immune signaling by RIG-I-like receptors, Immunity 34 (5) (2011) 680–692, https://doi.org/10.1016/j.immuni.2011.05.003 PubMed PMID: 21616437.
[28] M. Yoneyama, M. Kikuchi, K. Matsumoto, T. Imaizumi, M. Miyagishi, K. Taira, et al., Shared and unique functions of the DExD/H-box helicases RIG-I, MDA5, and LGP2 in antiviral innate immunity, J. Immunol. 175 (5) (2005) 2851–2858 PubMed PMID: 16116171.
[29] S.E. Keating, M. Baran, A.G. Bowie, Cytosolic DNA sensors regulating type I interferon induction, Trends Immunol. 32 (12) (2011) 574–581, https://doi.org/10.1016/j.it.2011.08.004 PubMed PMID: 21940216.
[30] F. Ma, B. Li, S.Y. Liu, S.S. Iyer, Y. Yu, A. Wu, et al., Positive feedback regulation of type I IFN production by the IFN-inducible DNA sensor cGAS, J. Immunol. 194 (4) (2015) 1545–1554, https://doi.org/10.4049/jimmunol.1402066 PubMed PMID: 25609843.
[31] Y. Zheng, Q. Liu, Y. Wu, L. Ma, Z. Zhang, T. Liu, et al., Zika virus elicits inflammation to evade antiviral response by cleaving cGAS via NS1-caspase-1 axis, EMBO J. 37 (18) (2018), https://doi.org/10.15252/embj.201899347 PubMed PMID: 30065070.
[32] S. Aguirre, P. Luthra, M.T. Sanchez-Aparicio, A.M. Maestre, J. Patel, F. Lamothe, et al., Dengue virus NS2B protein targets cGAS for degradation and prevents mitochondrial DNA sensing during infection, Nat. Microbiol. 2 (2017) 17037, https://doi.org/10.1038/nmicrobiol.2017.37 PubMed PMID: 28346446.
[33] R. Hamel, O. Dejarnac, S. Wichit, P. Ekchariyawat, A. Neyret, N. Luplertlop, et al., Biology of Zika virus infection in human skin cells, J. Virol. 89 (17) (2015) 8880–8896, https://doi.org/10.1128/JVI.00354-15 PubMed PMID: 26085147.
[34] H.M. Lazear, J. Govero, A.M. Smith, D.J. Platt, E. Fernandez, J.J. Miner, et al., A mouse model of Zika virus pathogenesis, Cell Host Microbe (2016), https://doi.org/10.1016/j.chom.2016.03.010 PubMed PMID: 27066744.
[35] D.J. Gough, N.L. Messina, L. Hii, J.A. Gould, K. Sabapathy, A.P. Robertson, et al., Functional crosstalk between type I and II interferon through the regulated expression of STAT1, PLoS Biol. 8 (4) (2010), https://doi.org/10.1371/journal.pbio.1000361 PubMed PMID: 20436908.
[36] N.A. de Weerd, T. Nguyen, The interferons and their receptors–distribution and regulation, Immunol. Cell Biol. 90 (5) (2012) 483–491, https://doi.org/10.1038/icb.2012.9 PubMed PMID: 22410872.
[37] A. Majoros, E. Platanitis, E. Kernbauer-Holzl, F. Rosebrock, M. Muller, T. Decker, Canonical and non-canonical aspects of JAK-STAT signaling: lessons from interferons for cytokine responses, Front. Immunol. 8 (2017) 29, https://doi.org/10.3389/fimmu.2017.00029 PubMed PMID: 28184222.
[38] S.V. Kotenko, J.E. Durbin, Contribution of type III interferons to antiviral immunity: location, location, location, J. Biol. Chem. 292 (18) (2017) 7295–7303, https://doi.org/10.1074/jbc.R117.777102 PubMed PMID: 28289095.
[39] A. Kelly, M.W. Robinson, G. Roche, C.A. Biron, C. O'Farrelly, E.J. Ryan, Immune cell profiling of IFN-lambda response shows pDCs express highest level of IFN-lambdaR1 and are directly responsive via the JAK-STAT pathway, J. Interferon Cytokine Res. 36 (12) (2016) 671–680, https://doi.org/10.1089/jir.2015.0169 PubMed PMID: 27617757.
[40] J. Pott, T. Mahlakoiv, M. Mordstein, C.U. Duerr, T. Michiels, S. Stockinger, et al., IFN-lambda determines the intestinal epithelial antiviral host defense, Proc Natl Acad Sci U S A. 108 (19) (2011) 7944–7949, https://doi.org/10.1073/pnas.1100552108 PubMed PMID: 21518880.
[41] J.W. Schoggins, C.M. Rice, Interferon-stimulated genes and their antiviral effector functions, Curr. Opin. Virol. 1 (6) (2011) 519–525, https://doi.org/10.1016/j.coviro.2011.10.008 PubMed PMID: 22328912.
[42] G.R. Stark, I.M. Kerr, B.R. Williams, R.H. Silverman, R.D. Schreiber, How cells respond to interferons, Annu. Rev. Biochem. 67 (1998) 227–264, https://doi.org/10.1146/annurev.biochem.67.1.227 PubMed PMID: 9759489.
[43] J.W. Schoggins, S.J. Wilson, M. Panis, M.Y. Murphy, C.T. Jones, P. Bieniasz, et al., A diverse range of gene products are effectors of the type I interferon antiviral response, Nature 472 (7344) (2011) 481–485, https://doi.org/10.1038/nature09907 PubMed PMID: 21478870.
[44] W.M. Schneider, M.D. Chevillotte, C.M. Rice, Interferon-stimulated genes: a complex web of host defenses, Annu. Rev. Immunol. 32 (2014) 513–545, https://doi.org/10.1146/annurev-immunol-032713-120231 PubMed PMID: 24555472.
[45] A. Grant, S.S. Ponia, S. Tripathi, V. Balasubramaniam, L. Miorin, M. Sourisseau, et al., Zika virus targets human STAT2 to inhibit Type I interferon signaling, Cell Host Microbe (2016), https://doi.org/10.1016/j.chom.2016.05.009 PubMed PMID: 27212660.
[46] A. Kumar, S. Hou, A.M. Airo, D. Limonta, V. Mancinelli, W. Branton, et al., Zika virus inhibits type-I interferon production and downstream signaling, EMBO Rep. 17 (12) (2016) 1766–1775, https://doi.org/10.15252/embr.201642627 PubMed PMID: 27797853.
[47] V. Chaudhary, K.S. Yuen, J.F. Chan, C.P. Chan, P.H. Wang, J.P. Cai, et al., Selective activation of Type II interferon signaling by Zika virus NS5 protein, J. Virol. 91 (14) (2017), https://doi.org/10.1128/JVI.00163-17 PubMed PMID: 28468880.
[48] H. Xia, H. Luo, C. Shan, A.E. Muruato, B.T.D. Nunes, D.B.A. Medeiros, et al., An evolutionary NS1 mutation enhances Zika virus evasion of host interferon induction, Nat. Commun. 9 (1) (2018) 414, https://doi.org/10.1038/s41467-017-02816-2 PubMed PMID: 29379028.
[49] Y. Wu, Q. Liu, J. Zhou, W. Xie, C. Chen, Z. Wang, et al., Zika virus evades interferon-mediated antiviral response through the co-operation of multiple nonstructural proteins in vitro, Cell Discov. 3 (2017) 17006, https://doi.org/10.1038/celldisc.2017.6 PubMed PMID: 28373913.
[50] L. Chatel-Chaix, M. Cortese, I. Romero-Brey, S. Bender, C.J. Neufeldt, W. Fischl, et al., Dengue virus perturbs mitochondrial morphodynamics to dampen innate immune responses, Cell Host Microbe 20 (3) (2016) 342–356, https://doi.org/10.1016/j.chom.2016.07.008 PubMed PMID: 27545046.
[51] F.M. Lum, D.C.B. Lye, J.J.L. Tan, B. Lee, P.Y. Chia, T.K. Chua, et al., Longitudinal study of cellular and systemic cytokine signatures to define the dynamics of a balanced immune environment during disease manifestation in Zika virus-infected patients, J. Infect. Dis. 218 (5) (2018) 814–824, https://doi.org/10.1093/infdis/jiy225 PubMed PMID: 29672707.
[52] D. Vremec, M. O'Keeffe, H. Hochrein, M. Fuchsberger, I. Caminschi, M. Lahoud, et al., Production of interferons by dendritic cells, plasmacytoid cells, natural killer cells, and interferon-producing killer dendritic cells, Blood 109 (3) (2007) 1165–1173, https://doi.org/10.1182/blood-2006-05-015354 PubMed PMID: 17038535.
[53] D. Michlmayr, P. Andrade, K. Gonzalez, A. Balmaseda, E. Harris, CD14 + CD16 + monocytes are the main target of Zika virus infection in peripheral blood mononuclear cells in a paediatric study in Nicaragua, Nat. Microbiol. 2 (11) (2017) 1462–1470, https://doi.org/10.1038/s41564-017-0035-0 PubMed PMID: 28970482.
[54] S.S. Foo, W. Chen, Y. Chan, J.W. Bowman, L.C. Chang, Y. Choi, et al., Asian Zika virus strains target CD14 + blood monocytes and induce M2-skewed immunosuppression during pregnancy, Nat. Microbiol. 2 (11) (2017) 1558–1570, https://doi.org/10.1038/s41564-017-0016-3 PubMed PMID: 28827581.
[55] J.R. Bowen, K.M. Quicke, M.S. Maddur, J.T. O'Neal, C.E. McDonald, N.B. Fedorova, et al., Zika virus antagonizes Type I interferon responses during infection of human dendritic cells, PLoS Pathog. 13 (2) (2017), https://doi.org/10.1371/journal.ppat.1006164 PubMed PMID: 28152048.
[56] M.C. Mladinich, J. Schwedes, E.R. Mackow, Zika virus persistently infects and is basolaterally released from primary human brain microvascular endothelial cells, MBio. 8 (4) (2017), https://doi.org/10.1128/mBio.00952-17 PubMed PMID: 28698279.
[57] M.T. Aliota, E.A. Caine, E.C. Walker, K.E. Larkin, E. Camacho, J.E. Osorio, Characterization of lethal Zika virus infection in AG129 mice, PLoS Negl Trop Dis. 10 (4) (2016), https://doi.org/10.1371/journal.pntd.0004682 PubMed PMID: 27093158.
[58] S.D. Dowall, V.A. Graham, E. Rayner, B. Atkinson, G. Hall, R.J. Watson, et al., A susceptible mouse model for Zika virus infection, PLoS Negl Trop Dis. 10 (5) (2016), https://doi.org/10.1371/journal.pntd.0004658 PubMed PMID: 27149521.
[59] S.L. Rossi, R.B. Tesh, S.R. Azar, A.E. Muruato, K.A. Hanley, A.J. Auguste, et al., Characterization of a novel murine model to study Zika virus, Am. J. Trop. Med. Hyg. 94 (6) (2016) 1362–1369, https://doi.org/10.4269/ajtmh.16-0111 PubMed PMID: 27022155.
[60] A. Elong Ngono, E.A. Vizcarra, W.W. Tang, N. Sheets, Y. Joo, K. Kim, et al., Mapping and role of the CD8 + T cell response during primary Zika virus infection in mice, Cell Host Microbe 21 (1) (2017) 35–46, https://doi.org/10.1016/j.chom.2016.12.010 PubMed PMID: 28081442.
[61] H. Li, L. Saucedo-Cuevas, J.A. Regla-Nava, G. Chai, N. Sheets, W. Tang, et al., Zika virus infects neural progenitors in the adult mouse brain and alters proliferation, Cell Stem Cell 19 (5) (2016) 593–598, https://doi.org/10.1016/j.stem.2016.08.005 PubMed PMID: 27545505.
[62] S. Tripathi, V.R. Balasubramaniam, J.A. Brown, I. Mena, A. Grant, S.V. Bardina, et al., A novel Zika virus mouse model reveals strain specific differences in virus pathogenesis and host inflammatory immune responses, PLoS Pathog. 13 (3) (2017), https://doi.org/10.1371/journal.ppat.1006258 PubMed PMID: 28278235.
[63] M.J. Gorman, E.A. Caine, K. Zaitsev, M.C. Begley, J. Weger-Lucarelli, M.B. Uccellini, et al., An Immunocompetent mouse model of Zika virus infection,

Cell Host Microbe 23 (5) (2018) 672–685 e6, https://doi.org/10.1016/j.chom.2018.04.003 PubMed PMID: 29746837.
[64] R.D. Pardy, M.M. Rajah, S.A. Condotta, N.G. Taylor, S.M. Sagan, M.J. Richer, Analysis of the T cell response to Zika virus and identification of a novel CD8+ T cell epitope in immunocompetent mice, PLoS Pathog. 13 (2) (2017), https://doi.org/10.1371/journal.ppat.1006184 PubMed PMID: 28231312.
[65] H. Huang, S. Li, Y. Zhang, X. Han, B. Jia, H. Liu, et al., CD8(+) T cell immune response in immunocompetent mice during Zika virus infection, J. Virol. 91 (22) (2017), https://doi.org/10.1128/JVI.00900-17 PubMed PMID: 28835502.
[66] S. Khan, E.M. Woodruff, M. Trapecar, K.A. Fontaine, A. Ezaki, T.C. Borbet, et al., Dampened antiviral immunity to intravaginal exposure to RNA viral pathogens allows enhanced viral replication, J. Exp. Med. 213 (13) (2016) 2913–2929, https://doi.org/10.1084/jem.20161289 PubMed PMID: 27852793.
[67] J.J. Miner, A. Sene, J.M. Richner, A.M. Smith, A. Santeford, N. Ban, et al., Zika virus infection in mice causes panuveitis with shedding of virus in tears, Cell Rep. 16 (12) (2016) 3208–3218, https://doi.org/10.1016/j.celrep.2016.08.079 PubMed PMID: 27612415.
[68] G.A. Kolumam, S. Thomas, L.J. Thompson, J. Sprent, K. Murali-Krishna, Type I interferons act directly on CD8 T cells to allow clonal expansion and memory formation in response to viral infection, J. Exp. Med. 202 (5) (2005) 637–650, https://doi.org/10.1084/jem.20050821 PubMed PMID: 16129706.
[69] M. Hassert, K.J. Wolf, K.E. Schwetye, R.J. DiPaolo, J.D. Brien, A.K. Pinto, CD4+T cells mediate protection against Zika associated severe disease in a mouse model of infection, PLoS Pathog. 14 (9) (2018), https://doi.org/10.1371/journal.ppat.1007237 PubMed PMID: 30212537.
[70] C.G.O. Lucas, J.Z. Kitoko, F.M. Ferreira, V.G. Suzart, M.P. Papa, S.V.A. Coelho, et al., Critical role of CD4(+) T cells and IFNgamma signaling in antibody-mediated resistance to Zika virus infection, Nat. Commun. 9 (1) (2018) 3136, https://doi.org/10.1038/s41467-018-05519-4 PubMed PMID: 30087337.
[71] K.A. Jurado, L.J. Yockey, P.W. Wong, S. Lee, A.J. Huttner, A. Iwasaki, Antiviral CD8 T cells induce Zika-virus-associated paralysis in mice, Nat. Microbiol. 3 (2) (2018) 141–147, https://doi.org/10.1038/s41564-017-0060-z PubMed PMID: 29158604.
[72] S.A. Rasmussen, D.J. Jamieson, M.A. Honein, L.R. Petersen, Zika virus and birth defects-reviewing the evidence for causality, N. Engl. J. Med. 374 (20) (2016) 1981–1987, https://doi.org/10.1056/NEJMsr1604338 PubMed PMID: 27074377.
[73] A.V.C. Coelho, S. Crovella, Microcephaly prevalence in infants born to Zika virus-infected women: a systematic review and meta-analysis, Int. J. Mol. Sci. 18 (8) (2017), https://doi.org/10.3390/ijms18081714 PubMed PMID: 28783051.
[74] T. Jaenisch, K.D. Rosenberger, C. Brito, O. Brady, P. Brasil, E.T. Marques, Risk of microcephaly after Zika virus infection in Brazil, 2015 to 2016, Bull. World Health Organ. 95 (3) (2017) 191–198, https://doi.org/10.2471/BLT.16.178608 PubMed PMID: 28250532.
[75] J.J. Miner, B. Cao, J. Govero, A.M. Smith, E. Fernandez, O.H. Cabrera, et al., Zika virus infection during pregnancy in mice causes placental damage and fetal demise, Cell 165 (5) (2016) 1081–1091, https://doi.org/10.1016/j.cell.2016.05.008 PubMed PMID: 27180225.
[76] L.J. Yockey, L. Varela, T. Rakib, W. Khoury-Hanold, S.L. Fink, B. Stutz, et al., Vaginal exposure to Zika Virus during pregnancy leads to fetal brain infection, Cell 166 (5) (2016) 1247–56 e4, https://doi.org/10.1016/j.cell.2016.08.004 PubMed PMID: 27565347.
[77] L.J. Yockey, K.A. Jurado, N. Arora, A. Millet, T. Rakib, K.M. Milano, et al., Type I interferons instigate fetal demise after Zika virus infection, Sci. Immunol. 3 (19) (2018), https://doi.org/10.1126/sciimmunol.aao1680 PubMed PMID: 29305462.
[78] G. Kochs, M. Anzaghe, S. Kronhart, V. Wagner, P. Gogesch, S. Scheu, et al., In vivo conditions enable IFNAR-independent Type I interferon production by peritoneal CD11b+ cells upon Thogoto virus infection, J. Virol. 90 (20) (2016) 9330–9337, https://doi.org/10.1128/JVI.00744-16 PubMed PMID: 27512061.
[79] T.R. Barnard, M.M. Rajah, S.M. Sagan, Contemporary Zika virus isolates induce more dsRNA and produce more negative-strand intermediate in human astrocytoma cells, Viruses 10 (12) (2018), https://doi.org/10.3390/v10120728 PubMed PMID: 30572570.
[80] S.L. Rossi, G.D. Ebel, C. Shan, P.Y. Shi, N. Vasilakis, Did Zika virus mutate to cause severe outbreaks? Trends Microbiol. 26 (10) (2018) 877–885, https://doi.org/10.1016/j.tim.2018.05.007 PubMed PMID: 29903417.
[81] S.D. Dowall, V.A. Graham, E. Rayner, L. Hunter, B. Atkinson, G. Pearson, et al., Lineage-dependent differences in the disease progression of Zika virus infection in type-I interferon receptor knockout (A129) mice, PLoS Negl Trop Dis. 11 (7) (2017), https://doi.org/10.1371/journal.pntd.0005704 PubMed PMID: 28672028.
[82] K.A. Tsetsarkin, H. Kenney, R. Chen, G. Liu, H. Manukyan, S.S. Whitehead, et al., A full-length infectious cDNA clone of Zika virus from the 2015 epidemic in Brazil as a genetic platform for studies of virus-host interactions and vaccine, Development. MBio. 7 (4) (2016), https://doi.org/10.1128/mBio.01114-16 PubMed PMID: 27555311.
[83] J.T. Ladner, M.R. Wiley, K. Prieto, C.Y. Yasuda, E. Nagle, M.R. Kasper, et al., Complete genome sequences of five Zika virus isolates, Genome Announc. 4 (3) (2016), https://doi.org/10.1128/genomeA.00377-16 PubMed PMID: 27174284.
[84] K. Fonseca, B. Meatherall, D. Zarra, M. Drebot, J. MacDonald, K. Pabbaraju, et al., First case of Zika virus infection in a returning Canadian traveler, Am. J. Trop. Med. Hyg. 91 (5) (2014) 1035–1038, https://doi.org/10.4269/ajtmh.14-0151 PubMed PMID: 25294619.
[85] C. Baronti, G. Piorkowski, R.N. Charrel, L. Boubis, I. Leparc-Goffart, X. de Lamballerie, Complete coding sequence of zika virus from a French polynesia outbreak, Genome Announc. 2 (3) (2014), https://doi.org/10.1128/genomeA.00500-14 PubMed PMID: 24903869.
[86] T. Tabata, M. Petitt, H. Puerta-Guardo, D. Michlmayr, C. Wang, J. Fang-Hoover, et al., Zika virus targets different primary human placental cells, suggesting two routes for vertical transmission, Cell Host Microbe 20 (2) (2016) 155–166, https://doi.org/10.1016/j.chom.2016.07.002 PubMed PMID: 27443522.