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REVIEW

Chikungunya Virus and Zika Virus, Two Different Viruses Examined with a Common Aim: Role of Pattern Recognition Receptors on the Inflammatory Response

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Chikungunya virus (CHIKV) and Zika virus (ZIKV) are 2 reemerging arboviruses that have been the focus of public health institutions worldwide, since the last decades and following a spate of outbreaks in tropical and subtropical areas. The disease caused by both viruses manifests itself first as an acute stage of severe inflammation into the infected tissues, which later progresses to arthritis and chronic polyarthralgia in the case of CHIKV or congenital microcephaly and neurological disorders such as Guillain–Barré syndrome in the case of ZIKV. This review aims to summarize on current knowledge of the role of different pattern recognition receptors that leads to an elevated production and secretion of antiviral response (interferon) and severe inflammation in response to CHIKV and ZIKV infection.

Keywords: PRRs, CHIKV, ZIKV, inflammation and arbovirus

Introduction

Diverse factors, including climate changes, rapid increase in deforestation, and growth of human populations in both urban and rural areas, have converted various mainly zoonotic and vector-borne agents to the most important causes of spread of emerging infectious diseases worldwide. Arboviruses (arthropod-borne viruses) are a diverse group of viruses that survive in nature by transmission from infected to susceptible hosts by vectors, including mosquitoes, ticks, sand flies, or biting midges (Beckham and Tyler 2015). Mosquitoes of the *Aedes* (*Ae.*) genus are the most important vectors of Dengue Virus (DENV), West Nile Virus, Yellow Fever Virus, Zika Virus (ZIKV), and Chikungunya Virus (CHIKV), in tropical and subtropical areas in the world, where these viruses cause thousands of deaths every year (Nene and others 2007; Pless and others 2017).

CHIKV and ZIKV are reemerging arboviruses that in the last 2 decades have been the causal agents of important epidemics worldwide. CHIK fever manifests itself first as an acute stage with severe joint inflammation and febrile illness that later progresses to a chronic stage that has been associated with the development of highly limiting diseases and chronic polyarthralgia (Zaid and others 2018). ZIKA fever is an inflammatory disease similar to dengue fever, whose major complication is the Guillain–Barré syndrome in adults (Cao-Lormeau and others 2016), and the infection has been associated with neurological diseases and microcephaly (Brickley and Rodrigues 2018). The acute phase of the disease caused by CHIKV and ZIKV is characterized by a marked increase of pro-inflammatory cytokines in the serum of CHIK and ZIK patients, an event that has been correlated with disease severity, indicating an important role of inflammation in the pathogenesis of both viruses (Wauquier and others 2011; Dupuis-Maguiraga and others 2012; Tappe and others 2016). Taken together, these manifestations suggest that both diseases are associated with pro-inflammatory complexes. In this study, we present the current state of our knowledge about the role of pattern recognition receptor (PRR) activation on inflammatory response (pro-inflammatory cytokine production) and antiviral response (through interferon induction) during the infection with either CHIKV or ZIKV.

Chikungunya virus

Like other alphaviruses, CHIKV, a zoonotic arthropod-borne virus, member of *Alphavirus* genus, *Togaviridae* family, is an enveloped virus 65–70 nm in diameter and an icosahedral capsid with a T = 4 symmetry (Joyce and others 2009). The virus contains a positive-sense, single-stranded RNA (ssRNA) of ~11.8 kb in length with 2 open reading

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frames (ORFs) that are translated into nonstructural (ns) and structural polyproteins. By proteolytic processing mediated by the viral protease nsP2, the viral ns polyprotein yields nsP1, nsP2, nsP3, and nsP4 (RNA-dependent RNA polymerase) implicated in viral genome replication, polyprotein processing, and counteraction of the host innate antiviral response (Joyce and others 2009; Zhang and others 2018). The structural polyprotein is expressed from a subgenomic RNA, which after translation is processed by the capsid protease and host proteases yielding 6 structural proteins, capsid protein, envelope (E) E3-E2–6K-E1 and transframe protein, that as a whole form the viral particle and are required for virus attachment/entry, nucleocapsid assembly, and virus budding from host cell membranes. CHIKV is directly co-inoculated with mosquito saliva through the epidermis and the dermis during the blood meal, where the virus can infect fibroblasts, keratinocytes, and resident macrophages (Schwartz and Albert 2010; Puiprom and others 2013). Then, CHIKV spreads to other organs, such as liver, skeletal muscle, joints, lymphoid organs, and central nervous system, presumably through the blood (Schwartz and Albert 2010).

In Africa, CHIKV is maintained within a sylvatic cycle by mosquitoes, including *Ae. furcifer, Ae. luteocephalus, Ae. Taylori,* and *Ae. Africanus*, that feed preferentially on primates (*Cercopithecus aethiops, Papio papio,* and *Erythrocebus patas*) (Diallo and others 1999). In urban areas, CHIKV is mainly transmitted within an urban cycle in interhuman transmission achieved essentially by the human-biting *Ae. aegypti* and *Ae. Albopictus*. CHIKV is a reemerging virus that was isolated for first time in 1953 in Tanzania in eastern Africa (Zeller and others 2016). During the last 50 years, CHIKV has caused a number of outbreaks in Central and South Africa, Southeast Asia, and in the Indian Ocean (Schuffenecker and others 2006; Weaver and Lecuit 2015). In 2013, the World Health Organization (WHO) reported the first case of local transmission of CHIKV in America on the Caribbean island of San Martín, and in 2014, more than 440,000 cases were reported in more than 20 countries in the Caribbean and Central and South America (Morrison 2014).

Overview of chikungunya fever

CHIKV is the etiological agent of chikungunya fever, a self-limiting disease that occurs in ~95% of individuals infected with the virus. CHIKV presents an incubation period of 2–7 days, and the acute phase is characterized by fever and arthralgia (70%–100% of cases), headache, myalgia, lymphopenia, rash (40%–69% of cases), neutropenia, thrombocytopenia, arthritis (10%–39% of cases), and hemorrhage (1%–10% of cases) (Lo Presti and others 2014; Restrepo-Jaramillo 2014; Gasque and others 2015; Petitdemange and others 2015; Goupil and Mores 2016). These symptoms usually disappear 2–3 weeks after the initial contact with CHIKV. In addition, although less frequently, serious clinical complications such as nephritis, myocarditis, acute hepatitis, or meningoencephalitis may occur, being more frequently in children and older adults (Solanki and others 2007; Economopoulou and others 2009; Labadie and others 2010; Goupil and Mores 2016). After the acute phase, about 55% of the affected individuals develop a subacute state of the disease, in which the pain in joints can last for several weeks or develop a chronic state of the disease where the pain in joints can last for several months or even years (Hoarau and others 2010; Chow and others 2011; Restrepo-Jaramillo 2014; Petitdemange and others 2015; Goupil and Mores 2016). Both, acute and chronic disease manifestations even though they are of significant concern, cannot be currently alleviated by specific, approved drug treatments.

During the acute phase, the CHIKV load can reach 1.0×10^5–1.0×10^8 viral particles/mL in blood accompanied by higher levels of Type I interferon (IFN-I), of CCL/CXC chemokines such as RANTES, CXCL-9, CXCL-10, CCL-2, CCL-3, and CCL-11, hepatocyte growth factor (HGF), basic fibroblast growth factor, granulocyte colony stimulating factor and granulocyte-macrophage colony-stimulating factor (GM-CSF), pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-7, IL-8, IL-12, and IL-15, as well as anti-inflammatory cytokines, including IL-1 receptor antagonist (IL-1Ra) and IL-4 (Wauquier and others 2011; Dupuis-Maguiraga and others 2012; Gasque and others 2015; Petitdemange and others 2015). Some of these cytokines/chemokines, such as IL-1β, IL-6, and RANTES, have been correlated with the severity of the disease, while others, such as CCL-2, CXCL-10, IFN-α, IL-1Ra, IL-6, IL-12, IL-16, IL-17, and IL-18, were correlated with high viral loads (Chow and others 2011; Dupuis-Maguiraga and others 2012; Goupil and Mores 2016). To date, the chronicity of CHIKV infection has been related to a strong and persistent inflammatory response. Indeed, a recent RNA sequence analysis of CHIKV-infected mouse tissue demonstrated that most genes were associated with inflammation (Wilson and others 2017), indicating consistent pro-inflammatory gene expression in both mouse and nonhuman primate models and CHIKV-infected patients (Zaid and others 2018).

In a longitudinal study of cases and control, it was established that individuals with high viral loads had high levels of cytokines such as IL-6 (which is associated with persistent arthralgias) and tumor necrosis factor-alpha (TNF-α) during the acute phase; however, when the disease progressed to a chronic phase, it was possible to detect CCL-2, IFN-α, IL-6, IL-8, IL-17, and matrix metalloproteinase 2 in synovial fluid (Chow and others 2011; Dupuis-Maguiraga and others 2012; Goupil and Mores 2016). It has been observed that the inflammatory profile, including cytokines and infiltrating cells, of chronic CHIKV infection is similar to that of rheumatoid arthritis (Waymouth and others 2013; Rolph and others 2015).

During chronic stages of the disease, no viral particles are detected in peripheral blood, but high levels of CHIKV RNA were detected in joints, muscle tissue, lymphoid organs, and liver, which may explain the permanence of symptoms for long periods (Labadie and others 2010). The ability of CHIKV to infect cells of the immune system such as monocytes and macrophages has also been reported, indicating that these are important targets of infection and replication of CHIKV, both *in vitro* and *in vivo* (Sourisseau and others 2007; Her and others 2010; Labadie and others 2010). In addition, CHIKV has the ability to infect and activate osteoblast and in the presence of pro-inflammatory environment promote osteoclast activity, favoring the development of arthralgia (Phuklia and others 2013). In addition, macrophages have been considered as the main reservoirs of the virus during persistent infections in macaques (a nonhuman primate model), given their ability to

chronically become infected with the virus (Labadie and others 2010).

Zika virus

Like other flaviviruses, ZIKV, a zoonotic arthropod-borne virus, member of *Flavivirus* genus, *Flaviviridae* family, is an enveloped virus 50 nm in diameter and with an icosahedral-like symmetry. The genome is a positive-sense ssRNA of ~10.7 kb in length with a single ORF that is translated into 1 large polyprotein of 3,423 amino acids that is processed by viral and host proteases yielding 3 structural proteins: the capsid (C), premembrane (prM), and envelope (E) proteins that form the virus particle and mediate virus attachment/entry, nucleocapsid assembly and virus budding from host cell membranes, and 7 NS proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5, that function in viral genome replication, polyprotein processing, and counteract host innate antiviral response (Chambers and others 1990; Wang and others 2017). ZIKV is directly co-inoculated by mosquito saliva through the epidermis and dermis during the blood meal, where the virus can infect dermal fibroblasts, epidermal keratinocytes, and immature dendritic cells (DCs) (Musso and others 2014; Lustig and others 2016; Shuaib and others 2016; Hamel and others 2015). From the skin, the virus spreads to the draining lymph nodes, where it is amplified resulting in viremia and dissemination through the blood to peripheral tissues and visceral organs such as liver, spleen, kidney, the central nervous system, eyes, testes in males, and the female genital tract (Barzon and others 2016a, 2016b; Freitasa and others 2017). ZIKV is mainly transmitted within an urban cycle by interhuman transmission achieved essentially by the human-biting *Ae. Aegypti*, through sexual contact, transfusions of blood, blood products, organ transplants, or from the mother to the fetus during pregnancy (Miner and others 2017).

ZIKV, a reemerging virus, was first isolated in 1947 from a Rhesus monkey in the Zika forest, Uganda (Dick and others 1952). In 2007 occurred the first large Zika outbreak in humans in the Pacific Island of Yap in the Federated States of Micronesia where an estimated 73% of Yap residents were infected with ZIKV (Duffy and others 2009). Between 2013 and 2014 a large outbreak occurred in 4 other groups of Pacific islands: French Polynesia, Easter Island, the Cook Islands, and New Caledonia where thousands of suspected infections were investigated and where the results revealed a possible association between ZIKV and congenital malformations and severe neurological and autoimmune complications (Cao-Lormeau and Musso 2014; Roth and others 2014). In 2015 the presence of ZIKV in the Americas was reported with local transition in Brazil, Colombia, Venezuela, and Cape Verde, events that were correlated with an abnormal increase in cases of congenital microcephaly and neurological disorders as in the Guillain–Barré syndrome (PAHO/WHO 2015; Méndez and others 2017).

In 2016 the presence of ZIKV RNA was confirmed in brain tissue samples from newborns and amniotic fluid of pregnant women infected with ZIKV, confirming the association between ZIKV infection in pregnant women and congenital microcephaly (WHO 2016a). In 2016 the WHO declared that the recent association of ZIKV infection with clusters of microcephaly and other neurological disorders constitutes a public health threat and emergency of international concern (WHO 2016b).

Overview of Zika fever

ZIKV is the etiological agent of Zika fever, a self-limiting disease that occurs in ~20% of individuals infected with the virus. The acute phase is present as a mild or unapparent form of dengue-like disease with myalgia, arthralgia, fever, conjunctivitis, maculopapular rash, headache, and prostration (Duffy and others 2009; Shuaib and others 2016). These symptoms usually disappear 2–7 days after the initial contact with ZIKV. In humans, ZIKV RNA is detectable in blood typically within the first 10 days after infection with viral load peaks occurring at the onset of the symptoms (Lanciotti and others 2008; Campos and others 2015). In blood, ZIKV appears to be cell-associated, since viral load is higher in whole blood than in plasma and serum (Lustig and others 2016). Human and animal model studies have demonstrated that ZIKV infection can result in the persistence of infectious virus and viral nucleic acid in several body fluids (e.g., semen, saliva, tears, and urine) and target organs, including immune-privileged sites (e.g., eyes, brain, testes, and female genital tract) (Barzon and others 2016a, 2016b; Freitasa and others 2017; Prisant and others 2016). During the viremia phase, ZIKV patients show typically low titer (about 1.0×10^3–1.0×10^4 ZIKV RNA copies/mL).

In a longitudinal study of cases and controls, Lum and others (2018) reported that patients with acute ZIKV infection had significantly higher levels of CCL/CXC chemokines (RANTES, CXCL-1, CXCL-10, CXCL-12, CCL-2, CCL-4), growth factors such as brain-derived neurotrophic factor, platelet-derived growth factor ββ, placenta growth factor 1 (PIGF-1), vascular endothelial growth factor, epidermal growth factor, HGF, and GM-CSF and also pro-inflammatory cytokines, including IFN-γ, TNF-α, IL-1β, IL-2, IL-6, IL-9, IL-12p70, IL-17A, IL-18, and IL-22 and equally anti-inflammatory cytokines such as IL-1RA, IL-4, IL-5, IL-10, and IL-21 and a transient leukopenia and neutropenia, compared with healthy controls (Lum and others 2018). High levels of some of these molecules, such as CXCL-10, CCL-2, PIGF-1, IL-8, and IL-1RA, were correlated with the severity of the disease and moderate viremia.

Our observations (data not published) and other reports (Quicke and others 2016; Bowen and others 2017; Michlmayr and others 2017; Miner and others 2017), showing that ZIKV is able to infect cells of the immune system such as monocytes, macrophages, and human DCs, demonstrate that these are an important target of infection and replication of ZIKV. In fact, monocytes have been considered the main target of ZIKV infection in blood (Michlmayr and others 2017).

Both CHIKV and ZIKV trigger PRRs that are key factors involved in the inflammatory and the antiviral response

Innate immunity response, the first line of defense against infection, is based on the role that PRRs play, which are found in diverse multicellular organisms and are conserved across evolution (Motta and others 2015). PRRs are important in the recognition of pathogen-associated molecular

patterns (PAMPs) or damage-associated molecular pattern (DAMP) and trigger intracellular signaling pathways that lead to the induction of cytokines and chemokines involved in maintaining host resistance to infections (Meylan and others 2006). Disruption of these signaling pathways has been identified as the core defect that results in chronic inflammation, generally defined as a response to invading pathogens or endogenous signals such as damaged cells that result in tissue repair or sometimes pathology, when the response goes unchecked. These processes not only trigger immediate host defensive responses, such as inflammation, but also prime and orchestrate antigen-specific adaptive immune responses (Janeway and Medzhitov 2002). Recent advances in research in innate immunity have revealed that this discrimination relies on PRRs, including Toll-like receptors (TLRs) (Kawai and Akira 2010; Kawasaki and Kawai 2014), RIG-I-like receptors (RLRs) (Loo and Gale 2011; Chow and others 2018), Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (Motta and others 2015; Kim and others 2016), other DNA sensors (Takaoka and others 2007; Nakaya and others 2017), and C-type lectin receptors (Dambuza and Brown 2015).

Both CHIKV and ZIKV replications result in abundant viral RNAs, dsRNA intermediates, and proteins that are recognized by PRRs to prevent virus replication, a consequence of the orchestration of an antiviral response. For example, viral ssRNA or dsRNA is recognized by TLR3, TLR7/8, and RIG-I/MDA5 that recruit adaptor molecules (ASC) and stimulate activation of transcription factors resulting in the expression of inflammatory mediators and IFN-I. The overall inflammation is important to limit virus replication and dissemination, but may be harmful to the host if an exacerbated uncontrolled response is triggered (Inohara and Nuñez 2003). In this study, we review recent knowledge that connects the interaction between PRRs and CHIKV and ZIKV components resulting in severe inflammation or antiviral response and the strategies that these 2 viruses use to counteract these cellular mechanisms and escape the innate immune response.

TLRs and their role in CHIKV and ZIKV sensing and induction of signaling pathways

The TLRs were the first PRRs to be identified and are the best characterized. The TLR family comprises 10 members (TLR1–TLR10) in humans and 12 (TLR1–TLR9, TLR11–TLR13) in mice. TLRs localize on the cell surface or intracellular compartments, including endosomes and lysosomes (Kawasaki and Kawai 2014). Upon PAMP recognition, TLRs recruit the Toll/IL-1 receptor (TIR)-domain containing adaptor proteins such as myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adaptor-inducing interferon-β (TRIF), which initiate signal transduction pathways that culminate in the activation of nuclear factor κB (NF-κB), Interferon response factors (IRFs), or Mitogen-activated protein kinases to regulate the expression of pro-inflammatory cytokines, chemokines, and IFN-I [for a review, see Refs. (Kawai and Akira 2010; Kawasaki and Kawai 2014)].

Since TLR3 recognizes viral dsRNA, small interfering RNAs (siRNAs), and self-RNAs derived from damaged cells (Bernard and others 2012; Pirher and others 2017), as well as induced IFN production in many cell types, it has been suggested that the TLR3 pathway contributes to the innate immune responses against many viruses, including CHIKV and ZIKV (Li and others 2012; Priya and others 2014; Dang and others 2016) (Figs. 1 and 2, respectively). Indeed, susceptibility to CHIKV infection was markedly increased in human and mouse fibroblasts with defective TLR3 signaling (Her and others 2015). Li and others (2012) reported that treatment of human bronchial epithelial-derived cells, BEAS-2B, with poly(I:C), a synthetic agonist of TLR3, suppressed the cytopathic effect induced by CHIKV infection and inhibited virus replication through the induction of IFN production and IFN-stimulated genes (ISGs), such as the 2′,5′-oligoadenylate synthetase (OAS)/RNase L pathway and the human myxovirus resistance protein A, suggesting that expression of ISGs is the first barrier against CHIKV since it leads to activation of inflammatory and antiviral defense mechanisms (Fig. 1A). Similar results were described in a murine model (Priya and others 2014; Her and others 2015).

The unusual severe manifestation of CHIKV infection, including neurological disorders, has been attributed to the novel East Central South African genotype with the A226V mutation in the E1 protein (Schuffenecker and others 2006). Interestingly, Priya and others (2013) found that the 226V mutant virus showed relatively less induction of IFN-β, OAS-3, MX-2, and TLR3/7 vs the nonmutant strain (A226), but that following poly(I:C) treatment CHIKV replication is inhibited. However, infection by either the A226 or the 226V strains induces the expression of IL-2, IL-6, IL-12, and TNF-α in neuronal infected cells, compared to mock infected cells. Another study suggested a probable association between single nucleotide polymorphisms on the TLR7/8 genes with CHIKV infection susceptibility and level of pro-inflammatory cytokine production (Dutta and Tripathi 2017). Taken together, these results suggest a possible link between TLR activation and pro-inflammatory cytokine production with CHIKV pathogenesis, since excessive release of these cytokines could contribute with tissue compromise together with the direct effect of viral replication (Table 1). However, the exact function and significance of TLRs in CHIKV pathogenesis require further investigation.

Like CHIKV, ZIKV induced TLR3 activation leads to the production of IFN-I and control of viral replication in human cerebral organoids and skin fibroblasts (Hamel and others 2015; Dang and others 2016). TLR3 expression is upregulated after ZIKV infection of human cerebral organoids and mouse neurospheres, and its inhibition reduced the phenotypic effects of ZIKV infection in brain. Furthermore, TLR3 activation highlights many genes involved in neurogenesis, differentiation of neural progenitor cells, and apoptosis, suggesting a mechanistic connection between TLR3 and neurological manifestations such as microcephaly in newborns induced by ZIKV infection (Faizan and others 2017).

Although many questions remain unanswered regarding the complications caused by different primary isolates of ZIKV and the role of TLR activation in response to virus infection, the virus can upregulate the expression of TLR3 in human astrocytes and human fibroblasts (Hamel and others 2015; Hamel and others 2017; Table 1). Furthermore, selective inhibition of either TLR3 or TLR8 through siRNA diminished inflammatory cytokine production, while neither IFN-β nor the levels of chemokines were affected in HTR8

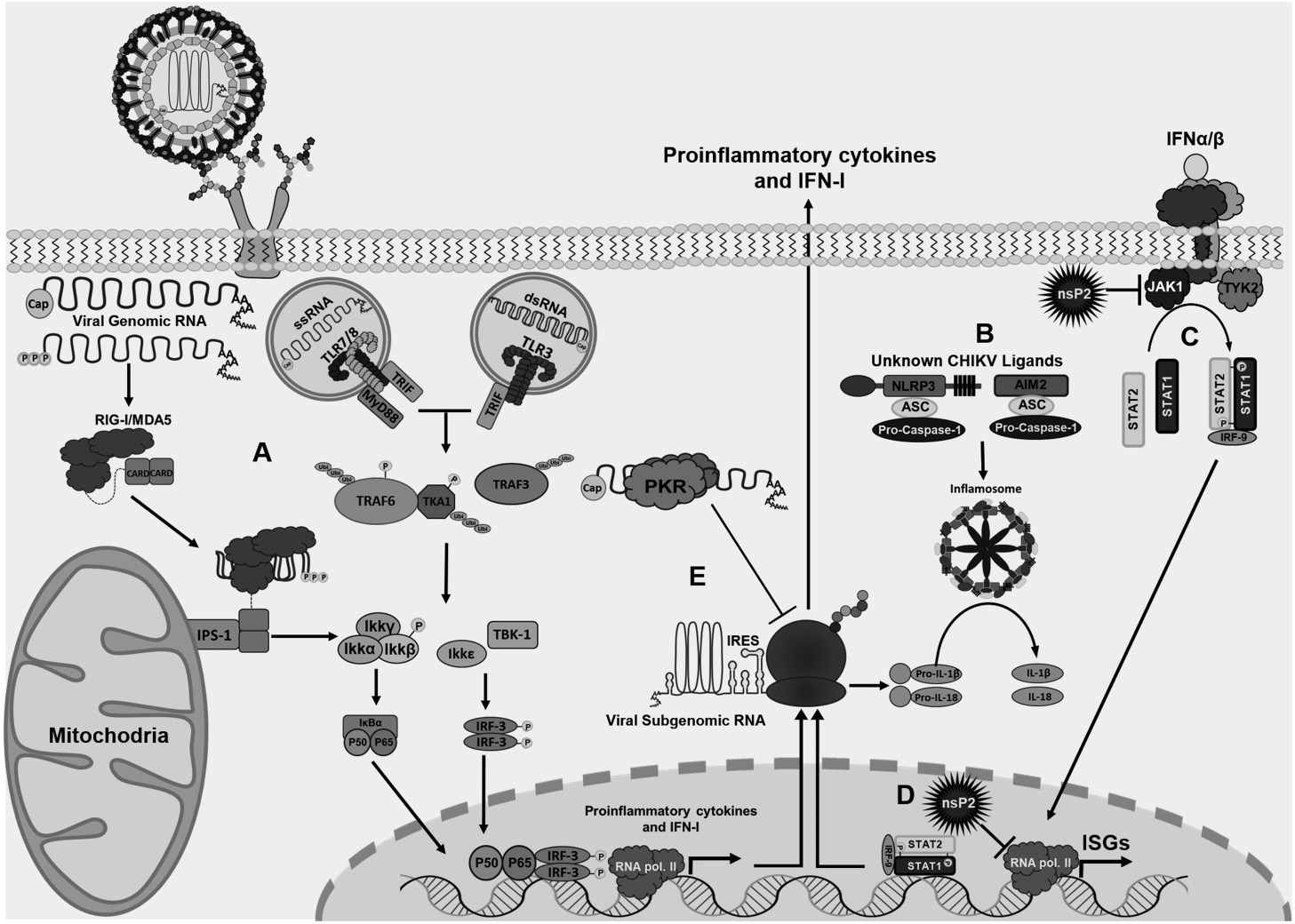

FIG. 1. Host innate immune recognition of CHIKV by PRRs and mechanisms of CHIKV subversion of type I IFN signaling. **(A)** CHIKV RNA is recognized by TLR3 (dsRNA), TLR7/8 (ssRNA), or RLRs as MDA5 and RIG-I (ssRNA), resulting in a signaling cascade that induces activation of NF-κB and IRFs, leading to the production of IFN-I and pro-inflammatory cytokines. **(B)**. Unknown component of CHIKV induces NLRP3 and AIM2 inflammasome activation, resulting in IL-1β and IL-18 maturation. **(C)** CHIKV nsP2 protein impairs IFN signaling in virally infected cells by blocking of the JAK/STAT signaling pathway, resulting in inhibition of STAT phosphorylation and translocation into the nucleus that affects the ISG expression. **(D)** CHIKV nsP2 induces the degradation of Rpb1, a catalytic subunit of RNA Polymerase II, late in infection, blocking the expression of cellular genes and downregulating cellular antiviral response. **(E)** CHIKV induces PKR dependent and independent translational shutoff, blocking translation of host mRNAs but not of CHIKV subgenomic RNA, which contains a cap and an 5′-IRES, and is translated in the absence of eIF2α. P, phosphorylated protein; Ubi, Ubiquitin chain; PRRs, pattern recognition receptors; ssRNA, single-stranded RNA; IFN, interferon; IL, interleukin; RLRs, RIG-I-like receptors; TLR, toll-like receptor; NF-κB, nuclear factor κB; IRF, interferon response factor; ISG, IFN-stimulated gene; MDA5, Melanoma Differentiation-Associated Protein 5; IRES, internal ribosome entry site; JAK-STAT, Janus kinase-signal transducer and activator of the transcription; eIF2α, eukaryotic translation initiation factor 2 subunit alpha; CHIKV, Chikungunya virus.

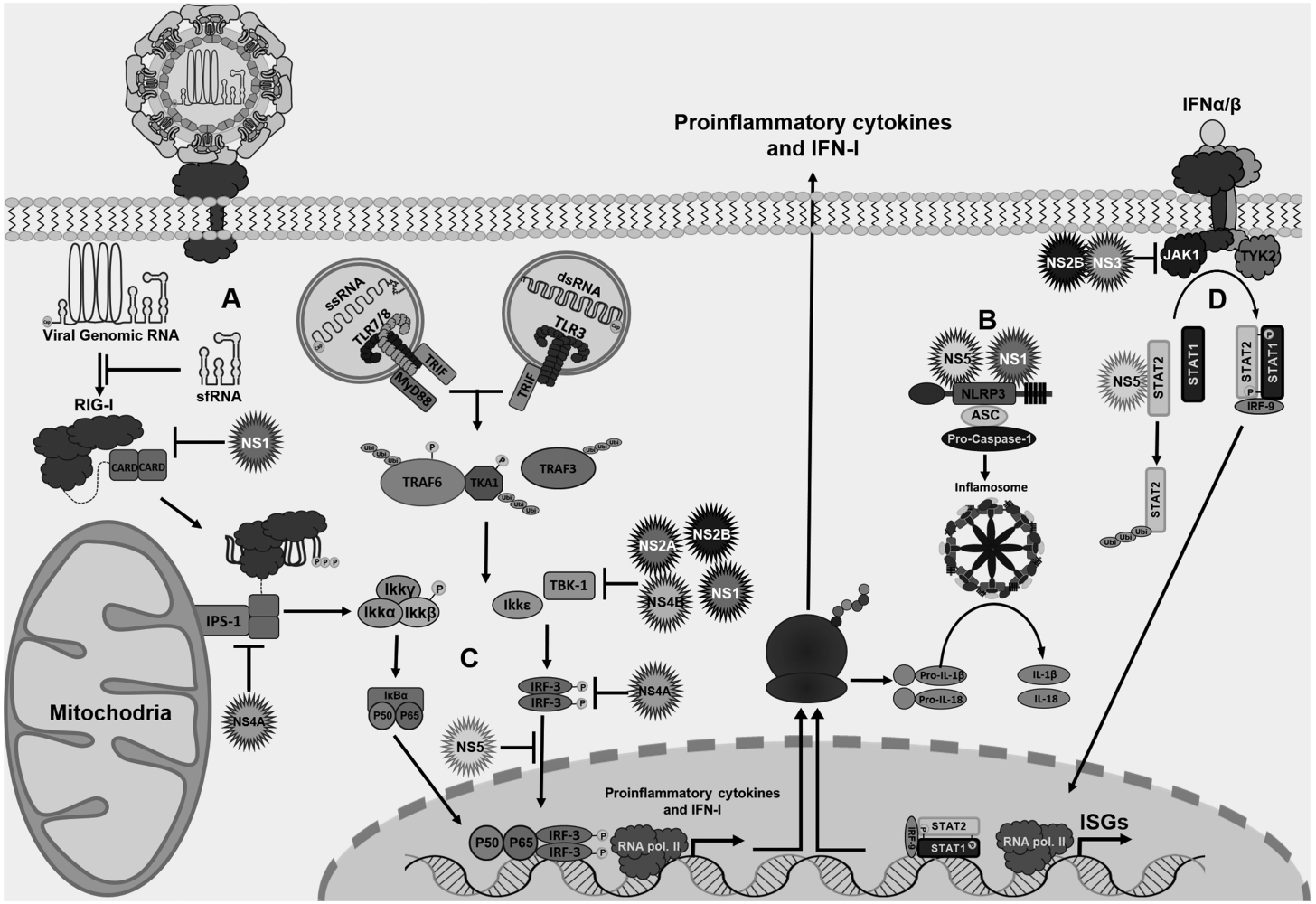

FIG. 2. Host innate immune recognition of ZIKV by PRRs and mechanisms of ZIKV subversion of type I IFN signaling. **(A)** ZIKV RNA is recognized by TLR3 (dsRNA), TLR7/8 (ssRNA), and RIG-I (ssRNA), resulting in a signaling cascade that induces activation of NF-κB and IRFs, leading to the production of IFN-I and pro-inflammatory cytokines. sfRNA present in ZIKV-infected cells acts as antagonist of RIG-I-dependent IFN-I production. **(B)** ZIKV NS1 and NS5 proteins induce NLRP3 inflammasome activation, resulting in IL-1β and IL-18 maturation. **(C)** ZIKV NS1 interacts with RIG-I and inhibits its activation. NS4A specifically binds to the CARD domain of IPS-1 and thus blocks its accessibility by RLRs. NS1, NS2A, NS2B, and NS4B block TBK-1 phosphorylation and activation. NS4A blocks IRF-3 phosphorylation, and NS5 inhibits its translocation into the nucleus, impeding IFN-I induction in virally infected cells. **(D)** The NS2B-NS3 complex impedes IFN signaling in virally infected cells by blocking the JAK/STAT signaling pathway by degrading JAK1. NS5 binds and degrades human STAT2, targeting this toward the proteasomal degradation pathway, thus preventing the formation of the STAT1/STAT2 heterodimer and its transcriptional induction of ISGs. P, phosphorylate protein; Ubi, Ubiquitin; IPS-1, interferon-beta promoter stimulator 1; TBK-1, TANK-binding kinase 1; ZIKV, Zika virus.

Table 1. Similitude and Difference on How Chikungunya Virus and Zika Virus Trigger Inflammatory Signaling and Regulated Antiviral Response

	Trigger inflammatory signaling and antiviral response		
Viruses	*PRRs implicated in viral recognition and induction of pro-inflammatory and antiviral response*	*Viral mechanisms to regulate IFN-I expression*	*Viral mechanisms to regulate ISG expression*
CHIK	-TLR3 [Viral RNA] (Li and others 2012; Her and others 2015). -TLR7/8 [Viral RNA] (Dutta and Tripathi 2017). -RIG-I/MDA5 [Viral RNA] (Olagnier and others 2014; Akhrymuk and others 2016). -NLRP3 [Unknown viral ligand] (Ekchariyawat and others 2015; Chen and others 2017). -AIM2 [Unknown viral ligand] (Ekchariyawat and others 2015).	Unknown	-nsP2 blocking the JAK/STAT signaling pathway (Fros and others 2010). -nsP2 induces degradation of Rpb1, a catalytic subunit of RNA Polymerase II, through the ubiquitin-proteasome system (Akhrymuk and others 2012). -Translational shutoff induced by CHIKV replication downregulates cellular antiviral response (White and others 2011).
ZIK	-TLR3 [Viral RNA] (Hamel and others 2015; Dang and others 2016; Faizan and others 2017). -TLR7/8 [Viral RNA] (Luo and others 2018; Vanwalscappel and others 2018). -RIG-I [Viral RNA] (Bowen and others 2017; Chazal and others 2018). -NLRP3 [NS1 and NS5] (Tricarico and others 2017; Wang and others 2018; Zheng and others 2018).	-sfRNA in ZIKV acts as antagonist of RIG-I-dependent IFN-I production (Donald and others 2016). -NS1 interacts with RIG-I and downregulates the antiviral signaling pathway (Kim and others 2018). -NS4A specifically binds to the CARD domain of IPS-1 and thus blocks its accessibility by RLRs (Ma and others 2018). -NS1, NS2A, NS2B, and NS4B interact directly with TBK-1 and block its phosphorylation and activation (Xia and others 2018). -NS4A suppresses IRF-3 phosphorylation (Xia and others 2018). -NS5 inhibits a step downstream of IFR-3 phosphorylation (Xia and others 2018).	-NS2B-NS3 complex impairs the JAK–STAT signaling pathway by degrading JAK1 (Wu and others 2017). -NS5 interacts with STAT2 and induces STAT2 degradation through ubiquitin-proteasome system (Chaudhary and others 2017).

CHIKV, Chikungunya virus; ZIKV, Zika virus; PRRs, pattern recognition receptors; IFN-I, Type I interferon; TLR, toll-like receptor; RLRs, RIG-I-like receptors; IRF, interferon response factor; ISG, IFN-stimulated gene; MDA5, Melanoma Differentiation-Associated Protein 5; IPS-1, interferon-beta promoter stimulator 1; TBK-1, TANK-binding kinase 1; JAK-STAT, Janus kinase-signal transducer and activator of the transcription.

cells (Luo and others 2018). This is interesting since TLR7/8 agonists have been used to treat inflammatory disorders and viral infection. Vanwalscappel and others (2018) tested the effect of the TLR7/8 agonist R-848 (resiquimod) on monocytes and found that it acts as a potent inhibitor of ZIKV replication on monocytes through viperin, an ISG that has antiviral activity against several RNA viruses. Taken together, these results suggest that TLR3 and TLR7/8 activation can play an important role in induction of inflammatory cytokine production and IFN-I secretion in response to CHIKV (Fig. 1A; Table 1) and ZIKV (Fig. 2A; Table 1) infection.

NOD-like receptor activation and its role in CHIKV and ZIKV recognition and inflammatory response

NOD-NLRs are a group of cytoplasmic receptors that like TLRs play a key role in recognition of PAMPs and DAMPs and subsequent activation of the innate immune response. These proteins share a common domain organization, present an NH_2-terminal protein–protein interaction domain, a central nucleotide-binding oligomerization (NOD/NACHT) domain that possess ATPase activity, and the Mg^{+2}-binding site and a COOH-terminal leucine-rich repeat [reviewed in references (Koonin and Aravind 2000; Motta and others 2015)]. The activation of NLRs exerts multiple downstream signaling that results in the assembly of a multiprotein platform called inflammasome, activation of the NF-κB pathway, and promoting inflammatory responses. Inflammasome platforms are composed of a protein that senses stimulation [NLRP (P for pyrin domain) 1, NLRP2, NLRP3, NLRP6, NLRP7, NLRP12, NLRC4, and NAIP], an ASC, and a catalytic protein (pro-caspase-1), and after a 2-step process of priming and activation, inflammasomes are responsible for the processing and maturation of IL-1β and IL-18 (Schroder and Tschopp 2010; Davis and others 2011), as well as inflammatory cell death (pyroptosis) (Man and others 2017).

It was described that CHIKV infection enhances IL-1β secretion and induces maturation of caspase-1 in primary human dermal fibroblasts, suggesting that CHIKV can elicit activation of the inflammasome program (Ekchariyawat and others 2015) (Fig. 1B; Table 1); the caspase-1 activation favors the control of CHIKV replication in human dermal fibroblasts. Ekchariyawat and others (2015) showed that NLRP3, AIM2, and ASC1 expression were upregulated 15-fold, 33-fold, and 24-fold, respectively, upon dermal fibroblast infection. Furthermore, it has been reported that patients during early stages of CHIKV infection show high serum levels of IL-1β (Venugopalan and others 2014). Moreover, in both individuals infected with CHIKV and in murine models of CHIKV infection, a correlation between NLRP3 expression and the peak of inflammatory symptoms was reported (Chen and others 2017). In fact, inhibition of NLRP3 activation in the murine model resulted in reduced CHIKV-induced inflammation (lower expression of CCL2, IL-6, and TNF-α in joint tissue), bone loss, and myositis, indicating an important role of NLRP3 inflammasome activation in immunopathogenesis of CHIKV (Chen and others 2017). This notion was further highlighted since another study showed that induction of an NLRP3-IL-1β axis in human peripheral blood mononuclear cells contributes to severe inflammation in influenza A virus infection (McAuley and others 2013).

Like CHIKV, ZIKV also induces NLRP3 inflammasome activation with subsequent IL-1β secretion, as was demonstrated in U87-MG cells, and ZIKV-infected patients (Tricarico and others 2017; Wang and others 2018). Mice infected with ZIKV exhibited severe inflammatory pathology, and high levels of IL-1β in the serum and brain were associated with inflammasome activation (He and others 2018). Furthermore, ZIKV NS1 and NS5 interact with NLRP3 and promote assembly of the NLRP3 inflammasome complex resulting in IL-1β production (Fig. 2B; Table 1) and stimulated ZIKV replication (Zheng and others 2018). In addition, NS1 interacts strongly with caspase-1 in 293T cells infected with ZIKV and inhibits proteasomal degradation of caspase-1. Likewise, stabilization of caspase-1 by NS1 promotes the cleavage of cyclic GMP-AMP synthase, which results in reduced IFN-I signaling and enhanced ZIKV replication (Zheng and others 2018). The NLRP3 deficiency increases IFN production and strengthens host resistance to viral infection *in vitro* and *in vivo* (Zheng and others 2018). In a fatal case of ZIKV-linked microcephaly, significantly high expression of NLRP1, NLRP3, and AIM2 and IL-1β and IL-18 was reported (De Sousa and others 2018), suggesting that *in situ* inflammasome activation could contribute to the development of neuroinflammatory response. In addition, NLRP3 inflammasome–derived IL-1β production has been associated as a critical feature of inflammation in brain, spleen, liver, and kidney of mice infected with ZIKV (Tappe and others 2016; He and others 2018; Wang and others 2018).

RIG-I-like receptor signaling and their role in CHIKV and ZIKV recognition: an orchestrated multilevel blocking of the IFN signaling pathway complex

Although distinction between self and nonself RNA is believed to rely on the molecular signatures found in PAMPs, the mechanism for which viral RNA is recognized by RLRs, a family of cytoplasmic dsRNA helicases that includes RIG-I, Melanoma Differentiation-Associated Protein 5 (MDA5), and Laboratory of Genetics and Physiology 2, is poorly understood (Koyama and others 2008; Lässig and Hopfner 2017). RIG-I can specifically recognize 5′-triphosphate or diphosphate groups on ssRNA and dsRNA (Hornung and others 2006; Pichlmair and others 2006; Goubau and others 2015), whereas MDA5 can specifically bind long dsRNA (Kato and others 2008). In addition, both RLRs are activated in response to recognition of 5′-Cap 0 structure present in viral mRNAs (Shuman 2002; Ghosh and Lima 2010).

Recognition of viral ssRNA or dsRNA by the RIG-I/MDA5 helicase induces a conformational change in these proteins that release the CARD domain to initiate signal transduction pathways. The complex of ssRNA or dsRNA with RIG-I/MDA5 is then transported to the mitochondrial surface where the CARD domain interacts with the mitochondrial protein Interferon-beta promoter stimulator 1 (IPS-1), also known as mitochondrial antiviral signaling protein (MAVS). This interaction induces the recruitment and activation of the I kappa B kinase family members, including Ikkα, β, γ, ε, and TANK-binding kinase 1 (TBK-1), that mediate activation of NF-κB and IRFs to regulate the expression of pro-inflammatory cytokines, chemokines,

and IFN-I [for a review, see (Loo and Gale 2011; Chow and others 2018)].

The presence of the 5′ cap structure is essential in Alphavirus and Flavivirus gene expression, since there are not internal ribosome entry site (IRES) elements present in some of the viral RNAs of these viruses. During the viral capping reaction in alphaviruses, nsP1 and nsP2 are implicated in the formation of viral type-0 cap structure that is found on both genomic and subgenomic RNAs (Ahola and others 1997; Vasiljieva and others 2000). In this context, it has been reported that RIG-I/MDA5 plays a crucial role in recognition of the alphavirus genome and stabilizing of the antiviral response (Olagnier and others 2014; Akhrymuk and others 2016), possibly by recognizing the viral 5′-Cap 0 structure or the triphosphate-uncapped RNAs (Fig. 1A; Table 1). CHIKV also alters the expression of RLRs. In HS 633T and HT-1080 (2 fibroblast cell lines), it was observed that CHIKV infection induces the expression of antiviral genes, such as IFN-I and RIG-I (Thon-Hon and others 2012). Similar results were observed in U-87 MG cell lines (Abraham and others 2013), a glioblastoma cell line of human astrocyte origin. Using 5′-triphosphorylated RNA (5′-pppRNA), a RIG-I agonist, inhibition of CHIKV replication was observed in monocytes and monocyte-derived DCs challenged with CHIKV (Olagnier and others 2014). The protection of these cells was dependent on an intact RIG-I/MAVS/TBK1/IRF3 axis, but independent of the IFN response.

CHIKV and ZIKV replication results in abundant viral RNA that is recognized by RIG-I/MDA5 leading to the production of inflammation mediators and IFNs, both involved in preventing virus infection and spread. It has been demonstrated that the ZIKV 5′-RNA is recognized by RIG-I (Chazal and others 2018); however, Donald and others (2016) reported that subgenomic flavivirus RNA (sfRNA) in ZIKV acts as antagonist of RIG-I-dependent IFN-I production (Fig. 2A; Table 1). In addition, during infection with ZIKV, minimal upregulation of DC activation markers, proinflammatory cytokine production, and impaired translation of IFN-I, despite high expression of RIG-I and MDA5, were reported (Bowen and others 2017). Furthermore, treatment with a highly specific RIG-I agonist, but not IFN-I, strongly restricted ZIKV replication in human DCs (Bowen and others 2017), indicating a viral antagonism of the IFN-I response.

Both CHIKV and ZIKV orchestrate a multilevel complex to block the IFN signaling pathway

IFN-I (IFN-α, -β, -ε, -κ, -ω, and -ζ) and IFN-III (IFN-λ1, 2, and 3) are large subgroups of IFN proteins that help regulate the activity of the immune system and induce the establishment of an antiviral state in infected cells (Stetson and Medzhitov 2006; De Weerd and Nguyen 2012; Le Bon and Tough 2002). IFN-I and -III bind to a specific cell surface receptor complex known as IFN-α receptor (IFNAR) that consists of the IFNAR1 and IFNAR2 chains (Piehler and others 2012). The IFN–IFNAR interaction results in the Janus kinase-signal transducer and activator of the transcription (JAK-STAT) signaling pathway, which along with Mitogen-activated protein kinases, Phosphoinositide 3-kinases, and Protein Kinase B signaling pathways leads to the expression of ISGs that classically result in a robust antiviral immune response (De Weerd and Nguyen 2012). [For review see Bayer and others 2016; Schneider and others 2014].

ISGs such as PKR, OAS/RNase L, viperin, and ISG15 (Werneke and others 2011; White and others 2011; Teng and others 2012; Li and others 2016) have been reported to play a crucial role in the control of CHIKV replication and dissemination in the tissues. Therefore, it is not surprising that CHIKV has developed mechanisms to block IFN signaling or ISG expression. One of the proteins implicated in the control of antiviral effects of IFNs is CHIKV nsP2, a polyfunctional protein with helicase activity, RNA triphosphatase, nucleoside triphosphatase, methyltransferase, and papain-like cysteine protease activity, implicated in viral replication (Ahola and others 1997; Vasiljieva and others 2000; Tang 2012). Furthermore, it is involved in orchestrating downregulation of IFN-dependent cellular antiviral state in multiple steps. Indeed, the CHIKV nsP2 protein inhibits transcription of ISGs by inhibiting IFN signaling blocking the JAK/STAT signaling pathway, an event that leads to inhibition of STAT phosphorylation and translocation into the nucleus (Fros and others 2010) (Fig. 1C; Table 1). In addition, CHIKV nsP2 induces the degradation of Rpb1, a catalytic subunit of RNA Polymerase II, through the ubiquitin-proteasome system and blocks the activation of cellular gene transcription and downregulation of cellular antiviral response late during the CHIKV replication cycle (Akhrymuk and others 2012) (Fig. 1D; Table 1).

Translational shutoff is an innate mechanism of cellular antiviral response that is frequently activated in response to viral infections to limit translation of viral genes (Walsh and Mohr 2011). In the case of CHIKV infection, translational shutoff is activated in response to viral replication by pathways dependent and independent of PKR activation in response to viral RNA (White and others 2011). Once activated, PKR phosphorylates the eukaryotic translation initiation factor 2 subunit alpha (eIF2α). This inhibits further cellular mRNA translation, thereby preventing viral protein synthesis (García and others 2007; Kim and others 2018). However, in the infection context of CHIKV, PKR is activated late during the CHIKV replication cycle, a time during which are expressed structural genes from viral subgenomic RNAs, which are translated in the absence of eIF2α (Alphavirus subgenomic RNA presents a 5′-IRES sequence) (Joyce and others 2009) (Fig. 1E; Table 1). Therefore, translational shutoff induced by CHIKV replication downregulates cellular antiviral response because phosphorylation of eIF2α blocks translation of cellular mRNA but not viral mRNAs; this strategy reduces the competition of ribosomes by both viral and host mRNAs.

The IFN-I and -III responses are crucial in the control of ZIKV replication (Bayer and others 2016; Van Der Hoek and others 2017) and as in DENV (Munoz-Jordan and others 2003; Mazzon and others 2009; Rodriguez-Madoz and others 2010), ZIKV has an extensive repertory of mechanisms to control IFN response. It has been reported that after recognition of the ZIKV genome, different ZIKV proteins antagonize IFN-β production through distinct cellular mechanisms, among them, the RIG-I pathway (Fig. 2A and C; Table 1), for example, (i) ZIKV NS1 interacts with RIG-I and downregulates the antiviral signaling pathway (Kim and others 2018), (ii) NS4A specifically binds to the CARD domain of IPS-1 and thus blocks its accessibility by

RLRs (Ma and others 2018), (iii) NS1, NS2A, NS2B, and NS4B interact directly with TBK-1 and block its phosphorylation and activation, (iv) NS4A suppresses IRF-3 phosphorylation, and (v) NS5 inhibits a step downstream of IFR-3 phosphorylation, possibly through IRF-3 nuclear translocation or its binding to the IFN-ß promoter (Xia and others 2018). In addition, it has been reported that the NS2B-NS3 complex of ZIKV impairs the JAK–STAT signaling pathway by degrading JAK1 and reduces virus-induced apoptotic cell death (Wu and others 2017) (Fig. 2D; Table 1). In addition, ZIKV NS5 is a potent suppressor of the IFN-I/III signaling pathway, but it enhances the IFN-II signaling pathway. Inversely, IFN-γ increases ZIKV replication (Chaudhary and others 2017). NS5 interacts with STAT2 and this later is degraded through the ubiquitin-proteasome system (Fig. 2D; Table 1) and induces the formation of a STAT1-STAT1 homodimer that is involved in the transcriptional activation of IFN-γ-stimulated genes, such as the gene encoding the pro-inflammatory chemokine CXCL10 (Kumar and others 2016; Bowen and others 2017; Chaudhary and others 2017).

What is common and what is different in the mechanisms by which the viruses CHIK and ZIK trigger the innate immune signaling?

In summary and as we describe it in this review, the aim of the recognition of viral components (PAMPs) of both CHIKV and ZIKV by PRRs is to disrupt the viral infection/replication process and/or contribute to the development of a strong adaptive immune response. However, both viruses have developed specific strategies to regulate their own benefit or to escape the innate immune signaling program of the host cell that is summarized in Table 1. However, as described above, prolonged activation of the innate immunity by PRRs can contribute to the different diseases associated with each of these 2 viruses. Just to mention an example, since the relationship between the activation of the PRRs and their consequence in viral pathogenesis was discussed above, the severe manifestation of CHIKV infection, including neurological disorders, has been attributed to the novel East Central South African genotype (Schuffenecker and others 2006), which showed relatively less induction of IFN-β, OAS-3, MX-2, and TLR3/7 versus the nonmutant strain, but that following poly(I:C) treatment CHIKV replication is inhibited (Priya and others (2013)). Furthermore, persistent polyarthralgia after CHIKV clearing from peripheral blood has been associated with chronic infection of macrophages in synovial fluid and the establishment of a persistent activation of PRRs that promotes an inflammatory environment (Labadie and others 2010). Likewise, TLR3 activation in response to ZIKV infection highlights many genes involved in neurogenesis, differentiation of neural progenitor cells, and apoptosis, suggesting a mechanistic connection between TLR3 and neurological manifestations such as microcephaly in newborns induced by ZIKV infection (Faizan and others 2017). Moreover, the activation of PRRs induces elevated production of pro-inflammatory cytokines involved in the development of an inflammatory state that is involved in the permeabilization of the hematoencephalic barrier, which is a common manifestation in response to infection with CHIKV or ZIKV.

Conclusions

CHIKV and ZIKV are 2 arboviruses that have caused important epidemics in tropical and subtropical areas worldwide in the last 2 decades. Collectively, the PRRs such as TLRs, NLRs, and RLRs play a crucial role in recognition and control of viral infection, replication, and spread of both CHIKV and ZIKV. Furthermore, based on what we discuss above, a synergy of TLR3 with diverse host RNA sensors (RIG-I/MDA5) might be necessary for specific interaction with intermediate viral components of replication such as dsRNA to restrict CHIKV and ZIKV by inducing a rapid antiviral response through IFN production together with pro-inflammatory cytokine and chemokine secretion. However, an exacerbated activation of PRRs can lead to a marked pro-inflammatory response that has been implicated in the development of immunopathologic diseases (fever) of CHIKV and ZIKV infection.

In the case of CHIKV, a marked pro-inflammatory response has been associated with the development of acute and chronic polyarthralgia. Persistent polyarthralgia after CHIKV clearing from peripheral blood has been associated with chronic infection of macrophages in synovial fluid and the establishment of a persistent activation of PRR that promotes an inflammatory environment. In the case of ZIKV, its ability to infect immune privileged tissues is a major determinant of viral pathogenesis. Thereafter, ZIKV infection has been associated with the development of important neurological disorders such as congenital microcephaly, since ZIKV has the ability to migrate transplacentally and infect neural progenitor cells in the fetus, leading to activation of TLR3 and factors involved in pro-inflammatory response in the brain that has been associated with the development of microcephaly. The findings discussed in this study provide a better knowledge of the role of the different receptors of the immune response whose activation induces protective anti-CHIKV and anti-ZIKV response and this will have critical implications in the future development of therapeutic strategies against both viruses that have serious global health impacts.

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