Host Immune Responses to Arthritogenic Alphavirus Infection, with Emphasis on Type I IFN Responses

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Abstract

Arthritogenic alphaviruses, such as Ross River virus, chikungunya virus and O’nyong-nyong virus, cause endemic disease globally and are a major public health concern. The hallmarks of arthritogenic alphavirus disease are debilitating pain, and potentially chronic inflammation of the muscles, thus influencing quality of life. The type I IFN response is a major component of the innate immune response against arthritogenic alphaviruses, and is essential in inhibiting viral replication and dissemination. Type I IFNs are induced during early stages of infection and are essential for the activation of the antiviral innate immune response. They also link the innate immune response and the activation of adaptive immunity. This review focuses on the host immune response, particularly that involving type I IFN, in arthritogenic alphavirus disease.

Key words: alphavirus, innate immune response, Type I IFN, antagonism

INTRODUCTION

Alphavirus, the only genus of the Togaviridae family, currently comprises 32 members. The first reported alphavirus infection in animals dates to the 18th century and is thought to have been Eastern equine encephalomyelitis virus (EEEV), on the basis of disease symptoms [1]. Chikungunya virus (CHIKV) was first identified in 1952 in Africa [2]. CHIKV has been observed in nearly 60 countries and has caused millions of clinical cases worldwide. Human infection with Ross River virus (RRV) was first recorded in Australia in 1928 [3]. Currently, RRV is the most widespread arbovirus in Australia and can be found throughout the South Pacific [4]. Each year in Australia, approximately 5,000 cases of RRV disease are reported [5,6]. In 2015, owing to extended periods of heavy rainfall, RRV disease cases reached a 23-year high in Australia, with 9,542 cases reported [7]. Diseases caused by alphaviruses have major economic and social costs. In the United States, CHIKV outbreaks have cost the healthcare system approximately US $14.8 to $33.4 million between the years 2014 and 2015 [8]. The annual cost of RRV in Australia, including testing, supportive therapies and loss of earnings, has been estimated to be approximately AU $20 million [6]. Nonetheless, no specific treatments or approved vaccines are currently available to protect against alphavirus infection, and only supportive care with analgesics and non-steroidal anti-inflammatory drugs is provided to symptomatic patients [9]. Therefore, investigation of the pathogenesis of alphavirus disease is imperative to identify potential targets for therapeutic intervention. Host type I interferon (IFN) is the first line of defence...
against invading viral pathogens [10]. However, many viruses, including alphaviruses, have evolved abilities to counteract the type I IFN system [11-13]. The mechanisms used by alphaviruses to antagonise the host type I IFN system have been investigated in recent years. However, very little is known in this regard, and further investigations on these mechanisms are required.

**Alphavirus structure and life cycle**

The alphavirus virion is composed of an envelope, a nucleocapsid and a positive sense single-stranded RNA genome [14]. The genomes of most alphaviruses contain approximately 12 kb nucleotides encoding two open reading frames (ORFs): a non-structural protein (nsP) ORF and a structural protein ORF [15]. The full length alphavirus genome comprises 5’-cap–nsp1–nsp2–nsp3–nsp4–(junction region)–CP–E3–E2–6k–E1–poly(A) tail–3’. The main stages of the alphavirus life cycle are shown in Fig 1 [16-21]. First, the virion attaches to the target host cytoplasmic membrane through cellular receptors, such as Mxra8 [22], C-type lectin receptor (CD209, also known as DC-SIGN) [23,24], TIM-1, NRAMP2, laminin, prohibitin1 [25] and heparan sulfate [26]. The virion enters cells through endocytosis. The viral envelope fuses with a mature endosome, and the viral core nucleocapsid disassembles under the low pH environment [27]. Next, the virus non-structural proteins are translated as poly-non-structural proteins p123 or p1234 from the viral genomic non-structural protein ORF. Cis-cleavage of the poly-non-structural proteins produces the mature non-structural proteins nsP1, nsP2, nsP3 and nsP4, which form a mature viral replicase that mediates viral RNA replication. The structural proteins are translated from the viral subgenomic RNA. The viral capsid protein interacts with viral RNA, and the virion is assembled in the cytoplasm. E1 and E2 proteins are secreted through the Golgi complex and embedded in the host cell membrane, which coats the virus nucleocapsid core during budding and formation of the mature virion [14].

**Alphavirus disease and host immune response**

Arthritogenic alphaviruses such as CHIKV, Mayaro virus (MAYV), RRV and O’nyong-nyong virus are associated with rheumatic disease and are the primary cause of infectious arthropathies worldwide [28]. Generally, acute fever, skin rash, malaise, fatigue, myalgia and arthralgia are the common clinical signs shared by most arthrogenic alphavirus infections. The main features of pathogenesis of alphavirus disease are summarised in Fig 2. Several of the host’s innate and adaptive immune responses are activated during alphavirus infection [29], including the induction of cellular responses associated with T cells [30], B cells [31], natural killer cells [32] and macrophages [33], as well as the induction of cytokines, chemokines [34-38] and...
complement factors [39]. Inflammatory mediators such as cytokines, chemokines, reactive oxygen and nitrogen species, and prostaglandins are released from leukocytes [40]. In inflamed tissues, these immune factors, which constitute the host natural defence system, potentially contribute to viral arthropathies.

Macrophages play important roles in rheumatoid arthritis (RA) [41], spondyloarthropathies [42,43] and gout-arthritis [44]. Notably, macrophages have also been found to be associated with the pathogenesis of infectious arthritis such as septic arthritis and Lyme arthritis [45–47]. A major component of the cellular infiltrate in alphavirus infected tissues is macrophages. The depletion of macrophages in RRV infected mice, compared with undepleted infected mice, significantly ameliorates rheumatic disease signs, thus suggesting that macrophages and macrophage derived factors are the primary cellular mediators of RRV induced arthritis and myositis disease [48]. A recent study has indicated a novel role of CX3CR1+ macrophages in tissue repair after RRV-induced myositis. The study has also highlighted a potential therapeutic approach using immune modifying IMP microparticles to decrease inflammation and enhance tissue repair in infected individuals [49].

Beyond the cellular response, soluble mediators have also been reported to play roles in RRV disease. Macrophage migration inhibitory factor (MIF) is a critical contributor to the severity of alphavirus-induced musculoskeletal disease. MIF is up-regulated in the serum and musculoskeletal tissues of mice with severe RRV disease [36]. Moreover, MIF has recently been found to correlate with CHIKV viral load in patients with CHIKV in Brazil [50]. Therefore, targeting this factor might aid in treating alphaviral arthritis in humans.

Monocyte chemotactic protein–1 (MCP–1; CCL2), tumour necrosis factor alpha (TNF-α) and IFN-γ are elevated in synovial effusions of alphavirus infected patients [48]. An in vitro study using human synovial cells infected with RRV has detected MCP-1, type I IFN, granulocyte macrophage colony stimulating factor (GM-CSF) and interleukin (IL)-8 at high levels [37]. Notably, treatment with Bindarit, an experimental drug that inhibits MCP-1 production, has been found to decrease macrophage infiltration and ameliorate rheumatic disease in a mouse model [38,51].

In a recent study, IL-17A has been reported to be associated with tissue inflammation as well as neutrophil infiltration in CHIKV-induced RA [28]. In another recent study on IL-17 in RRV disease, IL-17 has been found to be responsible for RRV-induced arthritis and myositis [52]. IL-17 expression is up-regulated in musculoskeletal tissues and sera of RRV infected mice and humans.
Blocking IL-17 has been suggested to decrease transcription of proinflammatory genes, cellular infiltration in synovial tissues and cartilage damage, thus ameliorating arthritic alphavirus diseases.

Interestingly, downregulation of IL-13 and MCP-3 has been observed in patients with CHIKV disease, representing a unique cytokine profile of acute CHIKV infection [53]. IL-13 negatively regulates IgG1 and IgG2a switching through IFN-γ dependent signalling, thus suggesting that IL-13 may play an important role in antibody class switching during acute CHIKV infection.

Beyond targeting joints and skeletal muscles, CHIKV, MAYV and encephalitic alphaviruses (new-world alphaviruses such as Venezuelan, eastern and western equine encephalitis viruses (VEEV, EEEV, and WEEV, respectively)) also infects the central nervous system (CNS) in humans [54–57]. VEEV and WEEV infection in the CNS is controlled by caveolin-1 (Cav-1)–mediated transcytosis across the blood brain barrier [55]. Several studies have indicated that type I IFN is highly important in preventing viral invasion into the host CNS.

The complement system has been shown to mediate immunopathogenesis during RRV infection. Activated complement proteins have been found in synovial fluids of RRV infected patients. Complement activation is involved in tissue destruction at the site of infection [58]. Moreover, mannose binding lectin (MBL) has been shown to be the essential receptor for complement activation in RRV infection. Mice deficient in MBL, C3 or CR3 complement receptor show less severe rheumatic symptoms than do wild type mice [58–60]. Another study has shown indicated that, compared with mice infected with wild type virus, infection with RRV missing both E2 glycans leads to diminished MBL binding and complement activation, thus resulting in mild tissue damage [61]. Consequently, MBL and the viral N-linked glycans appear to be highly important to the development of alphaviral disease.

Bone lesions have been reported in patients with CHIKV disease [62]. The disruption of the Receptor activator of nuclear factor kappa-B ligand (RANKL)/Osteoprotegerin (OPG) ratio has been shown to be a major contributor to bone loss in alphavirus induced arthritis disease. Primary human osteoblasts infected by RRV and CHIKV show a disrupted RANKL/OPG ratio and high levels of IL-6. However, the bone loss and the disrupted RANKL/OPG ratio are blocked by an IL-6 neutralising antibody treatment in a mouse model, thus suggesting that IL-6 plays a role in modulation of the RANKL/OPG ratio [35]. Furthermore, MCPs have been reported to play a role in CHIKV-induced osteoclastogenesis, because Bindarit treatment decreases CHIKV-induced bone loss in vivo [63].

Host type I IFN response

The innate immune system is the first line of defence against viral infection [10,64]. Its roles include detection of antigens, protection against viruses and activation of the adaptive immune system [65]. The interplay between type I IFN and alphavirus infection is discussed below.

The interplay between alphavirus and the type I IFN pathways is summarised in Fig 3. Type I IFN induction has shown indicated that, compared with mice infected with wild type virus, infection with RRV missing both E2 glycans leads to diminished MBL binding and complement activation, thus resulting in mild tissue damage [61]. Consequently, MBL and the viral N-linked glycans appear to be highly important to the development of alphaviral disease.

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pathways start when pattern recognition receptors (PRRs) identify the pathogen-associated molecular patterns (PAMPs) associated with the invading viruses [66]. PRRs can be divided into three classes on the basis of their subcellular localisation: membrane-bound PPRs, cytoplasmic PPRs and secreted extracellular PPRs. Activation of PRRs by PAMPs induces cascades of intracellular signalling, thus leading to type I IFN production. TLR and retinoic acid-inducible gene-I-like receptor (RLR) families are the major PPRs that activate these signalling cascades [67,68]. TLRs associated with type 1 IFN production include TLR3, TLR4, TLR7, TLR6 and TLR9. TLR3, TLR7, TLR8 and TLR9 localise to endosomes, whereas TLR4 localises to the cell membrane surface [69,70]. TLR4 is a robust type I IFN inducer that signals through adapter protein, TIR-domain containing adapter inducing interferon-β (TICAM1, TRIF) recognises lipopolysaccharide from bacteria. Within endosomal compartments, TLR3, TLR7, TLR8 and TLR9 react to double-stranded RNA, single-stranded RNA and unmethylated CpG DNA [68]. The RLR family includes three members: retinoic acid inductive gene-I protein (RIG-I), melanoma differentiation-associated gene 5 protein (MDA-5) and laboratory of genetics and physiology 2 protein (LGP2). MDA-5 recognises long foreign dsRNA [71]. RIG-I detects primarily foreign ssRNA containing 5’-triphosphate or short dsRNA, and is an essential regulator of dsRNA-induced IFN signalling [67,71-76]. LGP2 is a negative regulator of the RIG-I/MDA5 initiated type I IFN induction pathway [77]. Most cellular RNA contains short hairpin structures and a 3’ cap structure. In contrast, viral RNA is often double stranded, and viral ssRNAs contain a 5’ triphosphate. These structural differences allow for self/nonself discrimination by these receptors. The central downstream adaptor of the RLR family receptor is the IFN-β promoter stimulator (IPS)-1, which is attached to the mitochondrial membrane by a C-terminal hydrophobic region [78]. Downstream of IPS-1, the serine/threonine kinase TANK-binding kinase 1 (TBK-1) phosphorylates interferon regulatory factors (IRFs) 3 and 7. IRFs 3 and 7 are the key adaptor molecules in the induction of type I IFN. IPS-1 also induces the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein 1 (AP1) [72].

Type I IFN induction by alphavirus infection

Type I IFN responses are usually associated with alphaviral infection [79-85]. Multiple regulatory proteins are involved in the induction of IFN and contribute to antiviral effects. These include TLRs, IRF-3/7, 2, 5-oligoadenylate synthetase and RIG-I. During alphavirus infection, the IPS-1-dependent RIG-I pathway, Myd88-dependent TLR7 pathway and TRIF-dependent TLR3 pathway contribute to the expression of type I IFN [67,68,86-94]. A recent study has indicated that TRIF is a key player in IFN production during RRV infection as well as in inducing an optimal immune response against RRV, particularly B cell proliferation and T cell responses [95]. MDA-5 may also play a role in type I IFN induction after SINV infection [96]. A recent study has demonstrated that the TLR3 and RLR families both contribute to type I IFN in response to MAYV infection [57].

Interestingly, in RRV infected Tlr7-/- and Myd88-/- mice, despite showing more severe disease than that in WT infected mice, the expression of type I IFN is unaffected [86]. Additionally, studies have suggested that the TLR3 initiated type I IFN induction pathway is involved in host protection against CHIKV infection [94]. Moreover, type I IFN levels differ between Trif-/- and Ips-/- mice infected with CHIKV [93]. These findings suggest that the three induction pathways may act independently in host protection against invading alphaviruses.

Several factors have been associated with type I IFN induction after alphavirus infection. Viral non-structural protein processing and viral replicate are closely associated with type I IFN induction [87,97]. Mutations in the nsP1 and nsP2 regions, which are common in naturally occurring RRV strains, can increase sensitivity to type I IFN [97,98]. Temperature is another factor modulating type I IFN activity in alphaviral arthritis. A study in a CHIKV mouse model has indicated greater type I IFN activity at 30°C than 22°C, thus resulting in ~20-fold lower viral load in the animals [99]. In agreement with those findings, Lane et al. have shown that lower temperatures exacerbate CHIKV replication in mice [100]. The intestinal microbiome also plays a role in the type I IFN response following CHIKV infection. TLR7-MyD88-dependent type I IFN signalling is hampered in germ-free mice with a depleted intestinal microbiome, thus leading to more rapid CHIKV infection spread in the animals. However, the type I IFN response is restored by reconstitution with a gut microorganism derived product, bile acid deoxycholic acid [101].

Role of type I IFN in alphavirus infection

SINV proliferates extensively in cells lacking type I IFN induction signalling. In contrast, viral replication is impaired in cells that produce type I IFN [82,102]. Type I IFN appears to play a pivotal role in controlling alphavirus replication and protecting cells against alphaviral invasion, although alphaviruses differ in sensitivity to type I IFN [96].

Type I IFN clearly exerts broad antiviral functions by inducing a range of cellular interferon-stimulated genes (ISGs); however, the mechanistic details of this antiviral effect in host cells remain poorly defined. Among the ISGs elevated in response to alphavirus infection, Protein kinase R (PKR), Growth arrest and DNA-damaged protein 34 (GADD34), 2’,5’-oligoadenylate synthetase (OAS)/RNase L, ISG20, Interferon-induced proteins with tetratricopeptide repeats/IFN-induced transmembrane protein (IFIT/IFITM), Bone marrow stromal antigen 2 (BST2), Radical SAM domain-containing 2 (RSAD2), Promyelocytic leukemia zinc finger protein
(PLZF) and ISG15 have shown in vitro inhibitory effects against alphavirus replication (Fig 3) [103]. PKR and GADD34 exert their antiviral effects through eukaryotic initiation factor (eIF)-2α phosphorylation, thus impairing viral RNA translation [104,105]. Although SFV has been reported to overcome the effects of PKR through a stem-loop structure in the viral RNA genome [106], delayed viral clearance has been observed in SFV-infected Pkr−/− mice [107]. Similarly, in Gadd34−/− neonate mice, CHIKV replicates to a higher titre than that in wild type mice [108]. OAS proteins are a family that catalyses 2′, 5′-oligomers of ATP [109]. These oligomers activate RNase L, which degrades viral RNAs and thereby blocks viral replication [110]. Interestingly, despite showing in vitro antiviral activity against SFV, CHIKV, and SINV, mice deficient in RNase L or PKR develop only subclinical SINV infections [83], thus suggesting that RNase L and PKR may not have major roles in antiviral mechanisms against SINV.

ISG20 is a nuclear 3′-5′ exonuclease reported to inhibit viral replication through direct degradation of viral RNA [111]. ISG20 also interferes with viral protein translation in a 5′ cap-dependent manner [112,113]. However, the antiviral effect of ISG20 in mice has been observed only against an attenuated strain of VEEV, but not against CHIKV or VEEV virulent strains [113]. IFIT/IFITM family has been reported to inhibit viral replication by binding and preventing the viral RNA from recognising the 43S pre-initiation complex, thereby interfering with viral protein translation [114]. IFIT1 proteins are upregulated by ISG20 in response to alphavirus infection [115]. The antiviral role of IFITM has been demonstrated in CHIKV or VEEV-infected Ifitm3−/− mice, which show elevated viral load and tissue damage [115]. BST2 (Tetherin) is a cell-surface protein that blocks viral particle budding and therefore hampers viral release [116]. The in vivo antiviral effect of BST2 has been evidenced by an elevated viral load of CHIKV in Bat2−/− mice [117]. RSAD2 (Viperin) is an antiviral protein that interferes with viral replication by inhibiting viral RNA polymerase [118]. CHIKV and SINV both show elevated virulence in Rsad2−/− mice, as evidenced by viremia and mortality [119,120]. PLZF, a host transcriptional regulator in the nucleus, is involved in multiple biological processes, including haematopoiesis, osteogenesis and immune regulations [121]. In mice lacking PLZF, compared with wild type mice, SFV replicates to a significantly higher titre [122]. Notably, several ISGs are modulated by PLZF, including IFIT and RSAD2 [122]. Ubiquitin–like protein ISG15 is critical for the host antiviral response [123]. In mice deficient in ISG15, compared with wild type mice, CHIKV and SINV infection leads to higher levels of lethality [124,125].

The type I IFN response is also involved in RA pathogenesis [126]. Interestingly, IFNα and IFNβ have different roles in inflammatory arthritis. IFNα promotes TLR3, TLR4 and TLR7-associated signalling pathways, and increases the production of IL-6, TNF-α, IL-1β and IL-18 in synovial cells from patients with RA [127]. In contrast, IFNβ shows an anti-inflammatory effect by inhibiting the production of IL-1β and TNF-α in RA [128]. However, the role of elevated type I IFN in the pathogenesis of arthritic disease after alphavirus infection has not been fully studied. Notably, compared with healthy osteoblasts, osteoblasts from patients with osteoarthritis show a remarkable delay in the type I IFN response, thus resulting in higher susceptibility to RRV infection, higher RANKL/OPG ratios, and elevated production of osteotropic factors, such as IL-6, IL-1β, TNF-α and CCL2 [129]. The delayed type I IFN response in osteoblasts has therefore been suggested to be the cause of the increased alphaviral osteoclastogenesis. Further studies are warranted to elucidate the role of type I IFN in alphavirus disease pathogenesis.

**Alphaviral antagonism of the type I IFN system**

Many viruses have evolved mechanisms to counteract the host IFN system [130]. The main viral strategies for circumventing the IFN system can be classified into three types: 1) concealing the viral RNA to make the viral dsRNA inaccessible to host RLRs; 2) masking the viral RNA to change the viral dsRNA PAMP signatures and avoid recognition by RLRs; and 3) blocking of host signalling pathways to inhibit immune functions [131].

The antagonistic effect of alphavirus infection on type I IFN production has been described in several reports. Viral proteins are widely recognised to be the primary factors in the antagonism of type I IFN. For New World alphaviruses, such as VEEV and EEEV, the capsid protein is associated with IFN antagonism [11,132]. In EEEV, a region of the capsid between 55 and 75 amino acids is associated with inhibition of host gene expression and interferon sensitivity, whereas WEEV has a nucleocapsid arrangement targeting the PRR pathways downstream of IRF3 [133, 134]. In contrast, a study on VEEV and SINV has shown that the suppression of IFN-β and ISG mRNA production in neuron cells is associated with structural protein of VEEV but nonstructural protein of SINV [135]. SINV deficient in poly non-structural protein cleavage induces a much higher level of type I IFN than wild type SINV, and is quickly eliminated from infected cells [136]. Similarly, the descriptions of mutations at the cleavage site between nsP1 and nsP2 suggest that antagonism of type I IFN may be based on non-structural proteins [97,98]. A shutoff effect is one route of type I IFN antagonism: mutant viruses that are defective in the shutoff effect have been shown to be stronger IFN inducers [137]. The shutoff effect has been suggested to result from the nuclear localisation of nsP2 and the associated degradation of the host (DNA-directed RNA polymerase II subunit A) Rpβ1 [138]. In a recent study on MAYV, nsP2 has been shown to interact with Rpβ1 and transcription initiation factor II E subunit 2 (TFIIE2), thus inhibiting type I and type III IFN induction [139].
However, the growth, shutoff effect and type I IFN induction of an SFV mutant lacking nsP2 NLS have suggested that the viral shutoff effect may not be the main mechanism underlying type I IFN antagonism [12]. Another putative mechanism of IFN antagonism comes from the alphavirus transmission cycle. The highly structured glycans on alphavirus E1/E2 protein synthesised in mosquito cells are efficient ligands for cell entry [24]. In contrast, E1/E2 carbohydrate structures derived from mammalian host cells cannot efficiently attach to host cells. In a study in 2007, murine bone marrow-derived culture myeloid DCs infected with insect cell-derived RRV, VEEV or Barmah forest virus were found to produce much lower levels of type I IFN than myeloid DCs infected with mammalian cell-derived virus [140]. These findings suggest that different glycan structures on E1/E2 result in different type I IFN induction levels in certain cell types.

Antagonism of the type I IFN by invading alphaviruses is probably performed at multiple stages of the type I IFN system, including modulation of the signalling proteins in the IFN induction pathways and subversion of proteins in the canonical JAK-STAT pathway. SINV targets IPS-1 and consequently impedes the type I IFN system [90], whereas VEEV and CHIKV antagonise type I IFN by disrupting STAT signalling [91,141,142]. CHIKV has also been reported to play a role in suppressing activation of the IFN-β promoter induced MDA5/RIG-I receptor signalling pathway through nsP2, E1 and E2 [143]. The A532V mutation of RRV nsP1 has been shown to upregulate phosphorylated IRF3 [144], thus indicating that upstream effectors of the induction pathways may play roles in type I IFN modulation.

CONCLUDING REMARKS

Type I IFN plays a critical role in controlling the host’s innate antiviral responses and is known to trigger multiple downstream antiviral pathways. Through PRR dependent cascades, alphavirus infection in humans and animals is usually associated with a type I IFN response activating a range of downstream antiviral ISGs, including ISG15, PKR, OAS and ISG20. The activation of ISGs interferes with viral replication via various mechanisms including viral element degradation and modulation of immune responses. Alphavirus antagonises type I IFN mainly through viral non-structural proteins including nsP2 and capsid protein. However, the mechanisms through which alphavirus modulates type I IFN and the manner in which type I IFN orchestrates the activation of cellular immunity after alphavirus infection remain poorly understood. Because alphavirus infections have been gradually escalating worldwide, developing from periodic endemic outbreaks to global epidemics, understanding the mechanism of type I IFN responses to alphavirus infection is imperative to develop more targeted and effective therapeutic against these viruses as quickly as possible.

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CONFLICTS OF INTERESTS

We declare no competing interests.

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