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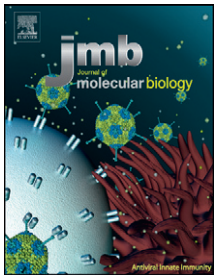

Innate Immune Response to Arenaviral Infection: A Focus on the Highly Pathogenic New World Hemorrhagic Arenaviruses

Takaaki Koma[1], **Cheng Huang**[1], **Olga A. Kolokoltsova**[1], **Allan R. Brasier**[2] **and Slobodan Paessler**[1]

1 - Department of Pathology and Institute for Human Infections and Immunity, *University of Texas Medical Branch, Galveston, TX 77550, USA*
2 - Division of Endocrinology, *Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX 77550, USA*

Correspondence to Slobodan Paessler: *Department of Pathology, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555, USA. slpaessl@utmb.edu*
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Abstract

Arenaviruses are enveloped, negative-stranded RNA viruses that belong to the family *Arenaviridae*. This diverse family can be further classified into OW (*O*ld *W*orld) and NW (*N*ew *W*orld) arenaviruses based on their antigenicity, phylogeny, and geographical distribution. Many of the NW arenaviruses are highly pathogenic viruses that cause systemic human infections characterized by hemorrhagic fever and/or neurological manifestations, constituting public health problems in their endemic regions. NW arenavirus infection induces a variety of host innate immune responses, which could contribute to the viral pathogenesis and/or influence the final outcome of virus infection *in vitro* and *in vivo*. On the other hand, NW arenaviruses have also developed several strategies to counteract the host innate immune response. We will review current knowledge regarding the interplay between the host innate immune response and NW arenavirus infection *in vitro* and *in vivo*, with emphasis on viral-encoded proteins and their effect on the type I interferon response.

Introduction

Arenaviruses are a family of RNA viruses that often establish chronic infection in their natural rodent hosts [1]. The geographic distribution of each arenavirus is determined by the range of habitats of its natural rodent hosts [2] (Table 1). Infection in humans is believed mainly through respiratory exposure to virus containing aerosols or by direct contact of abraded skin with infectious materials and may cause severe morbidity and mortality in humans [1,3]. Studies involving intragastric infection of rhesus macaques and mice experimentally and serological survey in rodent consumers suggest that gastric mucosa could also be targeted by the virus [4–6]. Based on the antigenicity, phylogeny, and geographical distribution, arenaviruses can be divided into the OW (*O*ld *W*orld) (Lassa–lymphocytic choriomeningitis complex) arenaviruses and the NW (*N*ew *W*orld) (Tacaribe complex) arenaviruses [7,8] (Table 1). The LCMV (lymphocytic choriomeningitis virus) from the OW arenaviruses is the prototype arenavirus and is often used in research laboratories. LCMV can cause central nervous system and immunopathological diseases in mice and in immunosuppressed humans [9–11]. OW LASV (Lassa virus) is the causative agent of Lassa fever, a major public health concern in western Africa [12,13]. The NW arenaviruses are further classified into clades A, B, and C NW arenaviruses [7]. The clade A NW arenavirus include PICV (Pichinde virus), Pirital virus, Parana virus, Flexal virus, and Allpahuayo virus, which are not known to cause disease in humans. The clade B contains many important human pathogens, such as JUNV (Junin virus), MACV (Machupo virus), GTOV (Guanarito virus), SABV (Sabia virus), and CHAV (Chapare virus). The pathogens listed above are the etiological agents of Argentine hemorrhagic fever (AHF), Bolivian hemorrhagic fever, Venezuelan hemorrhagic fever, and Brazilian hemorrhagic fever, respectively [2]. CHAV infection has been recently associated with human hemorrhagic fever cases in

Table 1. Arenaviridae family adapted from Salvato *et al.* [8].

Virus	Human pathogen	Reservoir	Distribution
OW arenaviruses			
Gbagroube virus	Unknown	*Mus setulosus*	Côte d'Ivoire
Ippy virus	Unknown	*Arvicanthis* sp.	Central African Republic
LASV	Lassa fever	*Mastomys natalensis*	West Africa
LCMV	Yes	*M. musculus*	Europe, Americas
Menekre virus	Unknown	*Hylomyscus* sp.	Côte d'Ivoire
Mobala virus	Unknown	*Praomys* sp.	Central African Republic
Mopeia virus	Unknown	*M. natalensis*	Mozambique, Zimbabwe
Morogoro virus	Unknown	*M. natalensis*	Tanzania
NW arenaviruses			
Clade A NW arenaviruses			
Allpahuayo virus	Unknown	*Oecomys* sp.	Peru
Flexal virus	Febrile	*Oryzomys* spp.	Brazil
Parana virus	Unknown	*Oryzomys buccinatus*	Paraguay
PICV	Asymptomatic infection	*Nephelomys albigularis*	Colombia
Pirital virus	Unknown	*Sigmodon alstoni*	Venezuela
Whitewater Arroyo virus	Hemorrhagic fever	*Neotoma albigula*	United States
Clade B NW arenaviruses			
AMAV	Unknown	*Oryzomys capito Neacomys guianae*	Brazil
CHAV	Chapare hemorrhagic fever	Unknown	Bolivia
Cupixi virus	Unknown	*O. capito*	Brazil
GTOV	Venezuelan hemorrhagic fever	*Zygodontomys brevicauda*	Venezuela
JUNV	AHF	*C. musculinus*	Argentine
MACV	Bolivian hemorrhagic fever	*Calomys callosus*	Bolivia
Sabiá virus	Brazilian hemorrhagic fever	Unknown	Brazil
TCRV	Yes	*Artibeus* spp.	Trinidad
Clade C NW arenaviruses			
Latino virus	Unknown	*C. callosus*	Bolivia
Oliveros virus	Unknown	*Necromys obscurus*	Argentina
Unassigned arenaviruses			
Dandenong virus	Febrile	Unknown	Unknown
Lujo virus	Hemorrhagic fever	Unkonwn	Zambia
Luna virus	Unknown	*M. natalensis*	Zambia
Merino Walk virus	Unknown	*Myotomys unisulcatus*	South Africa

Bolivia [14]. Clade B also contains the non-pathogenic TCRV (Tacaribe virus), AMAV (Amapari virus), and Cupixi virus. Clade C contains the non-pathogenic Oliveros virus and Latino virus [1,7].

Currently, there are no effective vaccines for viral hemorrhagic fever (VHF) caused by human pathogenic arenaviruses except the vaccine Candid#1 against JUNV in Argentina [15]. Ribavirin and immune plasma from recovered patients are effective treatments for VHFs caused by arenaviruses [16,17]. Because these pathogenic arenaviruses cause significant morbidity and high mortality, they have become public health concerns in their endemic regions and consequently are classified as the Category A Pathogen Agents by the National Institutes of Health (US). Many of these highly pathogenic viruses must be handled in Biosafety Level 4 facilities, which hamper research. However, infection of certain rodents with some PICV and TCRV strains can cause disease that is similar to VHF in humans [18–23]. These surrogate virus models are used in basic studies and preclinical safety evaluation at early stages [24].

Arenaviruses are enveloped, bi-segmented negative-stranded RNA viruses [1]. Each genomic RNA segment, L (ca 7.3 kb) and S (ca 3.5 kb), contains two open reading frames with opposite (ambisense) orientation divided by a non-coding intergenic region that serves as a transcription termination signal. The L segment genomic RNA encodes for the RNA-dependent RNA polymerase L protein and the small zinc-finger Z protein [1]. The Z protein is the arenavirus counterpart of the M (matrix) protein of many other negative-stranded RNA viruses and is the driving force of virus particle formation.

The S segment encodes for the viral nucleoprotein (NP) and the glycoprotein precursor (GPC). The GPC is cleaved into the SSP (*s*table *s*ignal *p*eptide) by signal peptidase, and the mature glycoproteins GP1 and GP2 are cleaved by the host subtilase SKI-1/S1P (*s*ubtilisin *k*exin *i*sozyme-*1*/*s*ite *1* *p*rotease) [1,25,26]. SSP association is required for the transport of GPC through the Golgi compartment, in which the active form of SKI-1/S1P resides [26,27]. GP1 and GP2 form the viral spikes on the surface of virion and mediate receptor recognition and virus entry. The SSP is also assembled with GP1 and GP2 into virus particles, which is unique for arenaviruses.

Pathogenic clade B NW arenaviruses (i.e., JUNV, MACV, GTOV, and SABV) use the hTfR1 (*h*uman *t*rans*f*errin *r*eceptor *1*) and the TfR1 orthologs of their

natural host as the cellular receptor for viral entry of host cells. For example, the pathogenic NW JUNV can use both hTfR1 and the TfR1 ortholog of its natural host, *Calomys musculinus*. Meanwhile, non-pathogenic clade B NW arenaviruses (i.e., AMAV and TCRV) use TfR1 orthologs but not the hTfR1 as the cellular receptor [28–32]. The OW and the clade A and C NW arenaviruses use the α-dystroglycan as their cellular receptor [33,34]. Exposure to the low-pH environment of the late endosome is required to enhance membrane fusion by GPCs, which are reported to be unusually resistant to low pH [35–38].

Innate Immune Response

The race between virus infection and host innate immune response often determines the outcome of virus infection. Type I interferons (IFNs) including different species of IFN-α and IFN-β are the essential components for host mucosal innate defense [39–42]. Type I IFNs are rapidly secreted from virus-infected cells and act to establish an antiviral state in infected cells and uninfected neighboring cells. Additionally, IFNs also stimulate and regulate cells involved in innate and adaptive immunity such as NK cells, NKT cells, T cells, macrophages, and dendritic cells. Different cytokines, chemokines and innate immune cells (e.g., macrophages, dendritic cells, and NK cells), also play critical roles in host innate response to virus infection.

Host germline-encoded PRRs (*p*attern *r*ecognition *r*eceptors) have broad specificity and can potentially bind to numerous PAMPs (*p*athogen-*a*ssociated *m*olecular *p*atterns), including PAMPs present in microbes [43]. Upon recognition of PAMPs, PRRs are rapidly activated and stimulate host cells to counteract virus infection by mounting the early innate immune response in order to prevent further infection and virus growth. Induction of type I IFN expression is controlled by three different classes of PRRs [44–46]: RLRs (*r*etinoic acid-inducible gene-I-*l*ike *r*eceptors), TLRs (*T*oll-*l*ike *r*eceptors), and NOD (*n*ucleotide *o*ligomerization *d*omain)-like receptors [43,47,48]. RLRs are composed of RIG-I (*r*etinoic acid-*i*nducible *g*ene-*I*), MDA5 (*m*elanoma *d*ifferentiation-*a*ssociated gene *5*), and LGP2 (*l*aboratory of *g*enetics and *p*hysiology *2*) that are cytosolic helicases sensing features unique to viral RNA [49]. RIG-I detects 5′-triphosphate single-stranded RNA (ssRNA) and short (<2 kb) double-stranded RNAs (dsRNAs) in most cell types, whereas MDA5 is responsible for recognition of virus-derived, long (>2 kb) dsRNA and a synthetic dsRNA [poly(I:C)] [46,50,51]. Upon binding to viral RNA, activated RIG-I and MDA5 transduce the signal to the downstream IPS-1 (*I*FN-β *p*romoter *s*timulator-*1*) (also known as MAVS, VISA, or CARDIF) [52] on mitochondrial membranes. IPS-1 serves as a scaffold to recruit the signal adapter, TRAF-3 (*t*umor necrosis factor-*r*eceptor-*a*ssociated *f*actor-*3*); the activated complex activates the IKKε/TBK-1 (serine/threonine kinases *I*κB *k*inase ε/*T*ANK-*b*inding *k*inase-*1*) complex and the IKKα/β complexes [53–55] (Fig. 1). Activated IKKε/TBK-1 complex phosphorylates IRF-3 (*I*FN *r*egulatory *f*actor-*3*) and/or IRF-7, while the IKKα/β/γ complex phosphorylates NF-κB. These transcription factors undergo nuclear translocation and initiate the expression of IFN-β, IFN-α, and other proinflammatory cytokines [44,56–58].

TLRs are a group of transmembrane proteins contributing to the recognition of various pathogen-specific molecules. Most TLRs are expressed on cell surfaces, while TLR7, TLR8, TLR9, and in some cases TLR3 are located in intracellular endosomal compartments [59]. TLR3 and TLR7/TLR8 play critical roles in recognizing viral dsRNA and ssRNA, respectively [60]. TLR2 detects measles virus hemagglutinin protein [61], and TLR4 is implicated in the detection of envelope proteins of respiratory syncytial virus and mouse mammary tumor virus [62,63]. All TLRs, with the exception of TLR3, rely on MyD88 (*my*eloid *d*ifferentiation factor *88*) as the adaptor molecule to activate the downstream TAK1 (*t*ransforming growth factor-β-*a*ctivated *k*inase *1*) [64,65]. Activated TAK1 phosphorylates and activates the IKK complex, followed by activation of NF-κB and expression of various proinflammatory cytokines [66,67]. TLR3 and TLR4 pathways are dependent on Toll/interleukin-1 receptor domain-containing adaptor-inducing INF-β [68,69] as the downstream adaptor molecule, which activates the TRAF-3–TBK-1/IKKε cascade and mediates the phosphorylation of IRF-3 to initiate IFN-β expression [70]. Expressed type I IFNs are secreted from infected cells and interact with the IFN receptor on cell surface in an autocrine or paracrine manner [71]. This triggers the expression of a spectrum of IFN-stimulated genes (ISGs) [72,73], which ultimately execute the IFN-induced antiviral activities in a collaborative manner by targeting various steps of viral life cycle [74]. Expression of some ISGs could also be mediated directly by IRF-3/IRF-7 independent of IFN production, particularly in dendritic cells and macrophages [75,76].

Innate Immune Response to OW Arenaviruses

OW LCMV infection in its natural host, *Mus musculus*, has been extensively studied as an important model in elucidating the immune response of natural hosts to arenaviruses. LCMV causes either an acute infection followed by virus clearance or a chronic/persistent infection in described murine models. The difference in the disease outcome is largely determined by the IFN response at the early stage of virus infection [77–79]. A potent IFN response may inhibit virus

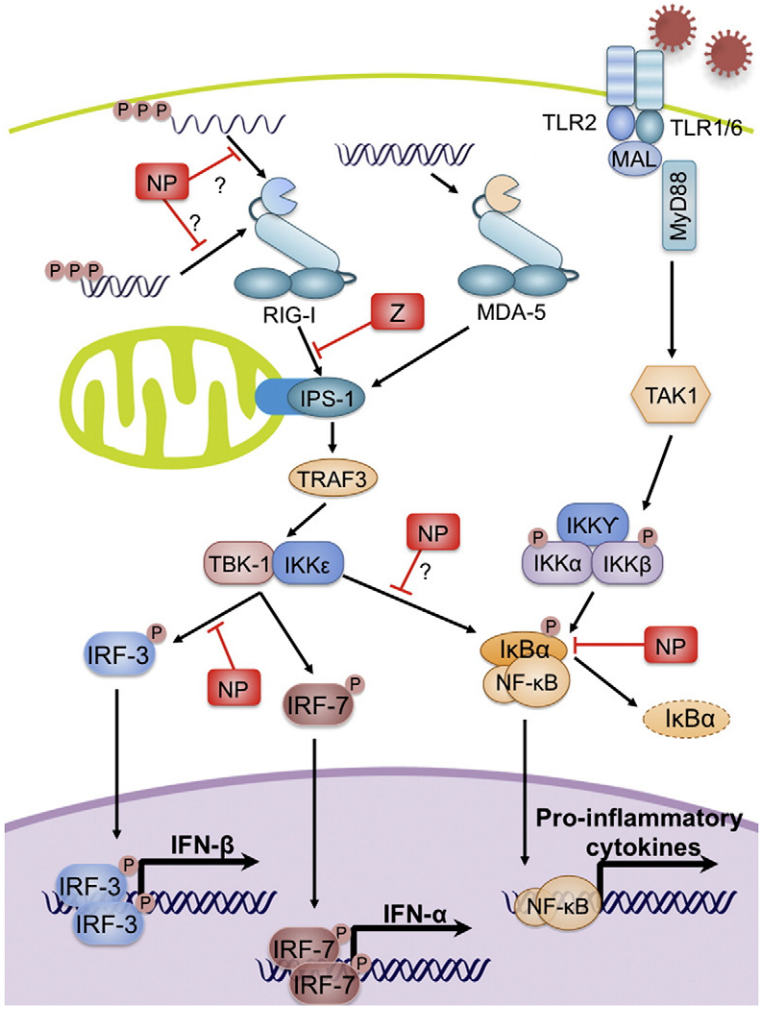

Fig. 1. Schematic diagram showing the interaction between NW arenaviruses and host innate immune response. Arenavirus NPs possess 3′ to-5′ exonuclease activity and are proposed to degrade viral dsRNA or ssRNA to reduce the exposure of viral RNA to RIG-I and MDA5. Z protein of the NW arenavirus, but not of the OW arenavirus, inhibits RIG-I signaling cascade probably as a result of its direct binding to RIG-I protein. NP further interacts with IKKε and inhibits TBK-1/IKKε activation to interfere with phosphorylation and activation of IRF-3 or IRF-7. NP prevents activation of NF-κB. It is still unclear whether suppression of TBK-1/IKKε complex by NP could directly lead to inhibition of NF-κB activation. On the other hand, NW arenavirus JUNV GP is recognized by TLR2 pathway and triggers IFN and cytokine production in mouse macrophages.

replication at early stage and induce virus-specific CD8+ T cell, resulting in virus clearance. However, a modest level of IFN production at early stage could eventually allow persistent infection, as IFN response is unable to suppress virus multiplication to the level that is required for virus clearance by CD8+ T cells later during infection [80–83]. On the other hand, the details of the immune response to other arenaviruses in their natural hosts are largely unknown. Experiments using NW JUNV and NW Catarina virus to infect of their natural hosts, *C. musculinus* and *Neotoma micropus*, respectively, showed age-dependent antibody elevation and persistent infection [84–86]. It is possible that arenaviruses may be maintained in their natural hosts by suppression of both innate and adaptive antiviral responses.

It is known that LASV infection causes immunosuppression in patients, as evidenced by the lack of induction of IFN production, proinflammatory response, or T cell activation *in vitro* or *in vivo* [1,87–90]. Lymphopenia and lymphoid depletion in spleen and lymph nodes has been reported in Lassa fever patients [91–93]. Furthermore, it has been reported that the level of type I IFNs and proinflammatory cytokines such as TNF-α (*t*umor *n*ecrosis *f*actor-*α*) and IL-1β (*i*nter*l*eukin-*1β*) are low in human macrophages and dendritic cells infected by LASV *in vitro* [94,95]. Lack of induction of costimulatory molecules,

such as CD86, has been reported in LASV-infected dendritic cells [94,95]. In addition, LASV-infected dendritic cells fail to activate virus-specific CD4+ T cells and CD8+ T cells [96]. Thus, insufficient immune responses in macrophages and dendritic cells probably contribute to severe disease progression of Lassa fever, particularly in fatal cases.

Immune responses to LASV have been studied in non-human primates. Lymphopenia has been identified in LASV-infected cynomolgus monkeys [97,98]; meanwhile, depletion or reduction of T cells and B cells has also been found in livers and spleens of LASV-infected marmosets [99]. Thus, lethal LASV infection in non-human primates seems to be accompanied with weak innate and cellular immune responses and uncontrolled viral replication, which are similar to that usually found in patients [24,97–99].

Innate Immune Response to NW Arenaviruses

For NW arenaviruses that cause VHF in humans, very few clinical studies are available regarding the innate immune response in humans, with the exception of AHF. Nevertheless, AHF clinical studies have revealed dysregulated IFN and cytokine production in patients. High levels of endogenous IFN-α (2000–64,000 IU/mL), along with elevated levels of cytokines IL-6, IL-8, IL-10, and TNF-α, are present in serum of patients in the acute stage of disease, whose cytokine levels are correlated with disease severity [100,101]. IFN induction has also been found in animal models of AHF [102,103]. IFN likely contributes to the AHF diseases as IFN-α level was linked to the severity of symptoms such as fever, chills, and backache [100]. Also, high levels of endogenous IFN-α in AHF patients have been linked to low platelet count (thrombocytopenia) and platelet abnormality [104]. This abnormality has been also demonstrated experimentally in an *in vitro* study showing that JUNV infection of human hematopoietic progenitor CD34+ cell and human megakaryocyte impairs platelet formation and function via type I IFN pathway [105]. Induction of type I IFNs has also been reported in the rhesus macaque model during JUNV and MACV infections [102,106], although it is still unclear if increased IFN is related to disease progression and time to death.

Rodent animal models have been used to study the pathogenesis of NW arenaviruses as well [18,107]. Adult mice are generally resistant to infection by VHF-causing NW arenaviruses. JUNV and TCRV cause diseases in IFN-α/βγR$^{-/-}$ mice with some histopathological changes similar to that found in AHF patients [108,109], suggesting the critical role of IFN pathway in host resistance to JUNV and TCRV infection in adult mice. TNF-α likely plays a key role in the pathogenesis in a lethal neonatal mice model of TCRV infection [19,20,110]. MACV infection causes diseases in STAT-1 (*s*ignal *t*ransducer and *a*ctivator of *t*ranscription-*1*) knockout mice [111], albeit with symptoms different from humans. Elevated levels of proinflammatory cytokines such as TNF-α, IFN-γ, IL-6, and G-CSF (*g*ranulocyte *c*olony-*s*timulating *f*actor) are detected in the serum of MACV-infected STAT1 knockout mice [111]. In contrast, LASV did not induce fatal infection in IFN-αβγR$^{-/-}$ mice [88]. However, STAT1 knockout mice develop lethal disease upon LASV infection [112]. These results indicate that IFN might play an important role in controlling some NW arenavirus infections and that cytokines might contribute to pathogenesis in the murine model.

Hamsters and guinea pigs are used in studying the pathogenesis of NW arenaviruses (reviewed in Vela [18]). PICV-infected hamsters display elevated level of type I IFN in serum [22]. PICV infection of guinea pigs has been used as a model to study the pathogenesis of the OW LASV. While the non-pathogenic P2 strain of PICV causes mild disease, the P18 strain, which has been serially passaged in guinea pigs, causes lethal hemorrhagic fever in guinea pigs [113]. Elevated levels of TNF in serum and spleen are initially observed in inbred guinea pigs during the late phases of the pathogenic P18 strain infection [21]. However, a later study reported that P18 strain-infected peripheral blood leukocytes had decreased transcripts for cytokines including TNF-α, IFN-γ, and RANTES (*r*egulated on *a*ctivation *n*ormal *T* cell *e*xpressed and *s*ecreted) relative to that of P2 strain-infected cells; meanwhile, reduced TNF-α, IL-8, and IL-12 p40 mRNAs have also been observed in peritoneal cells from P18 strain-infected guinea pigs relative to that of mock-infected animals [23]. The result of latter is also consistent with previous studies showing that JUNV and LASV infection either inhibit or fail to induce these cytokines in human macrophages [90,114]. Intriguingly, these IFNs and inflammatory cytokines seem to be basically elevated in human pathogenic NW arenavirus (e.g., JUNV and MACV) infections in patients and animal models but not in OW arenavirus (e.g., LASV) infection.

The innate immune response to NW JUNV infection has been studied in cultured cells. Monocytes, macrophages, dendritic, and epithelial cells involved in innate immune response are also suggested as the initial target cells for JUNV and other arenaviruses [115–118]. TLR2, but not TLR4, has been shown to recognize JUNV GPs and initiate IFN-β and TNF-α production in mouse macrophages [119]. Similarly, some strains of non-pathogenic OW LCMV are also recognized by TLR2 and MyD88/Mal pathway in murine central nervous system glial cells and macrophages [120,121]. However, no elevation in the levels of IFN-α, IFN-β, IL-6, IL-10, IL-12, or TNF-α was detected in cultures of human monocytes and macrophages infected with the pathogenic Romero

strain of JUNV, suggesting that these cells might not be the cellular source of IFN and cytokine production *in vivo* or that the cytokine production *in vitro* is different from the one detected *in vivo* [114]. Meanwhile, IL-6, IL-10, and TNF-α were expressed in non-pathogenic NW TACV-infected cells in the same study [114], indicating its inability to suppress innate immune response in these cells. On the other hand, RIG-I-mediated IFN production and ISG expression are readily detected in human lung epithelial A549 cells during the infection of both pathogenic and vaccine strains of JUNV [122], which also suggests that JUNV-infected parenchymal cells could be a cellular source of IFN *in vivo*. OW LCMV infection induces type I IFN responses in HEK293 cells and murine embryonic fibroblast cells in a RIG-I- and MDA5-dependent manner [123]. Further studies are required to clarify the involvement of MDA5 in IFN response during JUNV and other NW arenavirus infections.

The non-pathogenic PICV P2 strain has been shown to induce higher levels of IL-6 and TNF-α in murine monocyte-like cells than the pathogenic P18 strain [124]. PICV P2 infection produces an increased amount of the transcription-activating NF-κB p65/p50 heterodimer, whereas P18 strain infection induces accumulation of the transcription-repressing NF-κB p50/p50 homodimer [124,125]. Infection by the PICV P2 strain is also accompanied with enhanced activation of Janus kinase/STAT signaling pathway in murine monocyte-like cells [126]. These data suggest that a more potent innate immune response could possibly contribute to the protection of guinea pigs from PICV P2 strain infection.

Arenavirus Evasion of Host Innate Immune Response

Arenaviruses have utilized several strategies to evade host innate immune response, particularly to subvert the IFN pathway. NPs from almost all arenaviruses examined are capable of interfering with type I IFN induction *in vitro* [123,127–129]. In a co-transfection assay, NPs of LCMV, LASV, PICV, JUNV, and MACV inhibited the Sendai virus-induced nuclear translocation of IRF-3 in Vero cells [128] (Fig. 1). Sendai virus-induced IFN-β and IRF-3 promoter expression is dose dependently inhibited by different arenavirus NPs in 293T cells [128]. LCMV NP has been shown to directly interact with RIG-I and MDA5 [123]. However, a mutant NP lacking IFN inhibitory activity is still able to bind to both RIG-I and MDA5 proteins, suggesting that NP binding alone is not sufficient to interfere with RIG-I/MDA5 function. The IFN antagonist activity is mapped to the C terminal DIEGR motif (D382, G385, E384, and R386) of the LCMV NP [127–129]. Interestingly, this DIEGR motif also partially overlaps in amino acid sequence with the five amino acids (D382, E384, D459, H517, and D552) that are critical for NP 3′ to 5′ exonuclease activity as determined by structure studies [130,131]. Mutation of these five amino acids that are required for exonuclease activity diminishes the NP exonuclease activity and also coincidentally abolishes the NP IFN antagonistic activity in reporter assays [131]. It has been proposed that the exonuclease activity could reduce the opportunity of viral RNA to be exposed to RIG-I or MDA5, a hypothesis that still remains to be confirmed in virus-infected cells (Fig. 1). LASV with mutations of these key amino acid residues shows enhanced IFN and cytokine production in infected cells, supporting a link of exonuclease activity and NP-mediated suppression of IFN response [132]. Additionally, NP directly interacts to and blocks IKKε to interfere with IRF-3 phosphorylation and activation [133] (Fig. 1). Meanwhile, NPs from NW and OW arenaviruses (e.g., LCMV, LASV, PICV, JUNV, and MACV) inhibit the nuclear translocation and transcriptional activity of NF-κB [134]. This could allow arenavirus to down-regulate the NF-κB pathway that is required for expression of many proinflammatory cytokines and IFN.

Until recently, the NP of non-pathogenic TCRV was believed to be unable of inhibiting the IRF-3 pathway and the NF-κB pathway [128] due to its sequence variation in the DIEGR motif. However, it has been found that some TCRV isolates actually contain the important NP residues required for IFN antagonism [135] as NPs of other arenavirus, suggesting that, at least, some of the TCRV strains might also retain the IFN antagonistic activity of NP.

The arenavirus Z protein is another viral protein that contributes to the virus suppression of type I IFN response [136]. The Z proteins from NW arenaviruses (i.e., JUNV, MACV, GTOV, and SABV), but not from the OW arenaviruses (i.e., LCMV and LASV), bind to RIG-I and interfere with the interaction between RIG-I and IPS-1, resulting in inhibition of nuclear translocation of IRF-3 and IFN-β expression in A549 cells [136] (Fig. 1).

Furthermore, the short dsRNAs with the overhanging 5′ppp-G residue present at the 5′-end of arenavirus genomic and antigenomic RNA species are poor substrates for RIG-I binding and therefore are proposed to contribute to virus evasion from RIG-I recognition [137,138].

It seems that the IFN antagonistic activities of arenavirus NP and Z proteins could not absolutely abolish host innate immune response: infection by many OW and NW arenaviruses still induces IFN and cytokine production in the context of virus infection as shown in different studies [78,79,100,101,119,120,122,139]. It is possible that, in the early stage of virus infection, when viral NP and Z protein are at low level and mostly engaged in viral replication, host cells still could sense virus replication and activate the innate immune response.

Taken together, both NW and OW arenaviruses use several strategies to evade or subvert the host innate immune response by inhibiting IFN and inflammatory cytokine production. These activities might help the virus to counteract host innate immune response and contribute to viral pathogenesis.

Concluding Remarks

The NW arenaviruses include many important human pathogens. The impact of innate immune response on arenavirus infection and its role in pathogenesis varies remarkably depending on the virus, host, age, infection dose, infection route, and immune conditions. Based on studies on many non-pathogenic viruses, such as TACV [114], Mopeia virus (a non-pathogenic OW arenavirus closely related to LASV) [139], and some less virulent strains of PICV [126] or LCMV [77–79], it is tempting to conclude that the viral pathogenicity is often inversely associated with a higher level of cytokine or IFN response, indicative of the inhibitory effect of potent innate immune response against virus infection. In contrast, the pathogenic OW arenaviruses, such as LASV and LCMV, utilize several strategies to efficiently subvert or evade host innate immune response and cause severe diseases. However, the infection by VHF-causing NW arenavirus JUNV is distinct; JUNV triggers strong cytokine and IFN response in humans, which is associated with high mobility and mortality [100,101]. It is worthy to note that many arenaviruses (e.g., JUNV and MACV) are relatively resistant to IFN treatment *in vitro* [122,140]. As the innate immune response could be either beneficial or detrimental to the host, future studies are required to investigate whether dysregulated innate immune response could contribute to the pathogenesis of VHF-causing NW arenaviruses, similar to influenza virus [141] and severe acute respiratory syndrome virus infection in humans [142,143]. Also, studying the role of the innate immune response during the NW arenavirus infection will help us to design new strategies to develop vaccines and treatments against VHF-causing NW arenavirus infection.

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Abbreviations used:
VHF, viral hemorrhagic fever; AHF, Argentine hemorrhagic fever; NP, nucleoprotein; GPC, glycoprotein precursor; ssRNA, single-stranded RNA; dsRNA, double-stranded RNA; ISG, IFN-stimulated gene

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