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

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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 (Old World) and NW (New World) 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.

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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 (Old World) (Lassa–lymphocytic choriomeningitis complex) arenaviruses and the NW (New World) (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
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 (signal peptide) by signal peptidase, and the mature glycoproteins GP1 and GP2 are cleaved by the host subtilisin SKI-1/S1P (subtilisin kexin isozyme-1/site 1 protease) [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 (human transferrin receptor 1) and the TIR1 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 (pattern recognition receptors) have broad specificity and can potentially bind to numerous PAMPs (pathogen-associated molecular patterns), 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 (retinoic acid-inducible gene-I-like receptors), TLRs (Toll-like receptors), and NOD (nucleotide oligomerization domain)-like receptors [43,47,48]. RLRs are composed of RIG-I (retinoic acid-inducible gene-I), MDA5 (melanoma differentiation-associated gene 5), and LGP2 (laboratory of genetics and physiology 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 (IFN-β promoter stimulator-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 (tumor necrosis factor-receptor-associated factor-3); the activated complex activates the IKKε/IKKγ (serine/threonine kinases IκB kinase ε/TANK-binding kinase-1) complex and the IκKα/β complexes [53–55] (Fig. 1). Activated IKKε/IKKγ complex phosphorylates IRF-3 (IFN regulatory factor-3) and/or IRF-7, while the IκKα/β 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 (myeloid differentiation factor 88) as the adaptor molecule to activate the downstream TAK1 (transforming growth factor-β-activated kinase 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 IFN-β [68,69] as the downstream adaptor molecule, which activates the TRAF-3–TBK-1/IKKc 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 IFR-3/IFR-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...
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 (tumor necrosis factor-α) and IL-1β (interleukin-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/βR−/− 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 (signal transducer and activator of transcription-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 (granulocyte colony-stimulating factor) are detected in the serum of MACV-infected STAT1 knockout mice [111]. In contrast, LASV did not induce fatal infection in IFN-αβR−/− 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 (regulated on activation normal T cell expressed and secreted) 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 LASSV 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 and the NF-κB pathway [128] due to its 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, 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.

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 IFN-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, 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 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.

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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References

[1] Buchmeier MJ, de la Torre JC, Peters CJ. Arenaviridae: the viruses and their replication. In: Knipe DM, PM H, editors. Fields virology, 5th ed. Philadelphia: Wolter Kluwer Lippincott Williams & Wilkins; 2007.
[2] Charrel RN, de Lamballerie X. Arenaviruses other than Lassa virus. Antiviral Res 2003;57:89–100.
[3] Stephenson EH, Larson EW, Dominik JW. Effect of environmental factors on aerosol-induced Lassa virus infection. J Med Virol 1984;14:295–303.
[4] Rodas JD, Lukashevich IS, Zapata JC, Cairo C, Tikhonov I, Djavani M, et al. Murcosal arenavirus infection of primates can protect them from lethal hemorrhagic fever. J Med Virol 2004;72:424–35.
[5] Rai SK, Micales BK, Wu MS, Cheung DS, Pugh TD, Lyons GE, et al. Timed appearance of lymphocytic choriomeningitis virus after gastric inoculation of mice. Am J Pathol 1997;151:633–9.
[6] Ter Meulen J, Lukashevich I, Sidibe K, Inapogu A, Marx M, Dorfmann A, et al. Hunting of peridomestic rodents and consumption of their meat as possible risk factors for rodent-to-human transmission of Lassa virus in the Republic of Guinea. Am J Trop Med Hyg 1996;55:661–6.
[7] Charrel RN, de Lamballerie X. Emonet S. Phylogeny of the genus Arenavirus. Curr Opin Microbiol 2008;11:362–8.
[8] Salvato MS, Clegg JCS, Buchmeier MJ, Charrel RN, Gonzales JP, Lukashevich IS, et al. Family Arenaviridae. Virus Taxonomy. In: King AMQ, Adams MJ, Carstens EB, Gonsales JP, Lukashevich IS, et al. Family Arenaviridae. Virus Taxonomy. In: King AMQ, Adams MJ, Carstens EB, Lefkowitz EF, editors. Ninth Report of the International Committee on Taxonomy of Viruses. Oxford: Elsevier; 2012.
[9] Barton LL. Lymphocytic choriomeningitis virus: a neglected central nervous system pathogen. Clin Infect Dis 1996;22:197.
[10] Barton LL, Hyndman NJ. Lymphocytic choriomeningitis virus: reemerging central nervous system pathogen. Pediatr 2000;105:E35.
[11] Rivers TM, McNair Scott TF. Meningitis in man caused by a filterable virus. Science 1935;81:439–40.
[12] Briese T, Paweska JT, McMullan LK, Hutchison SK, Street C, Palacios G, et al. Genetic detection and characterization of Lujo virus, a new hemorrhagic fever-associated arenavirus from southern Africa. PLoS Pathog 2009;5:e1000455.
frame JD, Baldwin JM, Gocke DJ, Troup JM. Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings. Am J Trop Med Hyg 1970;19:670–6.

Delgado S, Erickson BR, Agudo R, Blair PJ, Vallejo E, Albarino CG, et al. Chapare virus, a newly discovered arenavirus isolated from a fatal hemorrhagic fever case in Bolivia. PLoS Pathog 2008;4:e1000047.

Maiztegui JJ, McKeen KT, Barrera Oro JG, Harrison LH, Gibbs PH, Feuillard MR, et al. Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. AHF Study Group. J Infect Dis 1998;177:277–83.

McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever. Effective therapy with ribavirin. N Engl J Med 1986;314:20–6.

Maiztegui JJ, Fernandez NJ, de Damielano AJ. Efficacy of immune plasma in treatment of Argentine haemorrhagic fever and association between treatment and a late neurological syndrome. Lancet 1979;2:1216–7.

Vela E. Animal models, prophylaxis, and therapeutics for arenavirus infections. Viruses 2012;4:1802–9.

Borden EC, Nathanson N. Tacaribe virus infection of the mouse: an immunopathologic disease model. Lab Invest 1974;30:465–73.

Pedras-Vasconcelos JA, Goucher D, Puig M, Tonelli LH, Wang V, Ito S, et al. Cpg oligodeoxynucleotides protect newborn mice from a lethal challenge with the neurotropic Tacaribe arenavirus. J Immunol 2006;176:4940–9.

Aronson JF, Herzog NK, Jerrells TR. Tumor necrosis factor and association between treatment and a late neurological disease model. Lab Invest 1974;30:465–73.

Aronson JF, Aronson JF, Herzog NK, Jerrells TR. Tumor necrosis factor and association between treatment and a late neurological disease model. Lab Invest 1974;30:465–73.

Lukashevich IS. The search for animal models for Lassa fever vaccine development. Expert Rev Vaccines 2008;7:975–80.

Scott EP, Aronson JF. Cytokine patterns in a comparative model of arenavirus haemorrhagic fever in guinea pigs. J Gen Virol 2008;89:2569–79.

Lukashevich IS. The search for animal models for Lassa fever vaccine development. Expert Rev Vaccines 2013;12:71–86.

Lenn O, ter Meulen J, Klenk HD, Seidah NG, Garten W. The Lassa virus glycoprotein precursor GP-C is proteolytically processed by subtilase SKI-1/S1P. Proc Natl Acad Sci USA 2001;98:12701–5.

Nunberg JY, York J. The curious case of arenavirus entry, and its inhibition. Viruses 2012;4:83–101.

Agnihothram SS, York J, Nunberg JH. Role of the stable signal peptide and cytoplasmic domain of G2 in regulating intracellular transport of the Junin virus envelope glycoprotein complex. J Virol 2006;80:5189–98.

Radoshitzky SR, Kuhn JH, Sporopoulou CF, Albarino CG, Nguyen DP, Salazar-Bravo J, et al. Receptor determinants of zoonotic transmission of New World hemorrhagic fever arenaviruses. Proc Natl Acad Sci USA 2008;105:2664–9.

Flanagan ML, Oldenburg J, Reigner T, Holt N, Hamilton GA, Martin VK, et al. New world clade B arenaviruses can use transferrin receptor 1 (TIR1)-dependent and -independent entry pathways, and glycoproteins from human pathogenic strains are associated with the use of TIR1. J Virol 2008;82:938–48.

Radoshitzky SR, Aronson JF, Sporopoulou CF, Kuhn JH, Nguyen D, Li W, et al. Transferrin receptor 1 is a cellular receptor for New World haemorrhagic fever arenaviruses. Nature 2007;446:92–6.

Helguera G, Jemielity S, Abraham J, Cordo SM, Martinez MG, Rodriguez JA, et al. An antibody recognizing the apical domain of human transferrin receptor 1 efficiently inhibits the entry of all new world hemorrhagic fever arenaviruses. J Virol 2012;86:4024–8.

Abraham J, Kwong JA, Albarino CG, Lu JG, Radoshitzky SR, Salazar-Bravo J, et al. Host-species transferrin receptor 1 orthologs are cellular receptors for nonpathogenic new world clade B arenaviruses. PLoS Pathog 2009;5:e1000358.

Cao W, Henry MD, Borrow P, Yamada H, Elder JH, Rakov EV, et al. Identification of alpha-dystroglycan as a receptor for lymphocytic choriomeningitis virus and Lassa fever virus. Science 1998;282:2079–81.

Sporopoulou CF, Kunz S, Rollin PE, Campbell KP, Oldstone MB. New World arenavirus clade C, but not clade A and B viruses, utilizes alpha-dystroglycan as its major receptor. J Virol 2002;76:5140–6.

Di Simone C, Zandonatti MA, Buchmeier MJ. Acidic pH triggers LCMV membrane fusion activity and conformational change in the glycoprotein spike. Virology 1994;198:455–65.

Di Simone C, Buchmeier MJ. Kinetics and pH dependence of acid-induced structural changes in the lymphocytic choriomeningitis virus glycoprotein complex. Virology 1995;209:3–9.

Castilla V, Mensich SE, Canduria NA, Danemonte EB. The entry of Junin virus into Vero cells. Arch Virol 1994;136:363–74.

Borrow P, Oldstone MB. Mechanism of lymphocytic choriomeningitis virus entry into cells. Virology 1994;198:1–9.

Versteeg GA, García-Sastre A. Viral tricks to grid-lock the type I interferon system. Curr Opin Microbiol 2010;13:508–16.

Diamond MS, Gale M. Cell-intrinsic innate immune control of West Nile virus infection. Trends Immunol 2012;33:522–30.

Borden EC, Sen GC, Uze G, Silverman RH, Ransohoff RM, Foster GR, et al. Interferons at age 50: past, current and future impact on biomedicine. Nat Rev Drug Discov 2007;6:975–90.

Bowie AG, Unterholzer L. Viral evasion and subversion of pattern-recognition receptor signalling. Nat Rev Immunol 2008;8:911–22.

Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature 2007;449:819–26.

Honda K, Yanai H, Negishi H, Asagiri M, Sato M, Mizutani T, et al. IRF-7 is the master regulator of type-I interferon-dependent immune responses. Nature 2005;434:772–7.

Loo YM, Fornek J, Crochet N, Bajwa G, Perwitasari O, Martinez-Sobrido L, et al. Distinct IRG-I and MDAS signaling by RNA viruses in innate immunity. J Virol 2008;82:335–45.

Takeuchi O, Akira S. Innate immunity to virus infection. Immunol Rev 2009;227:75–86.

Beutler B, Eidenschenk C, Crozat K, Imler JL, Takeuchi O, Hoffmann JA, et al. Genetic analysis of resistance to viral infection. Nature 2007;449:819–26.

Fujita T, Onoguchi K, Onomoto K, Hirai R, Yoneyama M. Triggering antiviral response by RIG-I-related RNA helicases. Biochimie 2007;89:754–60.

Yoneyama M, Fujita T. Structural mechanism of RNA recognition by the RIG-I-like receptors. Immunity 2008;29:178–81.

Kato H, Takahasi K, Fujita T. RIG-I-like receptors: cytoplasmic sensors for non-self RNA. Immunol Rev 2011;243:91–8.

Kato H, Sato S, Yoneyama M, Yamamoto M, Uematsu S, Matsui K, et al. Cell type-specific involvement of RIG-I in antiviral response. Immunity 2005;23:19–28.
Review: Innate Immune Response to Arenavirus Infection

Yoneyama M, Kikuchi M, Natsukawa T, Shinobu N, Imazumi T, Miyagishi M, et al. The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat Immunol 2004;5:730–7.

Kawai T, Takahashi K, Sato S, Coban C, Kumar H, Kato H, et al. IPS-1, an adaptor triggering RIG-I, and Mda5-mediated type I interferon induction. Nat Immunol 2005;6:981–8.

Tang ED, Wang CY. MAVS self-association mediates antiviral innate immune signaling. J Virol 2009;83:3420–8.

Baril M, Racine ME, Penin F, Lamarre D. MAVS dimer is a crucial sensing component of innate immunity and the target of hepatitis C virus NS3/4A protease. J Virol 2009;83:1299–311.

Fitzgerald KA, McWhiter SM, Faia KL, Rowe DC, Latz E, Golenbock DT, et al. IKKeptosin and TBK1 are essential components of the IRF3 signaling pathway. Nat Immunol 2003;4:491–6.

Sharma S, tenOever BR, Grandvaux N, Zhou GP, Lin R, Hiscott J. Triggering the interferon antiviral response through an IKK-related pathway. Science 2003;300:1148–51.

Honda K, Taniguchi T. IRFs: master regulators of signaling by Toll-like receptors and cytosolic pattern-recognition receptors. Nat Rev Immunol 2006;6:644–58.

Boehme KW, Compton T. Innate sensing of viruses by toll-like receptors. J Virol 2004;78:8677–73.

Blasius AL, Beutler B. Intracellular toll-like receptors. Immunity 2010;32:305–15.

Bieback K, Lien E, Klagge IM, Avota E, Schneider-Koch P, Yang X. A Drosophila kinase, Melk, is required for innate immunity. Proc Natl Acad Sci USA 2002;99:2281–6.

Li S, Strelow A, Fontana EJ, Wesche H, et al. Hemagglutinin protein of wild-type measles virus activates toll-like receptor 2 signaling. J Virol 2002;76:8729–36.

Kurt-Jones EA, Popova L, Kwinn L, Haynes LM, Jones LP, Tripp RA, et al. Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. Nat Immunol 2000;1:398–401.

Rassa JC, Meyers JL, Zhang Y, Kudaravalli R, Ross SR. Murine retroviruses activate B cells via interaction with toll-like receptor 4. Proc Natl Acad Sci USA 2002;99:2281–6.

Cao Z, Xiong J, Takeuchi M, Karama T, Goeddel DV. TRAF6 is a signal transducer for interleukin-1. Nature 1996;383:443–6.

Lu S, Strelov A, Fontana EJ, Wesche H. IRAK-4: a novel member of the IRAK family with the properties of an IRAK-kinase. Proc Natl Acad Sci USA 2002;99:5567–72.

Wesche H, Henzel WJ, Shillinglaw W, Li S, Cao Z, MyD88: an adapter that recruits IRAK to the IL-1 receptor complex. Immunity 1997;7:837–47.

Sakurai H, Shigemori N, Hasegawa K, Sugita T. TGF-beta-activated kinase 1 stimulates NF-kappa B activation by an NF-kappa B-inducing kinase-independent mechanism. Biochem Biophys Res Commun 1999;243:545–9.

Yamamoto M, Sato S, Hemmi H, Hoshino K, Kaisho T, Sanjo H, et al. Role of adaptor TRIF in the type I interferon signaling pathway. Science 2003;301:640–3.

Hoebe K, Du X, Georgel P, Janssen E, Tabeta K, Kim SO, et al. Identification of Lps2 as a key transducer of MyD88-independent TLR signaling. Nature 2003;424:743–8.

Tseng PH, Matsuzawa A, Zhang W, Mino T, Vignali DA, Karin M. Different modes of ubiquitination of the adaptor TRAF3 selectively activate the expression of type I interferons and proinflammatory cytokines. Nat Immunol 2010;11:70–5.

de Weerd NA, Samarajiwa SA, Hertzog PJ. Type I interferon receptors: biochemistry and biological functions. J Biol Chem 2007;282:20053–7.

Randall RE, Goodbourn S. Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures. J Gen Virol 2008;89:1–47.

Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006;124:783–801.

Schoggins JW, Wilson SJ, Panis M, Murphy MY, Jones CT, Bieniasz P, et al. A diverse range of gene products are effectors of the type I interferon antiviral response. Nature 2011;472:481–5.

Grandvaux N, Servant MJ, tenOever B, Sen GC, Balachandran S, Barber GN, et al. Transcriptional profiling of interferon regulatory factor 3 target genes: direct involvement in the regulation of interferon-stimulated genes. J Virol 2002;76:5532–9.

Lazear HM, Lancaster A, Wilkins C, Suthar MS, Huang A, Vick SC, et al. IRF-3, IRF-5, and IRF-7 coordinate the type I IFN response in myeloid dendritic cells downstream of MAVS signaling. PLoS Pathog 2013;9:e1003118.

Borrow P, Martinez-Sobrido L, de la Torre JC. Inhibition of the type I interferon antiviral response during arenavirus infection. Viruses 2010;2:2443–80.

Merigan TC, Oldstone MB, Welsh RM. Interferon production during lymphocytic choriomeningitis virus infection of nude and normal mice. Nature 1977;268:67–8.

Ou R, Zhou S, Huang L, Moskophidis D. Critical role for alpha/beta and gamma interferons in persistence of lymphocytic choriomeningitis virus by clonal exhaustion of cytolytic T cells. J Virol 2001;75:8407–23.

Bukowski JF, Biron CA, Welsh RM. Elevated natural killer cell-mediated cytotoxicity, plasma interferon, and tumor cell rejection in mice persistently infected with lymphocytic choriomeningitis virus. J Immunol 1983;131:991–6.

Saron MF, Riviere Y, Hovanessian AG, Guillou JC. Chronic production of interferon in carrier mice congenitally infected with lymphocytic choriomeningitis virus. Virology 1982;117:253–6.

Wilson EB, Yamada DH, Elsaesser H, Herskovitz J, Deng J, Cheng G, et al. Blockade of chronic type I interferon signaling to control persistent LCMV infection. Science 2013;340:202–7.

Kolumam GA, Thomas S, Thompson LJ, Sprent J, Murali-Krishna K. Type I interferons act directly on CD8 T cells to allow clonal expansion and memory formation in response to viral infection. J Exp Med 2005;202:637–50.

Milazzo ML, Fulhorst CF. Duration of Catarina virus infection in the southern plains woodrat (Neotoma microplus). Vector Borne Zoonotic Dis 2012;12:321–4.

Peters CJ, Liu CT, Anderson GW, Morrill JC, Jahrling PB. Exotic emerging viral diseases: natural reservoir, in experimentally infected adult Neotoma microplus). Vector Borne Zoonotic Dis 2012;12:321–4.

Vitullo AD, Hodara VL, Merani MS. Effect of persistent infection with Junin virus on growth and reproduction of its natural reservoir, Calomys musculinus. Am J Trop Med Hyg 1987;37:663–9.

Goldsbrough PB, Jahrling PB. Exotic emerging viral diseases: progress and challenges. Nat Med 2004;10:S110–9.

Yun NE, Poussard AL, Seregin AV, Walker AG, Smith JK, Aronson JF, et al. Functional interferon system is required for clearance of lassa virus. J Virol 2012;86:3389–92.

Eriksson PO, Andersson PW, Keyrouz W, Sprent J, Jawhing PB. Pathogenesis of viral hemorrhagic fevers: Rift Valley fever and Lassa fever contrasted. Rev Infect Dis 1989;11:S743–9.
Review: Innate Immune Response to Arenavirus Infection

[90] Baize S, Kaplon J, Faure C, Pannetier D, Georges-Courbot MC, Deubel V. Lassa virus infection of human dendritic cells and macrophages is productive but fails to activate cells. J Immunol 2004;172:2861–9.

[91] Walker DH, McCormick JB, Johnson KM, Webb PA, Komba-Kono G, Elliott LH, et al. Pathologic and virologic study of fatal Lassa fever in man. Am J Pathol 1982;107:349–56.

[92] Edington GM, White HA. The pathology of Lassa fever. Trans R Soc Trop Med Hyg 1972;66:381–9.

[93] Fisher-Hoch S, McCormick JB, Sasso D, Craven RB. Hematologic dysfunction in Lassa fever. J Med Virol 1986;26:127–35.

[94] Baize S, Pannetier D, Faure C, Marianneau P, Marandet I, Georges-Courbot MC, et al. Role of interferon in the control of Lassa virus replication in human dendritic cells and macrophages. Microbes Infect 2006;8:1194–202.

[95] Mahantu S, Hutchison K, Agarwal S, McRae M, Rollin PE, Pulendran B. Cutting edge: impairment of dendritic cells and adaptive immunity by Ebola and Lassa viruses. J Immunol 2003;170:2797–801.

[96] Pannetier D, Reynard S, Russier C, Joumeaux A, Tordo N, Deubel V, et al. Human dendritic cells infected with the nonpathogenic Mopeia virus induce stronger T-cell responses than those infected with Lassa virus. J Virol 2011;85:8293–306.

[97] Baize S, Marianneau P, Loth P, Reynard S, Joumeaux A, Chevallier M, et al. Early and strong immune responses are associated with control of viral replication and recovery in lassa virus-infected cynomolgus monkeys. J Virol 2009;83:5890–903.

[98] Hensley LE, Smith MA, Geisbert JB, Fritz EA, Daddario-DiCaprio KM, Larsen T, et al. Pathogenesis of Lassa fever in cynomolgus macaques. Virol J 2011;8:205.

[99] Carrion R, Brasky K, Mansfield K, Johnson C, Gonzales M, Ticer A, et al. Lassa virus infection in experimentally infected marmosets: liver pathology and immunophenotypic alterations in target tissues. J Virol 2007;81:6482–90.

[100] Levis SC, Saavedra MC, Cecconi C, Falcoff E, Feuillade MR, Enria DA, et al. Endogenous interferon in Argentine hemorrhagic fever. J Infect Dis 1984;159:428–33.

[101] Levis SC, Saavedra MC, Cecconi C, Falcoff MR, Enria DA, Maiztegui JI, et al. Correlation between endogenous interferon and the clinical evolution of patients with Argentine hemorrhagic fever. J Interferon Res 1985;5:383–9.

[102] Kenyon RH, McKee KT, Zack PM, Rippy MK, Vogel AP, York C, et al. Aerosol infection of rhesus macaques with Junin virus. Intervirology 1992;33:23–31.

[103] Dejean CB, Ayerra BL, Teyssie AR. Interferon response in the guinea pig infected with Junin virus. J Med Virol 1987;23:83–91.

[104] Lerer GD, Saavedra MC, Falcoff R, Maiztegui JI, Molinas FC. Activity of a plateau protein kinase that phosphorylates fibrinogen and histone in Argentine hemorrhagic fever. Acta Physiol Pharmacol Ther Latinoam 1991;41:377–86.

[105] Poznir RG, Ure AE, Jaquenod de Giusti C, D’Atri LP, Italiano JE, Torres O, et al. Junin virus infection of human hematopoietic progenitors impairs in vitro proplatelet formation and platelet release via a bystander effect involving type I IFN signaling. PLoS Pathog 2010;6:e1000847.

[106] Stephen EL, Scott SK, Eddy GA, Levy HB. Effect of interferon on togavirus and arenavirus infections of animals. Tex Rep Biol Med 1977;35:449–54.

[107] Grant A, Seregine A, Huang C, Kolokoltsova O, Brasier A, Peters C, et al. Junin virus pathogenesis and virus replication. Viruses 2012;4:2317–39.

[108] Kolokoltsova OA, Yun NE, Poussard AL, Smith JK, Smith JN, Salazar M, et al. Mice lacking alpha/beta and gamma interferon receptors are susceptible to Junin virus infection. J Virol 2010;84:13063–7.

[109] Gowen BB, Wong MH, Larson D, Ye W, Jung KH, Selig EJ, et al. Development of a new tacaribe arenavirus infection model and its use to explore antiviral activity of a novel aristeromycin analog. PLoS One 2010;5:e12760.

[110] Pedras-Vasconcelos JA, Puig M, Sauder C, Wolpert C, Ovanesov M, Goucher D, et al. Immunotherapy with CpG oligonucleotides and antibodies to TNF-alpha rescues neonatal mice from lethal arenavirus-induced meningoencephalitis. J Immunol 2008;180:8231–40.

[111] Bradfute SB, Stuthman KS, Strueffel AC, Bavarri S. A STAT-1 knockout mouse model for Machupo virus pathogenesis. J Virol 2011;85:300.

[112] Yun NE, Seregine AV, Walker DH, Popov VL, Walker AG, Smith JN, et al. Mice lacking functional STAT1 are highly susceptible to lethal infection with Lassa virus. J Virol 2013;87:10908–11.

[113] Aronson JF, Herzog NK, Jerrells TR. Pathological and virological features of arenavirus disease in guinea pigs. Comparison of two Pichinde virus strains. Am J Pathol 1994;145:228–35.

[114] Groseth A, Hoenen T, Weber M, Wolf S, Henwig A, Kaufmann A, et al. Tacaribe virus but not Junin virus infection induces cytokine release from primary human monocytes and macrophages. PLoS Negl Trop Dis 2011;5:e1137.

[115] Ambrosio AM, Enria DA, Maiztegui JI. Junin virus isolation from lympho-mononuclear cells of patients with Argentine hemorrhagic fever. Intervirology 1986;25:97–102.

[116] Ambrosio M, Vallezos A, Saavedra C, Maiztegui JI. Junin virus replication in peripheral blood mononuclear cells of patients with Argentine haemorrhagic fever. Acta Virol 1990;34:58–63.

[117] Gonzalez PH, Cossio PM, Arana R, Maiztegui JI, Laguens RP. Lymphatic tissue in Argentine hemorrhagic fever. Pathologic features. Arch Pathol Lab Med 1980;104:250–9.

[118] Maiztegui JI, Laguens RP, Cossio PM, Casanova MB, de la Vega MT, Ritchaco V, et al. Ultrastructural and immunohistochemical studies in five cases of Argentine hemorrhagic fever. J Infect Dis 1975;132:35–53.

[119] Cuevas CD, Lavanya M, Wang E, Ross SR. Junin virus infects mouse cells and induces innate immune responses. J Virol 2011;85:11058–68.

[120] Zhou S, Halle A, Kurt-Jones EA, Cerny AM, Porpiglia E, Rogers M, et al. Lymphocytic choriomeningitis virus (LCMV) infection of CNS glial cells results in TLR2-MyD88/MyD88-dependent inflammatory responses. J Neuroimmunol 2008;194:70–82.

[121] Zhou S, Kurt-Jones EA, Mandell L, Cerny A, Chan M, Golenbock DT, et al. MyD88 is critical for the development of innate and adaptive immunity during acute lymphocytic choriomeningitis virus infection. Eur J Immunol 2005;35:822–30.

[122] Huang C, Kolokoltsova OA, Yun NE, Seregine AV, Poussard AL, Walker AG, et al. Junin virus infection activates the type I interferon pathway in a RIG-I-dependent manner. PLoS Negl Trop Dis 2012;6:e1659.

[123] Zhou S, Cerny AM, Zacharia A, Fitzgerald KA, Kurt-Jones EA, Finberg RW. Induction and inhibition of type I interferon
responses by distinct components of lymphocytic choriomeningitis virus. J Virol 2010;84:9452–62.

[124] Fennewald SM, Aronson JF, Zhang L, Herzog NK. Alterations in NF-kappaB and RBP-Jkappa by arenavirus infection of macrophages in vitro and in vivo. J Virol 2002;76:1154–62.

[125] Bowick GC, Fennewald SM, Zhang L, Yang X, Aronson JF, Shope RE, et al. Attenuated and lethal variants of Pichinde virus induce differential patterns of NF-kappaB activation suggesting a potential target for novel therapeutics. Viral Immunol 2009;22:457–62.

[126] Bowick GC, Fennewald SM, Scott EP, Zhang L, Elsom BL, Aronson JF, et al. Identification of differentially activated cell-signaling networks associated with pichinde virus pathogenesis by using systems kinomics. J Virol 2007;81:1923–33.

[127] Martinez-Sobrido L, Emonet S, Giannakas P, Cubitt B, Garcia-Sastre A, de la Torre JC. Identification of amino acid residues critical for the anti-interferon activity of the nucleoprotein of the prototypic arenavirus lymphocytic choriomeningitis virus. J Virol 2009;83:11330–40.

[128] Martinez-Sobrido L, Giannakas P, Cubitt B, Garcia-Sastre A, de la Torre JC. Differential inhibition of type I interferon induction by arenavirus nucleoproteins. J Virol 2007;81:12696–703.

[129] Martinez-Sobrido L, Zuniga EI, Rosario D, Garcia-Sastre A, de la Torre JC. Inhibition of the type I interferon response by the nucleoprotein of the prototypic arenavirus lymphocytic choriomeningitis virus. J Virol 2006;80:9192–9.

[130] Hastie KM, Kimberlin CR, Zandonatti MA, MacRae IJ, Saphire EO. Structure of the Lassa virus nucleoprotein reveals a dsRNA-specific 3’ to 5’ exonuclease activity essential for immune suppression. Proc Natl Acad Sci USA 2011;108:2396–401.

[131] Qi X, Lan S, Wang W, Schelde LM, Dong H, Wallat GD, et al. Cap binding and immune evasion revealed by Lassa nucleoprotein structure. Nature 2010;468:779–83.

[132] Carnec X, Baize S, Reynard S, Diangcourt L, Caro V, Tordo N, et al. Lassa virus nucleoprotein mutants generated by reverse genetics induce a robust type I interferon response in human dendritic cells and macrophages. J Virol 2011;85:12093–7.

[133] Pythoud C, Rodrigo WW, Pasqual G, Rothenberger S, Martinez-Sobrido L, de la Torre JC, et al. Arenavirus nucleoprotein targets interferon regulatory factor-activating kinase IKKepsilon. J Virol 2012;86:7728–38.

[134] Rodrigo WW, Ortiz-Riano E, Pythoud C, Kunz S, de la Torre JC, Martinez-Sobrido L. Arenavirus nucleoproteins prevent activation of nuclear factor kappa B. J Virol 2012;86:8185–97.

[135] Harmon B, Kozina C, Maar D, Carpenter TS, Branda CS, Negrete OA, et al. Identification of critical amino acids within the nucleoprotein of Tacaribe virus important for anti-interferon activity. J Biol Chem 2013;288:8702–11.

[136] Fan L, Briese T, Lipkin WI. Z proteins of New World arenaviruses bind RIG-I and interfere with type I interferon induction. J Virol 2010;84:1785–91.

[137] Marq JB, Hausmann S, Veillard N, Kolakofsky D, Garcin D. Short double-stranded RNAs with an overhanging 5’ ppp-nucleotide, as found in arenavirus genomes, act as RIG-I decoys. J Biol Chem 2011;286:6108–16.

[138] Marq JB, Kolakofsky D, Garcin D. Unpaired 5’ ppp-nucleotides, as found in arenavirus double-stranded RNA panhandles, are not recognized by RIG-I. J Biol Chem 2010;285:18208–16.

[139] Pannetier D, Faure C, Georges-Courbot MC, Deubel V, Baize S. Human macrophages, but not dendritic cells, are activated and produce alpha/beta interferons in response to Mopeia virus infection. J Virol 2004;78:10516–24.

[140] Canonico PG, Kende M, Luscri BJ, Huggins JW. In-vivo activity of antivirals against exotic RNA viral infections. J Antimicrob Chemother 1984;14:27–41.

[141] Salomon R, Hoffmann E, Webster RG. Inhibition of the cytokine response does not protect against lethal H5N1 influenza infection. Proc Natl Acad Sci USA 2007;104:12479–81.

[142] Chen J, Subbarao K. The immunobiology of SARS*. Annu Rev Immunol 2005;23:443–72.

[143] Huang KJ, Su IJ, Theron M, Wu YC, Lai SK, Liu CC, et al. An interferon-gamma-related cytokine storm in SARS patients. J Med Virol 2005;75:185–94.