[Frontiers in Bioscience S4, 1065-1077 , January 1, 2012]

Antiviral escape strategies developed by bunyaviruses pathogenic for humans

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1. ABSTRACT

New or re-emerging pathogens for humans have emerged outside of their usual endemic range during the last decade originating severe public health concern and economical losses. Climate changes have played a significant role in the emergence or re-emergence of arboviruses. Among these pathogens, several viruses belong to the *Bunyaviridae* family. This family is composed of RNA viruses grouped into five genera *Orthobunyavirus*, *Hantavirus*, *Nairovirus*, *Phlebovirus* and *Tospovirus* characterized by their antigenic, genetic and ecological properties. These viruses use cellular proteins to promote their own replication/transcription and reciprocally the host induces, in response, an important transcriptional reprogramming to activate antiviral defences including the interferon type I pathways. The virulence of the pathogenic bunyaviruses is directly linked to the roles of viral virulence factors and their capacity to counteract the host pathways. This review summarizes the various strategies developed by the different genera of the *Bunyaviridae* family to overcome and escape the innate immune response and eventually other cellular functions.

2. INTRODUCTION

During the past decade, the emergence of either emerging or re-emerging virus diseases in new areas of the world occurred with increasing frequency and became a serious public health concern and economical losses. Arboviruses are distributed worldwide and represent approximately 30% of all emerging infectious diseases during the last decade (1). Viruses such as West Nile (WNV), Chikungunya (CHIKV), Dengue (DENV), Yellow Fever (YFV), Crimea-Congo Hemorrhagic Fever (CCHF) and Rift Valley Fever (RVFV) viruses, which are pathogenic for humans and/or animals have emerged outside of their usual endemic range and caused epidemics in North America, Europe and the Arabian Peninsula. Their emergence may be related to the climate fluctuations due to the global warming and/or human activities (human travel increasing, deforestation, political and military activities) that facilitate the dispersion of the arthropods beyond their current geographic boundaries (2, 3). As an example of new emerging pathogens, one should recall the newly identified phlebovirus isolated in China. It is transmitted by ticks and closely related to the tick borne Uukuniemi

Table 1. Human pathogens in the different genera of the *Bunyaviridae* family

Genus	Virus	Vector	Human Disease
Orthobunyavirus			
	La Crosse	Mosquito	Severe encephalitis, meningitis
	Ngari	Mosquito	Haemorrhagic Fever
	Oropouche	Midge	Acute febrile illness
	Tahyna	Mosquito	Non fatal flu-like illness
Hantavirus			
	Andes	Mouse	Hantavirus cardiopulmonary syndrome Fatality 40-50%
	Hantaan	Field Mouse	Severe haemorrhagic fever with renal syndrome Fatality 5-15%
	Puumala	Bank Vole	Mild haemorrhagic fever with renal syndrome Fatality 0.1%
	Seoul	Rat	Moderate haemorrhagic fever with renal syndrome Fatality 1%
	Sin Nombre	Deer Mouse	Hantavirus cardiopulmonary syndrome Fatality 50%
Nairovirus			
	Crimean Congo hemorrhagic Fever	Tick	Haemorrhagic Fever Fatality 20-80%
Phlebovirus			
	Naples sandfly Fever	Sandfly	"three day fever" with Influenza-like symptoms
	Punta Toro	Sandfly	Acute febrile illness
	Rift Valley Fever	Mosquito	Hepatitis, encephalitis, haemorrhagic fever Fatality 1-10%
	Toscana	Sandfly	Meningitis, meningoencephalitis, encephalitis
	Sicilian sandfly Fever	Sandfly	"three day fever" with Influenza-like symptoms
	Huaiyangshan	Tick	severe thrombocytosis and multiorgan dysfunction Fatality 30%

(UUKV) virus. However, in contrast with UUKV, which is not pathogenic for humans, this novel phlebovirus designated severe fever with thrombocytopenia syndrome virus or Huaiyangshan virus depending on the laboratory where it was isolated, is responsible for severe thrombocytosis and multi-organ dysfunction with high morbidity and mortality (initial fatality rate 30%) (4, 5). Studies on these arboviruses thus become a major issue since neither safe vaccine for protection nor antiviral treatments for therapy is currently available. Among these emerging pathogens, several viruses belong to the large family of RNA viruses, the *Bunyaviridae* family (Table 1).

The *Bunyaviridae* family comprises more than 350 members and is subdivided in five genera (i.e. *Orthobunyavirus*, *Hantavirus*, *Nairovirus*, *Phlebovirus* and *Tospovirus*) characterized by their antigenic, genetic and ecological properties. Orthobunyaviruses, nairoviruses and phleboviruses infect vertebrates and are vectored by haematophagous arthropods including mosquitoes, ticks, midges and sandflies whereas tospoviruses are plant pathogens and are vectored by different thrips (6). In contrast, hantaviruses are not transmitted by arthropods but by rodents and insectivores which act as reservoirs. Infections by hantaviruses are persistent in their reservoir hosts and humans become infected through contamination by excretions or carcasses of infected reservoirs (7).

All the members of this family, referred as bunyaviruses, are enveloped, spherical virions between 80-120 nm in diameter with its replicative cycle in the cytoplasm and maturation and budding of the newly formed particles in the Golgi apparatus (8, 9). These viruses possess single-stranded RNA genomes that consist of three segments L (Large), M (Medium) and S (Small) having a negative- or ambi-sense polarity (6). The L and M segments code respectively for the viral RNA-dependent RNA polymerase (L-RdRp) and a precursor to the envelope glycoproteins (Gn and Gc). The S segment codes for the internal protein N or nucleocapsid protein that is able to oligomerize and associate with the viral polymerase and the three different segments of the viral genome to form viral ribonucleoparticles (RNPs) packaged into virions. Depending on the genus, other proteins are encoded by the M and S segments, namely the non-structural proteins NSm1, NSm2 and NSs harbouring multiple roles. The virulence of the pathogenic bunyaviruses illustrates the permanent co-evolution between the viruses and their hosts. The virus utilizes cellular proteins or functions to promote their own replication/transcription. This is particularly well illustrated in the case of bunyaviruses which utilize capped oligonucleotides from host cell mRNAs to prime transcription through the cap-snatching mechanism mediated by the L-RdRp which possesses an endonuclease activity to cleave the capped oligonucleotides (10). In response to viral infection, the host induces an important transcriptional reprogramming to activate various defences including the innate immunity. However, viruses have developed strategies to overcome the numerous host responses; this will be described in the following sections of this review.

3. THE INNATE IMMUNITY

In many cases, arboviruses infect vertebrates through mosquito or tick bites, which inoculate the virus in the skin, making Dendritic Cells (DCs) such as skin Langerhans cells the primary cell targets (11, 12). Infected Langerhans cells migrate to the draining lymph node, allowing the virus to enter the bloodstream and disseminate. After pathogen intrusion, the first response of the cell or the organism is an inflammatory reaction

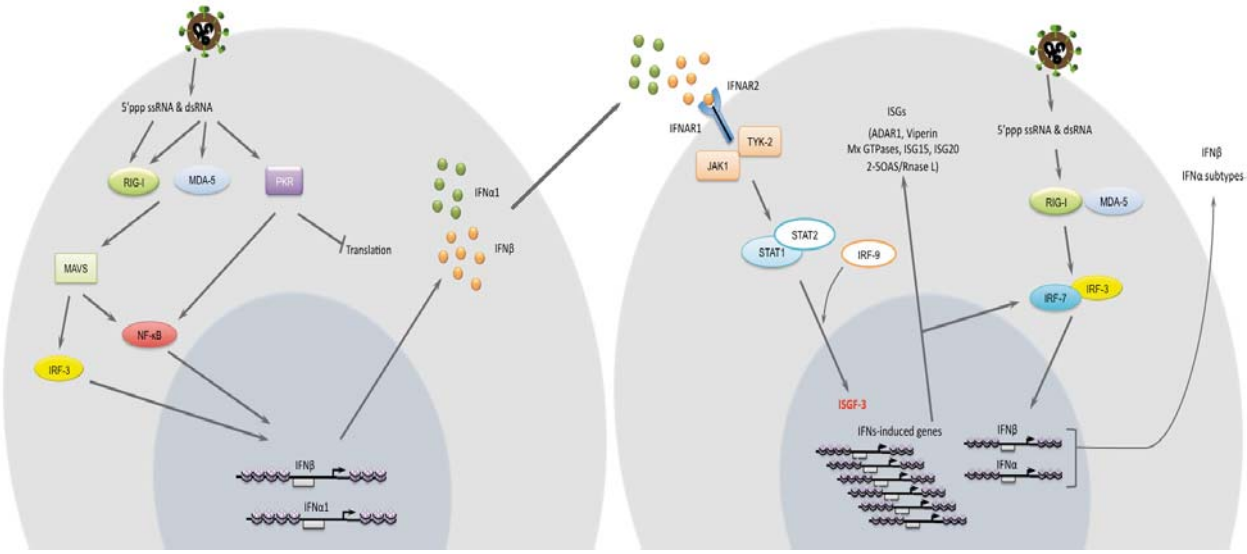

Figure 1. Induction and signaling pathways of the innate immunity. The viral replication of bunyaviruses can produce 5' triphosphate ssRNA and dsRNA that activate the cytoplasmic PAMPs RIG-I, MDA-5 and PKR. The RIG-I/MDA-5 dependent pathways induce the mitochondrial MAVS (IPS-1/Cardiff/VISA) that is necessary for the subsequent TBK-1-directed phosphorylation of IRF-3 and NF-κB that translocate into the nucleus and transactivate collectively the IFNβ and IFNα1 promoters. In parallel, activated PKR can phosphorylate eIF2α and inhibit the host and viral translation. The secreted IFNβ and IFNα1 acting in autocrine and paracrine manner bind and activate the IFNARs allowing the expression of numerous ISGs and IRF-7 through the JAK/STAT pathways. In these cells, bunyaviruses can be blocked through the products of these ISGs. Moreover, 5' triphosphate ssRNA and dsRNA produced during the viral replication activate the cytoplasmic RIG-I, MDA-5 and consequently IRF-7/IRF-3 leading to a positive-feedback loop that initiates the synthesis of IFNβ and several IFNα subtypes.

including secretion of soluble mediators such as cytokines and chemokines. Among these mediators, Interferons (IFNs) and especially type I IFNs (IFNα/β) are the most efficient to mount a rapid host response with the aim to block the viral replication (13, 14). The initial response to infection involves the production and secretion of IFNα1 and IFNβ followed by a subsequent amplification phase linked to induction of other IFNα subtypes. The secreted IFNs act in autocrine and paracrine manner to stimulate the expression of antiviral, antiproliferative and immunomodulatory genes.

The induction of type I IFNs occurs mainly by an intracellular pathway and necessitates the initial recognition between specific cellular Pattern Recognition Receptors (PRR) and viral inducers so-called Pathogen-Associated Molecular Patterns (PAMP). Double-stranded (ds) RNA or 5'-triphosphorylated single-stranded (ss) RNA from RNA viruses trigger several cytosolic PAMPs including two RNA helicases, RIG-I and MDA-5, and the dsRNA-dependent Protein Kinase R (PKR). The binding of viral RNA to RIG-I and MDA-5 induces a signaling chain, which leads to the activation and nuclear translocation of several transcription factors including the constitutive Interferon Regulatory Factor-3 (IRF3) and NF-κB. The RIG-I and MDA-5 dependent pathways result in the phosphorylation of IRF-3 by TBK1, the homodimerisation and nuclear translocation of IRF-3 being a prerequisite to initiate the messenger RNA (mRNA) IFNβ and human IFNα1 synthesis (15, 16). The kinase PKR is a constitutive protein that is activated by dsRNA inducing its auto-phosphorylation. The activated PKR can therefore phosphorylate several substrates including IκB and eIF-2α (eukaryotic Initiation Factor 2 alpha). The phosphorylated IκB is degraded through the proteasome activating the transcription factor NF-κB whereas its effect on eIF-2α leads to the inhibition of translation of cellular and viral mRNA.

The secreted IFNα1 and IFNβ, triggered through the IRF-3-dependent induction, are able to bind and activate IFNAR1 and IFNAR2 present on all host cells. These IFNARs dimerize and induce the phosphorylation of members of Janus Kinase (JAK), TYK-2 and JAK1 that are pre-associated with their cytoplasmic tails. The latent cytoplasmic transcription factors from the Signal Transducer and Activator of Transcription (STAT) family are therefore phosphorylated by JAK1 and TYK-2 leading to their activation (17, 18). Phosphorylated STAT1 and STAT2 heterodimerize and recruit IRF-9 to form a complex called IFN stimulated gene factor 3 (ISGF-3) that translocates to the nucleus, binds to IFN-stimulated response elements (ISRE) localized in numerous IFN-induced gene promoters such as IFN-Stimulated Genes (ISGs) and IRF-7 and activates the transcription of these genes (Figure 1). IRF-7 is not constitutively expressed in most cells (except in plasmacytoid Dendritic Cells, pDCs) and is an IFN-inducible and virus-inducible protein similar to IRF-3. Active IRF-7 homodimers or heterodimers with IRF-3, bind to promoter of all IFNα genes, and are

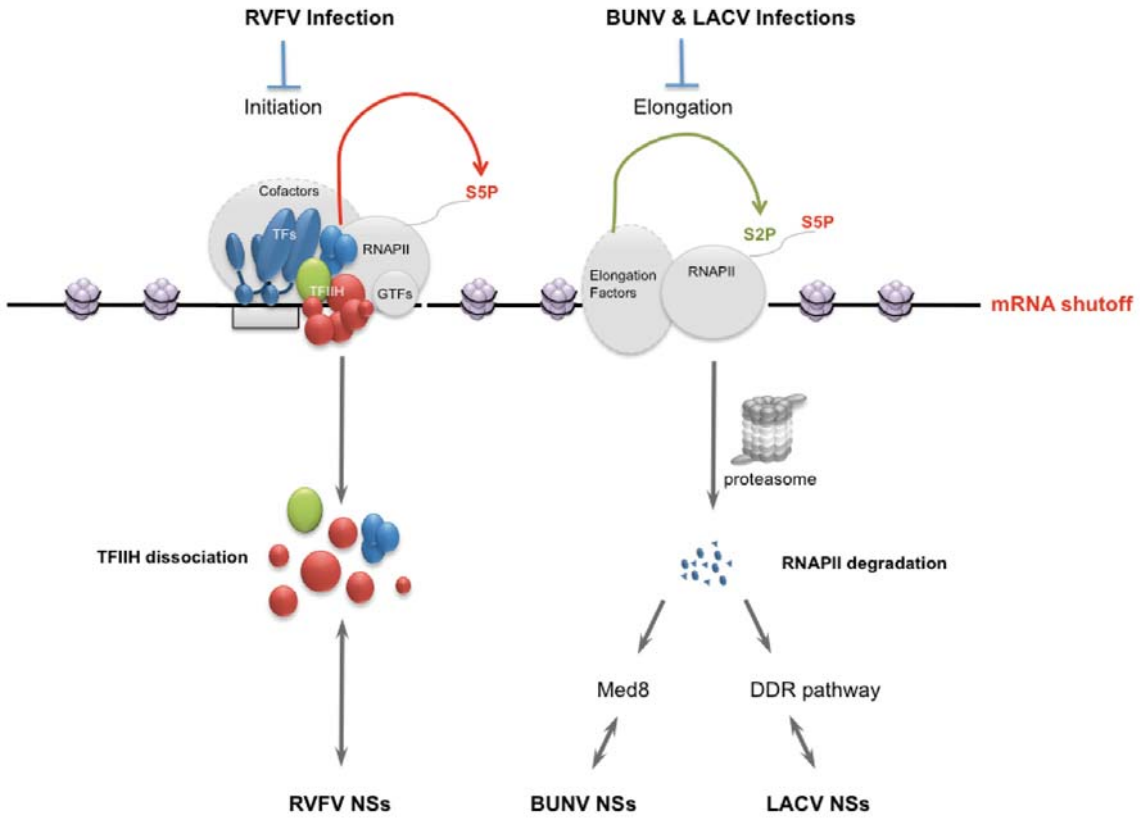

Figure 2. Mechanisms of immune escape targeting the cellular transcriptional machinery for BUNV, LACV and RVFV. NSs proteins from BUNV, LACV and RVFV block the type I IFN response and shut off the mRNA expression by targeting the cellular transcriptional machinery through different strategies. RVFV NSs protein inhibit the formation of the basal transcription TFIIH complex that is crucial for the initiation step by phosphorylating notably the CTD repeat serine 5 residue of RNAPII. BUNV and LACV NSs proteins induce the proteolysis of RNAPII engaged in elongation (characterized by the CTD repeat serine 2 phosphorylation) through their interactions respectively with the Mediator subunit Med8 and the DNA Damage Repair pathway.

therefore responsible for the induction of delayed type I IFNs and amplification of the IFN response (16) (Figure 1). IFNs also induce more than 350 ISGs, which have antiviral, antimicrobial, antiproliferative and immunomodulatory functions (19). The proteins induced by IFNs include enzymes, signalling proteins, chemokines, cytokines, transcription factors, heat shock proteins, surface glycoproteins or pro-apoptotic proteins. Among this list, only a few ones have been characterized with antiviral activities such as the Mx GTPases, PKR, the 2',5' Oligoadenylate Synthetases (2-5 OAS)/RNAse L system, the RNA-specific adenosine deaminase 1 (ADAR1), viperin, ISG20 or p56 which are largely described in more detailed in other reviews (20). In response to the type I IFNs action, each virus targets specific cellular proteins and usually possesses unique strategy to counteract these pathways. This review illustrates the diversity and originality in the strategies developed by different pathogenic bunyaviruses.

4. ORTHOBUNYAVIRUSES

This genus consists of more than 150 viruses; it is subdivided into 19 different serogroups: among which the California, Bunyamwera and Simbu serogroups comprise respectively, three serious human pathogens: La Crosse, Ngari and Oropouche viruses. Bunyamwera virus is the prototype for the *Orthobunyavirus* genus and the *Bunyaviridae* family. The orthobunyaviruses are able to replicate both in mammalians and in insects. The infection in mammalian cells is lytic and causes host cell shut off and cell death whereas it is noncytolytic and leads to viral persistent in invertebrate cells. Besides the classical organization, the M segment encodes a polyprotein precursor post-translationally cleaved into the envelope glycoproteins Gn and Gc and a third protein NSm of unknown function. In addition to the nucleocapsid, the S segment also encodes the NSs protein in an overlapping reading frame. The NSs protein has been reported to act as an interferon antagonist playing an important role in viral pathogenesis (21-23). The innate immune escape mediated by NSs protein was more precisely studied for two orthobunyaviruses Bunyamwera (BUNV) and La Crosse (LACV) viruses. The NSs protein impairs the antiviral response by preventing cellular transcription through the proteolysis of RNA polymerase II (RNAPII) (Figure 2).

4.1. Bunyamwera virus

The BUNV NSs protein is predominantly cytoplasmic although a significant fraction was also observed in the nucleus of cells transfected with a Flag-NSs expressing plasmid (22). Upon infection with wild type (wt) BUNV, the induction of IFN or IRF-3 mediated pro-apoptosis genes is abolished although the activation of IRF-3 and PKR is maintained indicating the NSs effect is downstream the primary signaling chain of innate immunity (24, 25). In BUNV-infected mammalian cells, NSs inhibits the phosphorylation of serine 2 in heptapeptide repeat of the CTD of RNA polymerase II and induces also its degradation (26, 27). Such a dysregulation of the host transcription machinery results from the interaction between the C-terminal region of NSs and Med8, a subunit of mediator complex (27). Mediator regulates RNAPII phosphorylation CTD-ser-5 residue and contacts the CTD-ser-2 kinase P-TEFb (28, 29). Moreover, Med8 can form an ubiquitin E3 ligase with Elongin B/C, Cul2 and Rbx1 targeting putatively RNAPII. Thus, NSs can evade the innate immune response by a general block of transcription of all cellular protein-coding genes including type I IFNs. This inhibition of the host transcription machinery caused by NSs is at least partially responsible for the shut off of cell protein synthesis (23, 26). Indeed, a recent study demonstrated the interaction with Med8 alone is not sufficient to impair the cellular gene expression and that other host partners requiring the N-terminal region of NSs are involved in this process (30).

4.2. La Crosse virus

LACV causes severe encephalitis and meningitis in children in the Midwestern United States including 300,000 cases per year with more than 10% developing long-lasting neurological defaults. LACV NSs protein was identified as a type I IFNs antagonist without affecting the PKR activity and the RIG-I pathway that is normally induced in infected cells (21, 31, 32). Two studies have ascribed the LCAV NSs protein as RNAi suppressor and pro-apoptotic protein since it has similarities with the Reaper protein from Drosophila involved in translation inhibition and apoptosis in insects (33-35). However, these two putative functions seem to be side effects of the NSs molecular mechanisms to inhibit IFN induction. Indeed, expression of NSs has no apparent pro-apoptotic activity in insects and no advantage conferred by NSs was detected for the RNAi inhibition in insects and mammalian cells (21). A recent study indicates that NSs acts downstream the canonical RIG-I/IRF-3 signaling pathway and its effect is based on the shutdown of RNAPII-dependent transcription. LACV NSs exploits the response of cells to damaged DNA to induce the degradation of the elongating RNAPII. Indeed, DNA damage causes the arrest of elongating RNAPII, which in turn triggers the proteolysis through the ubiquitin/proteasome pathway. In LACV-infected cells, NSs activates part of the DDR machinery such as the DDR pak6 gene and the phosphorylation of H2A.X (32). The authors suggest that such an effect can lead to a general mRNA shut off. However the precise mechanism inhibiting and degrading the elongating RNAPII through LACV NSs remains to be characterized.

5. HANTAVIRUSES

Contrary to other bunyaviruses, hantaviruses are not transmitted by arthropods. They are rodent-borne viruses, present throughout the world. They are classified into New World or Old World based on their geographic location. Pathogenic New World hantaviruses (Andes, ANDV, Sin Nombre, SNV and New York1, NY-1V viruses) cause a Hantavirus Cardiopulmonary Syndrome (HCPS) in Americas whereas pathogenic Old World hantaviruses (Hantaan, HNTV, Puumala, PUUV and Seoul, SEOV viruses) cause a Hemorrhagic Fever with Renal Syndrome (HFRS) in Europe and Asia. The New World hantaviruses Andes and Sin Nombre are responsible for mortality rate of 50% while the Old World hantavirus Hantaan can reach a mortality rate of 15% (7). Hantaviruses developed species-specific mechanisms to escape the innate immune responses. However, even non-pathogenic viruses (Tula TULV, Prospect Hill PHV viruses) antagonize some IFN pathways indicating that the IFN dysregulation alone is insufficient for hantaviruses to cause disease (36, 37). The different hantaviral strategies may involve several viral proteins including the glycoproteins, the nucleocapsid and the NSs proteins that can collectively block different steps in the type I IFNs pathways (Figure 3).

5.1. Glycoproteins Gn and Gc

Two reports have demonstrated that the ectopic expression of the glycoprotein Gn cytoplasmic tail from NY-1V was sufficient to inhibit the NF-κB and IRF-3-directed transcriptional responses. The TBK1 and RIG-I-directed steps were involved in such dysregulation and especially the components of TBK1 complexes (38, 39). TBK1 plays a crucial role in the IFN regulation since it directs the activation of both IRF-3 and NF-κB (15, 40). TRAF3 forms a complex with TBK1 and links upstream IFN signaling responses of the RIG-I/MDA-5 induced MAVS (IPS-1/Cardiff/VISA) to the TBK-1-directed phosphorylation of IRF-3 (41). TBK1 also activates NF-κB through interactions with TRAF2 (40). The NY-1V Gn cytoplasmic tail interacts with the TRAF3 N-terminus and consequently impairs cellular TBK-1-TRAF3 complex formation (39) (Figure 3). It was also suggested that such viral glycoprotein could block, through a similar mechanism, the TRAF2-directed NF-κB activation. For other pathogenic hantaviruses, both glycoproteins Gn and Gc could be necessary to overcome the IFN response. Indeed, the expression of the glycoprotein precursor (GPC) of SNV and ANDV is sufficient to inhibit the IFNβ induction, IRF-3 activation and the JAK/STAT signaling through the blockage of the phosphorylation and the nuclear translocation of STAT1/STAT2 (36, 42).

5.2. Nucleocapsid

The nucleocapsid is the most abundant viral protein in bunyavirus-infected cells. It is essential for the replicative cycle playing multiple functions. In the case of hantaviruses, it was shown to be involved in the formation of RNP through its homotrimerization and its interaction with viral RNA (43, 44). The nucleocapsid participates to the translation initiation mechanism through its interaction

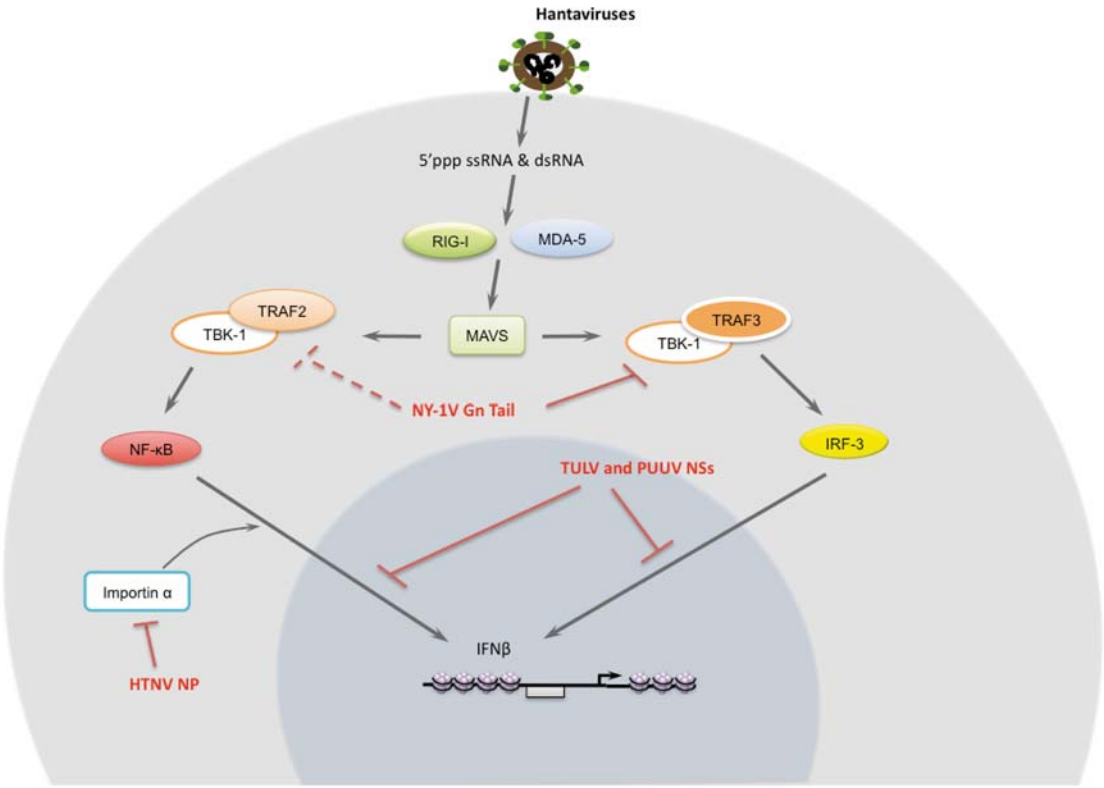

Figure 3. Hantaviral strategies played by Gn glycoprotein, nucleocapsid and NSs protein to evade the type I IFN response. The NY-1V Gn cytoplasmic tail can inhibit the activation of the transcription factors IRF-3 and putatively NF-κB by blocking their phosphorylation through TBK-1 that necessitates the formation of complexes with respectively TRAF3 and TRAF2. The viral glycoprotein interacts with the TRAF3 N-terminus and consequently impairs cellular TBK-1-TRAF3 complex formation. The HTNV nucleocapsid block the NF-κB-directed transcriptional response by interacting with importin α proteins impairing the nuclear translocation of activated NF-κB that remains into the cytoplasm. Finally, the NSs protein of TULV and PUUV localized in perinuclear area inhibits the induction of IFNβ and the activation of IRF-3 and NF-κB responsive promoters.

with Ribosomal Protein S19 (RPS19) (45). The IFN antagonism was also associated to this viral protein. Indeed, N proteins from PUUV, HTNV and TULV have been shown to interact respectively with the apoptotic protein Daxx, the Ubiquitin-conjugating enzyme 9 (Ubc9) and the Small Ubiquitin-like Modifier 1 (SUMO-1) (46-48). However the link between these interactions and the IFN escape remains to be determined. HTNV can also block the activation of NF-κB via the TNF-α through its nucleocapsid. It was demonstrated that the N protein interacts with importin α proteins, impairing the nuclear translocation of activated NF-κB that remains into the cytoplasm (49, 50). Another role linked to the nucleocapsid of ANDV is the inhibition of STAT1 phosphorylation, nuclear translocation and IFNβ-induced ISRE activity. However, the ANDV N protein alone is not sufficient but rather functions in synergy with the glycoprotein precursor (GPC) to inhibit significantly these different steps of IFN signaling (36).

5.3. NSs proteins

The S segment of some hantaviruses possesses an additional open reading frame (ORF) coding for a non-structural protein NSs and overlapping the N ORF. This is a coding strategy resembling to the one observed for the orthobunyaviruses. Such an ORF is found in the S segments of hantaviruses transmitted by Arvicolinae and Sigmodontinae rodents (voles and lemmings of the north hemisphere and New world mice and rats) whereas it is absent for hantaviruses associated with Old World mice and rats (51). Recent studies have demonstrated that the NSs of TULV could accumulate in perinuclear area and was necessary for the viral survival in IFN-competent cells but not in IFN-deficient cells (52, 53). Moreover, the NSs protein of TULV and PUUV expressed via recombinant plasmids inhibited the induction of IFNβ and the activation of IRF-3 and NF-κB responsive promoters but to a weaker extent compared to the NSs protein from BUNV or RVFV (54). The host protein synthesis is not importantly impaired in TULV and PUUV-infected cells arguing for a weak effect of the NSs protein on cellular transcription. Contrary to the other bunyaviruses, hantaviruses have developed a different strategy to avoid more gently the IFN response. Indeed the hantaviruses are the only bunyaviruses causing an asymptomatic persistent infection in their rodent hosts (55). Such viruses encode several proteins antagonizing multiple cellular targets collectively inhibiting different steps of the antiviral response.

6. NAIROVIRUSES: CRIMEA-CONGO HEMORRHAGIC FEVER VIRUS

The *Nairovirus* genus includes 34 viruses grouped into seven different serotypes. All of the members are transmitted by argasid or ixodid ticks, but only three have been implicated as causes of human disease: the Dugbe (DUGV) and Nairobi sheep disease (NSD) and Crimean Congo hemorrhagic fever (CCHF) viruses, which is the most important human pathogen amongst them. CCHF is the causative agent of severe hemorrhagic fever in human transmitted either through bites by infected ticks or by nosocomial contamination (56). The average mortality rate is 30% but can reach 70% in some outbreaks. Mice lacking IFNAR or STAT1 are very sensitive to the CCHF infection, indicating the strong antiviral effect of type I IFNs (57, 58). Moreover, pre-treatment with type I IFNs inhibits CCHF replication, involving the activity of ISGs like MxA, whereas an established CCHF infection is insensitive to subsequent treatment (59, 60). CCHF can counteract the IFN signaling through at least three independent mechanisms involving different viral elements. Firstly, the RIG-I dependent pathway is not activated since CCHFV does not produce significant amounts of the well-known inducers, which include the dsRNA and the 5' triphosphate ssRNA (61). It was proposed that CCHF cleaves the 5' triphosphate group during the replication to evade the recognition by this PRR. Secondly, it was demonstrated that the virus possesses at least one factor of virulence as an IFN antagonist that can delay the activation of IRF-3 (62). However, the factor is not identified yet. The existence of a coding capacity for a NSs-like gene in the S segment has been suggested but the protein remains to be determined. Thirdly, an ovarian tumor (OTU) domain has been identified on the L-RdRp of CCHF, DUGV and NSD (63). Proteins with an OTU domain belong to proteases super family deconjugating a broad spectrum of proteins modified with Ubiquitin (Ub) or ubiquitin-like proteins like IFN-Stimulated Gene product 15 (ISG15). The expression of a mutant L-RdRp defective in OTU protease function did not impair the replication and the transcription of a CCHF minigenome system indicating that the L-OTU activity is not required for these functions of L-RdRp (64). However, a role in the innate immunity escape has been suggested. The L-OTU activity would deconjugate ubiquitin and ISG15 from different cellular targets dysregulating their activities notably related to the antiviral responses (63).

7. PHLEBOVIRUSES: RIFT VALLEY FEVER VIRUS

Rift Valley Fever Virus (RVFV) is a mosquito-borne zoonotic pathogen that has caused large outbreaks in sub-Saharan countries, Yemen, Saudi Arabia, South Africa and Madagascar. RVFV infection is lethal for newborn animals and causes febrile illness and a high rate of abortion in adult ruminants. Humans infected with RVFV usually develop an acute febrile myalgic syndrome. However, in a small proportion of patients, RVFV infection leads to hepatic damage, hemorrhagic fever-like illness, encephalitis and/or retinal vasculitis that result in a lethal illness. The S segment utilizes an ambisense strategy and codes for the nucleoprotein N and the non-structural NSs protein in opposite polarities (65). This later protein is not essential for the viral replication. In addition, while the replication cycle occurs in the cytoplasm as it is the case for all bunyaviruses, NSs is located in the nucleus of infected cells, forming a filamentous structure that is unique among bunyaviruses (66). It was also demonstrated that the virulence was linked to the absence of IFN production due to NSs, which was shown to block transcription of the IFNβ (67, 68).

7.1. The multifunctionality of the RVFV NSs protein

At least, three complementary mechanisms linked to the interaction of NSs with three different cellular partners, enable RVFV to evade the innate antiviral host responses (Figure 4). These mechanisms target the expression of IFN-ß, the activity of cellular transcription and translation.

The specific inhibition of IFNβ mRNA induction by NSs occurs as early as 3-4 h post-infection (p.i.). The molecular mechanism sustaining the transcriptional repressed state of the IFNβ promoter is correlated to the interaction between YY1 (the activator/repressor of IFNβ transcription Ying Yang 1), NSs and SAP30 (Sin3A Associated Protein 30) that is a subunit of Sin3A co-repressor complexes (such as NcoR/SMRT). It has been shown that SAP30 binds both NSs on and YY1 proteins, forming a complex that contains NcoR, HDAC1 and HDAC3, repressing the recruitment of CBP, the acetylation of histone H3 and consequently the transcriptional activation at the IFNβ promoter. To ascertain the role of this interaction, we created through a reverse genetic system, a recombinant ZH548 RVFV (ZH548-NSsΔ210-230) that expresses a mutated NSs protein unable to interact with SAP30. Such recombinant virus cannot inhibit the IFN production and is avirulent in mice (69).

Later during the viral cycle, after 8 h p.i., a second mechanism leads to the inhibition of the cellular RNA synthesis; it involves the interaction between NSs and the TFIIH factor. This complex is one of the basal transcription factors that can be resolved in two sub-complexes: the core that contains XPB, p62, p52, p44, p34 and TTD-A p8 is bridged by the XPD subunit to the CAK (Cdk- Activating Kinase) composed of cdk7, cyclin H, and MAT1 proteins. TFIIH possesses several enzymatic activities during transcription: (1) the XPB participates in promoter opening through a helicase/ATPase activity; (2) cdk7 phosphorylates RNA polymerase II (CTD-ser-5 residue) and numerous transcription factors controlling gene expression (70). The RVFV NSs protein suppresses the synthesis of host RNA by interacting and sequestrating p44 and XPB into the NSs nuclear filament. Through this interaction, NSs competes also with the usual partner of p44, XPD, unabling it to enter into the nucleus. The RVFV NSs protein also promotes the proteolysis of the TFIIH subunit p62 through the proteasome (71). Altogether, the effects of the NSs/p44 and NSs/p62 interactions inhibit the formation of TFIIH. Consequently, its concentration strongly decreases in RVFV infected cells leading to the inhibition of the cellular transcription (72).

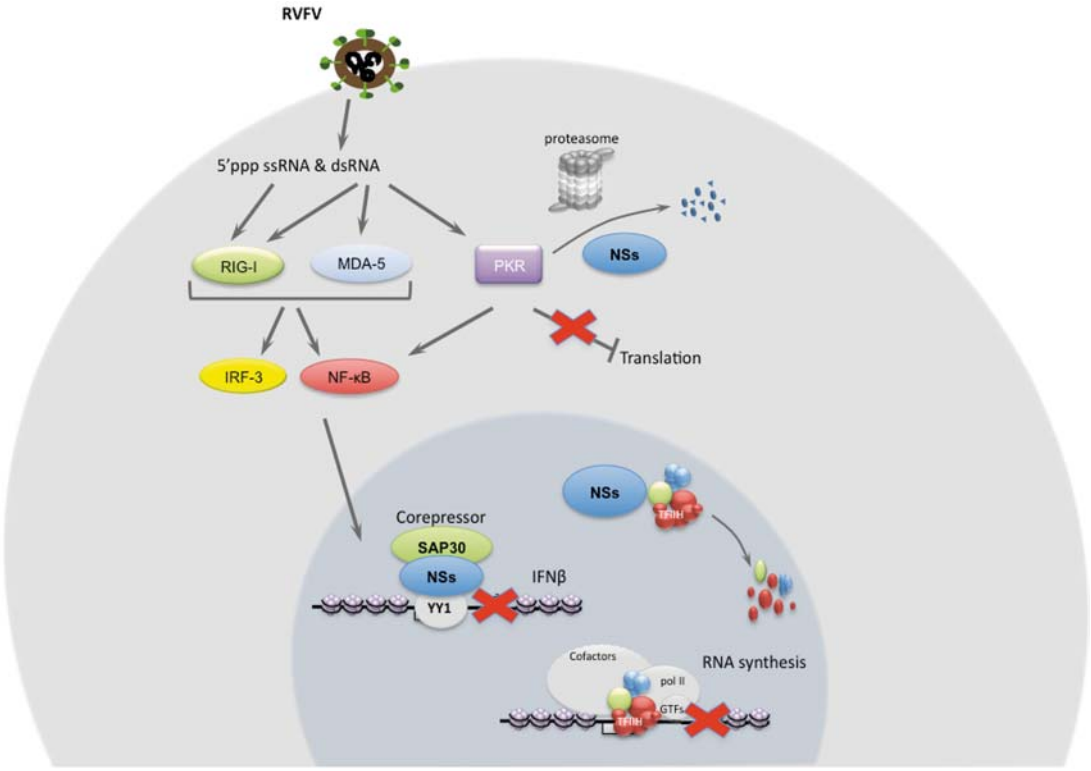

Figure 4. Multifunctional RVFV NSs protein overcomes the host response. The RVFV NSs protein has multiple activities targeting several cellular partners and inhibiting different steps of the type I IFN response. Through an interaction with SAP30, NSs can maintain via YY1 a co-repressor complex containing NcoR and HDACs at the IFNβ promoter although IRF-3 and NF-κB are recruited. Such repressive environment specifically blocks the formation of transcriptional machinery and consequently the induction of IFNβ mRNA. Later in the viral replicative cycle, NSs can also inhibit the global cellular mRNA synthesis through its interaction with TFIIH subunit that disrupts the entire complex (see also Figure 2). The RVFV NSs protein can also induce the proteolysis of PKR blocking the inhibition of viral and host translation linked to the PKR-dependent phosphorylation of eIF2α.

A third function for NSs was recently described preventing the inhibition of host and viral translation (31, 73). RVFV is resistant to the PKR-mediated virus inhibition early in the course of the infection. Such a role is linked to the post-transcriptional down-regulation of PKR degraded through the proteasome and consequently the impairment of the phosphorylation of eIF2α.

In addition, it was shown that the formation of NSs filament strongly disturbs the architecture of nucleus of RVFV-infected cells and affects chromosome cohesion leading to segregation defects in murine and ovine cells. The genomic DNA is largely excluded from the NSs filament. However, specific DNA regions associated with heterochromatin can interact with NSs such as pericentromeric gamma-satellite sequences (74). Such a nuclear reorganization may be involved in the foetal deformities, necrosis of the placenta and abortions observed in infected ruminants. Although it seems likely that NSs proteins of different bunyaviruses have their specific partners (31, 69), the NSs proteins from other phleboviruses like Toscana (TOSV) and Punta Toro (PTV) viruses are also involved in the inhibition of IFNβ-induction (75, 76), strongly indicating that NSs proteins have conserved functions through unique mode of actions.

7.2. Anti-apoptotic role of RFVF NSm proteins

A recent analysis of RVFV infection in cells of the lung epithelium indicated a viral strategy that aims at controlling cellular apoptosis (77). Indeed, a recombinant RVFV lacking the expression of NSm proteins, encoded by the M segment, can induce extensive cell death. The expression of NSm, dispensable for viral replication, suppresses apoptosis triggered through the cleavage of caspase-8 and -9 induced by staurospine (78). However, the control of apoptosis by RVFV seems complex since significant changes in PI3K-AKT, caspase, MAPK and p53 pathways, involved in survival and death of cells, were also observed (77).

8. PERSPECTIVE

Altogether the data on how bunyaviruses evade the cellular response indicate that each virus has developed its own strategy. For orthobunyaviruses and phleboviruses, NSs and to a lesser extend NSm proteins play a crucial role but in the case of hantaviruses, also other proteins such as

the nucleocapsid and the glycoproteins appear to have IFN antagonist functions. For nairoviruses, less is known on the IFN antagonistic activities but the L polymerase may be the virulent factor. Such studies were important for the production of rationally designed attenuated vaccines, which have been developed so far, for RVFV. The naturally avirulent Clone 13 carrying a large deletion in the NSs ORF appears as a good vaccine candidate to protect against virulent RVFV (79). Other viruses obtained by reverse genetics were also produced with the deletion of the complete NSs ORF and /or the preglycoprotein region corresponding to NSm (33, 78, 80). Creation of mutated viruses by reverse genetics has been a valuable tool to decipher the function of the non-structural proteins (21, 23, 69) but the methodology is not yet available for hantaviruses and nairoviruses. Other investigations are needed for the development of antivirals targeting the different steps of the viral cycle, which would be of great value for the treatment of these infections. Up to now, most of the studies focused on the viral functions antagonizing the innate immune response which is an immediate and the first line of defence. However, viruses have evolved other strategies to target cellular functions, which participate to the viral pathogenesis and will deserve to be studied in the near future.

9. ACKNOWLEDGEMENTS

N.L.M. is recipient from the ARC and a young investigator contract from the Institut National de la Sante et de la Recherche Medicale. The financial support from the Agence nationale de la Recherche (ANR-08-MIE-022) is greatly acknowledged**.**

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Abbreviations: CHIKV: Chikungunya Virus, DENV: Dengue Virus, YFV: Yellow Fever Virus, CCHF: Crimea-Congo Hemorrhagic Fever Virus, RVFV: Rift Valley Fever Virus, UUKV: Uukuniemi Virus, L: Large, M: Medium, S: Small, L-RdRP: viral RNA-dependent RNA polymerase, RNPs: ribonucleoparticles, IFN: Interferon, DC: Dendritic Cell, pDC: plasmacytoid Dendritic Cell, PRR: Pattern Recognition Receptors, PAMP: Pathogen-Associated Molecular Patterns, ds: double-stranded, ss: single-stranded, PKR: Protein Kinase R, IRF-3: Interferon Regulatory Factor 3, mRNA: messenger RNA, eIF-2α: eukaryotic Initiation Factor 2 alpha, IFNAR: Type I IFN receptor, JAK: Janus Kinase, STAT: Signal Transducer and Activator of Transcription, ISGF-3: IFN stimulated gene factor 3, ISRE: IFN-stimulated response elements, ISGs: IFN-stimulated genes, ADAR1: adenosine deaminase 1, BUNV: Bunyamwera Virus, LACV: La Crosse Virus, RNAPII: RNA polymerase II, ANDV: Andes Virus, SNV: Sin Nombre Virus, NY-1V: New York Virus 1, HNTV: Hantaan Virus, PUUV: Puumala Virus, SEOV: Seoul Virus, HCPS: Hantavirus Cardiopulmonary Syndrome, HFRS: Hemorrhagic Fever with Renal Syndrome, GPC: Glycoprotein Precursor, RPS19: Ribosomal Protein S19, Ubc9: Ubiquitin-conjugating enzyme 9, SUMO-1: the Small Ubiquitin-like Modifier 1, ORF: Open Reading Frame, OTU: ovarian tumor, ISG15: IFN-stimulated gene product 15, Ub: Ubiquitin, TULV: Tula Virus, PHV: Prospect Hill Virus, DUGV: Dugbe Virus, NSD: Nairobi Sheep Disease, SAP30: Sin3A associated protein, CAK: Cdk-Activating Kinase, TOSV: Toscana Virus, PTV: Punta Toro Virus, YY1: Ying Yang 1.

Key Words: Bunyaviruses, Innate Immunity, Escape, Virulence Factors

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