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Virus-host interactions during tick-borne bunyavirus infection

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The *Bunyavirales* order is the largest grouping of RNA viruses, comprising emerging and re-emerging human, plant and animal pathogens. Bunyaviruses have a global distribution and many members of the order are transmitted by arthropods. They have evolved a plethora of mechanisms to manipulate the regulatory processes of the infected cell to facilitate their own replicative cycle, in hosts of disparate phylogenies. Interest in virus-vector interactions is growing rapidly. However, current understanding of tick-borne bunyavirus cellular interaction is heavily biased to studies conducted in mammalian systems. In this short review, we summarise current understandings of how tick-borne bunyaviruses utilise major cellular pathways (innate immunity, apoptosis and RNAi responses) in mammalian or tick cells to facilitate virus replication.

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Introduction

The taxonomy of bunyaviruses has evolved drastically since 2016, with the promotion of the *Bunyaviridae* family to the *Bunyavirales* order and its subsequent division into 13 viral families by the International Committee on Taxonomy of Viruses (ICTV) [1,2]. Bunyaviruses share a common genetic organisation, with a segmented negative- or ambisense RNA genome composed of a small (S), medium (M) and large (L) genome segment. These segments encode orthologous structural proteins for all known bunyaviruses. The S segment encodes the nucleocapsid protein (N), the M segment encodes the virion glycoproteins (Gn) and (Gc) and the L segment encodes for an RNA-dependent RNA polymerase (RdRp). In addition to these structural proteins, the genome of bunyaviruses can encode non-structural proteins, in a negative- or positive-sense orientation, on the S segment (NSs) and/or the M segments (NSm, Gp160/85 and Gp38) [3]. The genome organisation of the *Phenuivirus* and *Nairovirus* genera is shown in Figure 1.

Infection of invertebrates with most members of the *Bunyavirales* order appears to result in an apathogenic infection. Five of the viral families contain arboviruses capable of causing diseases that affect human and animal health [4,5]. With the exception of Hantaviruses and Arenaviruses, most bunyaviruses are arthropod-borne and are transmitted by vectors, such as mosquitos, ticks, midges, sandflies and thrips [6–9]. These viruses infect disparate mammalian hosts and have a truly global geographical distribution [10–12]. The increased frequency of outbreaks and the spread of competent vectors for bunyaviruses has led to several bunyaviruses being designated as priority pathogens by the World Health Organization and other medical bodies [11].

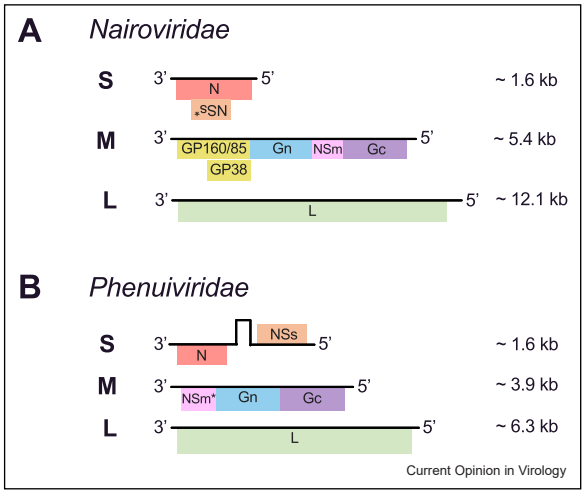
In this review, we will examine how select tick-borne members of the *Bunyavirales* (*Nairoviridae* and *Phenuiviridae*) interact with arthropod vectors or mammalian hosts to facilitate the replication of their genomic material and propagate their onward transmission.

Nairoviridae family

The *Nairoviridae* family is comprised of seven genera, however, it is the *Orthonairovirus* genus that is considered the most impactful and includes tick-borne viruses that are pathogenic to humans and animals. Based on antibody cross-reactivity, seven serogroups are identified within the *Orthonairovirus* genus [8,13].

Nairoviruses differ from phenuiviruses in respect to the coding strategy adopted for the expression of the non-structural proteins. The M segment encodes for non-structural proteolytic products, an NSm protein, as well as Gp160/85 and Gp38 proteins, which are absent from the *Phenuiviridae* genome. The NSs protein of nairoviruses is expressed from the positive-sense S RNA encoded within the N ORF (Figure 1) [8,13–17]. Crimean-Congo haemorrhagic fever virus (CCHFV) is

Figure 1



Organisation of the viral genomes. The coding strategies for both the *Nairoviridae* **(a)** and *Phenuiviridae* **(b)** are depicted. Proteins encoded within the genome are highlighted: structural proteins: N (red), Gn (blue), Gc (purple) and L (green); non-structural proteins: NSm (pink), NSs (orange), GP160/85 or GP38 (yellow). (*) Not present in all viruses within the family. The figure has been adapted from [6,15].

the most widespread tick-borne human disease and an ever-increasing risk for human health [16]. Human infection by the virus causes a haemorrhagic disease that ranges from mild to severe and has a fatality rate of up to 30%. CCHFV has been shown to be maintained in *Hyalomma spp*. tick populations by transstadial or transovarial transmission [15,17–20].

Human infection with another nairoviruses, such as Nairobi sheep disease virus (NSDV) or Dugbe virus (DUGV), has been rarely reported but it is highly pathogenic to livestock [21–24].

Phenuiviridae family

The ICTV created the *Phenuiviridae* family in 2016, and it has been expanded and reorganised multiple times since [1,25–28]. Unlike tick-borne orthonairoviruses, phleboviruses do not encode GP160/85 or GP38 nonstructural proteins within their M segment [6,29•,30]. Phleboviruses utilise an ambisense coding strategy on the S segment to temporally express the N and NSs proteins during infection [4,6,31] (Figure1).

Tick-borne members of the *Phenuiviridae* family that affect human and/or animal health are classified within the *Bandavirus* genus. *Uukuniemi uukuvirus* (genus *Uukuvirus*) was isolated from ticks in 1959 and has been used as a safe Hazard Group (HG) 2 surrogate for the study of highly pathogenic phenuiviruses [32,33]. *Dabie Bandavirus* severe fever with thrombocytopenia syndrome virus (SFTSV), a novel bunyavirus responsible for severe fever with thrombocytopenia syndrome (SFTS), emerged in China in 2009 [34]. It is spread by the bite of *Haemaphysalis longicornis* and *Dermacentor silvarum* tick species and is prevalent throughout East Asia [35–37]. In humans, SFTS is characterised by a febrile illness, thrombocytopenia, and leukocytopenia, with an average case fatality rate of 20%, due to multiple organ failure in the later stages of disease [38]. Heartland virus (HRTV) has been isolated from several life stages of the lone star tick *Amblyomma americanum* [39]. Similar to SFTSV, HRTV causes a febrile illness that can be fatal [40,41]. Guertu virus (GTV) was recently isolated from *D. nuttalli* ticks in China. Closely related to SFTSV and HRTV, serological evidence of GTV human infection has been described, but disease manifestations associated with infection have not yet been observed in man [42].

Mammalian immune responses to bunyavirus infection

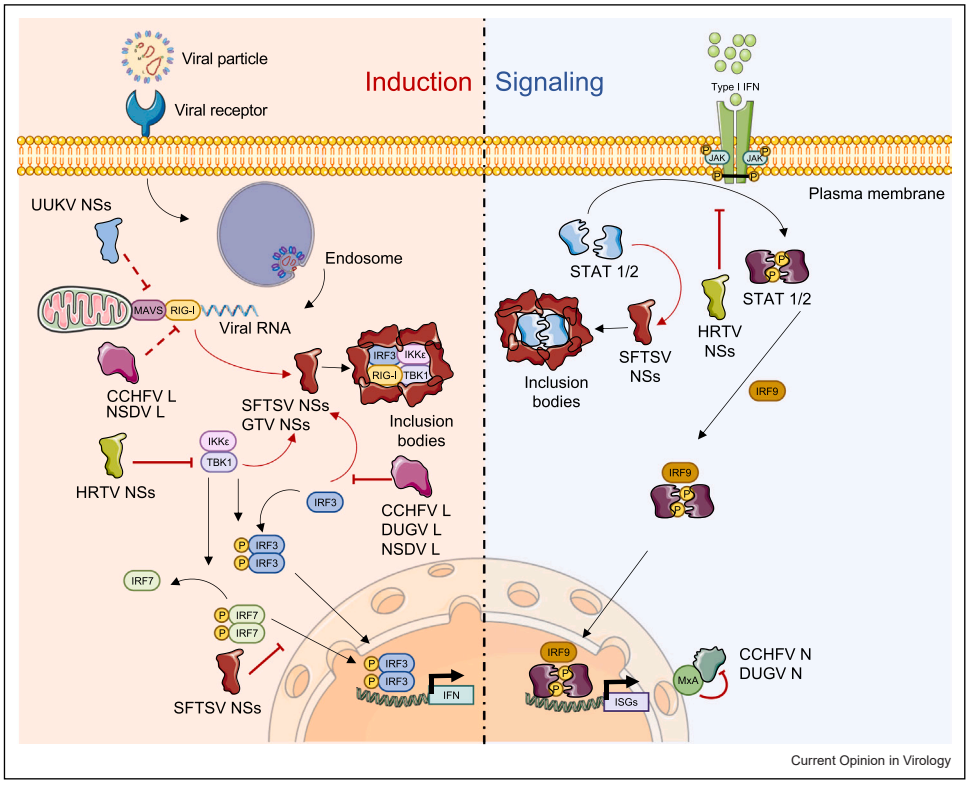
To successfully replicate in their host, it is vital for viruses to interact with and antagonise antiviral pathways to allow for efficient replication and spread. Bunyaviruses are well adept at antagonising the mammalian IFN response and have developed different strategies to manipulate cellular responses, summarised in Figure 2 [43,44]. While an efficient innate immune response is essential for the host control of viral replication, it is often an excessive immune response to infection that is the cause of tissue damage and aberrant pathologies [45].

In *in vitro* studies, CCHFV has been shown to be sensitive to IFNα treatment as early as 6 h post infection [46]. Whereas for SFTSV infection, infected patients with higher IFN-β expression levels had lower viral loads and fatal outcomes were observed less frequently [47]. Immunocompetent adult mice and hamsters have been demonstrated to be refractory to SFTSV or CCHFV infection, whereas newborn or IFN-α/β receptor knockout mice succumb to infection, reinforcing the role of type-I interferon in host defence against SFTSV infection [48•,49].

MxA has been reported to efficiently inhibit CCHFV and DUGV replication through its interaction and sequestration of the viral nucleocapsid protein [50,51]. This MxA-N interaction has also been described for the mosquito-borne La Crosse virus [52,53], which suggests that this antiviral mechanism could be broadly conserved within bunyaviruses.

NF-κB activation is induced by SFTSV infection *in vitro*, observed in infected Hela cell lines, while infection of PBMCs with SFTSV triggered IL-1β maturation and release in a dose-dependent manner [54,55]. Levels of cytokines, such as IL-6 and TNF-α, were significantly

Figure 2



Bunyaviral antagonism of the mammalian innate immune response. Schematic representation of how the N, NSs or L proteins encoded by the tick-borne bunyaviruses CCHFV, NSDV, SFTSV, HRTV or GTV antagonise the interferon induction and/or signalling pathways within infected cells. Interactions (red arrow), inhibitory effects (bar-headed arrow) and suggested interactions (dashed lines) are shown. The figure has been adapted from [44].

higher in the serum of patients experiencing severe disease, while IL-1β expression inversely correlated with the disease severity [47,56].

Evidence for a potential IFN-I suppressive role for CCHFV N protein is scarce in the literature. CCHFV N protein from strain YL04057 (isolated from ticks) was not able to suppress an IFN response induced by Sendai virus infection [57–59]. While similar observations have been described for the non-pathogenic CCHFV strains IbAr10200 and AP92 (isolated from ticks), the Hoti strain (considered pathogenic and isolated from a fatal human case) has been shown to suppress IFN promoter activity [60], suggesting that inhibition of IFN by CCHFV N is strain-specific.

Sensing of viral infection

Viral infections are sensed by pattern-recognition receptors (PRR), such as retinoic acid-inducible gene I (RIG-I), which subsequently induces the activation of the adaptor MAVS. CCHFV has been shown to prevent RIG-I activation by post-transcriptionally cleaving the RIG-I-activating 5′ terminal triphosphate group from the viral genomic RNAs [61]. While such post-transcriptional modification has not been observed for phenuiviruses, they are also able to inhibit RIG-I activation. SFTSV NSs protein interacts with RIG-I and TRIM25 complexes, sequestering them into inclusion bodies consequently inhibiting the activation of IFN-β [62]. SFTSV NSs has also been shown to directly interact with RIG-I, thereby indirectly reducing the activation of the IFN-β promoter. The authors demonstrate it possible to partially recover RIG-I levels through the chemical inhibition of proteasome-dependent processes [63,64]. SFTSV NSs also interacts with LSm14A, a cellular sensor for viral RNA and an activator of interferon-stimulated response elements (ISRE), to antagonise LSm14A binding to RIG-I and leading to the modulation of IFN-β expression [65]. UUKV NSs was shown to induce a weak repression of IFN activation by interacting with MAVS but not RIG-I or by inducing the degradation of RIG-I in a proteasome-mediated manner [64,66] (Figure 2).

Toll-like receptor (TLR) sensing may be involved in the detection of bunyaviruses within cells. SFTSV does not

activate host immune responses in cell lines that are deficient for TLR3 [67]. Moreover, in SFTS patients, there was a positive correlation between TLR3 expression in myeloid dendritic cells or monocytes and disease severity [47].

TBK1, IRF3 and interference within the IFN induction pathway

Downstream of sensing viral infection by PRRs, TBK1 sits at the crossroad of multiple antiviral innate immunity pathways. TBK1 forms a complex with IKKε that mediates the activation of IRF3, IRF7 and NF-κB signalling pathways [68,69].

CCHFV has been demonstrated to antagonise the activation of IRF3 [46]. Inhibition of IFN activation by nairoviruses could be mediated by an ovarian tumour (OTU) domain, belonging to the superfamily of ubiquitin (Ub)-deconjugating proteases. CCHFV, DUGV and NSDV harbour an OTU domain on the RdRp protein, which has not been reported for other bunyaviruses [70]. The OTU domain inhibits two important pathways for innate immunity: ubiquitination, involved in NF-κB activation by TNFα; and ISGylation, in which the Ub-like protein ISG15 induces covalent protein modifications that are important for the antiviral response [71,72]. However, it is unclear if the OTU domain directly interacts with IRF3 and NF-κB or other molecules whose activation and regulation are dependent on ubiquitination [73]. Similarly, the RdRp of NSDV antagonized IFN production through the OTU domain. In this case, the expression of the N protein or the glycoproteins of NSDV had minimal antagonistic effect on the induction of IFNβ promoter [74].

Tick-borne phenuiviruses have developed different mechanisms to interfere with IFN induction. SFTSV and HRTV target IRF3 activation downstream of MAVS through the interaction of NSs with TBK1, blocking its autophosphorylation, which in turn inhibits IRF3 phosphorylation and subsequent IFN-β production [66,75,76]. Both SFTSV and HRTV NSs proteins block the phosphorylation of TBK1 at Ser172, the mechanism by which this occurs remains to be elucidated [66]. Interestingly, while both SFTSV NSs and HRTV NSs proteins interact with TBK1, SFTSV NSs sequestrates TBK1 into inclusion bodies, while HRTV NSs retains a diffuse cytoplasmic distribution when colocalised with TBK1 [66]. GTV induced similar inclusion bodies to SFTSV NSs, but also induced the formation of extended cytoplasmic filamentous structures [77••]. This interaction led to the sequestration of not only TBK1 but also other interacting proteins of the IKK complex into NSs-mediated cytoplasmic inclusion bodies [78,79]. Reported observations about whether GTV NSs subsequently attenuates NF-κB promoter activation seem contradictory or cell-type specific [76,80]. The specific interaction between SFTSV NSs and TBK1, leading to its sequestration into inclusion bodies, was shown to be dependent on two amino acid residues at position 21 and 23 within the N-terminus of the NSs protein [75].

Interactions with the IFN signalling pathway

Interference with the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is a common feature in pathogenic tick-borne phenuiviruses. NSs of SFTSV and HRTV, but not UUKV, have been shown to inhibit type-I and -III IFN signalling by preventing the phosphorylation of STAT2. Both NSs proteins cause the re-localisation of STAT1 and STAT2 complexes, either into viral inclusion bodies (SFTSV) or holding the proteins in the cytoplasm (HRTV), thereby blocking their nuclear translocation [66,81,82]. SFTSV NSs can also inhibit the full activation of STAT1 by decreasing its phosphorylation on two important residues: S727 and, in a cell-dependent manner, Y701 [67,80,82–84]. Finally, SFTSV NSs interferes with signalling downstream JAK/STAT by preventing the relocalisation and recruitment of STAT1/2 to the ISRE promoters of interferon-stimulated genes (ISG), such as IFI6 and ADAR1 [80].

NSDV was shown to inhibit the cellular IFN signalling pathway by blocking STAT1/2 phosphorylation. However, no role for the OTU domain has been demonstrated, as ISGylation and ubiquitination does not appear to be required for STAT1 phosphorylation [74]. Whereas, other viral proteins such as SFTSV N, NSDV N or NSDV Gc did not have any influence on the nuclear translocation or phosphorylation of STAT1/2 complexes [74,82].

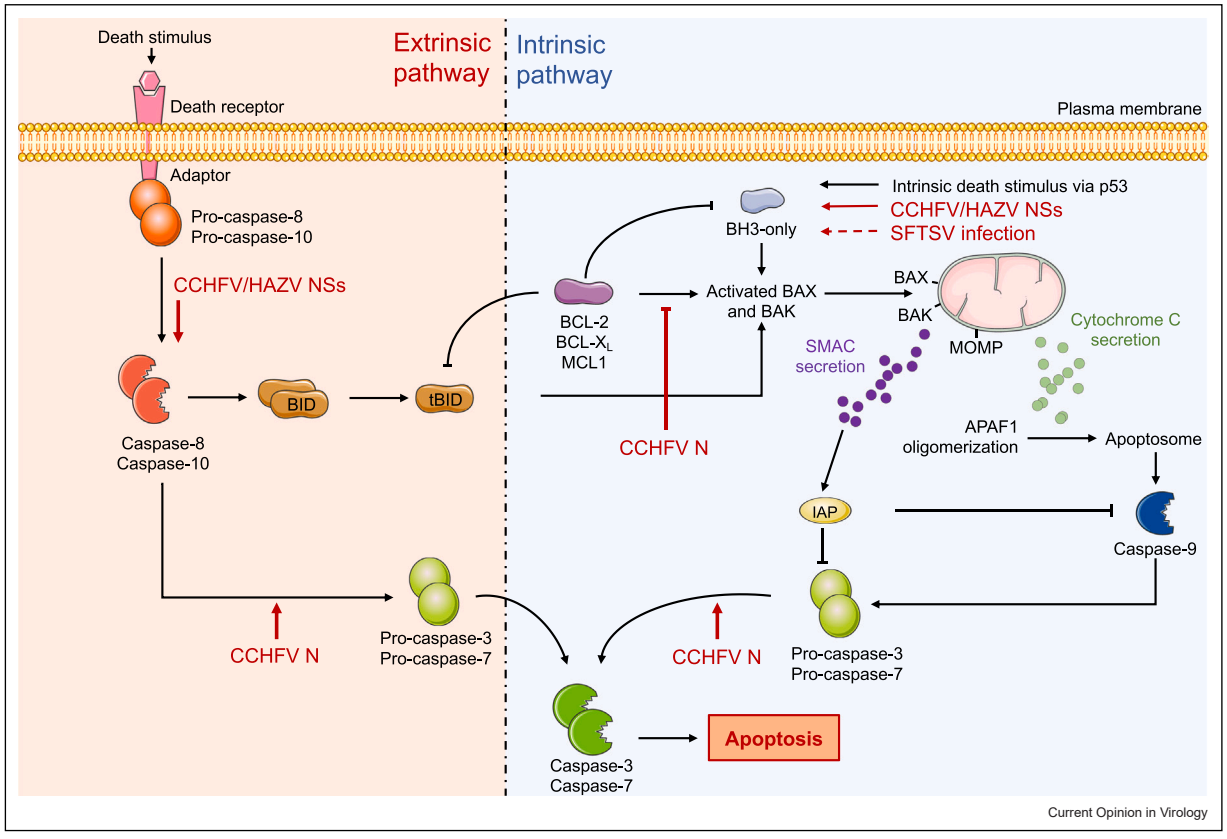
Apoptosis

Viruses have evolved to regulate apoptosis induction or suppression to benefit their dissemination or persistence, respectively. The apoptotic process is divided into two interlinked parts, the extrinsic or intrinsic pathways, mediated by the sequential activation of caspase proteins. Pathways converge with the activation of executioner caspases, leading to cell death [85]. Viral protein interaction with the apoptotic pathways is described in Figure 3.

CCHFV and Hazara virus (HAZV) induce apoptosis through caspase-3 cleavage in multiple cell types derived from mammalian hosts [14,86,87], and activation of intrinsic and extrinsic apoptosis pathways has been observed in adult patients with CCHF disease [88].

In early stages of infection, suppression of apoptosis by CCHFV was mediated by the N protein that inhibited the induction of the intrinsic pathway [87,89]. CCHFV

Figure 3



Bunyaviral antagonism of the apoptotic cascade. Schematic model recapitulating tick-borne bunyavirus manipulation of apoptosis during infection. CCHFV, HAZV and SFTSV interactions are depicted. Interactions (red arrow), inhibitory effects (bar-headed arrow) and suggested interactions (dashed lines) are shown.
The figure has been adapted from [106].

and HAZV N proteins contain a caspase-3-specific proteolytic cleavage site and N-protein cleavage was observed at the time of infection-induced caspase-3 activation [86,87]. This suggests that N protein of nairoviruses may act as a decoy substrate for caspases, aiming to delay host cell apoptosis [87,90] (Figure 3).

In the latter stages of nairovirus infection, the induction of apoptosis was shown to be mediated by the NSs protein. Overexpression of CCHFV or HAZV NSs proteins induced apoptosis via both intrinsic and extrinsic pathways, in a caspase-3/7-dependent manner [14]. In CCHFV NSs, the C-terminal Leu-127 or Leu-135 were identified as key residues for mitochondrial membrane potential disruption and the induction of apoptosis [14]. DUGV, a mildly pathogenic *Nairovirus*, did not induce either cytopathic effect (CPE) or apoptosis in a Huh7 hepatocyte cell line [91]. The late expression of CCHFV NSs [14] is consistent with a role in late apoptosis induction, and suggests a minimal role in interferon antagonism, unlike that seen with other members of the *Phenuiviridae* family.

In contrast to the defined role apoptosis plays in CCHFV infection, comparatively little is known about the induction or mechanisms of apoptosis in SFTSV-infected cell cultures. SFTSV induces apoptosis through the intrinsic and extrinsic pathways in liver cells and in endothelial cells [92,93•]. This subsequently triggers NLRP3 and activates the inflammasome pathway. SFTSV infection also induced IL-1β and IL-18 secretion, which led to catalytic processing of GSDMD and pyroptosis [55,94,95].

These reports contrast with experimental evidence showing the absence or weak induction of apoptosis by SFTSV [55,76,96]. This questions whether apoptosis induction is linked to the proinflammatory response rather than intrinsic viral signalling [55,93]. There are no reports of apoptosis in HRTV infection, but apoptotic

debris has been observed in haematoxylin and eosin staining of livers of HRTV-infected AG129 mice [97].

Tick-virus interactions

In ticks, the humoral immunity revolves around three signalling pathways: Toll, immune deficiency and JAK/STAT, and their activation leads to the expression of antimicrobial peptides [98,99]. However, RNAi is considered the most important antiviral defence mechanism against viruses in arthropods [98,100]. SFTSV infection induced the production of virus-derived siRNAs in *H. longicornis* ticks, which were predominantly 22-nucleotides long [101••]. SFTSV NSs was suggested to be a viral suppressor of the induced RNAi response [101••]. Furthermore, for nairoviruses, HAZV-derived viral DNAs have been detected in infected HAE/CTVM8 tick cell cultures, and described as suppressors of viral replication and promoters of viral persistence and survival of infected tick cells [102••].

Tick-borne bunyaviruses have been described to persistently infect tick cell lines. UUKV and HAZV persisted in tick cell lines derived from their natural vectors, *Ixodes ricinus* (IRE/CTVM19 and IRE/CTVM20) and *Hyalomma anatolicum* (HAE/CTVM8 and HAE/CTVM9), respectively [32,102••]. The cellular viability of the infected tick cell lines was not affected and no CPE was observed after extended periods of infection [102••,103]. Interestingly, unlike mammalian hosts, neither cleavage of N protein nor apoptosis were observed in HAE/CTVM9 tick cell lines infected with HAZV [86•], which suggests that the lack of apoptosis induction may be a key mechanism for the ability of nairoviruses to persistently infect their arthropod vectors [104].

Infection of tick hosts is not without consequence to the virus, and changes have been observed both structurally (in glycosylation patterns, electrophoretic mobility and global structural organisation of the glycoproteins), and genetically (nonsynonymous mutations, greater intra-host diversity) compared with mammalian-derived counterparts [32,105].

The mechanism of responses to bunyavirus infection in ticks remains understudied, and thorough studies are required to better understand these bunyavirus-induced antiviral responses. These works and information are important to assess the nature and consequence of viral infection for ticks and how this impacts the infectivity, transmission and the life cycle of bunyaviruses.

CRediT authorship contribution statement

M.F.: Conceptualisation, Formal analysis, Visualisation, Writing – original draft, Writing – review & editing; **B.B.:** Formal analysis, Project administration, Supervision, Validation, Visualisation, Writing – original draft, Writing – review & editing.

Conflict of interest statement

The authors declare no conflict of interest for this paper or work.

Data availability

No data were used for the research described in the article.

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- • of special interest
- •• of outstanding interest.

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