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Orthobunyaviruses and innate immunity induction: alieNSs vs. PredatoRRs☆

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ABSTRACT

The taxonomic group of Orthobunyaviruses is gaining increased attention, as several emerging members are causing devastating illnesses among humans and livestock. These viruses are transmitted to mammals by arthropods (mostly mosquitoes) during the blood meal. The nature of their genomic RNA predisposes orthobunyaviruses for eliciting a strong innate immune response mediated by pathogen recognition receptors (PRRs), especially the cytoplasmic RIG-I. However, the PRR responses are in fact disabled by the viral non-structural protein NSs. NSs imposes a strong block of cellular gene expression by inhibiting elongating RNA polymerase II. In this review, we will give an overview on the current state of knowledge regarding the interactions between orthobunyaviruses, the PRR axis, and NSs.

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1. Orthobunyaviruses

Newly emerged and well-established members of orthobunyaviruses are responsible for diseases that range from febrile illnesses, polyarthritis, encephalitis, or even hemorrhagic fever among humans, to abortion, stillbirths and teratogenic effects in livestock (Elliott, 2014; Elliott and Weber, 2009; Soldan and Gonzalez-Scarano, 2005). In humans, Oropouche virus (OROV) has caused more than 30 recorded epidemics of debilitating fever in Latin America (mostly Brazil), involving an estimated 500,000 cases (Vasconcelos et al., 2011). Members of the Mapputta orthobunyavirus group are associated with an acute epidemic polyarthritis-like illness in Australia and Papua-New Guinea (Gauci et al., 2015). La Crosse virus (LACV) causes the most common arboviral infection of North American children under 15 years of age, with about 100 reported cases per year that require hospitalizations or even intensive care (McJunkin et al., 2001). Residual epilepsy and long-lasting neurological deficits can occur (Utz et al., 2003). Since the majority of human LACV infections are considered to have a subclinical course, it is estimated that more than 300,000 infections occur annually (Calisher, 1994; Haddow and Odoi, 2009). A novel orthobunyavirus, Ngari virus, was recently identified as a cause of hemorrhagic fever in East Africa (Briese et al., 2006; Gerrard et al., 2004; Groseth et al., 2012). An important novel orthobunyavirus of animals is Schmallenberg virus (SBV), which has emerged 2011 in Europe and caused stillbirths, abortions, and congenital malformations in thousands of ruminants (Beer et al., 2013; Conraths et al., 2013; Pawaiya and Gupta, 2013). The related Akabane virus, that is prevalent in tropical and subtropical areas of the old world and Australia, exhibits a similar host tropism and pathogenesis (Hubalek et al., 2014).

Taxonomically, the genus orthobunyavirus is one of the five genera that constitute the family *Bunyaviridae* (Elliott, 2014). The prototype of both the whole virus family (containing more than 350 named viruses) and the genus orthobunyavirus (containing more than 170 named viruses) is Bunyamwera virus (BUNV), which was first isolated in 1943 from *Aedes* mosquitoes in Uganda (reviewed in Elliott, 2014). The other bunyavirus genera include pathogens like Hantaviruses, Crimean-Congo hemorrhagic fever virus, Rift Valley fever virus, or Tomato spotted wilt virus, that are responsible for substantial medical, veterinary, and agricultural damages.

Orthobunyaviruses are enveloped particles of approximately 100 nm in diameter. They are pleomorphic in shape but contain locally ordered patches of glycoprotein spikes (Bowden et al., 2013). The particles contain a genome of negative-sense RNA that is divided into three segments, named L, M, and S, according to their relative size (Fig. 1A). The L segment encodes the RNA-dependent RNA polymerase (RdRP, also called L protein), the M segment

☆ This article is dedicated to the memory of Richard M. Elliott, the great bunyavirologist.

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encodes the viral envelope proteins (Gn and Gc), and the S segment encodes the nucleocapsid protein (N). These structural proteins constitute the viral particles, with Gn and Gc inserted in the lipid envelope that enwraps the viral nucleocapsids (also called RNPs, for ribonucleoprotein particles). Nucleocapsids consist of one of the genomic RNA segments and are encapsidated by N and associated with L (Fig. 1B). Each N protein binds 11 nucleotides of the genome, forming a compact, flexible, and partially helical nucleocapsid structure with a diameter of 10 nm (Ariza et al., 2013; Dong et al., 2013; Li et al., 2013; Niu et al., 2013; Reguera et al., 2013). Importantly, the RNA segments contain untranslated regions (UTRs) at their 3′ and 5′ ends that are partially complementary to each other. The ensuing RNA structure (the "panhandle") acts as promoter for viral transcription and replication, and results in pseudo-circularization of the nucleocapsids (Elliott, 2014; Obijeski et al., 1976; Walter and Barr, 2011; Weber et al., 2013; Weber and Weber, 2014b) (see Fig. 1A and B).

Orthobunyaviruses also express two non-structural proteins, NSm (encoded by the M segment as part of a larger polyprotein), and NSs (translated from a +1 shifted reading frame within the 5′ part of the N mRNA) (see Fig. 1A). Both NSm and NSs are mostly dispensable for virus replication (Bridgen et al., 2001; Kraatz et al., 2015; Pollitt et al., 2006; Shi et al., 2006). While NSm seems to be involved in virus assembly and budding, NSs plays an important role as a virulence factor countering host defences (see below) (Eifan et al., 2013; Elliott, 2014).

Orthobunyavirus particles attach to cells of mammals and insects via unknown receptors, though mammalian DC-SIGN can be used as an attachment factor (Lozach et al., 2011). Mammalian cells are entered through the early endosome in a Rab5-, dynamin- and clathrin-dependent manner, requiring a drop in pH and serine protease activity (Hofmann et al., 2013; Hollidge et al., 2012).

The first event after entering the cytoplasm is primary transcription, defined as mRNA synthesis by the L polymerase brought along by the incoming nucleocapsids. Initiation of transcription requires short 12–18 nt long capped RNA primers hat were cleaved off host cell mRNAs (Patterson et al., 1984). The endonuclease domain responsible for this so-called cap-snatching is located on the N terminus of the L polymerase (Klemm et al., 2013; Reguera et al., 2010). Curiously, in mammalian cells orthobunyavirus transcription depends on translation (Abraham and Pattnaik, 1983; Raju et al., 1989). The current model posits that secondary structures build up on the nascent mRNA strand which act as transcription stop signals if they are not ironed out by translocating ribosomes (Barr, 2007; Bellocq and Kolakofsky, 1987). In mosquito cells, however, orthobunyavirus transcription is not dependent on translation (Raju et al., 1989), suggesting the existence of insect-specific factors that prohibit formation of the inhibitory RNA structures. Orthobunyavirus mRNAs are also peculiar in lacking a poly(A) tail. To compensate for the absence of this important translation-promoting sequence element, orthobunyavirus mRNAs (shown for the S segment) contain a specific stem-loop structure in their 3′ UTR (Blakqori et al., 2009). Moreover, Bunyamwera N protein interacts with the cellular poly(A)- binding protein (PABP) in the cytoplasm, and PABP is retained in the nucleus later in infection. Apparently, the cytoplasmic N protein, aided perhaps by the nuclear NSs (as shown for the phlebovirus Rift Valley fever virus (Copeland et al., 2013)), is responsible for locking up the shuttling protein PABP in the nucleus (Blakqori et al., 2009). The removal of PABP tips the balance towards translation of viral mRNAs over polyadenylated host cell mRNAs.

Despite having an influence on nuclear events (see also below), the replication cycle of orthobunyaviruses is confined to the cytoplasm and most likely takes place in virus "factories", protected by tubular structures with a small opening (Fontana et al., 2008). The viral genome is faithfully multiplied and encapsidated by newly synthesized L and N proteins. The progeny nucleocapsids then assemble with newly synthesized glycoproteins on Golgi

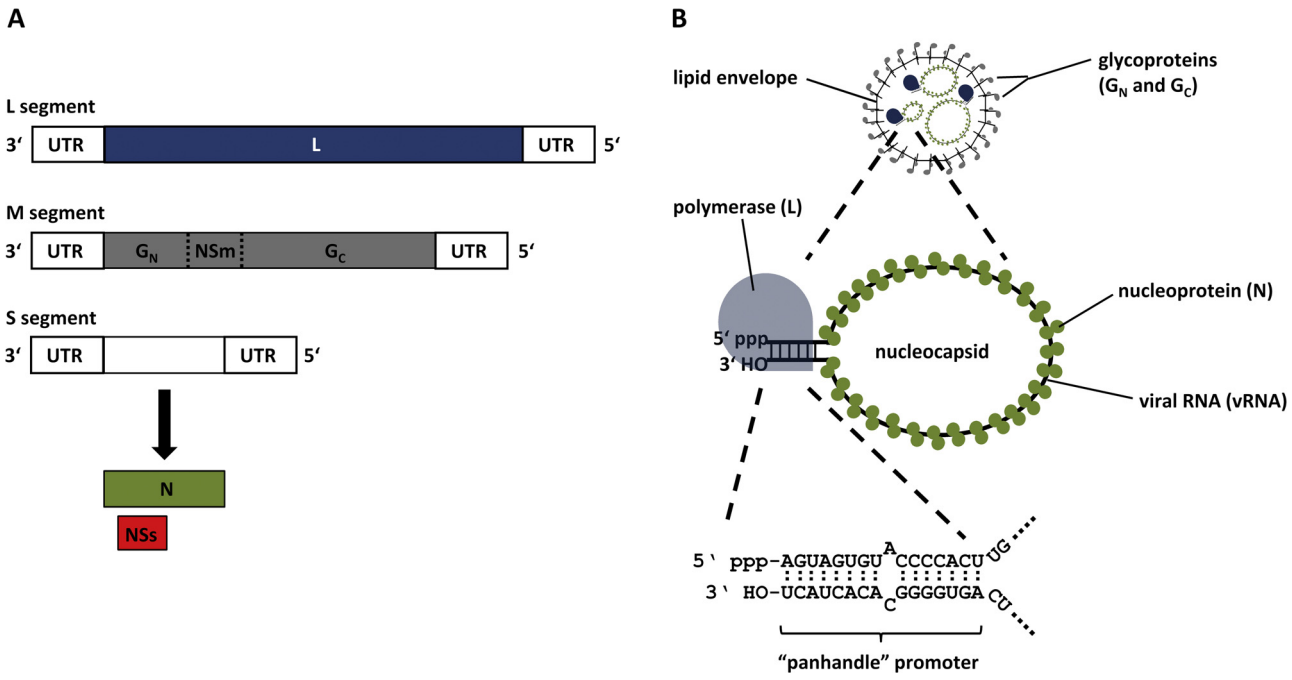

Fig. 1. Orthobunyavirus genomic organization and virion structure. (A) Coding strategies of the three orthobunyaviral single-stranded negative-sense RNA segments. The L segment encodes the RNA-dependent RNA-polymerase (L). A polyprotein is encoded by the M segment that is cleaved into the two glycoproteins (Gn and Gc) and a non-structural protein (NSm). The S segment encodes the nucleoprotein (N) and the non-structural protein NSs in overlapping reading frames. (B) Orthobunyavirus nucleocapsids and the panhandle. The two surface glycoproteins are embedded in the viral envelope as spike-forming heterodimers (Bowden et al., 2013). Three nucleocapsids are inside the enveloped orthobunyavirus particles. The nucleocapsids are pseudo-circularized due to base-pairing of their 5′ triphosphate dsRNA panhandle. The nucleotide sequence of the La Crosse virus S segment panhandle is depicted.

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