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Review

Orthobunyavirus entry: receptors, endocytosis, and fusion cues

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Orthobunyaviruses (OBVs) are medically and veterinary important arboviruses with simple genomes yet complex entry mechanisms enabling infection of diverse mammalian hosts. Understanding of the molecular and cellular processes mediating OBV attachment, internalization, endosomal trafficking, and membrane fusion has advanced recently. Here, we review how OBVs engage host receptors, notably the low-density lipoprotein receptor-related protein 1 (Lrp1), utilize clathrin-mediated endocytosis, and respond to endosomal acidification and potassium ion accumulation to trigger fusion via their class II Gc glycoprotein. Live-cell imaging has elucidated single-particle entry dynamics, revealing the interplay of viral and host factors in timing and efficiency of genome release. These findings refine the model of OBV entry, highlighting coordinated physicochemical cues and receptor usage that influence tropism and pathogenesis. Improved mechanistic insights offer potential avenues for broad-spectrum antiviral development and enhance understanding of OBV epidemiology, exemplified by Oropouche virus emergence in South America.

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Introduction

Orthobunyaviruses (OBVs, genus *Orthobunyavirus*, family *Peribunyaviridae*, class *Bunyaviricetes*) encompass a large and genetically diverse group of segmented negative-strand RNA viruses [1] transmitted mainly by mosquitoes and biting midges, and more rarely by ticks and other arthropods [2]. Several members are established human or veterinary pathogens. La Crosse virus (LACV) is a leading cause of pediatric arboviral encephalitis in the United States [3], while Schmallenberg virus (SBV) emerged in Europe in 2011 as a major teratogenic agent in ruminants [4]. Oropouche virus (OROV) has become a major cause of arboviral fever in South America and now drives large urban outbreaks, with occasional exported cases [5]. Newly detected zoonotic OBVs, such as Cristoli and Umbre viruses in Europe [6,7], further illustrate the expanding ecological and geographical range of these viruses.

Their capacity to emerge is reinforced by their intrinsic ability to reassort. Ngari virus, a natural reassortant with the M segment of Bunyamwera virus (BUNV) and the S/L segments of Batai virus, caused severe hemorrhagic fever outbreaks in East Africa with case fatality rates reminiscent of Rift Valley fever [8]. This example shows how genetic exchange can rapidly generate more virulent or epidemiologically fit variants. The close relationship between OROV and SBV, one primarily affecting humans and the other livestock, provides a comparative framework to examine how small genomic differences shape distinct epidemiological outcomes.

Despite this diversity, OBVs share the property of replicating their genome and expressing genes in the cytosol [9], while productive infection also depends on endocytic entry and fusion within acidified intracellular compartments [10]. Thus, early virion–host cell interactions, including attachment, receptor engagement, clathrin-mediated internalization, endosomal trafficking, and fusion-triggered uncoating, critically shape tropism, neuroinvasion, and disease outcome.

Recent advances have substantially enriched this picture. The identification of low-density lipoprotein receptor-related protein 1 (Lrp1) as an essential entry receptor for OROV represents the first genetically and functionally validated OBV receptor [11], and LACV and Jamestown Canyon virus (JCV) have since been added to the list of OBVs relying on Lrp1 for efficient entry [12,34]. High-resolution structural analyses have refined our view of the Gn/Gc spike, revealing how a conserved class II fusion core is paired with a highly variable Gc

head domain that shapes antigenicity and neutralization sensitivity [13]. Work on OBVs has also highlighted the importance of endosomal ionic remodeling, particularly potassium (K+) accumulation in late endosomes (LEs), as a second checkpoint beyond low pH that promotes fusion and uncoating [14]. Finally, advances in live-cell imaging and single-particle tracking now allow individual OBV particles to be followed as they enter, traffic, and fuse within mammalian cells, providing a dynamic and quantitative framework for dissecting the entry process [15].

In the following sections, we summarize how these structural, cellular, and biophysical insights have reshaped the OBV entry field. We focus on virion architecture, receptors and attachment factors, endocytic uptake, intracellular trafficking, and the physicochemical cues that drive fusion and uncoating. We also highlight outstanding questions likely to guide future work.

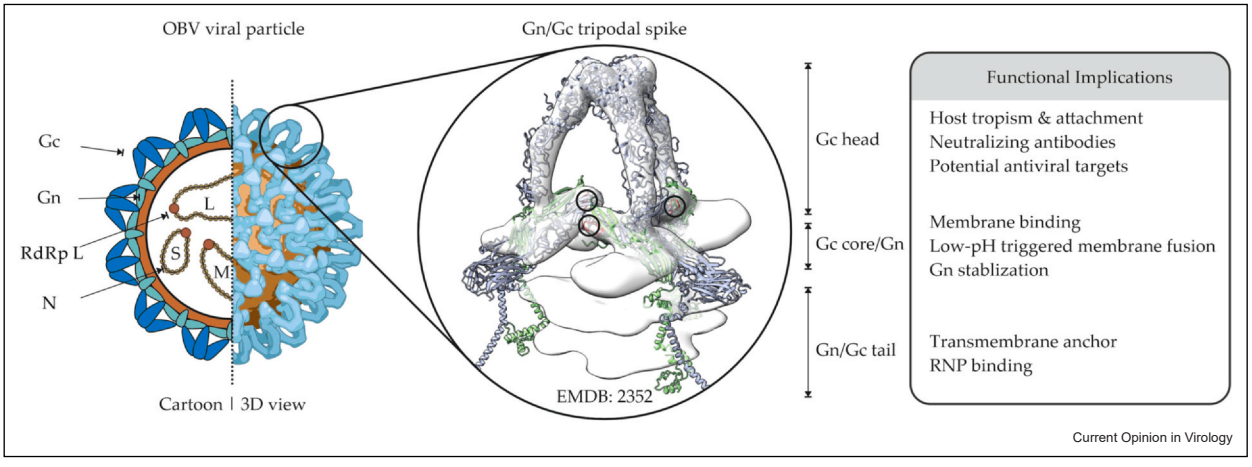
Virions and spike structure

OBV particles are enveloped virions with an average diameter of 90–110 nm [16]. The three genomic RNA segments of OBVs each associate with nucleoprotein N and the polymerase L to form ribonucleoprotein (RNP) complexes [9] (Figure 1). While nothing is currently known about the number and orientation of RNA segments in OBV particles, bunyaviruses outside this genus can contain variable numbers of each segment, sometimes including both negative- and positive-sense copies [17,18]. Unlike many enveloped viruses, OBVs lack a canonical matrix protein linking the envelope to the RNPs, which likely results in a more flexible and less structurally defined interior.

The viral envelope displays the two transmembrane glycoproteins Gn and Gc, produced as an M-segment polyprotein and processed in the endoplasmic reticulum and Golgi apparatus [19]. Cryo-electron tomography of BUNV shows that Gn and Gc ectodomains assemble into a characteristic tripodal spike extending ~18–20 nm from the membrane (Figure 1). Each spike comprises three Gn/Gc heterodimers arranged around a central axis [20]. Although this tripodal architecture is conserved across multiple OBVs, including LACV, SBV, and BUNV, spike density, spacing, and orientation vary across virions, contributing to their variable shapes and sizes (pleomorphic appearance) in electron microscopy [13].

Functionally, the tripodal spike serves as an integrated platform for receptor engagement, immune recognition, and membrane fusion [21]. Structural studies established that Gc is a class II fusion protein with a conserved fusion core and a highly variable N-terminal region [20]. The conserved core contains the fusion loops and undergoes low-pH-triggered refolding to drive membrane merger [22]. Mutations in the *ij* loop, a discrete subregion of the fusion loop (Figure 1), disrupt this refolding step, markedly reducing viral replication and infectivity and underscoring the essential contribution of this element to fusion competence and overall viral fitness [23]. The N-terminal 'head' dominates the exposed spike surface and constitutes the main target of

Figure 1



Modular architecture of orthobunyavirus (OBV) particles and the Gn/Gc spike. OBV virions contain three ribonucleoprotein complexes (L, M, and S segments), and their surface is decorated with heteromultimeric Gn/Gc spikes arranged in a characteristic tripodal organization. Structural analyses show that Gc adopts the fold of a class II fusion protein, comprising a conserved C-terminal fusion core and a highly variable N-terminal head that forms most of the exposed spike and serves as the dominant target of neutralizing antibodies. Gn likely acts as a chaperone that stabilizes and escorts Gc. Three BUNV Gn/Gc heterodimer models were fitted into the BUNV cryo-EM density map (EMDB: 2352). Gn and Gc are highlighted in light green and light blue, respectively. The ij loop within the Gc fusion loop is indicated by black circles. *Abbreviation*: RdRp L, RNA-dependent RNA polymerase L; RNP, ribonucleoprotein.

neutralizing antibodies; its pronounced variability across OBVs suggests adaptation to immune pressure while preserving essential fusion functions (Figure 1). Recent analyses further implicate the Gc head in neurovirulence and host cell entry, raising the possibility that it functions as a key attachment interface and a potential site for therapeutic intervention [24]. In contrast, Gn remains less well characterized, but by analogy with other bunyaviruses, it is thought to chaperone and stabilize Gc during folding and transport [10].

Together, Gn and Gc form a multifunctional module coordinating attachment, antigenicity, and fusion. Increasing evidence indicates that OBV Gc plays a more central and multifaceted role in entry than fusion proteins of other bunyaviruses, underscoring its expanded contribution within the tripodal spike [25].

Receptors and attachment factors

In mammals, OBVs are introduced into the skin during the blood meal of infected arthropods [26]. Virions first encounter extracellular matrix components and a heterogeneous population of dermal dendritic cells (DCs), macrophages, endothelial cells, and fibroblasts. Initial contact often involves low-affinity interactions with ubiquitous heparan sulfate proteoglycans (HSPG), which enhance infection by SBV and Akabane virus (AKAV) [27,28] (Figure 2). These glycans act as attachment factors that increase local virion concentration at the plasma membrane but are not strictly required for entry.

Several C-type lectins expressed by DCs and macrophages, including DC-SIGN, L-SIGN, Mincle, Dectin-1, and Dectin-2, can bind OBVs or pseudotyped particles displaying their glycoproteins [29–31] (Figure 2). These lectins recognize high-mannose glycans typical of mosquito-derived virions and strongly enhance infection of DC-like cells, but OBVs efficiently infect many lectin-negative cell types, indicating that they act mainly as attachment factors or entry enhancers rather than universal receptors [32,33].

A major conceptual advance is the identification of Lrp1 as a *bona fide* entry receptor for OROV [11] and subsequently for other OBVs [12,34] (Figure 2). CRISPR-Cas9 knockout, receptor blocking, and gain-of-function assays showed that Lrp1 is necessary for efficient OROV internalization in multiple mammalian cell lines. Lrp1 is a large endocytic receptor widely expressed in the central nervous system, liver, and vascular endothelium. Its implication in the entry of other bunyaviruses, such as Rift Valley fever virus [35], suggested a receptor hub potentially shared across genera. Lipid transfer receptors, including Lrp1 and other members of the LDL-R family, have also been shown in recent years to mediate entry of diverse viruses from multiple families and orders [36,37], highlighting their role as conserved viral entry hubs. Whether other OBVs also use Lrp1, how it cooperates with HSPG and lectins, and whether alternative receptors operate in specific tissues or species remain open questions.

Additional genetic and *in vivo* work is also needed, and several studies have reported the isolation of fully infectious OBV variants lacking the head or stalk of the glycoprotein spikes, which can influence cell entry, transmission, and escape from neutralizing antibodies [38]. Nonetheless, current evidence supports a modular receptor system combining ubiquitous hubs with context-dependent attachment factors to generate broad yet tunable tropism.

Recent work expanded this view by identifying an unexpected mode of attachment. Phenuiviruses can incorporate the host-derived glycolipid glucosylceramide (GlcCer) into their envelope and use it as a determinant of cell binding [39]. In Uukuniemi virus (UUKV), the glucose headgroup of GlcCer is required for attachment, implying engagement of a yet-unidentified carbohydrate-specific receptor. Competition with soluble GlcCer similarly reduced Germiston virus (GERV) attachment, suggesting that some OBVs may exploit a related glycolipid-dependent interaction [39]. This broadens the range of bunyavirus attachment strategies and highlights lipid-lectin interactions as an emerging area of interest.

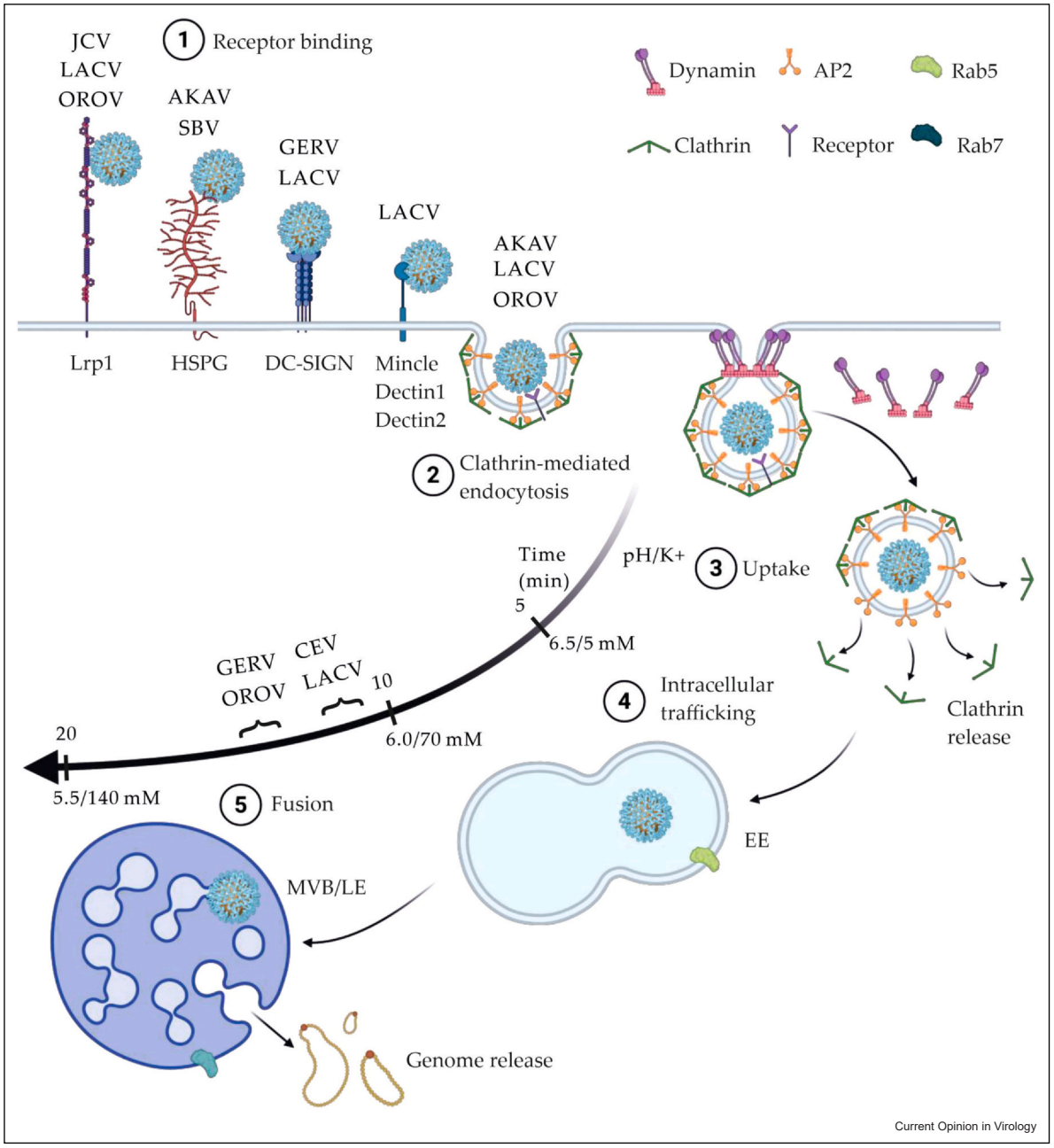
Endocytosis and intracellular trafficking

Following receptor engagement, OBVs are internalized predominantly through clathrin-mediated endocytosis (Figure 2). Pharmacological inhibition of clathrin assembly, AP2 function, or dynamin activity, as well as dominant-negative forms of these factors, markedly reduces infection by LACV, OROV, and AKAV [32,40,41]. Disrupting cholesterol-rich microdomains likewise impairs uptake [40,41], which may reflect a role for lipid rafts in organizing receptor clusters and curvature-generating platforms at the plasma membrane.

Once internalized, virions enter the endosomal network (Figure 2). Live-cell imaging and perturbation studies indicate that Rab5 activity and early endosome (EE) maturation are essential for productive infection [15]. Dominant-negative Rab5 blocks LACV entry [32], and OROV co-localizes with EEA1-positive intracellular vesicles shortly after uptake [41]. From EEs, virions traffic toward LEs, a route accompanied by progressive acidification, lipid remodeling, and pronounced shifts in luminal ion concentrations [10,42].

The precise fusion compartment varies among OBVs and may depend on cell type. Using fluorescently labeled virions, GERV was shown to rely on Rab7 activity and intact LEs for penetration [15], placing it among

Figure 2



Entry pathways of orthobunyaviruses (OBVs) in mammalian cells. OBVs attach to the cell surface via various factors (HSPG, DC-SIGN, Lrp1, etc.) before entering through clathrin-mediated endocytosis. Internalized particles traffic from Rab5-positive early endosomes (EEs) to Rab7-positive late endosomes (LEs), where progressive acidification (H+), increasing luminal K+ levels, and lipid remodeling activate Gc. Fusion typically occurs within multivesicular bodies (MVBs) or LEs, releasing ribonucleoproteins directly into the cytosol to initiate transcription. *Abbreviations*: AKAV, Akabane virus; BUNV, Bunyamwera virus; CEV, California encephalitis virus; GERV, Germiston virus; JCV, Jamestown canyon virus; LACV, La Crosse virus; OROV, Oropouche virus; SBV, Schmallenberg virus.

'late-penetrating' viruses [42] (Figure 2). OROV infection exhibits similar Rab7 dependence [41]. In contrast, LACV displays a stringent Rab5 requirement but limited Rab7 dependence, suggesting fusion in a subset of maturing EEs or early LEs [32]. These differences indicate that OBVs exploit the full range of endosomal compartments with notable flexibility.

Quantitative single-particle tracking further refines this spatial and temporal map [15,38,43]. Individual virions

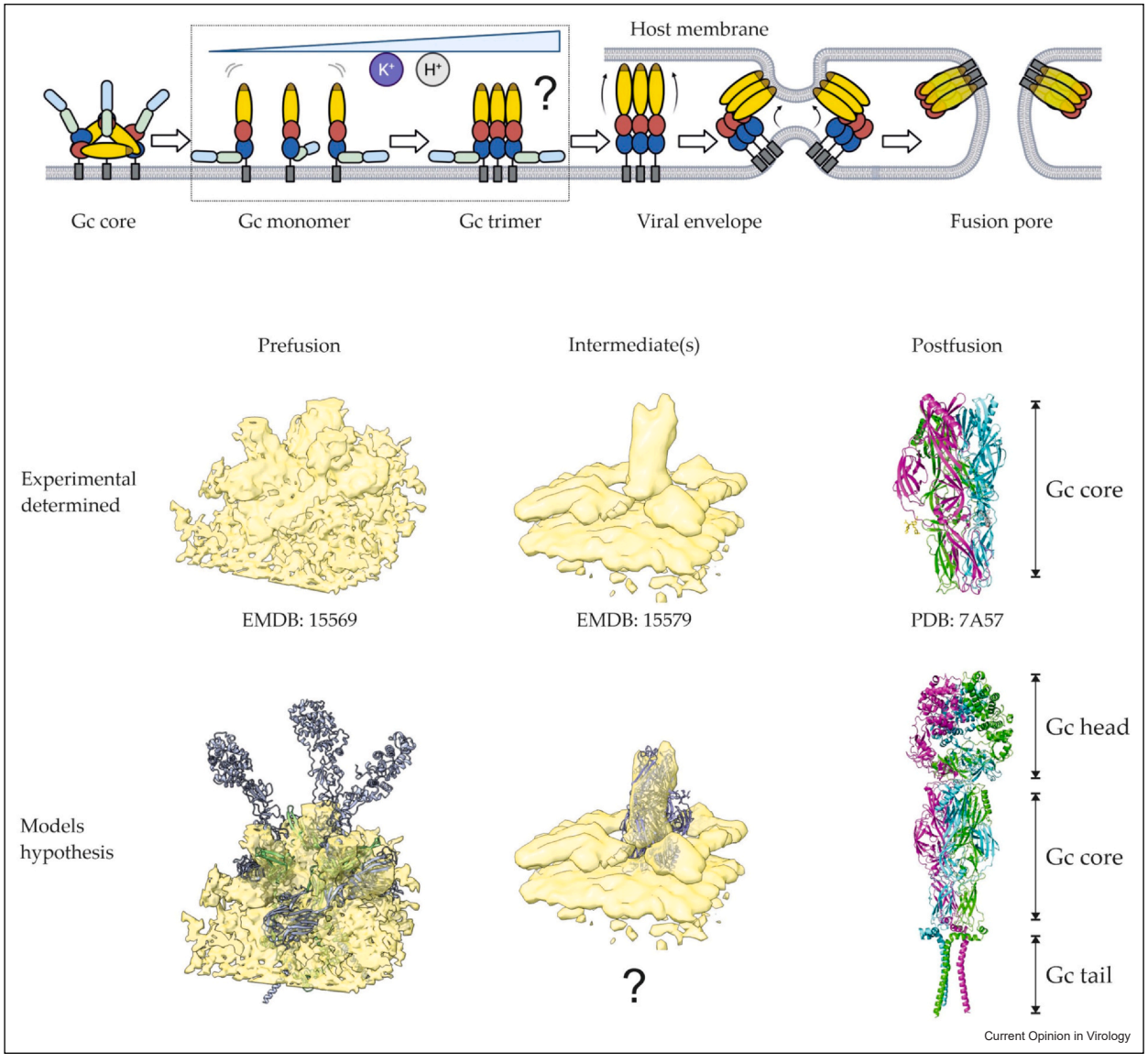
can be followed from the cell surface to fusion, revealing dwell times within successive endosomal compartments and showing that penetration is gated by sequential checkpoints, that is, receptor-dependent uptake, Rab5-mediated endosomal maturation, and acquisition of a physicochemical environment permissive for fusion.

Fusion, ionic cues, and uncoating

Fusion of the OBV envelope with endosomal membranes is triggered by the acidic pH generated by proton (H+) accumulation in maturing endosomes [10]. Exposure of virions or Gc-expressing cells to acidic buffers induces class II-like changes in Gc, including ectodomain extension and exposure of hydrophobic fusion loops [44–48]. For LACV and other OBVs, fusion is optimal within the pH range of LEs [46,47,49–51], consistent with the endocytic pathways discussed above (Figure 2).

However, H+-driven acidification alone does not fully account for the timing or efficiency of fusion. A recent

Figure 3



Acid- and ion-dependent activation of the Gc fusion machinery. The class II fusion protein Gc undergoes sequential conformational changes in response to the physicochemical environment of late endosomes (LEs). Rising K+ levels together with decreasing pH remodel the Gc head and promote extension of the conserved fusion core, thereby exposing the fusion loops and driving merger of the viral envelope with cellular membranes, ultimately enabling genome release. Three BUNV Gn/Gc heterodimer models were fitted into the BUNV floor domain cryo-EM density map (EMDB: 15569). The postfusion trimer of LACV Gc (PDB: 7A57) was fitted into the BUNV intermediate cryo-EM density map (EMDB: 15579). Question marks indicate steps for which structural information or model data are currently lacking.

development is the demonstration that endosomal K+ accumulation is also required for the entry of BUNV and SBV [52,53] (Figure 3). Inhibiting K+ channels or transporters reduces infection, and manipulating K+ gradients alters fusion efficiency. Cholesterol content in endosomal membranes modulates K+ accumulation [54], thereby linking membrane composition, ionic remodeling, and the fusion competence of incoming virions. Emerging evidence thus supports a model in which OBV fusion depends on the coordinated sensing of multiple ionic cues — H+ and elevated K+ — acting within a permissive lipid environment (Figure 3). The precise sequence, hierarchy, and mechanistic interplay of these signals, however, remain largely to be elucidated.

These signals promote Gc refolding into its postfusion conformation, drive membrane merger, and prime RNPs for cytosolic release. A related concept was recently illustrated for the Toscana virus, whose fusion reaction appears at least partly reversible and triggered by progressive acidification rather than a strict pH threshold [55]. Whether OBVs follow a similar model remains unknown, an issue particularly relevant given their divergent fusion phenotypes and the requirement for elevated endosomal K+ reported for several OBVs. Understanding how OBVs sense and integrate H+, K+, and membrane lipids may uncover additional regulatory layers in their entry program.

The molecular mechanism of uncoating, that is, how RNPs are released from the envelope and become transcription-competent, remains largely unknown. By analogy with other enveloped viruses [56], changes in ion concentrations and interactions with host factors likely contribute to loosening the contact between RNPs and the viral membrane or associated proteins, but direct evidence is still scarce.

Conclusions and perspectives

Recent work has transformed OBV entry from a simple 'clathrin plus low pH' model into a multi-parameter process in which virion architecture, receptor usage, endocytic routing, and endosomal ion homeostasis are tightly intertwined. The identification of Lrp1 as an essential OROV receptor provides a molecular anchor for dissecting tropism and pathogenesis and supports the notion that a restricted set of receptor hubs may be shared across the *Bunyaviricetes*. In parallel, the discovery of glycolipid-dependent attachment in UUKV, and its possible extension to OBVs such as GERV, suggests that additional carbohydrate-recognizing receptors involved in cell entry remain to be identified, likely extending beyond the *Orthobunyavirus* genus and the *Bunyaviricetes* class.

Structural analyses of the Gn/Gc spike reveal how a conserved class II fusion core is capped by a highly variable antigenic head domain, explaining both cross-reactivity and antigenic drift. The recognition of K+ as a fusion cofactor reframes endosomal acidification as only one of several cues that incoming virions must integrate before committing to fusion. Because entry represents a critical bottleneck in the viral cycle, it is an attractive target for antiviral intervention.

Several questions remain. Key priorities include determining whether Lrp1 or related LDL-receptor family members act as universal receptors for additional OBVs, and how receptor usage differs between mammalian and arthropod hosts. Comparative studies of virions produced in vector versus vertebrate cells should clarify how glycosylation and lipid composition influence receptor engagement, endocytic routing, and fusion. A deeper understanding of how H+, K+, and other ions are sensed by Gc and by the RNPs could reveal targets for broad-spectrum antivirals. Such targets may include host-directed agents that modulate endosomal ion channels or cholesterol homeostasis. Finally, integrating high-resolution imaging, structural biology, and systems-level genetic screens in relevant *in vitro* and *in vivo* models will be essential to connect molecular mechanisms of entry with OBV epidemiology, exemplified by the expansion of OROV and recurrent SBV activity.

Overall, available evidence suggests that OBVs have evolved highly adaptable yet tightly regulated entry programs that enable infection of a broad range of hosts. Understanding this flexibility at the molecular level will be critical for anticipating future emergence events and for designing effective vaccines and antivirals against this still underestimated group of arboviruses.

Author contributions

PYL: Conceptualization, Writing – original draft, Writing – review & editing. QX: Preparation of figures, Writing – review & editing.

Data Availability

We used publicly available cryo-EM density maps from the EMDB and structural models from the PDB referenced in the figure legends.

Declaration of Competing Interest

Nothing declared.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors used ChatGPT for English language correction and stylistic improvement. Structural models were generated using AlphaFold3 (https://alphafoldserver.com/).

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- •• of outstanding interest

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