Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Adv Virus Res. Author manuscript; available in PMC 2024 August 09.

Published in final edited form as:

Adv Virus Res. 2023 ; 117: 121–136. doi:10.1016/bs.aivir.2023.09.001.

Host entry factors of Rift Valley Fever Virus infection

Safder S. Ganaie[1], **Daisy W. Leung**[1,2], **Amy L. Hartman**[3,4], **Gaya K. Amarasinghe**[1,*]

[1]Department of Pathology and Immunology, Washington University School of Medicine, St Louis, MO 63110, USA;

[2]Department of Medicine, Washington University School of Medicine, St Louis, MO 63110, USA;

[3]Center for Vaccine Research, University of Pittsburgh, Pittsburgh, PA, USA

[4]Department of Infectious Diseases and Microbiology, School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

SUMMARY

Rift Valley Fever Virus (RVFV) is a negative sense segmented RNA virus that can cause severe hemorrhagic fever. The tri-segmented virus genome encodes for six (6) multifunctional proteins that engage host factors at a variety of different stages in the replication cycle. The S segment encodes nucleoprotein (N) and nonstructural protein S (NSs), the M segment encodes viral glycoproteins Gn and Gc as well as nonstructural protein M (NSm) and the L segment encodes the viral polymerase (L). Viral glycoproteins Gn and Gc are responsible for entry by binding to a number of host factors. Our recent studies identified a scavenger receptor, LDL receptor related protein 1 (Lrp1), as a potential pro-viral host factor for RVFV and related viruses, including Oropouche virus (OROV) infection. Coincidentally, several recent studies identified other LDL family proteins as viral entry factors and receptors for other viral families. Collectively, these observations suggest that highly conserved LDL family proteins may play a significant role in facilitating entry of viruses from several distinct families. Given the significant roles of viral and host factors during infection, characterization of these interactions is critical for therapeutic targeting with neutralizing antibodies and vaccines.

Keywords

Rift Valley Fever Virus; RVFV; viral entry; LDL receptors; Lrp1

1. INTRODUCTION

Rift Valley Fever Virus (RVFV) is a negative sense segmented RNA virus. RVFV belongs to the genus *Phlebovirus* and family *Phenuiviridae* in the in the order *Bunyavirales*(Kuhn et al., 2022). RVFV is known to cause diseases including severe hemorrhagic fever in livestock and in humans(Ikegami and Makino, 2011;Kwaśnik, Rożek and Rola, 2021) and is transmitted through *Aedes* and *Culex* mosquito species (Kwaśnik, Rożek and Rola, 2021). Initially identified in east Africa, RVFV is now endemic throughout many regions

*Correspondence: gamarasinghe@wustl.edu (G.K.A.).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

of Africa(Ikegami, 2012). RVFV displays low-level enzootic activity, interspersed with large, explosive epizootic outbreaks in ruminant animals, and epidemics in humans during heavy rainfall seasons when mosquito populations are abundant(Chamchod et al., 2015), (Fontenille et al., 1998). Additionally, RVFV can be transmitted through bodily fluids of infected animals, but a significant route of transmission to humans appears to be through mosquito bites(Tantely, Boyer and Fontenille, 2015). RVFV related epidemics are increasing in frequency, possibly due to rainfall alterations associated with climate change(Chevalier et al., 2010). The widespread distribution of mosquito vectors that are RVFV-competent, emphasizes the emerging nature of RVFV (Turell et al., 2013). In 2018–2019, at least 10 African countries endured RVF disease in both animals and people(Organization, 2018a;Organization, 2018b;Organization, 2018c). RVF is highly lethal in young animals including cattle, sheep, goats, and camels(Daubney and Hudson, 1931;Easterday et al., 1962;Findlay and Daubney, 1931). In humans, RVF is primarily an acute febrile illness accompanied by headache, body aches and joint pain, with occasional progression to hepatic disease, hemorrhagic fever, or encephalitis(Connors and Hartman, 2022;Laughlin et al., 1979;Madani et al., 2003;McIntosh et al., 1980).

Rift Valley Fever (RVF) outbreaks have been reported in various countries. In 2000, Saudi Arabia and Yemen reported unexplained hemorrhagic fever cases in humans and animal deaths(Jupp et al., 2002). Uganda has been experiencing RVF outbreaks since March 2016, with subsequent outbreaks occurring (Nyakarahuka et al., 2023). Mayotte, a French overseas territory, witnessed a significant RVF outbreak from 2018 to 2020, with 143 human cases and 126 cases in livestock (Asad Khan et al., 2022) . Previous RVF outbreaks have also occurred in Mauritania in 1987, 2010, 2012, 2015, and 2020 (Caminade et al., 2014). In October 2020, Mauritania and Sudan reported RVF outbreaks, leading to human cases and livestock deaths (Asad Khanet al., 2022). Libya reported 30 RVF cases and four deaths in 2020. Kenya experienced an outbreak in Isiolo County in February 2021, with at least 11 deaths reported in both animals and humans. In Mauritania, an outbreak occurred between August and October 2022, resulting in 47 confirmed cases and 23 deaths, mainly among animal breeders (Mohapatra et al., 2023).

2. THE TRIPARTITE VIRAL GENOME ENCODES A SMALL NUMBER OF PROTEINS

The tri-segmented virus genome encodes for six (6) multifunctional proteins that engage host factors at a variety of different stages in the replication cycle (Figure 1). The S segment encodes for nucleoprotein (N) and nonstructural protein S (NSs); the M segment encodes viral glycoproteins Gn and Gc as well as nonstructural protein M (NSm); and the L segment encodes the viral polymerase (L) (Struthers, Swanepoel and Shepherd, 1984). Of these, the viral glycoproteins Gn and Gc are responsible for entry by engaging attachment factors, receptors, or other host factors (Ellis et al., 1979). Over the past two decades, significant progress has been made in advancing our knowledge of specific RVFV proteins and their interactions with host proteins for viral entry. The following sections summarize our current knowledge of the RVFV proteins and their interactions.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2.1 Non Structural Protein, NSs:

The RVFV NSs protein plays a central role in the pathogenesis of the virus by suppressing the antiviral type I interferon response (Billecocq et al., 2004)· (Bouloy et al., 2001). The NSs is present in both the cytoplasm and nucleus of infected cells, where it forms a filamentous structure in the nucleus (Yadani et al., 1999). This protein is made up of 265 amino acids and has an estimated size of 31 kDa. The acidic C-terminus, consisting of 17 amino acids, plays a crucial role in the formation of the filamentous structure within the nucleus (Ly and Ikegami, 2016),(Yadaniet al., 1999). Moreover, the NSs protein of RVFV disrupts the general transcription activity of the cell by directly interacting with components of the transcription factor (TF) IIH (Le May et al., 2004). Specifically, it interacts with TFIIH p62 and promotes its post-translational degradation (Kalveram, Lihoradova and Ikegami, 2011). The NSs protein also facilitates the reduction of protein kinase PKR through post-transcriptional processes while also suppressing the phosphorylation of eIF2α (Ikegami et al., 2009).

2.2 Non Structural Protein, NSm:

RVFV NSm is approximately 14 kDa in size and is generally considered to have no significant role in virus replication (Gerrard et al., 2007;Won et al., 2006). Instead, NSm has been shown to play a role in determining the virulence of RVFV in mice and in modulating host responses, including potentially limiting the impact of apoptosis during viral infeciton(Bird, Albariño and Nichol, 2007;Terasaki, Won and Makino, 2013;Won et al., 2007). NSm is anti-apoptotic and exerts its anti-apoptotic function by integrating into the mitochondrial outer membrane, with its N-terminus exposed to the cytoplasm(Terasaki, Won and Makino, 2013;Wonet al., 2006). The NSm protein spans approximately 115 amino acids and contains a hydrophobic amino acid cluster at its C-terminus. Within this context, two presumed transmembrane helices span amino acids 95 to 112 and 99 to 115. Amino acids 71 to 115 located in the C-terminal domain of RVFV NSm play a pivotal role in directing the protein to the mitochondrial outer membrane (MOM), facilitating its antiapoptotic role. For the MOM targeting of proteins, NSm has two basic amino acids preceding the potential transmembrane domain are imperative for efficient MOM targeting (Terasaki, Won and Makino, 2013) (Wonet al., 2006). The precise mechanism by which C-terminus of NSm executes its anti-apoptotic activity warrants further investigation.

In addition, NSm plays a crucial role in regulating p38 mitogen-activated protein kinase response in mammalian cells and is essential for virus infectivity in mosquitoes(Crabtree et al., 2012;Narayanan et al., 2011).

2.3 Nucleocapsid Protein, NP:

RVFV NP, molecular weight of 27-kDa, serves as a crucial structural protein within RVFV (Le May et al., 2005). It plays important roles in viral replication and assembly by actively participating in the formation of viral ribonucleoprotein complexes (vRNPs) (Zamoto-Niikura et al., 2009). The RVFV NP is involved in the encapsidation of viral genomic RNA, which is essential for various steps in the replicative cycle, including transcription and replication by the RNA-directed RNA polymerase (RdRp), as well as genome packaging into virions (Lopez et al., 1995). NP is thought to interact with the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

viral RdRp, and it also plays a role in virus assembly through interactions with viral envelope glycoproteins (Gn and Gc)(Barr et al., 2020) Additionally, the NP is a significant target of the host immune response, triggering antibody production and cellular immune responses(Ragan et al., 2018). NP is the most abundantly expressed protein. NP is also highly immunogenic, and many NP specific antibodies are observed during infections in multiple animal models, their impact in limiting infection and disease appears to be limited.

2.4 L (RdRp) protein:

The RVFV L protein is a multifunctional enzyme, approximately 238 kDa in size, responsible for catalyzing genome replication and viral gene transcription (Lopezet al., 1995). Genome replication occurs through a prime-and-realign mechanism, while viral gene transcription involves cap-snatching (Gogrefe et al., 2019;Wang et al., 2022). The L protein is essential for viral RNA synthesis, but its specific mechanisms and interactions with host factors remain poorly understood. The L protein consists of N -terminal endonuclease domain, a central RdRp domain and a C-terminal cap-binding domain. Cap-snatching involves cleavage of 5’ cap along with 10–18 nucleotides of host mRNAs by the L- endonuclease domain, which serve as primers for viral mRNAs ((Gogovi et al., 2019;Gogrefeet al., 2019). Recent, cryoEM structure of RVFV L revealed that a single template is required for initiation the RNA synthesis which is enhanced by 5’ vRNA (Wanget al., 2022). Another report suggested that RVFV L protein forms biologically active oligomers within cells and oligomerization is essential for RNA synthesis (Zamoto-Niikuraet al., 2009).

2.5 Gn and Gc Glycoproteins:

RVFV glycoproteins Gn (~57 kDa) and Gc (~55 kDa) are initially expressed as a precursor polypeptide and undergo co-translational cleavage, presumably by signal peptide peptidase (SSP), before maturing into envelope glycoproteins (Gerrard and Nichol, 2007;Huiskonen et al., 2009;Hulswit et al., 2021). As type-I integral membrane proteins anchored in the envelope, they play crucial roles in receptor recognition, binding to target cells, and viral entry through membrane fusion (Dessau and Modis, 2013). Unlike other negative-stranded RNA viruses, bunyaviruses lack a matrix protein, and Gn and Gc interact directly with the ribonucleoprotein complex inside the virus particle (de Boer et al., 2012b). Gn and Gc form oligomers and organize as cylindrical hollow spikes on the virus surface, arranged into distinct capsomers. The virus surface has 122 capsomers in an icosahedral lattice with a triangulation number of 12 (Bouloy and Weber, 2010). RVFV Gn consists of an N-terminal Gn ectodomain, succeeded by a stalk domain, transmembrane region, and a cytoplasmic tail. The cystal structure analysis of Gn ectodomain has unveiled a tripartite architecture comprising three distinct domain. These include a mixed α-helical/β-stranded N-terminal domain, referred to as domain A and a b-ribbon domain and a domain B (Hulswitet al., 2021;Wu et al., 2017). On the other hand, RVFV Gc falls under the category of Class-II fusion proteins. The crystallography studies of Gc etodomain regions has uncovered a trio of Gc domains designated as I, II and III. The domains are primarily from β-sheets. Importantly, fusion loop has been pinpointed within domain II, which are responsible for insertion into host target membrane. Adjacent to the fusion loop, there is a conserved cavity that interacts with glycerophospholipids and significantly contribute to

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

the interaction of Gc and the target membrane(Dessau and Modis, 2013;Guardado-Calvo et al., 2017;Halldorsson et al., 2016;Vaney and Rey, 2011). Due to their significance in virion maturation, receptor binding, and fusion with host cells, both glycoproteins are attractive targets for designing antiviral drugs to block receptor binding and/or fusion processes. Like other viral glycoproteins, RVFV virus glycoproteins Gn and Gc each have specialized functions. Together, they engage in with host receptors in order to promote fusion. Gn and Gc forms dimers, and the heterodimer subsequently forms higher order oligomers likely hexamer. The Gn/Gc hexamers are thought to promote type II fusion. While RVFV is an envelop virus, how the glycoproteins are selected during egress is unclear, but the cytoplasmic region of Gn is thought to be critical. Overall, Gn and Gc glycoproteins are critical for infection and for the continuation of the virus replication cycle.

Much progress has been made in defining molecular insights, including the availability of three-dimensional structures of multiple proteins from RVFV (Figure 1). Availability of these molecular insights, coupled with numerous studies that have defined host factor interactions, the field is poised to future explore how host-pathogen interactions contribute to infection and disease. However, one major limitation in the current literature is the lack of insight on membrane proximal regions, including structural insights into transmembrane regions of Gn and Gc. These crucial details are missing from the currently available structures of Gn/Gc ectodomains. Such insights will enhance our ability to better define how viral proteins engage host proteins during viral entry.

3. TARGET CELLS AND RECEPTORS

Transmission of RVFV typically occurs after an arthropod bite (Balenghien et al., 2013). During the initial stage of infection, the virus is recognized by dendritic cells (DCs) and macrophages in the skin, which are also permissive for RVFV infection (McElroy and Nichol, 2012;Oreshkova et al., 2015). While viral glycoproteins Gn and Gc are known to support entry into cells, prior studies have identified a plethora of host proteins as receptors and entry factors. Among them, lectin DC-SIGN on DCs has been shown to potentially mediate internalization of RVFV, and many other viruses through a poorly defined mechanism (Lozach et al., 2011;Phoenix et al., 2016). Importantly, in these previous studies, DC-SIGN interaction depended on the glycosylation of RVFV Gn. Elimination of Gn glycosylation by PNGase F and Endo H (glycolytic enzymes) resulted in reduced binding without impacting infectivity, demonstrating that DC-SIGN may be important for attachment, but not sufficient for infection (Lozachet al., 2011). Lectin molecules closely related to DC-SIGN, such as L-SIGN and DC-SIGNR, are found on RVFV-permissive cells, including hepatic and placental cells, but have no role in RVFV internalization (Hofmann et al., 2013). Heparan sulfate was also identified as a potential attachment factor for RVFV; however, removal of heparan sulfate reduced RVFV infection, but did not eliminate it. Adding heparan sulfate to virus led to inhibition through charge-charge interactions between basic clusters of glycoproteins and heparan sulfate (de Boer et al., 2012a;Riblett et al., 2016). While the liver is the main target of RVFV infection in rodents, ruminants, and primates, most cell and tissue types, including neurons, epithelial cells, macrophages, granulocytes, pancreatic islet cells, adrenal glands, ovaries, testes, and placenta, are susceptible (Gaudreault et al., 2015;Gommet et al., 2011;Gray et al.,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2012;Hartman et al., 2014;Ikegami et al., 2017;Odendaal et al., 2019;Scharton et al., 2015). Given its broad cellular and host tropism, yet unidentified host factors are likely to mediate RVFV entry.

Recently, a number of studies have used CRISPR-based genomic screens to identify host factors that provide entry receptors and attachment factors (Carette et al., 2011;Ma et al., 2020;Zhang et al., 2018). Following these studies and to define proteinaceous host factors for RVFV entry, we conducted a similar screen, which resulted in a series of prioritized hits, including a low-density lipoprotein (LDL) receptor family protein known as the LDL receptor-related protein 1 (Lrp1) (Ganaie et al., 2021) (Fig. 2A). Work from this study also showed that deletion of Lrp1 from multiple cell lines and from primary mouse embryonic fibroblast (MEF) cells resulted in reduced RVFV infection. Lrp1 is a scavenger receptor with a number of known ligands, including receptor associated protein (RAP), which binds LDL- receptor family members during its processing through the ER-Golgi network to keep these proteins in a ligand free conformation. Mouse RAP domain 3 ($mRAP_{D3}$), which binds to multiple clusters within Lrp1 was used to show that the RVFV glycoprotein Gn and mRAPD3, similar ligand binding sites within Lrp1 that are known as cysteine rich domains (CRDs). These CRDs are also known as LA domains. Importantly, mRAPD3 can reduce RVFV infection of taxonomically distinct cell lines, further demonstrating a shared role across different species. Finally, the same study highlighted a role for Lrp1 in an intracranial infection model, where co-injection of mRAPD3 was able to significantly protect mice from otherwise lethal disease. In contrast to blocking Lrp1, tissue specific removal of Lrp1 from the liver in a mouse model led to delayed time to death (Schwarz et al., 2023). In Lrp1 liver deleted mice, most exhibited high levels of neurological abnormalities relative to those with intact Lrp1 in the liver. While additional studies are required to fully explore the impact of Lrp1 in distinct tissues for tropism, dissemination, and zoonotic potential, these studies collectively highlight an important role for Lrp1 in RVFV virus entry. In addition to RVFV, additional bunyaviruses may also use Lrp1 (Schwarz et al., 2022), but the exact nature of the role played by Lrp1 in these infection models requires additional studies. In particular, Lrp1 is known to play multiple roles in endocytosis and therefore, the molecular mechanisms by which Lrp1 impacts virus infection may be more complex than currently appreciated.

In unrelated studies, several other LDLR-family proteins have been shown as to be entry factors for Semliki Forest virus (SFV), Eastern equine encephalitis virus (EEEV), Sindbis virus (SINV), and Venezuelan Equine Encephalitis Virus (VEEV) (Clark et al., 2022;Maet al., 2020;Zhanget al., 2018). These studies further highlight the importance of scavenger receptors such as LDLRs for virus entry. Importantly, these studies raise the potential that these evolutionarily conserved lipoprotein receptors also serve as a back-door for viral entry, where mutations in the host receptors that limit infection may be deleterious for the host, as it may also prevent the physiological roles of the scavenger receptors. Additionally, closer examination of the receptors themselves show a wide range in the number of binding sites. Distantly related LDLRAD3 contains 3 CRD/LA domains while Lrp1 contains 34 CRD/LA domains (Figure 2A). Biochemical and biophysical studies, including a recent cryoEM structure of Lrp8 (ApoER2) bound to SFV, revealed that different CRD domains can bind viral glycoproteins with different affinities. This variability, which results in an affinity gradient may play an important role in engaging the viral glycoproteins resulting

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

in virus retention (longer half-life) on cell surface (Cao et al., 2023). Increased half-life of cell surface attachment can enhance infectivity. Parameterization of such a model will require more data than currently available. However, these initial observations set up a potential model where the balance between high affinity binding sites (CRDs) and low affinity binding sites provide a kinetic advantage for virus entry (Figure 2B).

Recent studies in RVFV, described above, and other viruses are important contributions that help explain how some viruses display broad tissue and species tropism. Recent findings also point to numerous opportunities to develop animal models where LDLR family receptors can be targeted to therapeutic development and to better determine how RVFV and related viruses contribute to disease. Since many LDL family receptors are embryonically lethal, thus global deletion of such receptors are not feasible. Instead, conditional removal, using cre/lox methods, may enable investigators to probe the role of different LDL family proteins in viral infection. Additionally, there are numerous potential links between lipoprotein receptors and their impact on other signaling proteins at the membrane. Membrane lipid compositions can also impact phagocytosis, micropinocytosis, and endocytosis. Thus, there are many remaining questions, including gaps in genetic, molecular, and structural insights of viral entry. Therefore, additional studies are required to fully explore links between these important cellular processes and viral infections. Findings reviewed here further illustrate the exciting new avenues of research to come in the near future.

ACKNOWLEDGEMENTS

We would like to acknowledge Ms. Lydia Wheat for critical reading of the manuscript. We thank members of the Leung, Hartman, and Amarasinghe groups for discussion and input. The authors declare no competing interests. We also acknowledge funding from the National Institutes of Health awards R01 AI161765, R01AI169850, R56AI171920, and R21 AI163603.

ABBREVIATIONS

Lrp1	Low-density lipoprotein receptor-related protein 1
RVFV	Rift Valley Fever virus
OROV	Oropouche virus
CRD	Cysteine-rich domain
RdRp	RNA-dependent RNA polymerase
VLDLR	Very low-density lipoprotein receptor
LDLRAD3	Low density lipoprotein receptor class A domain containing 3
EpoER2	Apoliporpotein E receptor 2

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

References

Asad Khan FM, Islam Z, Kazmi SK, Hasan MM, Yasmin F, Costa A, Ahmad S, and Essar MY (2022). The concomitant viral epidemics of Rift Valley fever and COVID-19: A lethal combination for Kenya. Trop Doct 52, 6. [PubMed: 34866495]

Balenghien T, Cardinale E, Chevalier V, Elissa N, Failloux AB, Jean Jose Nipomichene TN, Nicolas G, Rakotoharinome VM, Roger M, and Zumbo B (2013). Towards a better understanding of Rift Valley fever epidemiology in the south-west of the Indian Ocean. Vet Res 44, 78. [PubMed: 24016237]

Barr J, Weber F, Schmaljohn C, Bunyaviridae KD, and Howley PJFV (2020). Fields virology. 1, 706.

Billecocq A, Spiegel M, Vialat P, Kohl A, Weber F, Bouloy M, and Haller O (2004). NSs protein of Rift Valley fever virus blocks interferon production by inhibiting host gene transcription. J Virol 78, 9798. [PubMed: 15331713]

Bird BH, Albariño CG, and Nichol ST (2007). Rift Valley fever virus lacking NSm proteins retains high virulence in vivo and may provide a model of human delayed onset neurologic disease. Virology 362, 10. [PubMed: 17412386]

Bouloy M, Janzen C, Vialat P, Khun H, Pavlovic J, Huerre M, and Haller O (2001). Genetic evidence for an interferon-antagonistic function of rift valley fever virus nonstructural protein NSs. J Virol 75, 1371. [PubMed: 11152510]

Bouloy M, and Weber F (2010). Molecular biology of rift valley Fever virus. Open Virol J 4, 8. [PubMed: 20517489]

Caminade C, Ndione JA, Diallo M, MacLeod DA, Faye O, Ba Y, Dia I, and Morse AP (2014). Rift Valley Fever outbreaks in Mauritania and related environmental conditions. Int J Environ Res Public Health 11, 903. [PubMed: 24413703]

Cao D, Ma B, Cao Z, Zhang X, and Xiang Y (2023). Structure of Semliki Forest virus in complex with its receptor VLDLR. Cell 186, 2208. [PubMed: 37098345]

Carette JE, Raaben M, Wong AC, Herbert AS, Obernosterer G, Mulherkar N, Kuehne AI, Kranzusch PJ, Griffin AM, Ruthel G, Dal Cin P, Dye JM, Whelan SP, Chandran K, and Brummelkamp TR (2011). Ebola virus entry requires the cholesterol transporter Niemann-Pick C1. Nature 477, 340. [PubMed: 21866103]

Chamchod F, Cosner C, Cantrell RS, Beier JC, and Ruan S (2015). Transmission Dynamics of Rift Valley Fever Virus: Effects of Live and Killed Vaccines on Epizootic Outbreaks and Enzootic Maintenance. Front Microbiol 6, 1568. [PubMed: 26869999]

Chevalier V, Pepin M, Plee L, and Lancelot R (2010). Rift Valley fever--a threat for Europe? Euro Surveill 15, 19506. [PubMed: 20403309]

Clark LE, Clark SA, Lin C, Liu J, Coscia A, Nabel KG, Yang P, Neel DV, Lee H, Brusic V, Stryapunina I, Plante KS, Ahmed AA, Catteruccia F, Young-Pearse TL, Chiu IM, Llopis PM, Weaver SC, and Abraham J (2022). VLDLR and ApoER2 are receptors for multiple alphaviruses. Nature 602, 475. [PubMed: 34929721]

Connors KA, and Hartman AL (2022). Advances in Understanding Neuropathogenesis of Rift Valley Fever Virus. Annu Rev Virol 9, 437. [PubMed: 36173701]

Crabtree MB, Kent Crockett RJ, Bird BH, Nichol ST, Erickson BR, Biggerstaff BJ, Horiuchi K, and Miller BR (2012). Infection and transmission of Rift Valley fever viruses lacking the NSs and/or NSm genes in mosquitoes: potential role for NSm in mosquito infection. PLoS Negl Trop Dis 6, e1639. [PubMed: 22563517]

Daubney R, and Hudson JR (1931). Enzootic hepatitis or Rift Valley Fever: an undescribed virus disease of sheep, cattle, and man from east Africa. J. Path. Bact 34, 545.

de Boer SM, Kortekaas J, de Haan CAM, Rottier PJM, Moormann RJM, and Bosch BJ (2012a). Heparan Sulfate Facilitates Rift Valley Fever Virus Entry into the Cell. Journal of Virology 86, 13767. [PubMed: 23015725]

de Boer SM, Kortekaas J, Spel L, Rottier PJ, Moormann RJ, and Bosch BJ (2012b). Acid-activated structural reorganization of the Rift Valley fever virus Gc fusion protein. J Virol 86, 13642. [PubMed: 23035232]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Dessau M, and Modis Y (2013). Crystal structure of glycoprotein C from Rift Valley fever virus. Proc Natl Acad Sci U S A 110, 1696. [PubMed: 23319635]

Easterday BC, Mc GM, Rooney JR, and Murphy LC (1962). The pathogenesis of Rift Valley fever in lambs. Am J Vet Res 23, 470. [PubMed: 13888969]

Ellis DS, Simpson DI, Stamford S, and Abdel Wahab KS (1979). Rift Valley fever virus: some ultrastructural observations on material from the outbreak in Egypt 1977. J Gen Virol 42, 329. [PubMed: 422955]

Findlay GM, and Daubney R (1931). The virus of Rift Valley fever or enzootic hepatitis. Lancet 221, 1350.

Fontenille D, Traore-Lamizana M, Diallo M, Thonnon J, Digoutte JP, and Zeller HG (1998). New vectors of Rift Valley fever in West Africa. Emerg Infect Dis 4, 289. [PubMed: 9621201]

Ganaie SS, Schwarz MM, McMillen CM, Price DA, Feng AX, Albe JR, Wang W, Miersch S, Orvedahl A, Cole AR, Sentmanat MF, Mishra N, Boyles DA, Koenig ZT, Kujawa MR, Demers MA, Hoehl RM, Moyle AB, Wagner ND, Stubbs SH, Cardarelli L, Teyra J, McElroy A, Gross ML, Whelan SPJ, Doench J, Cui X, Brett TJ, Sidhu SS, Virgin HW, Egawa T, Leung DW, Amarasinghe GK, and Hartman AL (2021). Lrp1 is a host entry factor for Rift Valley fever virus. Cell 184, 5163. [PubMed: 34559985]

Gaudreault NN, Indran SV, Bryant PK, Richt JA, and Wilson WC (2015). Comparison of Rift Valley fever virus replication in North American livestock and wildlife cell lines. Front Microbiol 6, 664. [PubMed: 26175725]

Gerrard SR, Bird BH, Albariño CG, and Nichol ST (2007). The NSm proteins of Rift Valley fever virus are dispensable for maturation, replication and infection. Virology 359, 459. [PubMed: 17070883]

Gerrard SR, and Nichol ST (2007). Synthesis, proteolytic processing and complex formation of N-terminally nested precursor proteins of the Rift Valley fever virus glycoproteins. Virology 357, 124. [PubMed: 16963099]

Gogovi GK, Almsned F, Bracci N, Kehn-Hall K, Shehu A, and Blaisten-Barojas E (2019). Modeling the Tertiary Structure of the Rift Valley Fever Virus L Protein. Molecules 24.

Gogrefe N, Reindl S, Günther S, and Rosenthal M (2019). Structure of a functional cap-binding domain in Rift Valley fever virus L protein. PLoS Pathog 15, e1007829. [PubMed: 31136637]

Gommet C, Billecocq A, Jouvion G, Hasan M, Zaverucha do Valle T, Guillemot L, Blanchet C, van Rooijen N, Montagutelli X, Bouloy M, and Panthier JJ (2011). Tissue tropism and target cells of NSs-deleted rift valley fever virus in live immunodeficient mice. PLoS Negl Trop Dis 5, e1421. [PubMed: 22163058]

Gray KK, Worthy MN, Juelich TL, Agar SL, Poussard A, Ragland D, Freiberg AN, and Holbrook MR (2012). Chemotactic and inflammatory responses in the liver and brain are associated with pathogenesis of Rift Valley fever virus infection in the mouse. PLoS Negl Trop Dis 6, e1529. [PubMed: 22389738]

Guardado-Calvo P, Atkovska K, Jeffers SA, Grau N, Backovic M, Perez-Vargas J, de Boer SM, Tortorici MA, Pehau-Arnaudet G, Lepault J, England P, Rottier PJ, Bosch BJ, Hub JS, and Rey FA (2017). A glycerophospholipid-specific pocket in the RVFV class II fusion protein drives target membrane insertion. Science 358, 663. [PubMed: 29097548]

Halldorsson S, Behrens AJ, Harlos K, Huiskonen JT, Elliott RM, Crispin M, Brennan B, and Bowden TA (2016). Structure of a phleboviral envelope glycoprotein reveals a consolidated model of membrane fusion. Proc Natl Acad Sci U S A 113, 7154. [PubMed: 27325770]

Hartman AL, Powell DS, Bethel LM, Caroline AL, Schmid RJ, Oury T, and Reed DS (2014). Aerosolized rift valley fever virus causes fatal encephalitis in african green monkeys and common marmosets. J Virol 88, 2235. [PubMed: 24335307]

Hofmann H, Li X, Zhang X, Liu W, Kühl A, Kaup F, Soldan SS, González-Scarano F, Weber F, He Y, and Pöhlmann S (2013). Severe fever with thrombocytopenia virus glycoproteins are targeted by neutralizing antibodies and can use DC-SIGN as a receptor for pH-dependent entry into human and animal cell lines. Journal of virology 87, 4384. [PubMed: 23388721]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Huiskonen JT, Overby AK, Weber F, and Grünewald K (2009). Electron cryo-microscopy and single-particle averaging of Rift Valley fever virus: evidence for GN-GC glycoprotein heterodimers. J Virol 83, 3762. [PubMed: 19193794]

Hulswit RJG, Paesen GC, Bowden TA, and Shi X (2021). Recent Advances in Bunyavirus Glycoprotein Research: Precursor Processing, Receptor Binding and Structure. Viruses 13.

Ikegami T (2012). Molecular biology and genetic diversity of Rift Valley fever virus. Antiviral Res 95, 293. [PubMed: 22710362]

Ikegami T, Balogh A, Nishiyama S, Lokugamage N, Saito TB, Morrill JC, Shivanna V, Indran SV, Zhang L, Smith JK, Perez D, Juelich TL, Morozov I, Wilson WC, Freiberg AN, and Richt JA (2017). Distinct virulence of Rift Valley fever phlebovirus strains from different genetic lineages in a mouse model. PLoS One 12, e0189250. [PubMed: 29267298]

Ikegami T, and Makino S (2011). The pathogenesis of Rift Valley fever. Viruses 3, 493. [PubMed: 21666766]

Ikegami T, Narayanan K, Won S, Kamitani W, Peters CJ, and Makino S (2009). Rift Valley fever virus NSs protein promotes post-transcriptional downregulation of protein kinase PKR and inhibits eIF2alpha phosphorylation. PLoS Pathog 5, e1000287. [PubMed: 19197350]

Jupp PG, Kemp A, Grobbelaar A, Lema P, Burt FJ, Alahmed AM, Al Mujalli D, Al Khamees M, and Swanepoel R (2002). The 2000 epidemic of Rift Valley fever in Saudi Arabia: mosquito vector studies. Med Vet Entomol 16, 245. [PubMed: 12243225]

Kalveram B, Lihoradova O, and Ikegami T (2011). NSs protein of rift valley fever virus promotes posttranslational downregulation of the TFIIH subunit p62. J Virol 85, 6234. [PubMed: 21543505]

Kuhn JH, Adkins S, Alkhovsky SV, Avšič-Županc T, Ayllón MA, Bahl J, Balkema-Buschmann A, Ballinger MJ, Bandte M, Beer M, Bejerman N, Bergeron É, Biedenkopf N, Bigarré L, Blair CD, Blasdell KR, Bradfute SB, Briese T, Brown PA, Bruggmann R, Buchholz UJ, Buchmeier MJ, Bukreyev A, Burt F, Büttner C, Calisher CH, Candresse T, Carson J, Casas I, Chandran K, Charrel RN, Chiaki Y, Crane A, Crane M, Dacheux L, Bó ED, de la Torre JC, de Lamballerie X, de Souza WM, de Swart RL, Dheilly NM, Di Paola N, Di Serio F, Dietzgen RG, Digiaro M, Drexler JF, Duprex WP, Dürrwald R, Easton AJ, Elbeaino T, Ergünay K, Feng G, Feuvrier C, Firth AE, Fooks AR, Formenty PBH, Freitas-Astúa J, Gago-Zachert S, García ML, García-Sastre A, Garrison AR, Godwin SE, Gonzalez JJ, de Bellocq JG, Griffiths A, Groschup MH, Günther S, Hammond J, Hepojoki J, Hierweger MM, Hongō S, Horie M, Horikawa H, Hughes HR, Hume AJ, Hyndman TH, Jiāng D, Jonson GB, Junglen S, Kadono F, Karlin DG, Klempa B, Klingström J, Koch MC, Kondō H, Koonin EV, Krásová J, Krupovic M, Kubota K, Kuzmin IV, Laenen L, Lambert AJ, Lǐ J, Li JM, Lieffrig F, Lukashevich IS, Luo D, Maes P, Marklewitz M, Marshall SH (2022). 2022 taxonomic update of phylum Negarnaviricota (Riboviria: Orthornavirae), including the large orders Bunyavirales and Mononegavirales. Arch Virol 167, 2857. [PubMed: 36437428]

Kwaśnik M, Rożek W, and Rola J (2021). Rift Valley Fever - a Growing Threat To Humans and Animals. J Vet Res 65, 7. [PubMed: 33817390]

Laughlin LW, Meegan JM, Strausbaugh LJ, Morens DM, and Watten RH (1979). Epidemic Rift Valley fever in Egypt: observations of the spectrum of human illness. Trans R Soc Trop Med Hyg 73, 630. [PubMed: 575446]

Le May N, Dubaele S, Proietti De Santis L, Billecocq A, Bouloy M, and Egly JM (2004). TFIIH transcription factor, a target for the Rift Valley hemorrhagic fever virus. Cell 116, 541. [PubMed: 14980221]

Le May N, Gauliard N, Billecocq A, and Bouloy M (2005). The N terminus of Rift Valley fever virus nucleoprotein is essential for dimerization. J Virol 79, 11974. [PubMed: 16140773]

Lopez N, Muller R, Prehaud C, and Bouloy M (1995). The L protein of Rift Valley fever virus can rescue viral ribonucleoproteins and transcribe synthetic genome-like RNA molecules. J Virol 69, 3972. [PubMed: 7769655]

Lozach PY, Kuhbacher A, Meier R, Mancini R, Bitto D, Bouloy M, and Helenius A (2011). DC-SIGN as a receptor for phleboviruses. Cell Host Microbe 10, 75. [PubMed: 21767814]

Ly HJ, and Ikegami T (2016). Rift Valley fever virus NSs protein functions and the similarity to other bunyavirus NSs proteins. Virol J 13, 118. [PubMed: 27368371]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ma H, Kim AS, Kafai NM, Earnest JT, Shah AP, Case JB, Basore K, Gilliland TC, Sun C, Nelson CA, Thackray LB, Klimstra WB, Fremont DH, and Diamond MS (2020). LDLRAD3 is a receptor for Venezuelan equine encephalitis virus. Nature 588, 308. [PubMed: 33208938]

Madani TA, Al-Mazrou YY, Al-Jeffri MH, Mishkhas AA, Al-Rabeah AM, Turkistani AM, Al-Sayed MO, Abodahish AA, Khan AS, Ksiazek TG, and Shobokshi O (2003). Rift Valley fever epidemic in Saudi Arabia: epidemiological, clinical, and laboratory characteristics. Clin Infect Dis 37, 1084. [PubMed: 14523773]

McElroy AK, and Nichol ST (2012). Rift Valley fever virus inhibits a pro-inflammatory response in experimentally infected human monocyte derived macrophages and a pro-inflammatory cytokine response may be associated with patient survival during natural infection. Virology 422, 6. [PubMed: 22018491]

McIntosh BM, Russell D, dos Santos I, and Gear JH (1980). Rift Valley fever in humans in South Africa. S Afr Med J 58, 803. [PubMed: 7192434]

Mohapatra RK, Kutikuppala LVS, Kandi V, Mishra S, Rabaan AA, Costa S, Al-Qaim ZH, Padhi BK, and Sah R (2023). Rift valley fever (RVF) viral zoonotic disease steadily circulates in the Mauritanian animals and humans: A narrative review. Health Sci Rep 6, e1384. [PubMed: 37404448]

Narayanan A, Popova T, Turell M, Kidd J, Chertow J, Popov SG, Bailey C, Kashanchi F, and Kehn-Hall K (2011). Alteration in superoxide dismutase 1 causes oxidative stress and p38 MAPK activation following RVFV infection. PLoS One 6, e20354. [PubMed: 21655261]

Nyakarahuka L, Whitmer S, Klena J, Balinandi S, Talundzic E, Tumusiime A, Kyondo J, Mulei S, Patel K, Baluku J, Akurut G, Namanya D, Kamugisha K, Cossaboom C, Whitesell A, Telford C, Graziano J, Montgomery J, Nichol S, Lutwama J, and Shoemaker T (2023). Detection of Sporadic Outbreaks of Rift Valley Fever in Uganda through the National Viral Hemorrhagic Fever Surveillance System, 2017–2020. Am J Trop Med Hyg 108, 995. [PubMed: 36913925]

Odendaal L, Clift SJ, Fosgate GT, and Davis AS (2019). Lesions and Cellular Tropism of Natural Rift Valley Fever Virus Infection in Adult Sheep. Vet Pathol 56, 61. [PubMed: 30343650]

Oreshkova N, Wichgers Schreur PJ, Spel L, Vloet RP, Moormann RJ, Boes M, and Kortekaas J (2015). Nonspreading Rift Valley Fever Virus Infection of Human Dendritic Cells Results in Downregulation of CD83 and Full Maturation of Bystander Cells. PLoS One 10, e0142670. [PubMed: 26575844]

Organization, W. H. (2018a). Rift Valley fever – Gambia. In Disease Outbreak News.

Organization, W. H. (2018b). Rift Valley fever – Kenya. In Disease Outbreak News.

Organization, W. H. (2018c). South Sudan declares Rift Valley fever outbreak in parts of Eastern Lakes State.

Phoenix I, Nishiyama S, Lokugamage N, Hill TE, Huante MB, Slack OAL, Carpio VH, Freiberg AN, and Ikegami T (2016). N-Glycans on the Rift Valley Fever Virus Envelope Glycoproteins Gn and Gc Redundantly Support Viral Infection via DC-SIGN. Viruses 8, 149. [PubMed: 27223297]

Ragan IK, Davis AS, McVey DS, Richt JA, Rowland RR, and Wilson WC (2018). Evaluation of Fluorescence Microsphere Immunoassay for Detection of Antibodies to Rift Valley Fever Virus Nucleocapsid Protein and Glycoproteins. J Clin Microbiol 56.

Riblett AM, Blomen VA, Jae LT, Altamura LA, Doms RW, Brummelkamp TR, and Wojcechowskyj JA (2016). A Haploid Genetic Screen Identifies Heparan Sulfate Proteoglycans Supporting Rift Valley Fever Virus Infection. J Virol 90, 1414. [PubMed: 26581979]

Scharton D, Van Wettere AJ, Bailey KW, Vest Z, Westover JB, Siddharthan V, and Gowen BB (2015). Rift Valley fever virus infection in golden Syrian hamsters. PLoS One 10, e0116722. [PubMed: 25607955]

Schrodinger, LLC. (2015). The PyMOL Molecular Graphics System, Version 1.8.

Schwarz MM, Ganaie SS, Feng A, Brown G, Yangdon T, White JM, Hoehl RM, McMillen CM, Rush RE, Connors KA, Cui X, Leung DW, Egawa T, Amarasinghe GK, and Hartman AL (2023). Lrp1 is essential for lethal Rift Valley fever hepatic disease in mice. Sci Adv 9, eadh2264. [PubMed: 37450601]

Schwarz MM, Price DA, Ganaie SS, Feng A, Mishra N, Hoehl RM, Fatma F, Stubbs SH, Whelan SPJ, Cui X, Egawa T, Leung DW, Amarasinghe GK, and Hartman AL (2022). Oropouche

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

orthobunyavirus infection is mediated by the cellular host factor Lrp1. Proc Natl Acad Sci U S A 119, e2204706119. [PubMed: 35939689]

Struthers JK, Swanepoel R, and Shepherd SP (1984). Protein synthesis in Rift Valley fever virus-infected cells. Virology 134, 118. [PubMed: 6710870]

Tantely LM, Boyer S, and Fontenille D (2015). A review of mosquitoes associated with Rift Valley fever virus in Madagascar. Am J Trop Med Hyg 92, 722. [PubMed: 25732680]

Terasaki K, Won S, and Makino S (2013). The C-terminal region of Rift Valley fever virus NSm protein targets the protein to the mitochondrial outer membrane and exerts antiapoptotic function. J Virol 87, 676. [PubMed: 23097454]

Turell MJ, Britch SC, Aldridge RL, Kline DL, Boohene C, and Linthicum KJ (2013). Potential for mosquitoes (Diptera: Culicidae) from Florida to transmit Rift valley fever virus. Journal of Medical Entomology 50, 1111. [PubMed: 24180117]

Vaney MC, and Rey FA (2011). Class II enveloped viruses. Cell Microbiol 13, 1451. [PubMed: 21790946]

Wang X, Hu C, Ye W, Wang J, Dong X, Xu J, Li X, Zhang M, Lu H, Zhang F, Wu W, Dai S, Wang HW, and Chen Z (2022). Structure of Rift Valley Fever Virus RNA-Dependent RNA Polymerase. J Virol 96, e0171321. [PubMed: 34787453]

Won S, Ikegami T, Peters CJ, and Makino S (2006). NSm and 78-kilodalton proteins of Rift Valley fever virus are nonessential for viral replication in cell culture. J Virol 80, 8274. [PubMed: 16873285]

Won S, Ikegami T, Peters CJ, and Makino S (2007). NSm protein of Rift Valley fever virus suppresses virus-induced apoptosis. J Virol 81, 13335. [PubMed: 17913816]

Wu Y, Zhu Y, Gao F, Jiao Y, Oladejo BO, Chai Y, Bi Y, Lu S, Dong M, Zhang C, Huang G, Wong G, Li N, Zhang Y, Li Y, Feng WH, Shi Y, Liang M, Zhang R, Qi J, and Gao GF (2017). Structures of phlebovirus glycoprotein Gn and identification of a neutralizing antibody epitope. Proc Natl Acad Sci U S A 114, E7564. [PubMed: 28827346]

Yadani FZ, Kohl A, Préhaud C, Billecocq A, and Bouloy M (1999). The carboxy-terminal acidic domain of Rift Valley Fever virus NSs protein is essential for the formation of filamentous structures but not for the nuclear localization of the protein. J Virol 73, 5018. [PubMed: 10233964]

Zamoto-Niikura A, Terasaki K, Ikegami T, Peters CJ, and Makino S (2009). Rift valley fever virus L protein forms a biologically active oligomer. J Virol 83, 12779. [PubMed: 19812169]

Zhang R, Kim AS, Fox JM, Nair S, Basore K, Klimstra WB, Rimkunas R, Fong RH, Lin H, Poddar S, Crowe JE Jr., Doranz BJ, Fremont DH, and Diamond MS (2018). Mxra8 is a receptor for multiple arthritogenic alphaviruses. Nature 557, 570. [PubMed: 29769725]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

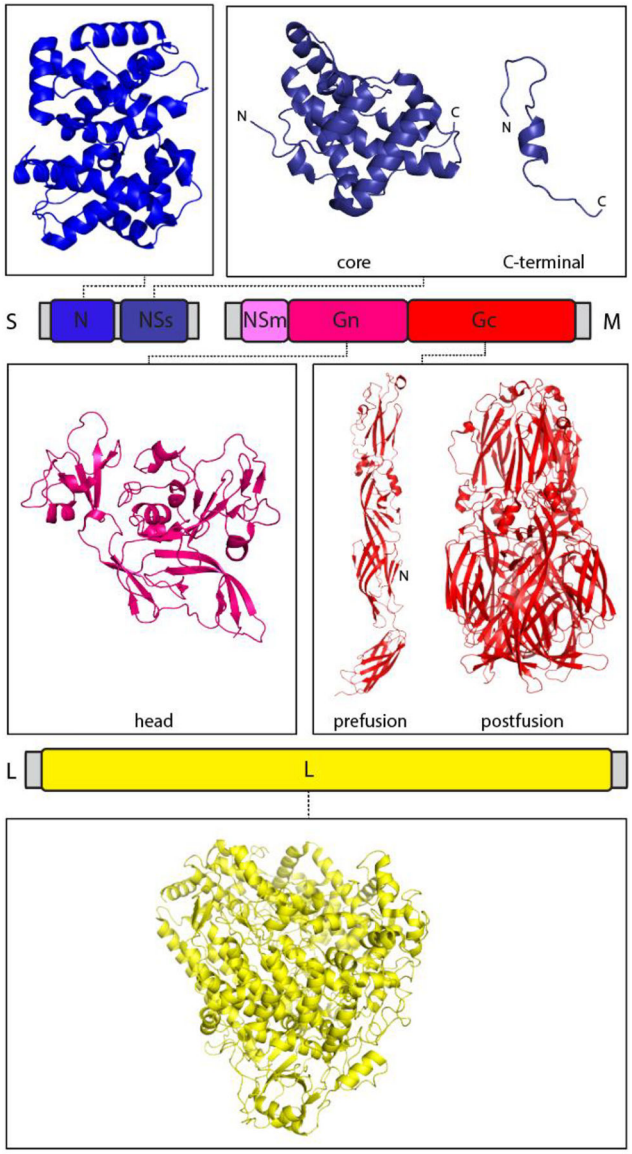

Figure 1.

Tri-segmented viral genome of RVFV encodes a handful of gene products. The tri-segmented virus genome encodes for six (6) multifunctional proteins that engage host factors at a variety of different stages in the replication cycle. The S segment encodes for nucleoprotein (N) and nonstructural protein S (NSs); the M segment encodes viral glycoproteins Gn and Gc as well as nonstructural protein M (NSm); and the L segment encodes the viral polymerase (L). Representative three-dimensional structures individual proteins or fragments for N (3LYF), NSs core (5OOO), NSs C-term (2N0Y), Gn head (5Y0W), Gc pre-fusion (6IEB), Gc post fusion (6EGT) and L (7EEI) rendered with PyMol Software (Schrodinger, 2015).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

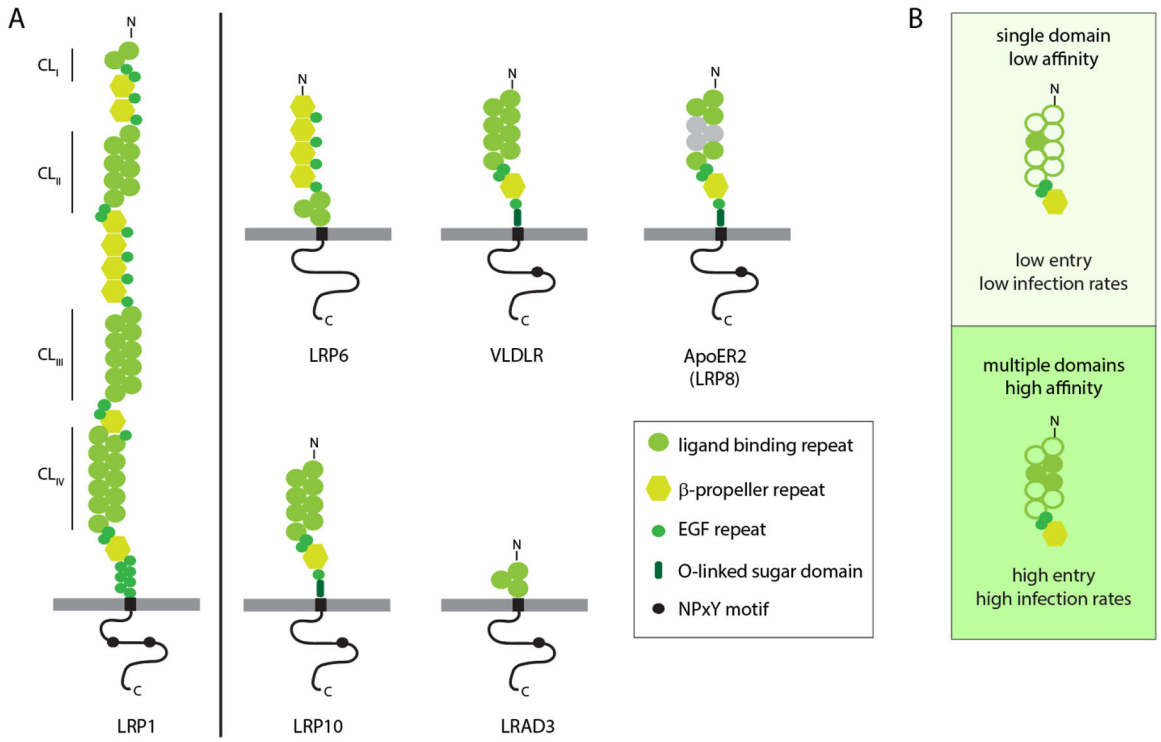

Figure 2.

LDL family receptors play a role in bunyaviral infections. A. Cartoon representation of select LDL family members include LDL receptor family protein (Lrp) 1 (Lrp1), Lrp6, Lrp10, very low-density lipoprotein receptor (VLDLR), Lrp8 (also known as apolipoprotein E receptor 2-ApoER2), and low-density lipoprotein receptor class A domain containing 3 (LDLRAD3). Each of these LDL family proteins contain repeating units including the ligand binding domain (LA or CRD), β-propeller repeats, epidermal growth factor repeat (EGF repeat), O-linked sugar domains, and NPxY, an endocytic motif, are shown in the inset. B. Model for ligand binding and viral entry. Single site binding result in low efficiency infections while multiple domain engagement results in apparent increased receptor/attachment factor engagement and therefore high levels of infectivity.