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A. Hejran[1*], F. Niazay[2], B. Sawicka[3], P. Niazi[4]

[1]Helmand University, Helmand, Afghanistan
[2]Mirwise Neeka University, Kandahar, Afghanistan
[3]University of Life Science, Lublin, Poland
[4]Kandahar University, Kandahar, Afghanistan
*e-mail: abdulbari.hejran94@gmail.com

MECHANISMS OF LANGYA HENIPAVIRUS (LAYV) PATHOGENESIS: GENOME FUNCTION, HOST CELL INFECTION, AND STRATEGIES OF IMMUNE EVASION

Langya henipavirus (LayV) is a novel zoonotic pathogen of the Henipavirus genus of the *Paramyxoviridae* family that is phylogenetically related to the virulent Nipah and Hendra viruses. First identified in the eastern part of China in 2018, the pathogen captured the attention of scientific researchers because of the genomic structure, postulated animal host and its possible impact on human health. This review focuses on the virus pathogenesis of LayV, especially its genomic model, the way it infects the cells and evades immune system. The purpose of the review is to summarize the current knowledge of LayV at the molecular and virological level, with the focus put on the functioning of the genome, the method of penetration into the host cell, and the possibility to influence the immune system. Additional emphasis is placed upon comparative genomic study, the use of glycoproteins to provide attachment and fusion activity, and suggested immune evasion strategies with comparison to other species of Henipavirus. The research is scientific and practical in nature and provides some background opinions on the biology of a new virus that has pandemic potential. The methodology would include a thorough review of publishing genomic terminations, scientific studies of molecular virology published in NCBI, and such comparative tests as Nipah and Hendra viruses. Key observations denote that LayV has a pattern of replication similar to other this type of henipaviruses, with a 6-gene RNA genome and potentially suppresses host innate immune responses. However, there are still significant uncertainty sheds, in particular with efforts to define host receptors and transmission forms. This review contributes to the field of emergent viral pathogenesis since it defines the viral pathogens biological dynamics of the LayV, thus setting the basis of future surveillance work, antiviral responses, and preparedness plans based on One Health.

Keywords: Langya henipavirus (LayV), viral pathogenesis, Genome structure, Host cell infection, Immune evasion, emerging zoonotic viruses.

А. Хеджран[1*], Ф. Ниязай[2], Б. Савицка[3], П. Ниязи[4]

[1]Гильменд университеті, Гильменд, Ауғанстан
[2]Мирвайс Ника университеті, Қандағар, Ауғанстан
[3]Өмір туралы ғылымдар университеті, юблин, Польша
[4]Қандағар университеті, Қандағар, Ауғанстан
*e-mail: abdulbari.hejran94@gmail.com

Ланъя вирусының (LayV) патогенез механизмдері: геномның функциялары, иесінің жасушасын жұқтыру және иммундық жүйеден жасырыну стратегиялары

Ланъя хенипавирусы (LayV) – *Paramyxoviridae* тұқымдасына жататын, *Henipavirus* тегіне кіретін, Nipah және Hendra вирустарымен филогенетикалық жағынан туыстас жаңа зоонозды патоген. Алғаш рет 2018 жылы Қытайдың шығыс бөлігінде анықталған бұл вирус өзінің геномдық құрылымы, ықтимал жануарлық резервуары және адам денсаулығына төндіретін қауіпі тұрғысынан ғылыми қауымдастықтың назарын аударды. Бұл шолу LayV вирусының патогенезіне, атап айтқанда оның геномдық құрылымына, иесінің жасушасын жұқтыру механизмдеріне және иммундық жүйеден жалтару стратегияларына арналған. Шолудың мақсаты – LayV туралы қазіргі таңдағы молекулалық және вирологиялық білімді жүйелеу, геномның қызмет ету ерекшеліктерін, жасушаға ену жолдарын және иммундық жауапқа ықтимал әсерін сипаттау.

салыстырмалы геномдық зерттеулерге, гликопротеиндердің жасушаға жабысу және мембранамен қосылу процесіндегі рөліне, сондай-ақ басқа хенипавирустармен салыстыра отырып, болжамды иммундық жалтару механизмдеріне ерекше назар аударылады. Бұл зерттеу ғылыми және практикалық маңызға ие, пандемиялық әлеуеті бар жаңа вирустың биологиясын түсінуге теориялық негіз қалыптастырады. Әдістемеге геномдық мәліметтерді талдау, NCBI-де жарияланған молекулалық вирология саласындағы ғылыми зерттеулер және Nipah пен Hendra вирустарымен жүргізілген салыстырмалы талдаулар кіреді. Негізгі қорытындылар LayV вирусының 6 геннен тұратын РНҚ геномына ие екенін, басқа хенипавирустарға ұқсас репликация үлгісін көрсететінін және иесінің туа біткен иммундық жауабын тежеуге қабілетті болуы мүмкін екенін көрсетеді. Дегенмен, вирустың жасушалық рецепторларын анықтау және берілу жолдарын нақтылау бағытында бірқатар белгісіздіктер әлі де сақталып отыр. Бұл шолу жаңа вирустық патогенез саласына өз үлесін қосып, «Бір Денсаулық» тұжырымдамасы аясында эпидемиологиялық бақылау, вирусқа қарсы шаралар мен дайындық жоспарларын әзірлеуге негіз қалайды.

Түйін сөздер: Ланъя хенипавирусы (LayV), вирустық патогенез, геномдық құрылым, иесінің жасушасын жұқтыру, иммундық жауаптан жалтару, жаңа зоонозды вирустар.

А. Хеджран[1*], Ф. Ниязай[2], Б. Савицка[3], П. Ниязи[4]

[1]Гильмендский университет, Гильменд, Афганистан
[2]Медицинский факультет, Университет Мирвайс Ника, Кандагар, Афганистан
[3]Университет естественных наук, Люблин, Польша
[4]Кандагарский университет, Кандагар, Афганистан
*e-mail: abdulbari.hejran94@gmail.com

Механизмы патогенеза вируса Ланъя (LayV): функции генома, заражение клеток хозяина и стратегии уклонения от иммунного ответа

Ланъя хенипавирус (LayV) – это новый зоонозный патоген, относящийся к роду *Henipavirus* семейства *Paramyxoviridae*, филогенетически близкий к высоковирулентным вирусам Nipah и Hendra. Впервые выявленный в восточной части Китая в 2018 году, данный вирус привлёк внимание научного сообщества благодаря своей геномной структуре, предполагаемому животному-резервуару и потенциальному воздействию на здоровье человека. Настоящий обзор посвящён патогенезу LayV с особым акцентом на геномную организацию вируса, механизмы инфицирования клеток хозяина и стратегии уклонения от иммунного ответа. Цель обзора – обобщить существующие знания о LayV на молекулярном и вирологическом уровнях, сосредоточив внимание на функционировании генома, механизмах проникновения в клетки хозяина и возможностях модификации иммунной реакции. Дополнительно рассматриваются сравнительные геномные исследования, роль гликопротеинов в обеспечении прикрепления и слияния с клеточной мембраной, а также предполагаемые механизмы иммунного уклонения, сопоставленные с другими представителями рода *Henipavirus*. Исследование носит как научный, так и практический характер и формирует теоретическую базу по биологии нового вируса с потенциальной пандемической угрозой. Методология включает всесторонний анализ опубликованных геномных данных, научные исследования в области молекулярной вирологии (включая базы NCBI) и сравнительные данные по вирусам Nipah и Hendra. Ключевые выводы показывают, что LayV имеет 6-генный РНК-геном и схожий с другими хенипавирусами механизм репликации, а также потенциально способен подавлять врождённый иммунный ответ хозяина. Тем не менее остаются значительные пробелы, особенно в вопросах идентификации клеточных рецепторов и путей передачи. Настоящий обзор вносит вклад в изучение патогенеза новых вирусных инфекций и формирует основу для дальнейшего эпиднадзора, разработки противовирусных стратегий и планов готовности в рамках концепции «Единое здоровье».

Ключевые слова: Ланъя хенипавирус (LayV), вирусный патогенез, структура генома, инфицирование клеток хозяина, уклонение от иммунного ответа, новые зоонозные вирусы

Introduction

Three recognized viral species classified within the genus *Henipavirus* include Hendra virus, Nipah virus, and Cedar virus. Hendra and Nipah viruses possess non-segmented, single-stranded, negative-sense RNA genomes, characteristic of all mononegaviruses. According to multiple reports, Langya virus, a novel member of this genus, has thus far been identified exclusively within China, with 35 confirmed human infections to date. Langya represents a newly discovered henipavirus. A limited number

of goats and dogs exhibited Langya virus-specific antibodies, and viral RNA was detected in 27% of the 262 shrews tested [1]. Henipaviruses, members of the *Paramyxoviridae* family, are enveloped, negative-sense, single-stranded RNA viruses with approximately 18 kb genomes that encode six principal structural proteins–N, P, M, F, G, L–as well as accessory proteins (V/W/C) [2, 3]. Hendra and Nipah viruses, archetypal henipaviruses, are highly fatal zoonotic agents with established bat reservoirs [3]. LayV is phylogenetically situated within the same genus and exhibits analogous zoonotic characteristics. Initially isolated from febrile patients in eastern China in 2018, LayV was genomically sequenced in 2022. Its genome (~18,402 nucleotides) conforms to the henipavirus structure, encoding six structural proteins and accessory proteins generated via RNA editing of the P gene. Panel A displays the scaled genome structure of Langya henipavirus (LayV), with *nt* indicating nucleotides. Panel B presents a phylogenetic tree based on the full amino acid sequence of the L protein, constructed using the maximum likelihood method and including recognized *Paramyxoviridae* species. LayV sequences from humans and shrews are marked in red and blue. The scale bar shows nucleotide substitutions per site; bootstrap values (1000 replicates) are indicated. Abbreviations include CedV, DARV, GAKV, GhV, HeV, HeV-g2, MojV, NiV, and SDQD. Panel C summarizes patients' provincial location, occupation, sex, and infection timeline (Figure 1) [2, 4]. LayV shares over 80% sequence identity in the L and N proteins with Nipah and Hendra viruses; however, its P gene and accessory proteins display divergence that may influence virulence. Transmission is presumed to occur via zoonotic spillover, with no evidence of human-to-human transmission documented. A serological survey of domestic animals revealed that LayV RNA was predominantly identified in *Crocidura lasiura* shrews, a species prevalent in Northeast Asia. Among 121 tested *C. lasiura* specimens, 52.1% tested positive for LayV. The virus was also detected in 20% of *Crocidura shantungensis* samples, 5% of dogs, and 2% of domestic goats, indicating multiple potential hosts, with shrews likely serving as the natural reservoir (Figure 2) [5].

Cryo-EM analysis of the LayV-F ectodomain revealed conserved pre- and postfusion states, with distinct antigenic features at the prefusion apex [6]. Prefusion-stabilizing mutations effective in NiV F also stabilize LayV F, informing cross-reactive vaccine design [7]. The crystal structure of LayV-G CTD demonstrates structural deviation from NiV/HeV G proteins and absence of ephrinB receptor binding, indicating a novel cellular receptor [8]. LayV F and G mediate membrane fusion in human, mouse, and hamster cells through an unidentified receptor, suggesting distinct host entry strategies [9]. Although precise human receptor identification remains unresolved, LayV replicates in Vero and endothelial cells and induces lung pathology in animal models, resembling that of related henipaviruses [10]. The P/V/W proteins of henipaviruses inhibit STAT1/2 signaling; the LayV P protein retains conserved motifs likely enabling similar antagonism of innate immune responses. LayV antigenic epitopes are markedly distinct from NiV/HeV, as shown by minimal monoclonal antibody cross-reactivity, highlighting unique immune evasion strategies. Detection of LayV RNA in approximately 27% of shrews and seropositivity in goats and dogs suggests a multi-host reservoir ecology (Table 1) [5]. By mid-2022, 35 human cases had been reported, with no fatalities or confirmed human-to-human transmission [3].

Finally, Recurrent COVID-19 outbreaks persist due to the continual emergence of SARS-CoV-2 variants. In 2022, the global health landscape was further complicated by monkeypox outbreaks. Concurrently, a novel pathogen, LayV, was identified in eastern China, with 35 confirmed cases. *Henipavirus*, classified as a biosafety level 4 pathogen, is associated with reservoirs such as bats, rodents, and shrews, with the Common Shrew posited as a potential transmission vector. The pathogenesis of the virus is modulated by key cytokine responses, and elucidating these mechanisms may facilitate the development of immunogenic viral proteins, as well as targeted vaccines and therapeutics. Presently, no approved vaccine or antiviral treatment exists for Henipavirus infections; however, a subunit vaccine based on the Hendra virus G glycoprotein (HeV-G) has demonstrated efficacy in preclinical models. Structural characterization of the virus, notably its 'tree-like' prefusion conformation of the F protein, indicates that a trivalent or tetravalent vaccine formulation may be required to achieve broad immunogenic coverage [11-13].

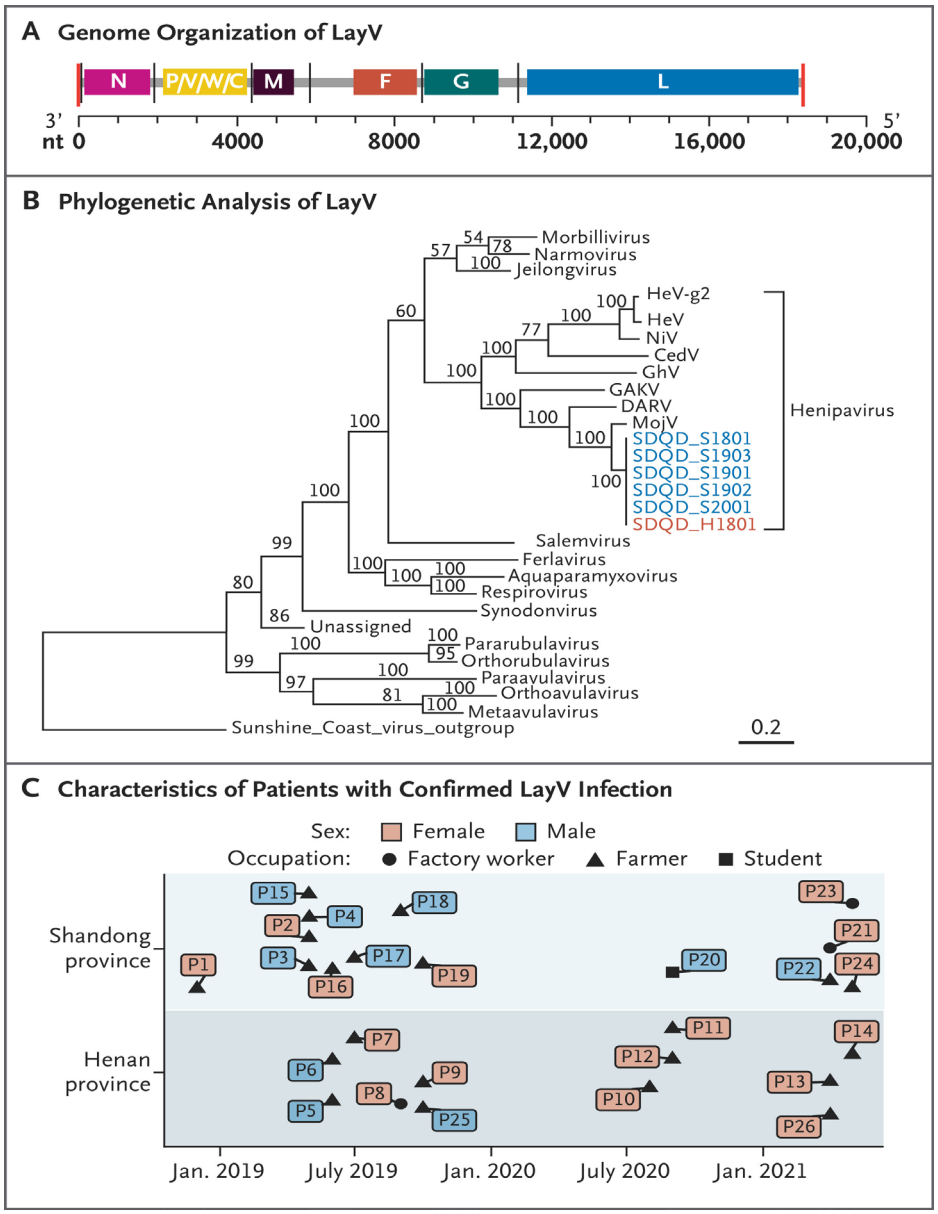

Figure 1 – LayV is characterized by its genome structure, phylogeny, and case distribution [4]

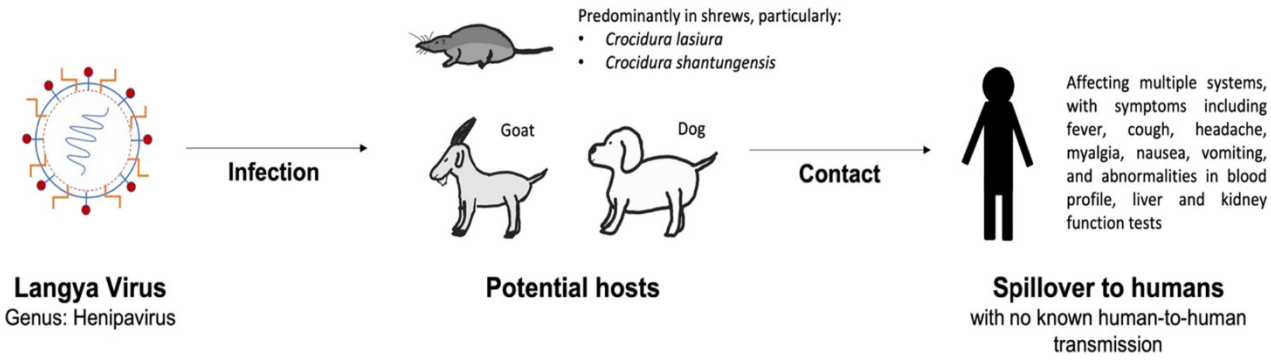

Figure 2 – Transmission of LayV [5]

Table 1 − Epidemiological patterns of henipaviruses outbreak in China and Southeast Asia

Species of henipavirus	Year	Countries affected	Outbreak to humans	Source of transmission
Nipah virus	1998	Malaysia, Singapore	Yes	Pig
	2001	Bangladesh, India	Yes	Date palm sap (Bangladesh), Nosocomial (India)
	2003	Bangladesh	Yes	
	2007	India	Yes	
	2018	India	Yes	Bats
	2019	India	Yes	Bats
	2000	Cambodia	No	Bats
	2002–2004	Thailand	No	Bats
	2008	Indonesia	No	Bats
	2007–2008	Vietnam	No	Bats
Hendra virus	1994–2022	Australia	No	Horse
Langya virus	2022	China	Yes	Shrews

Literature review

The structural preservation observed in the F glycoprotein of LayV substantiates its classification within the *Paramyxoviridae* family; however, notable antigenic divergence from NiV and HeV complicates current frameworks of vaccine cross-reactivity [9]. The «spring-loaded» fusion mechanism and prefusion conformational stability of LayV-F affirm its suitability for structure-guided vaccine development, though its antigenic distinctiveness necessitates the generation of LayV-specific immunogens [6]. Likewise, the unique glycosylation profile and "head-down" orientation of LayV-G underscore the imperative for customized receptor-binding investigations, as interactions with ephrin-B2/B3 appear improbable [2, 14]. Nevertheless, comprehensive cytokine profiling and characterization of in vivo infection kinetics remain incomplete for LayV, in contrast to the extensively studied NiV and HeV [9]. The current absence of confirmed human-to-human transmission, along with subclinical zoonotic spillover events, aligns LayV more closely with MojV in ecological terms; however, dedicated infection models are required to evaluate its transmissibility and tissue tropism [15].

Critically, the antiviral efficacy of neutralizing antibodies or epitope-driven vaccines targeting LayV G/F antigens has not yet been experimentally validated. Preliminary immunoinformatics analyses yield promising *in silico* predictions, but empirical substantiation is necessary [16]. Moving forward, research must prioritize receptor identification, detailed profiling of innate and adaptive immune responses, and the establishment of animal models to support One Health-based surveillance and the development of LayV-specific countermeasures, thereby reducing the risk of future henipavirus emergence.

Genomic Features of Langya Henipavirus

Genome Structure and Organization

LayV harbors a non-segmented, negative-sense RNA genome of approximately 18 kb, encoding six principal structural proteins N (nucleocapsid), P (phosphoprotein), M (matrix), F (fusion), G (attachment glycoprotein), and L (large polymerase) alongside accessory V/W proteins generated through RNA editing of the P gene [3, 17, 18]. Guo et al. (2024) demonstrates that LayV exhibits a uniquely mushroom-shaped architecture. The LayV-G glycoprotein lacks binding affinity for receptors utilized by other henipaviruses, such as ephrin B2/B3, and presents antigenic properties distinct from those of HeV-G and NiV-G. The near-complete structural elucidation of LayV-G highlights this distinctive morphology, setting it apart from other *Henipavirus* attachment glycoproteins. Its stalk and transmembrane domains resemble the stem and base of a mushroom cap, potentially mediating interactions with the F protein and modulating the membrane fusion process. As an attachment glycoprotein within the *Paramyxoviridae* family, LayV-G shares approximately 86% overall sequence identity with MojV-G, particularly within the conserved receptor-binding region. Prior investigations have shown that MojV-G fails to engage any known paramyxovirus receptor, and the receptor-binding capability of LayV-G to established paramyxovirus receptors remains undetermined. To elucidate the molecular

mechanism of LayV-G, the extracellular domain (residues 63–624 a.a.) was initially purified via recombinant expression. The C-terminal Flag-tagged LayV-G exhibited stability and homogeneity in size exclusion chromatography (SEC), and its UV absorption peak was assessed through non-reducing and reducing SDS-PAGE followed by Coomassie brilliant blue staining and western blotting, confirming the tetrameric conformation of LayV-G (Figure 3) [17].

Structural investigations employing cryo-electron microscopy and X-ray crystallography have verified that the LayV F and G proteins adopt the canonical class I fusion trimer and six-bladed β-propeller conformations, respectively, both of which are essential for host cell entry. Importantly, the LayV F protein preserves the "spring-loaded" prefusion conformation, with conserved stabilizing residues adjacent to the fusion peptide, thereby enabling structure-based antigen design [7].

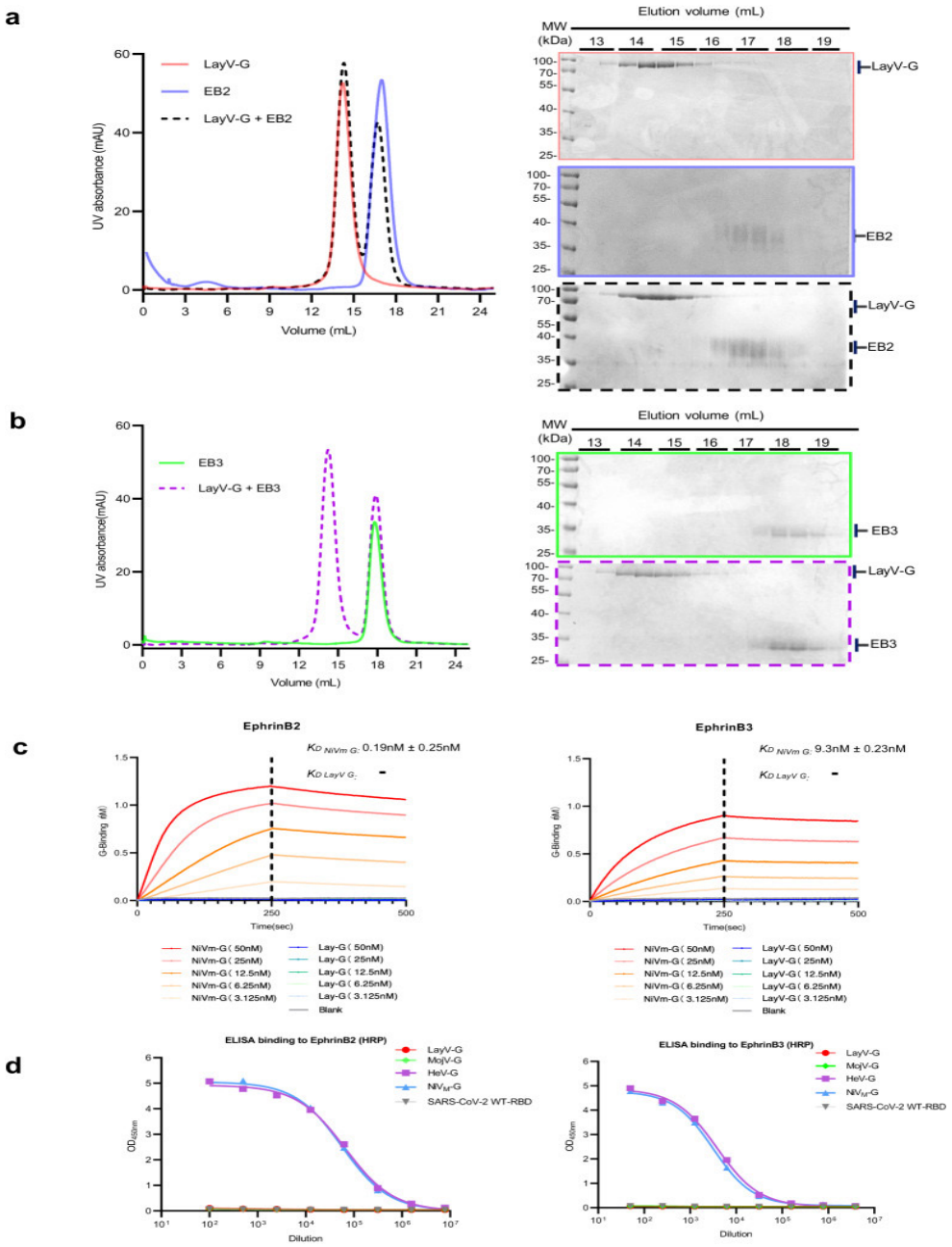

Figure 3 − Biochemical profiling of the LayV-G glycoprotein and its binding interactions with Henipavirus receptors ephrinB2 and ephrinB3 [17]

Comparison with Other Henipaviruses:- In comparison to its highly pathogenic counterparts, LayV demonstrates substantial genomic conservation in critical proteins such as N and L, sharing over 80% sequence identity with Nipah virus (NiV) and Hendra virus (HeV), while exhibiting greater divergence in the P, F, and G proteins particularly within antigenic and receptor-binding domains.The presence of a unique glycosylation motif at Asn189 in LayV-G, absent in NiV and HeV, implies altered host interactions and antigenic properties [15]. Structural analysis of LayV-G reveals a distinct "mushroom-like" tetrameric arrangement with four downward-tilted head domains, differing from the bidirectional configuration of NiV/HeV G proteins and suggesting alternative receptor specificity [17]. These conformational differences are supported by functional evidence indicating that LayV-G does not interact with ephrinB2 or B3, in contrast to NiV and HeV, thereby indicating a novel cellular entry mechanism. Ongoing comparative genomics and reverse genetics investigations are critical to elucidate the functional consequences of these molecular variations on LayV's pathogenic potential and zoonotic risk [8].

Mechanisms of Host Cell Infection

Viral Attachment and Entry

The G (attachment) glycoprotein of LayV plays a critical role in mediating host cell entry. Cryo-EM and crystallographic analyses reveal that LayV-G forms a tetrameric, mushroom-shaped structure characteristic of henipaviruses, featuring a six-bladed β-propeller head and a stalk domain that facilitates interaction with the fusion (F) protein [17]. In contrast to Nipah (NiV) and Hendra (HeV), LayV-G fails to bind ephrin-B2 or ephrin-B3 receptors, as demonstrated by SPR and ELISA assays, suggesting engagement with an unidentified receptor [8]. Structural comparison indicates approximately 86% sequence identity with Mojiang virus (MojV), which similarly lacks binding to known receptors, supporting this notion [17] Functional fusion assays confirm that LayV-G and LayV-F together mediate membrane fusion and syncytia formation in human, mouse, and hamster cell lines, validating receptor-dependent activation of F [9].

Functional Evaluation of LayV F and G Glycoproteins: LayV F harbors a presumptive cleavage motif at residue R104, analogous to R109 in NiV and K109 in HeV, but lacks the canonical YXXΦ sorting signal and one of two downstream tyrosine residues found in the C-terminal domains of NiV/HeV F, which mediate endosomal recycling and cathepsin L-dependent cleavage. Nonetheless, transient expression of LayV F, or co-expression with LayV G, in CHO-K1, HEK293T, or Neuro-2a cells produced both the F0 precursor and proteolytically processed F1 (and F2) in proportions comparable to other henipaviruses. These findings parallel those for MojV F and suggest that LayV/MojV employ a cleavage mechanism distinct from that of NiV and HeV. To investigate this, the general cysteine protease inhibitor Aloxistatin (E64d) was applied to transiently transfected Neuro-2a cells expressing LayV F, MojV F, NiV F, or HeV F. E64d impaired cleavage of NiV F and HeV F but had no effect on LayV or MojV, indicating that a distinct protease mediates F processing in this divergent HNV subgroup. LayV F contains a putative cleavage site at residue 104 (R104), analogous to NiV (R109) and HeV (K109), but lacks the canonical YXXΦ motif and one of the two downstream tyrosine residues found in the C-terminal cytoplasmic domains of NiV/HeV F, which facilitate endosomal recycling and subsequent cathepsin L-mediated cleavage (Figure 4) [9].

Structural Characterization of LayV F in Prefusion and Postfusion States*:* – To delineate LayV F architecture, an ectodomain construct fused to a GCN4 trimerization motif was produced. EM imaging of negatively stained samples confirmed compact homotrimer formation characteristic of the prefusion state, though spontaneous refolding to the postfusion form occurred. Consequently, two cryo-EM datasets were collected four months apart, resolving prefusion and postfusion structures at 2.5 Å and 3.9 Å, respectively. The prefusion LayV F adopts a ~90 Å-high and ~90 Å-wide pyramidal trimer, analogous to prefusion NiV F, despite sharing only 44% sequence identity. A LayV F protomer aligns with NiV F at a root-mean-square deviation (rmsd) of 2.3 Å over 432 Cα atoms, compared to 1.1 Å over 436 Cα atoms between NiV F and HeV F. All five disulfide bonds in LayV F are conserved relative to NiV/HeV F, supporting correct folding. The resolved LayV F structure closely resembles a recent LayV F model (rmsd 0.6 Å). The fusion peptide (residues 110–122) is identical to MojV F and conserved across NiV/HeV F, exhibiting an identical conformation. N-linked glycans at N65 and N459 are resolved, whereas NiV/HeV F possess at least four such glycans. The N65 glycan emerges from the trimer apex similarly to the N67 glycan of NiV/HeV, an epitope for neutralizing antibodies. LayV F's divergent sequence and glycosylation suggest unique antigenic properties [9].

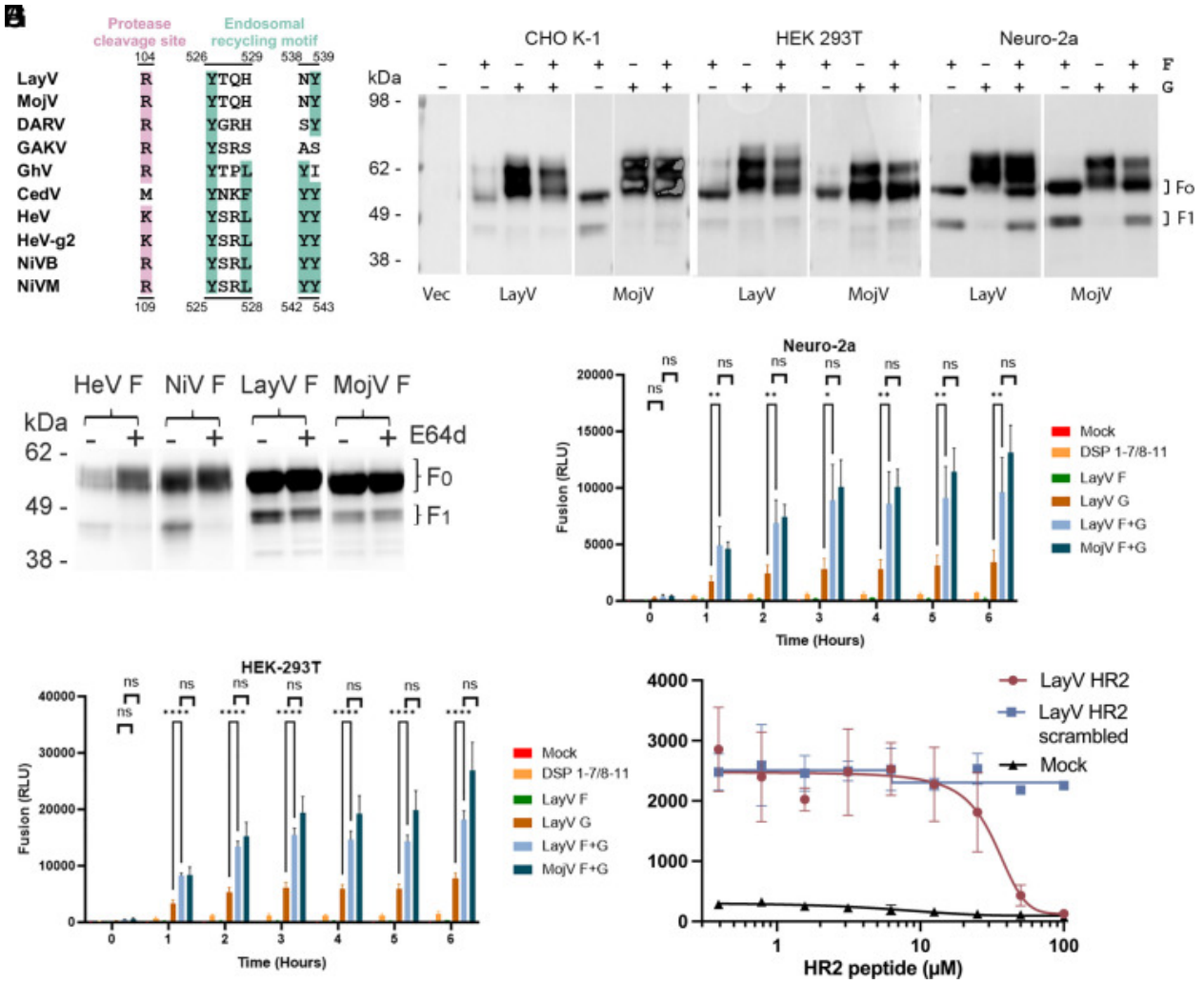

Figure 4 − (A) Alignment reveals conserved cleavage and recycling motifs in LayV and related Henipavirus F proteins. (B–D) Western blot shows LayV F is cleaved into F1/F2 in multiple cell lines. (E) E64d does not affect LayV/MojV F cleavage, indicating a different protease from NiV/HeV. (F–G) LayV and MojV F/G drive cell–cell fusion, confirmed by luciferase assays. (H) LayV HR2 peptide inhibits fusion dose-dependently; scrambled peptide shows no effect [9]

The postfusion LayV F presents as a ~150 Å-high and ~70 Å-wide conical trimer, with a central triple helix and HR1 domain enveloped by three antiparallel HR2 helices, forming a six-helix bundle. The opposite end forms a triangular base. HR1 and HR2 from each protomer interact exclusively with the other two protomers, forming an interlaced structure. Glycans at N65 and N459 localize to the outer region of the elongated trimer. In this conformation, the fusion peptide and transmembrane domain are repositioned to the same end to facilitate membrane fusion. The topology mirrors other paramyxovirus and coronavirus postfusion trimers, indicating evolutionary conservation of fusion mechanisms. While extensive conformational shifts occur, the N-terminus, β-rich domains (residues 281–420), and upstream helix largely retain their structure, aside from changes in orientation. This transition increases the buried surface area between protomers more than twofold–from ~2,180 Å² in prefusion to ~5,220 Å² in postfusion–highlighting the irreversible nature of this refolding [9].

A Generalizable Strategy for Prefusion Stabilization of HNV F Glycoproteins: – The spontaneous refolding of LayV F underscores its metastability, a common feature of viral fusion proteins. Immunization with prefusion, but not postfusion, NiV or HeV F induces neutralizing antibodies, prompting evaluation of NiV/HeV prefusion-stabilizing mutations in LayV F. These included i) NiV L172F and S191P (corresponding to LayV I167F and S186P) and ii) an engineered disulfide bond across F2 and

F1 (NiV/HeV N100C/A119C, LayV N95C/A114C) near the cleavage site. LayV F I167F/S186P produced primarily postfusion trimers, while N95C/A114C yielded well-folded prefusion trimers. The combination of all four mutations resulted in prefusion trimers with some aggregation. The engineered disulfide bond effectively stabilized prefusion LayV F and restored expression of otherwise postfusion constructs. Spontaneous refolding of LayV F highlights its metastable nature, characteristic of viral fusion proteins (40–42, 45–50). Immunization with prefusion, but not postfusion, NiV F or HeV F induced neutralizing antibodies (46, 51), prompting assessment of the applicability of NiV/HeV F prefusion-stabilizing mutations to LayV F. Evaluated were: i) the NiV L172F (cavity-filling; LayV F I167F) and S191P (postfusion central helix breaker; LayV F S186P) substitutions (51), and ii) the engineered disulfide bond bridging the F2 and F1 subunits (NiV/HeV F N100C/A119C; LayV F N95C/A114C), proximal to the F cleavage site (12, 22), all of which appear structurally compatible with LayV F (Fig. 5 A–C). LayV F I167F/S186P primarily yielded postfusion trimers (Fig. 5 E and F), whereas LayV F N95C/A114C facilitated production of well-folded prefusion F trimmers. The combination of all four mutations produced prefusion F trimers along with some aggregates (Figure 5) [9].

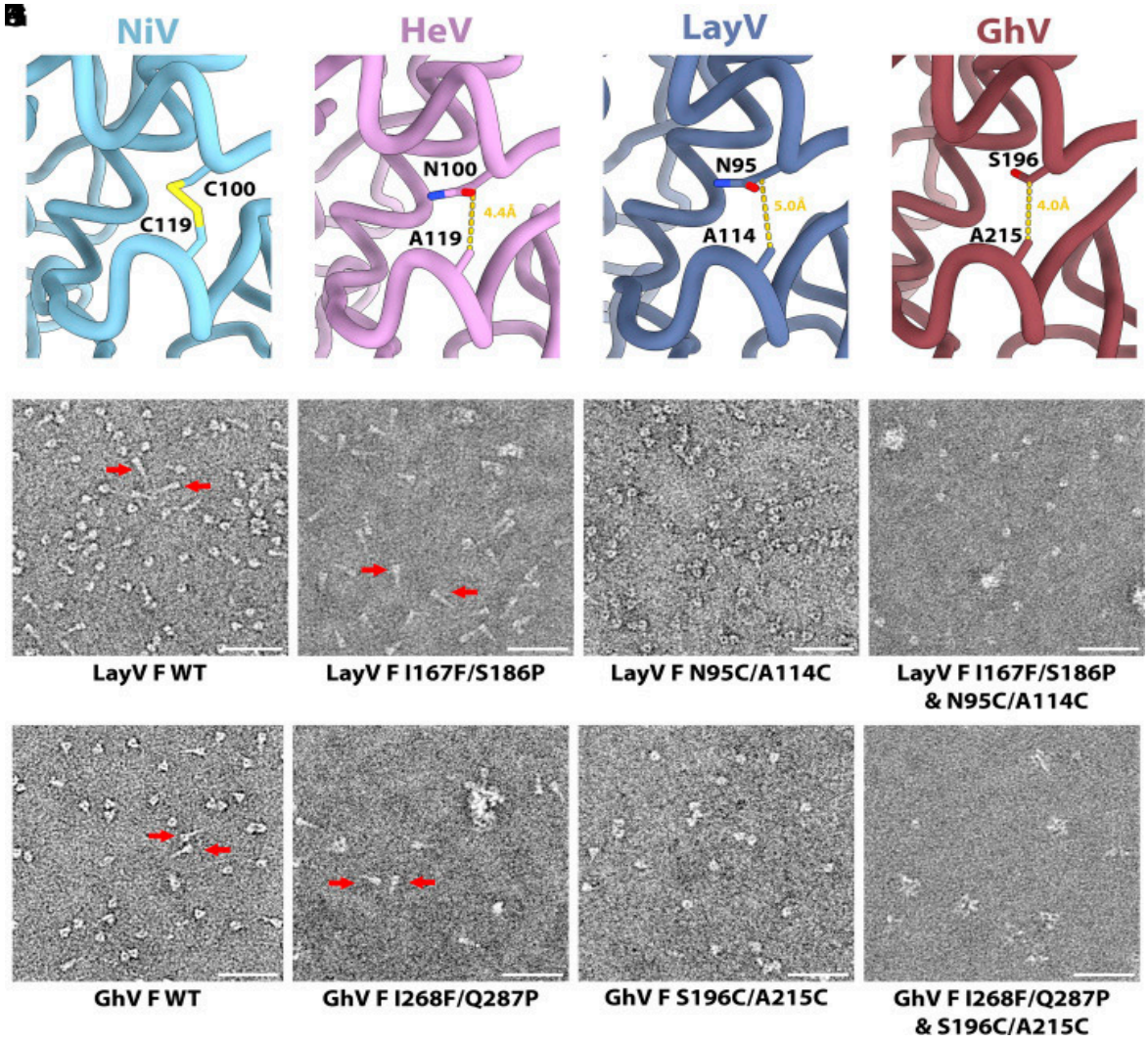

Figure 5 − (A–D) Structural analysis of NiV, HeV, LayV, and GhV F glycoproteins demonstrates spatial feasibility for disulfide bond engineering to enhance prefusion conformational stability. (E–H) Electron microscopy of wild-type and mutant LayV F variants indicates that the N95C/A114C substitution maintains the prefusion state, whereas I167F/S186P favors postfusion configuration. (I–L) EM evaluation of GhV F mutants exhibits analogous stabilization effects with I268F/Q287P and S196C/A215C substitutions; red arrows denote postfusion structures [9]

Discovery of a LayV F Cross-Reactive Monoclonal Antibody: – Monoclonal antibodies targeting NiV and HeV F proteins neutralize infection and confer protection in animal models. To assess cross-reactivity, biolayer interferometry (BLI) was used to test NiV/HeV F-directed mAbs against LayV F. Neither 5B3 nor 12B2 IgGs bound LayV F, likely due to structural discrepancies. However, 4G5 IgG, but not 3C4 IgG, exhibited binding, both derived from MojV F immunizations. These results highlight the close evolutionary and antigenic relationship between LayV F and MojV F sharing 90% sequence identity and their divergence from other henipaviruses [9].

Viral Replication and Transcription

LayV undergoes complete replication within the cytoplasm, utilizing an RNA-dependent RNA polymerase complex composed of the L (large) protein and its cofactor P (phosphoprotein), in conjunction with the N (nucleocapsid) protein. Structural analyses of NiV/HeV L–P complexes indicate a multi-domain organization including RNA polymerase, capping, and methyltransferase domains functionally integrated through P-mediated oligomerization [19, 20]. Gene expression adheres to a classical transcriptional gradient, with 3′-proximal genes such as N being transcribed at higher levels than distal genes, thereby promoting early nucleocapsid formation [21]. Genome replication involves synthesis of a full-length antigenome, with nascent RNA being encapsidated by nucleocapsid proteins. The M (matrix) protein plays a pivotal role in virion assembly and budding by mediating interactions between the nucleocapsid and viral envelope [19]. A recently established RT-qPCR assay targeting the LayV L gene has verified active viral replication in vitro, consistent with polymerase activity profiles reported in NiV/HeV systems.

Host Range and Tropism

LayV has been epidemiologically associated with shrews as its principal reservoir. Molecular surveillance in eastern China demonstrated that 27% of sampled shrews (Crocidura lasiura and C. shantungensis) harbored LayV RNA, strongly implicating these species in viral persistence and zoonotic transmission [22]. These observations are consistent with previous detections of henipavirus-like sequences in shrews across Asia and Africa. The widespread ecological distribution and growing adaptability of shrews to anthropogenic environments increase the likelihood of interspecies viral transmission [23]. Beyond wildlife reservoirs, domestic animals appear to serve as incidental hosts. Serological investigations revealed LayV-specific antibodies in approximately 2% of goats and 5% of dogs, whereas pigs and cattle showed no evidence of seropositivity [2]. These findings are congruent with historical accounts of domestic species such as pigs, cattle, and horses acting as amplifiers in past Nipah and Hendra virus outbreaks [22].

Human LayV infections remain sporadic, with 35 confirmed cases between 2018 and 2022, all involving documented contact with animals, predominantly shrews [24]. Clinical monitoring and contact tracing of approximately 15 individuals per case revealed no indications of human-to-human transmission [25]. This transmission profile reflects the ecological patterns observed in other non-bat henipaviruses with limited human spread [22]. However, the restricted sample size and absence of confirmed transmission clusters do not preclude the possibility of infrequent human-to-human transmission.

Pathogenesis

A hallmark of henipavirus pathogenesis is the induction of cell–cell fusion among adjacent host cells, facilitating direct viral dissemination without reliance on viral budding. The replication dynamics of LayV and MojV remain incompletely characterized, as MojV has never been isolated and LayV was only recently identified. Experimental evidence demonstrates that LayV is capable of replicating in Vero cells *in vitro*. MojV has been non-causatively implicated in cases of human pneumonia. LayV has been associated with febrile respiratory illness in humans, notably without evidence of encephalitis or neurological involvement. The clinical manifestations of LayV infection resemble those caused by other respiratory pathogens, including influenza viruses and SARS-CoV-2, thereby complicating diagnosis based solely on symptomatology (Table 2). MojV remains a controversial etiological agent in human pneumonia, lacking definitive pathogenic association [18].

Table 2 − Pathogenic Differences in Henipavirus Outbreaks

Symptoms/Signs	Nipah-M	Hendra	Langya	Mojiang
Fever	97%		100%	100%
Headache	65%		35%	50%
Cough	13%		50%	100%
Neurological Signs	11%	50%	0	0
Vomiting	27%		35%	16%
Elevated Neutrophils			50%	
Thrombocytopenia	30%		57%	
Leukopenia	11%		54%	33%
Death	32%	57%	0	50%

Strategies of Immune Evasion

Innate Immune System Avoidance by Langya Henipavirus

LayV likely adopts a complex strategy to circumvent the host innate immune response, paralleling mechanisms observed in related henipaviruses such as Nipah (NiV) and Hendra (HeV). Central to this evasion are proteins encoded by the P gene–P, V, and W–as well as the C protein produced via alternative reading frames. These viral proteins disrupt type I and II interferon (IFN) signaling by binding to STAT1 and STAT2, thereby inhibiting their phosphorylation and subsequent nuclear translocation [26]. In NiV and HeV, the V protein sequesters STAT1 and STAT2 into cytoplasmic aggregates, while the W protein confines STAT1 within the nucleus, suppressing IFN-stimulated gene (ISG) transcription [27-30].

Although less potent, the P protein also contributes by retaining STAT1 in the cytoplasm [31]. LayV's P/V/W proteins contain conserved N-terminal STAT-binding motifs including glycine-121 and serine-130/131 previously identified as critical for STAT interaction in NiV and HeV, suggesting analogous IFN antagonism in LayV [32]. The study evaluated the inhibitory effects of NiV-N, HeV-N, and MV-N proteins on host interferon (IFN) responses. Reporter assays demonstrated that henipavirus N proteins suppressed ISRE- and GAS-driven gene expression in a dose-dependent manner. Although less potent than P gene products against type I IFN, N proteins more effectively attenuated type II IFN responses. The core domain of NiV-N and HeV-N significantly inhibited IFN-α and IFN-γ signaling, whereas their tail domains showed no effect. NiV-N also impaired STAT1/2 nuclear translocation by disrupting interactions with importins α5, α6, and α7 [27]. Similarly, the M protein of NiV suppresses innate immunity by interacting with TRIM6 to inhibit TBK1 activation and downstream IFN signaling. NiV minigenome systems were pivotal in elucidating the bipartite replication promoter structure, confirming the applicability of the rule of six to NiV, evaluating the roles of noncoding regions, and conducting functional analyses of the NiV N, P, and L gene products (Figure 6) [33]. Given the conserved structure and function of LayV's N and M proteins, comparable mechanisms are plausible. Nonetheless, direct experimental validation such as STAT localization and ISG reporter assays is required to substantiate these immune evasion strategies in LayV infection.

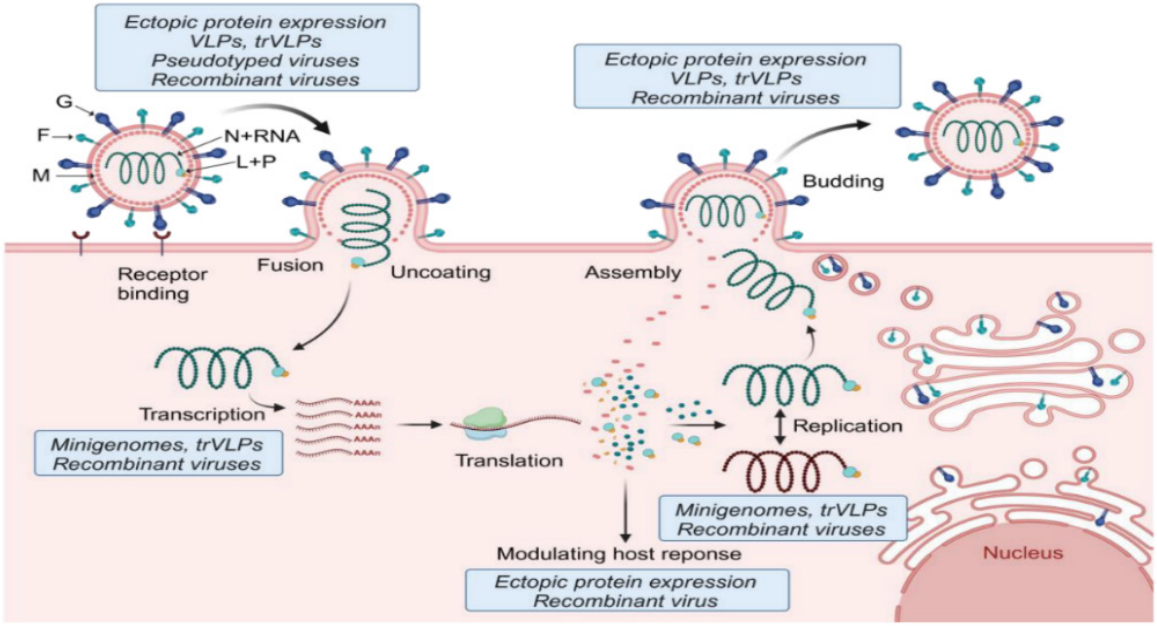

Figure 6 − The henipavirus replication cycle begins with G glycoprotein-mediated attachment to host cell receptors such as ephrin-B2/B3. Membrane fusion, facilitated by both G and F proteins, allows viral entry, releasing the helical nucleocapsid into the cytoplasm. Primary transcription is initiated, followed by translation of viral mRNAs, secondary transcription, and genome replication within cytoplasmic inclusion bodies. Viral proteins P, V, W, and C modulate host antiviral responses. Newly synthesized genomes are packaged with N, P, and L proteins into nucleocapsids and transported to the plasma membrane. The M protein directs viral assembly and budding. Experimental tools for each stage are outlined in blue boxes, including fusion (F), attachment (G), polymerase (L), matrix (M), nucleocapsid (N), phosphoprotein (P), transcription- and replication-competent virus-like particles (trVLPs), and virus-like particles (VLPs) [33]

Modulation of Host Signaling Pathways in LayV

LayV employs conserved molecular tactics akin to other henipaviruses to inhibit essential host innate immune signaling cascades, particularly the JAK/STAT and pattern recognition receptor (PRR) pathways. Accessory proteins P, V, and W produced via RNA editing of the P gene play central roles in this immune modulation. Studies on Nipah virus (NiV) reveal that the V protein binds STAT1/STAT2, forming high-molecular-weight aggregates that obstruct phosphorylation and nuclear translocation, thereby suppressing JAK/STAT signaling. And Interferons (IFNs) are key modulators of the innate antiviral immune response, triggered upon detection of pathogen-associated molecular patterns by host pattern recognition receptors. This activation initiates a signaling cascade that culminates in the secretion of type I IFNs and subsequent phosphorylation of STAT1 and STAT2 [34]. Simultaneously, the W protein disrupts nuclear import mechanisms, such as those mediated by importin-α, impeding transcriptional activation of interferon-stimulated genes (ISGs) [35]. Specific mutations, such as Y116E within the STAT-interacting domain, reduce antagonistic activity and attenuate virulence in animal models, highlighting the clinical significance of this immune evasion. The N-terminal region of the NiV P protein, shared with the V and W proteins, contains a STAT1-binding domain. Prior investigations employing diverse methodologies identified seven distinct amino acid substitutions within this domain, specifically: Y116E, G121E, G127E, G135E, G125E24, S130A, and S131A (Figure 7) [36]. Moreover, the NiV V protein suppresses PRR signaling by inhibiting host sensors including RIG-I, MDA5, IRF-3, and NF-κB through interactions with cellular proteins such as PP1 and 14-3-3 [37]. Transcriptomic analyses of henipavirus-infected cells reveal marked repression of both JAK/STAT-responsive and PRR-activated gene expression [38].

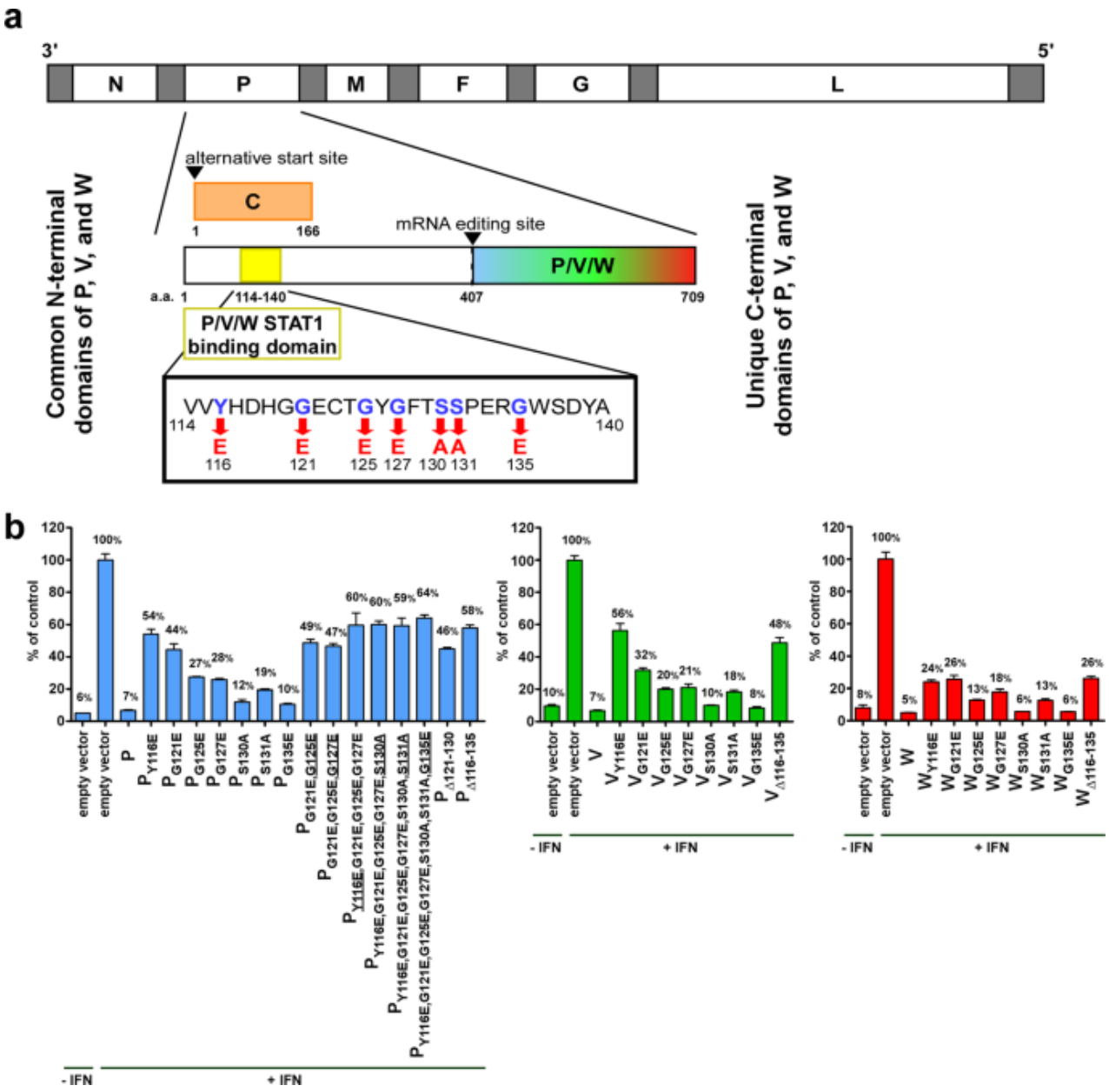

Figure 7 − (a) The STAT1-binding domain shared by NiV P, V, and W proteins encompasses amino acids 114–140, overlapping the open reading frame of the C protein; seven critical residues within this region mediate STAT1 interaction, with mutagenesis abrogating binding capability. (b) Luciferase reporter assays in 293T cells demonstrate that targeted mutations in the P, V, and W proteins attenuate IFN-α-induced signaling, corroborating the involvement of these residues in interferon antagonism [36]

Persistence and Latency (Hypothetical)

While LayV has not been conclusively shown to establish latency, insights from related henipaviruses, particularly Nipah virus (NiV), suggest the potential for prolonged viral persistence in specific tissues, especially the central nervous system (CNS) [39].

1. Evidence of NiV Persistence*:* – NiV has been identified in survivors several years post-infection, with delayed-onset encephalitis occurring up to 11 years later [39]. Post-mortem and neuroimaging analyses have demonstrated viral persistence in neurons and microglia of the brainstem and cortex, accompanied by lymphohistiocytic inflammation and demyelination. Experimental non-human primate models have shown that although viremia is initially acute, viral RNA and antigens persist in brain tissue during convalescence, indicating the possibility of recrudescence [39, 40].

2. Mechanisms of Persistence*:* – NiV persistence likely relies on immune evasion and residence in immune-privileged compartments. Suppression of interferon (IFN) signaling via accessory proteins may facilitate survival in neural tissues. Additionally, gradual viral release from endothelial and neural reservoirs may contribute to latent infection [26].

3. Implications for LayV: – Given LayV's structural and functional homology with NiV, particularly in replication and immune evasion, it is plausible that LayV may also exhibit tissue persistence [33]. However, no direct evidence currently confirms LayV latency. Longitudinal studies, including cerebrospinal fluid and brain tissue sampling in experimental models, are essential [41].

4. Research Needs:- Investigation into LayV persistence necessitates:

- Development of long-term animal models (e.g., ferret, hamster) [42].
- Use of molecular techniques (e.g., RT-qPCR, in situ hybridization) to detect viral RNA in neural and lymphoid tissues [43].
- Application of immunohistochemistry to localize viral proteins and characterize inflammatory responses (e.g., gliosis, microglial activation) [44].

Current Knowledge Gaps in Langya Henipavirus (LayV) Research

Despite progress, several pivotal gaps remain in the understanding of LayV pathogenesis, hindering effective surveillance, treatment, and prevention [17]:

1. Host Receptor Identification: – LayV's entry mechanism is unclear, as it does not bind the ephrin-B2/B3 receptors used by Nipah and Hendra viruses. Although LayV-G adopts a novel tetrameric architecture, its cellular receptor remains unidentified. Clarifying this is critical for understanding host range, tissue targeting, and therapeutic development [17].

2. Human-to-Human Transmission Potential: – As of August 2022, 35 human LayV cases were reported in China, all linked to animal contact with no evidence of person-to-person spread. However, limited sample size restricts conclusions; robust cohort studies and contact tracing are needed to assess low-frequency transmission [25, 45, 46].

3. Immune Modulation Mechanisms: – LayV encodes P/V/W proteins with conserved STAT-binding and RNA editing motifs, implying potential disruption of JAK/STAT and PRR signaling. However, experimental data confirming LayV-mediated immune suppression, including STAT sequestration or IRF-3 inhibition, is lacking [19, 47, 48, 49].

4. Lack of Animal Models: – No animal model currently exists for LayV, contrasting with validated models for other henipaviruses (e.g., ferrets, hamsters, AGMs). This absence impedes studies on LayV's in vivo pathogenesis, transmission, and immune interactions [50, 51].

5. Absence of Antiviral or Vaccine Testing: – No antivirals or vaccines target LayV. While m102.4 and ribavirin show efficacy against other henipaviruses, LayV's distinct F and G glycoproteins necessitate evaluation of cross-reactivity and the development of tailored immunotherapies [26].

Conclusion

Langya henipavirus (LayV) is a recently discovered new representative of the genus of henipaviruses with growing zoonotic significance and possible implications on public health. Being closely related to highly pathogenic Nipah and Hendra viruses on a genetic level, LayV possesses vital structural and functional similarities with a non- segmented negative sense RNA genome that encodes six key proteins (N, P, M, F, G and L) organizing the viral replication, cell entry, and immune modulation processes. Although its natural reservoir is assumed (probably) to be shrews, serological findings in domestic animals point to a larger host range and to the possibility of cross-species transmission. LayV pathogenesis is still unexplored with regard to its molecular mechanisms. The virus is, however, expected to infect its host cells with the help of glycoproteins G and F, and could utilize recruits to immune evasion similar to those of other henipaviruses, that includes, but is not limited to, inhibition of the JAK/STAT signalling pathway and suppression of the interferon responses through its accessory proteins. Although there is no documented human-to-human transmission, the presence of several human cases with fever and respiratory manifestations makes it clear that the virus has the potential of an occasional zoonotic spillover, a fact that necessitates heightened active surveillance. Substantial knowledge gaps still remain, mainly in the identity of host receptors, the dynamics of human transmission and immune escape. Additionally, the absence of established animal models of LayV significantly restrains the research capacities to understand its pathogenesis and to test the therapeutic activities. The future studies should focus more on the creation of in vivo models, functional assays of immune signaling disruption, and development of specific antivirals or vaccines. To conclude, there

is an increasingly One Health challenge of LayV. Spreading knowledge of this virus at the molecular and epidemiological level is crucial to identifying it early enough, manage the risks, and design specific strategies of outbreak prevention and international health preparedness.

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Авторлар туралы мәлімет:

Абдул Бари Хеджран (корреспондент-автор) – вирусология магистрі, Гильменд университетінің білім беру факультетінің биология кафедрасының асистенті (Гильменд, Ауганстан, e-mail: abdulbari.hejran94@gmail.com)

Фаридон Ниязай – Анестезиология кафедрасы, Мирвайс аймақтық ауруханасы және Жалпы медицина кафедрасы, Медицина факультеті, Мирвайс Ника университеті (Қандагар, Ауганстан, e-mail: faridoonniazay@gmail.com)

Барбара Савицка – Ауыл шаруашылығы ғылымдарының профессоры (Өсімдік өндірісі технологиясы және тауартану), Өсімдік өндірісі технологиясы және тауартану кафедрасы, Өмір туралы ғылымдар университеті (Люблин, Польша, e-mail: barbara.sawicka@gmail.com)

Парвиз Ниязи – ботаника магистрі (өсімдіктерді қорғау және нематология), Кандагар университетінің білім беру факультетінің биология кафедрасының оқу ассистенті (Кандагар, Ауганстан e-mail: parwiz60@gmail.com)

Information about authors:

Abdul Bari Hejran (corresponding author) – Master of Virology, Teaching Assistant at the department of Biology, Faculty of Education, Helmand University (Helmand, Afghanistan e-mail: abdulbari.hejran94@gmail.com)

Faridon Niazay – Department of Anesthesia, Mirwais Regional Hospital, Kandahar, and Department of General Medicine, Faculty of Medical, Mirwise Neeka University (Kandahar, Afghanistan e-mail: faridoonniazay@gmail.com)

Barbara Sawicka – Professor of Agricultural Sciences (Plant Production Technology and Commodities Science), Department of Plant Production Technology and Commodities Science, University of Life Sciences (Lublin, Poland, e-mail: barbara.sawicka@gmail.com)

Parwiz Niazi – Master of Botany (Plant Protection and nematology), Teaching Assistant at the department of Biology, Faculty of Education, Kandahar University (Kandahar, Afghanistan e-mail: parwiz60@gmail.com)

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