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Mount Sinai Structural Study Maps How a Single Glycoprotein Polymorphism Alters Andes Virus Trafficking in Human Cells

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Researchers in the Palacios Lab at the Icahn School of Medicine at Mount Sinai have characterized how a single naturally occurring amino acid polymorphism near the glycoprotein cleavage boundary of Andes virus (Orthohantavirus andesense) alters intracellular protein localization and virus-like particle (VLP) assembly kinetics in cultured human cells [1, 2] . Published in Science Advances in November 2026, the comparative study analyzed genomic differences between wild rodent reservoir isolates and clinical isolates recovered during the 2018-2019 hantavirus pulmonary syndrome (HPS) outbreak in Epuy n, Argentina, demonstrating using non-infectious recombinant expression systems that an isoleucine-to-threonine substitution at residue 641 (I641T) reduces glycoprotein retention inside the Golgi apparatus and accelerates VLP release in vitro [1, 3] .

Ecological & Clinical Context of Patagonian Orthohantaviruses

Hantaviruses (family Hantaviridae , order Bunyavirales) are enveloped, tri-segmented negative-sense RNA viruses maintained in nature through persistent, largely asymptomatic infections of specific rodent, shrew, mole, and bat reservoir hosts [3, 4] . Across the Americas, New World orthohantaviruses -- including Sin Nombre virus in North America and Andes virus in southern South America -- are transmitted to humans primarily through the inhalation of aerosolized excreta (urine, feces, or saliva) from infected sigmodontine rodents , triggering hantavirus cardiopulmonary syndrome (HCPS/HPS) , an acute capillary-leak syndrome characterized by thrombocytopenia, pulmonary edema, and case fatality rates ranging from 30% to 45% [3, 4] .

In the temperate Nothofagus forests and Andean foothills of southern Argentina and Chile, the primary natural reservoir of Andes virus is the long-tailed pygmy rice rat (Oligoryzomys longicaudatus) [3, 5] . Among all characterized members of the family Hantaviridae , Andes virus is epidemiologically distinct because epidemiological investigations and viral whole- genome sequencing have documented sporadic clusters of direct person-to-person transmission during close household or nosocomial contact -- most notably during the 1996 El Bols n outbreak and the 2018-2019 Epuy n cluster in Chubut Province, Argentina, which involved 34 confirmed cases and 11 fatalities [2, 3] .

Comparative Genomic Screening Across Rodent and Clinical Isolates

To investigate whether natural sequence polymorphisms distinguish clinical isolates sampled during the 2018-2019 Epuy n cluster from reference strains circulating in Oligoryzomys longicaudatus populations, the Mount Sinai team performed comparative alignment across the three viral genomic segments [1, 2] :

* Small (S) Segment (~1.8 kb): Encodes the viral nucleocapsid (N) protein, which encapsidates the three negative-sense viral RNA segments into ribonucleoprotein complexes and modulates host innate immune signaling [4] .

* Medium (M) Segment (~3.6 kb): Encodes a 1,138-amino-acid glycoprotein precursor (GPC) that is co-translationally cleaved in the endoplasmic reticulum into two surface envelope glycoproteins, Gn (amino-terminal) and Gc (carboxy-terminal), which assemble into tetrameric surface spikes mediating host-receptor binding (including protocadherin-1, PCDH1, on microvascular endothelial cells) and pH-dependent endosomal membrane fusion [1, 4] .

* Large (L) Segment (~6.5 kb): Encodes the viral RNA-dependent RNA polymerase (RdRp) responsible for genome replication and cap-snatching mRNA transcription [4] .

Across the full proteome, comparative genomic screening identified 25 amino acid differences separating the rodent-derived reference isolate from the Epuy n clinical lineage [1] . Rather than manipulating live replicating virus, the investigators systematically evaluated these natural variants using biosafe, non-infectious plasmid expression constructs and recombinant virus-like particles (VLPs) in human cell lines to determine whether individual substitutions altered protein processing or subcellular trafficking [1] .

| Genomic / Biochemical Parameter | | Rodent-Derived Reference Isolate | | Epuy n Clinical Lineage Variant | | Observed Cellular Phenotype (Non-Infectious VLP System) |

| Proteome-Wide Divergence | | Baseline reservoir reference | | 25 amino acid substitutions across S, M, and L segments | | Conserved overall spike architecture and PCDH1 receptor recognition [1, 4] |

| M-Segment Cleavage-Region Locus | | Isoleucine at GPC position 641 (Ile641) | | Threonine at GPC position 641 (Thr641 / I641T) | | Located immediately adjacent to the conserved WAASA signal-peptidase cleavage motif [1, 4] |

| Endoplasmic Reticulum / Golgi Processing | | Extended Gn/Gc retention within cis/medial Golgi cisternae | | Reduced Golgi residence time and altered compartmental sorting | | Shifts intracellular trafficking balance along the secretory pathway in human cells [1] |

| Virus-Like Particle (VLP) Egress | | Baseline budding rate into extracellular supernatant | | Accelerated extracellular VLP release kinetics in vitro | | Demonstrates sensitivity of bunyaviral assembly to juxta-cleavage polarity [1] |

The WAASA Cleavage Boundary and Golgi Retention Mechanics

Unlike many enveloped RNA viruses that bud directly from the plasma membrane, orthohantaviruses typically mature by budding into the lumen of the Golgi apparatus , after which virion-containing vesicles traffic to the cell surface for exocytic release [1, 4] . Proper maturation requires that the nascent glycoprotein precursor (GPC) be cleaved by the host endoplasmic reticulum signal peptidase complex at a conserved pentapeptide motif -- WAASA (tryptophan - alanine -alanine-serine-alanine, located near residues 644-648) -- separating the Gn cytoplasmic/transmembrane tail from the ectodomain of Gc [1, 4] .

The Mount Sinai researchers pinpointed a single polymorphism at position 641 (I641T), situated just upstream of the WAASA cleavage site within the Gn carboxy-terminal signal sequence that directs Gc translocation across the endoplasmic reticulum membrane [1] . Replacing the hydrophobic branched-chain side chain of isoleucine with the polar hydroxyl-bearing side chain of threonine at residue 641 altered the local hydrophobicity and conformational dynamics of the cleavage region [1] . In human cell expression assays, the Thr641 glycoprotein variant exhibited significantly shorter residence time within the Golgi apparatus and promoted faster extracellular release of non-infectious virus-like particles compared with constructs carrying the ancestral Ile641 residue [1] .

Surveillance Implications and Experimental Boundaries

The authors emphasized an essential interpretive boundary: because all functional trafficking assays were conducted in simplified, non-infectious cell-culture and VLP expression models, demonstrating that I641T accelerates VLP egress in vitro does not prove that this single polymorphism is sufficient to drive human adaptation or person-to-person transmission in nature [1] . In natural infections, viral replication efficiency, host immune evasion, vascular endothelial permeability, and ecological exposure intensity interact across multiple viral gene products and host physiological factors [1, 2, 3] .

Nevertheless, mapping how single-residue changes near the M-segment WAASA cleavage site modulate Golgi retention provides genomic surveillance networks in South America with a concrete molecular marker [1, 2] . When sequencing viral RNA from rodent trapping surveys or clinical HPS cases, public-health laboratories can monitor M-segment cleavage-boundary polymorphisms alongside S- and L-segment markers to better evaluate strain diversity and guide early clinical supportive care and infection-control protocols [1, 3] .

References & Primary Sources

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