Commentary

Hantavirus Pathophysiology: Insights from Tissue and Cellular Perspectives

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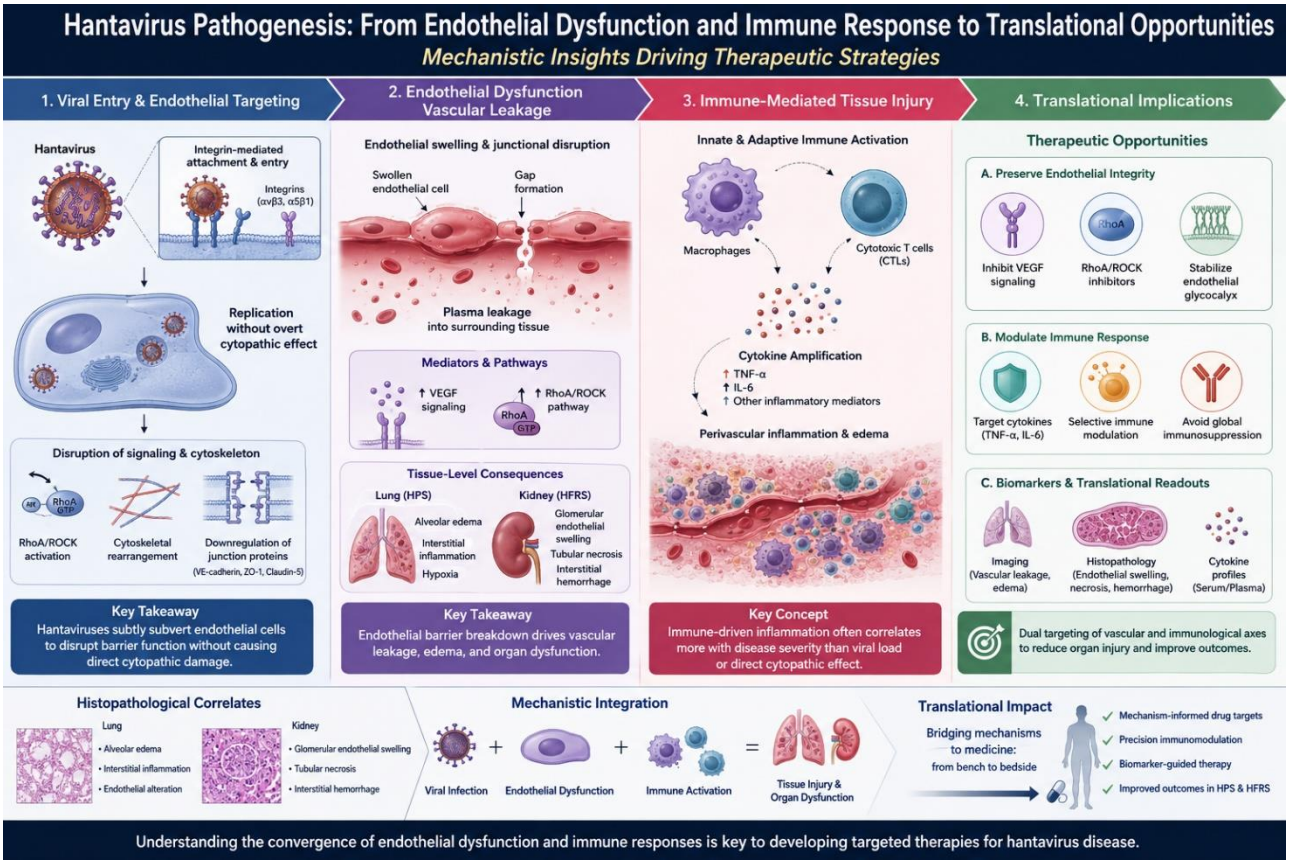
Received: March 12, 2026; **Revised:** April 23, 2026; **Accepted**: May 04, 2026; **Published online:** May 09, 2026.
Nex. Pathophysiol. Ther. J. 2026; 1:004, https://doi.org/10.22034/npt.2026.1.004

Abstract:

Hantavirus infections are primarily acquired through inhalation of aerosolized particles originating from rodent excreta and lead to severe pulmonary and renal syndromes. Although clinical features are well characterized, tissue-level mechanisms remain unclear. Histopathology consistently shows endothelial swelling, edema, and immune cell infiltration, indicating combined viral and host immune contributions to disease pathogenesis. The lungs and kidneys are the principal target organs, where microvascular dysfunction drives the most severe clinical manifestations. Hantaviruses preferentially infect endothelial cells of the microvasculature in these organs through integrin-mediated entry. Following infection, viral replication proceeds without marked cytopathic effects; instead, disruption of endothelial junctional proteins and cytoskeletal remodeling leads to progressive loss of barrier integrity. This results in increased vascular permeability, plasma leakage, and tissue edema. Activation of signaling pathways such as VEGF and RhoA/ROCK further amplifies endothelial dysfunction, contributing to pulmonary edema and renal impairment. In parallel, immune-mediated mechanisms play a central role in tissue injury. Recruitment of macrophages and cytotoxic T cells, together with elevated levels of proinflammatory cytokines including TNF-α and IL-6, intensifies vascular leakage and exacerbates organ damage. Disease severity appears to correlate more strongly with the magnitude of the host immune response than with direct viral cytotoxicity, emphasizing the importance of immunopathology in disease progression. From a mechanistic and translational perspective, hantavirus disease represents a paradigm of combined endothelial and immune-driven injury. The disruption of vascular integrity identifies potential therapeutic targets aimed at stabilizing endothelial junctions and modulating permeability-related signaling pathways such as VEGF and RhoA/ROCK. In addition, strategies that selectively attenuate excessive cytokine responses without inducing broad immunosuppression may reduce tissue damage and improve clinical outcomes. Histopathological features including endothelial swelling, tubular necrosis, and interstitial hemorrhage further provide measurable biomarkers for evaluating disease severity and therapeutic efficacy, bridging mechanistic insights with clinical application and supporting the development of targeted interventions.

Keywords: Hantavirus, endothelial dysfunction, vascular permeability, immune response, pathogenesis.



Graphical Abstract: Hantavirus Pathogenesis—Immune Activation, Endothelial Dysfunction, and Vascular Leakage. Following inhalation of aerosolized rodent excreta, hantaviruses primarily infect endothelial cells within the pulmonary and renal microvasculature, while also activating innate and adaptive immune responses. Viral replication occurs with minimal direct cytopathic effect but induces profound endothelial and immunological dysregulation. Infection promotes macrophage activation, cytotoxic T-cell infiltration, and excessive cytokine release, including TNF-α and IL-6, which amplify local and systemic inflammation. Concurrent activation of VEGF-, bradykinin-, and RhoA/ROCK-associated signaling pathways disrupts cytoskeletal organization and destabilizes endothelial junctions, resulting in increased vascular permeability and capillary leakage. These alterations lead to plasma extravasation, tissue edema, hypoxia, and organ dysfunction, particularly in the lungs and kidneys. Histopathological manifestations include endothelial swelling, interstitial inflammation, alveolar edema, tubular injury, and hemorrhage. Collectively, these mechanistic insights identify endothelial barrier preservation and targeted immunomodulation as key translational strategies for reducing vascular injury and improving clinical outcomes in hantavirus disease.

Introduction

Hantaviruses infect humans primarily through inhalation of viral particles from rodent excreta (1). The disease targets the lungs and kidneys and can involve multiple organs (2). While clinical features are well characterized, the tissue-level mechanisms remain less understood. Histopathological studies reveal endothelial swelling, edema, and infiltration of immune cells (3). These observations indicate that both viral replication and host immune responses contribute to disease progression. Investigating these mechanisms at cellular and tissue levels is essential for developing effective therapies.

Viral Entry and Cellular Targets

Hantaviruses predominantly target endothelial cells, particularly those lining the microvasculature of the lungs and kidneys (4, 5). Viral attachment and entry are primarily mediated through integrins expressed on the host cell surface (6). Following entry, the virus initiates intracellular replication without inducing extensive cytopathic effects (6). Instead of causing direct cellular destruction, infection alters

several hosts signaling pathways. These alterations affect cytoskeletal organization and disrupt junction-associated proteins (6). The integrity of endothelial tight junctions gradually becomes compromised. Loss of barrier function increases vascular permeability (6). As permeability rises, plasma components leak into surrounding tissues (7). This process contributes to pulmonary edema in HPS and renal dysfunction in HFRS.

Endothelial Dysfunction and Vascular Leakage

Endothelial cells swell and lose their normal shape (7). Gaps form between adjacent endothelial cells, allowing fluid to escape into surrounding tissues, a process driven in part by VEGF signaling and RhoA/ROCK pathway activation (8). Histological analysis of the lungs reveals alveolar edema and interstitial inflammation (9). In hantavirus-infected kidneys, the glomeruli show endothelial swelling, and tubular epithelial cells exhibit degenerative changes. These tissue-level alterations reflect underlying cellular and molecular disruption caused by endothelial dysfunction and immune-mediated injury (10). They provide a direct link between microscopic alterations and the clinical manifestations of the disease.

Immune-Mediated Tissue Injury

Hantavirus infection induces a strong immune response characterized by excessive immune activation and cytokine production (11). Mononuclear phagocytes and CD8+ cytotoxic T cells infiltrate affected tissues during hantavirus infection (11), contributing to local inflammatory responses. This immune activation is accompanied by markedly increased levels of cytokines, including TNF-α and IL-6, which further amplify inflammation and exacerbate tissue damage (12). Histological analysis often reveals perivascular inflammation and tissue edema, consistent with cytokine-mediated vascular dysfunction (13). Notably, disease severity frequently correlates more with the magnitude of the immune response than with direct viral cytopathic effects (14). Understanding these mechanisms may guide the development of therapies that modulate immune activity without causing global immunosuppression.

Histopathological Correlates

The lungs exhibit alveolar edema, interstitial inflammation, and alterations in endothelial cells (15). Histopathological findings in hantavirus-infected kidneys may include glomerular endothelial alterations, tubular injury, and interstitial hemorrhagic changes (10). These pathological features are consistently reported in both human and animal studies. They reflect disruption of the endothelial barrier, activation of inflammatory signaling, and immune-mediated tissue injury (16). Examining tissue morphology offers insight into disease mechanisms. Recognizing these patterns can inform experimental research and guide therapeutic development.

Conclusion

Hantavirus disease is driven by viral replication, endothelial dysfunction, and immune-mediated tissue injury. Histopathological examination provides critical insight into these underlying mechanisms. Lung and kidney tissues show consistent patterns of edema, endothelial swelling, and inflammation. These changes link cellular events to organ-level outcomes. Future research should integrate molecular, cellular, and tissue-level analyses. Such a comprehensive approach can guide the development of targeted therapies and improve patient outcomes.

Mechanistic and Translational Relevance

Hantavirus infection exemplifies a paradigm in which tissue-level pathology arises not solely from

viral replication, but from a complex interplay between endothelial dysfunction and host immune responses. Mechanistically, the virus targets endothelial cells in the microvasculature of the lungs and kidneys, subtly disrupting tight junction integrity and cytoskeletal organization without overt cytopathic effects. This endothelial compromise leads to capillary leakage, edema, and local hypoxia, establishing the structural basis for organ-specific manifestations such as pulmonary edema in HPS and acute kidney injury in HFRS. Concurrently, immune-mediated mechanisms, including infiltration by macrophages and cytotoxic T cells and cytokine-driven amplification of inflammation (e.g., TNF-α, IL-6), exacerbate tissue injury, often correlating more strongly with disease severity than direct viral cytotoxicity.

These mechanistic insights have direct translational relevance. Understanding how hantaviruses perturb endothelial barrier function identifies potential therapeutic targets aimed at preserving vascular integrity, such as modulators of VEGF signaling, RhoA/ROCK pathways, or strategies to stabilize endothelial glycocalyx. Simultaneously, characterizing the immune-mediated component highlights the need for interventions that attenuate excessive inflammation without inducing generalized immunosuppression, offering a precision-medicine approach to mitigate organ damage. Histopathological correlates, including endothelial swelling, tubular necrosis, and interstitial hemorrhage, provide measurable biomarkers for preclinical and clinical evaluation of candidate therapies. Integrating these cellular and tissue-level insights bridges mechanistic understanding with actionable strategies for clinical management and therapeutic development, making it possible to target both vascular and immunological axes of hantavirus pathogenesis.

Conflict of Interests

The author declares that there is no conflict of interest.

Acknowledgement

The authors would like to express their sincere gratitude and appreciation to all individuals who contributed to and supported this research, as well as to the Vice Presidents for Research and Technology of Lorestan University of Medical Sciences and Shahid Beheshti University of Medical Sciences for their valuable assistance and encouragement.

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