

## Endothelial Dysfunction and Immune Dysregulation in Hantavirus Infection: Mechanisms of Vascular Leakage and Disease Severity

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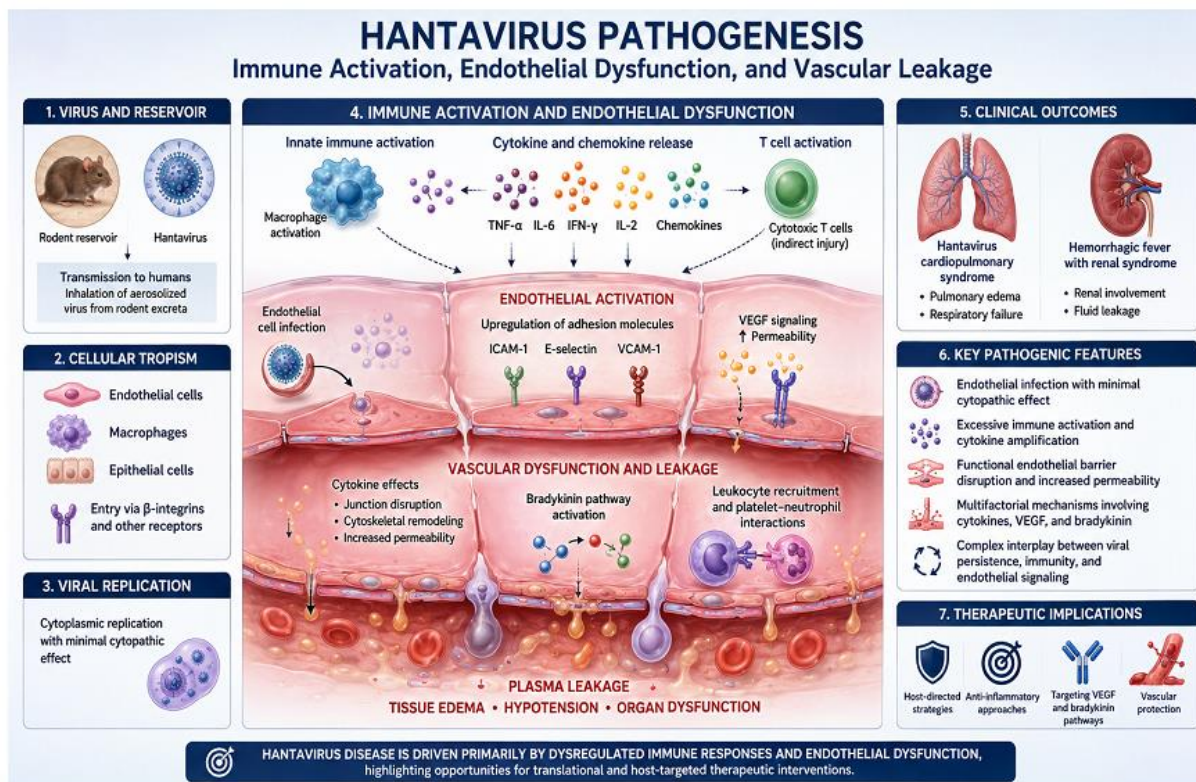
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### Abstract:

Hantaviruses are zoonotic RNA viruses that cause a spectrum of diseases, including hemorrhagic fever with renal syndrome and hantavirus cardiopulmonary syndrome. Although clinical manifestations vary among hantavirus species, increasing evidence suggests that disease severity is driven primarily by dysregulated host immune responses and vascular dysfunction rather than direct viral cytopathic effects alone. Hantaviruses exhibit a marked tropism for endothelial and immune cells, where infection alters inflammatory signaling pathways and disrupts vascular homeostasis. Increased endothelial permeability and capillary leakage are central features of severe disease and are associated with cytokine amplification, leukocyte recruitment, and endothelial barrier dysregulation. Multiple mediators, including tumor necrosis factor- $\alpha$ , interleukin-6, interferon- $\gamma$ , vascular endothelial growth factor, and bradykinin-related pathways, have been implicated in the pathogenesis of tissue edema and vascular instability. Current evidence further suggests that endothelial injury in hantavirus infection is predominantly functional rather than structurally destructive, reflecting complex interactions between viral persistence, host inflammatory responses, and vascular signaling networks. This review summarizes current understanding of the molecular and immunopathogenic mechanisms underlying hantavirus-associated vascular disease, with particular emphasis on endothelial dysregulation, cytokine-mediated injury, and permeability signaling pathways.

**Keywords:** Hantavirus, Endothelial dysfunction, Vascular permeability, Cytokine storm, Immunopathogenesis



**Graphical Abstract: Hantavirus Pathogenesis: Immune Activation, Endothelial Dysfunction, and Vascular Leakage.** Following inhalation, hantaviruses infect endothelial and immune cells and replicate with minimal cytopathic effect. Dysregulated immune responses lead to cytokine release, endothelial activation, and disruption of vascular barrier integrity through multiple pathways, including VEGF and bradykinin signaling. These events result in plasma leakage, tissue edema, and organ dysfunction. Targeting host and vascular pathways may offer therapeutic benefit.

### Introduction

Hantaviruses belong to the Hantaviridae family and are primarily maintained in rodent reservoirs (1). Human infection usually occurs through inhalation of aerosolized viral particles derived from rodent excreta (2). Different hantavirus species are associated with distinct geographic and clinical patterns (3).

Old World hantaviruses are more commonly linked to renal involvement, whereas New World hantaviruses often produce severe pulmonary disease (4). Despite differences in clinical presentation, several pathogenic mechanisms appear to be shared across hantavirus syndromes (5).

A growing body of evidence indicates that disease severity is not solely related to direct viral cytotoxicity (5). Instead, dysregulated host immune

responses, together with alterations in endothelial barrier function and increased vascular permeability, contribute to tissue injury and vascular instability (6).

The complex virus–host interactions, incomplete knowledge of viral replication, and dual endothelial–immune pathogenesis highlight hantavirus infection as a model for virus-induced vascular disease in translational research (7). Understanding the mechanisms of hantavirus-induced vascular dysfunction provides opportunities for therapeutic intervention.

### Viral Entry and Cellular Tropism

Hantaviruses show a strong tropism for endothelial cells, macrophages, and epithelial cells (8, 9). Viral attachment is mediated partly through  $\beta$ -integrins and other surface receptors expressed on vascular

endothelial cells (2). Following entry, viral replication occurs with relatively limited direct cytopathic effects (5). The non-lytic nature of hantavirus infection, together with evidence that vascular leakage is primarily driven by dysregulated endothelial and immune responses rather than direct viral cytopathic effects, has shifted research attention toward host-response mechanisms as central drivers of disease pathogenesis (10). Endothelial infection alters intracellular signaling pathways associated with vascular permeability and inflammatory activation (11). Several studies suggest that infected endothelial cells become highly responsive to inflammatory mediators, including Tumor Necrosis Factor-Alpha (TNF- $\alpha$ ) and Vascular Endothelial Growth Factor (VEGF) (12). These signals may amplify barrier dysfunction and contribute to plasma leakage (13). The interaction between viral proteins and innate immune signaling pathways also appears important (14). Hantaviruses evade type I interferon responses early in infection, which compromises innate antiviral control and permits sustained viral replication associated with later immune dysregulation and inflammatory disease manifestations (14).

### **Immunopathology and Cytokine-Mediated Injury**

One of the most important features of severe hantavirus disease is excessive immune activation (15). Elevated levels of pro-inflammatory cytokines, chemokines, and activated immune cells have been detected in both pulmonary and renal syndromes (16). Cytotoxic T lymphocytes are believed to contribute to endothelial injury indirectly through immune-mediated inflammation (5). In parallel, macrophage activation and cytokine release may intensify vascular leakage and tissue edema (13). This process resembles aspects of

cytokine dysregulation observed in other severe viral infections (17).

Importantly, endothelial dysfunction in hantavirus infection occurs without major structural endothelial destruction, instead reflecting functional barrier disruption rather than direct cytotoxicity, consistent with the absence of marked cytopathic effects in infected endothelial cells (5). This finding supports the concept of functional endothelial dysregulation rather than irreversible vascular injury during early disease stages (5). Several mediators have been implicated in this process, including Intercellular Adhesion Molecule (ICAM), Endothelial Selectin (E-Selectin), Interleukin (IL)-2, Interferon-Gamma (IFN- $\gamma$ ), TNF- $\alpha$ , IL-6, VEGF, and bradykinin-related signaling pathways (5, 13). These pathways are now being explored as potential therapeutic targets.

### **Mechanisms of Vascular Leakage**

Capillary leakage is considered a hallmark of severe hantavirus disease (5). The molecular basis remains unclear, but evidence suggests a multifactorial process involving immune signaling, endothelial junction disruption, and vascular dysfunction (18). VEGF-associated signaling may increase endothelial permeability by affecting adherens junction proteins. (19). Inflammatory cytokines further destabilize endothelial integrity and promote leukocyte recruitment (20). In addition, Platelet-neutrophil interactions via  $\beta$ 2 integrins may contribute to neutrophil activation and microvascular dysfunction (20).

Interestingly, some studies suggest that bradykinin pathway activation may participate in hypotension and vascular leakage (21). These findings have raised interest in therapeutic strategies targeting the kallikrein-bradykinin pathway, particularly in severe hantavirus infections characterized by vascular leakage and hypotension (21). The pathophysiology of hantavirus-associated leakage

therefore appears to involve dynamic interactions between viral persistence, host immunity, and endothelial signaling networks rather than a single dominant mechanism (5).

### **Cytokine-Mediated Endothelial Dysregulation and Therapeutic Implications**

Severe hantavirus infection is characterized by a marked dysregulation of host immune responses (17). Cytokine and chemokine networks play a central role in driving endothelial dysfunction and vascular leakage (22). Elevated levels of pro-inflammatory mediators, including TNF- $\alpha$ , IL-6, IFN- $\gamma$ , are consistently associated with disease severity in both hemorrhagic fever with renal syndrome and hantavirus cardiopulmonary syndrome (23). These cytokines do not act in isolation; rather, they form an interconnected signaling network that amplifies endothelial activation and disrupts vascular homeostasis (6). At the endothelial interface, cytokine signaling induces upregulation of adhesion molecules such as ICAM-1 and E-selectin (24). This promotes leukocyte recruitment and sustains local inflammatory responses (24).

In parallel, inflammatory mediators enhance VEGF-dependent signaling (25). VEGF-VEGFR2 signaling regulates endothelial junction integrity and increases vascular permeability through SRC-dependent pathways (26). Importantly, VEGFR signaling primarily regulates vascular barrier function, including junctional remodeling, permeability, and cellular trafficking, rather than inducing direct endothelial cell death (26). Rather, it leads to functional barrier disruption with largely reversible permeability changes (27). This reflects endothelial hyper-responsiveness rather than overt cytopathic injury (28). Cytokine signaling is also tightly integrated with both innate immune pathways and vascular regulatory systems (29). These include the bradykinin and complement cascades (30). Cross-talk between these pathways

may further increase endothelial leakage. It also contributes to systemic hypotension and tissue edema (30). Overall, disease severity appears to depend not only on viral load, but also on the magnitude and persistence of the host inflammatory response. From a therapeutic perspective, this supports the concept of host-directed interventions alongside antiviral strategies (31). Targeting cytokine signaling, modulating endothelial activation, or interfering with downstream permeability pathways such as VEGF or bradykinin may reduce vascular leakage (31).

However, cytokine networks are highly redundant and pleiotropic (32). This limits the effectiveness of single-target approaches and suggests that combination strategies may be required to balance viral control with controlled immunomodulation. In summary, cytokine-mediated endothelial dysregulation represents a central axis in hantavirus pathogenesis (5). It links innate immune activation to vascular dysfunction (33). It also provides a mechanistic framework for future therapeutic development.

### **Knowledge Gaps and Future Directions**

The determinants of hantavirus disease severity remain incompletely understood and are likely influenced by complex interactions among viral genetic diversity, host susceptibility factors, immune response variability, and environmental conditions. Current evidence suggests that disease progression and tissue injury arise from overlapping mechanisms involving endothelial dysfunction and dysregulated immune-vascular interactions, which may also contribute to differences in organ involvement, including pulmonary and renal manifestations. In addition, the identification of reliable biomarkers capable of predicting severe disease outcomes remains an important area of ongoing investigation. Further refinement of experimental and translational models that more accurately reproduce human vascular pathology

will be essential for improving mechanistic understanding and supporting therapeutic development. Beyond host and viral factors, ecological and climate-related changes affecting rodent reservoir populations may significantly influence future disease dynamics. Increasing human exposure to infected reservoirs could further enhance the global clinical relevance of hantavirus-associated diseases and highlight the need for improved surveillance and preventive strategies.

### **Conclusion**

Hantavirus infections represent a spectrum of zoonotic diseases that provide important insights into how viral–host interactions can perturb endothelial homeostasis and contribute to immune-mediated organ dysfunction. Current evidence supports a model in which vascular leakage and disease severity are largely driven by dysregulated host immune and inflammatory responses, rather than direct viral cytopathic effects alone, although the relative contribution of these mechanisms may vary depending on viral strain and host context. As understanding of these processes continues to evolve, therapeutic opportunities may emerge from targeting key nodes in endothelial signaling, inflammatory pathways, and host–pathogen interactions. Further integration of molecular virology, vascular biology, and immunopathology will be essential to refine mechanistic models and support the development of more effective translational interventions for hantavirus-associated disease.

### **Mechanistic and Translational Relevance**

The pathogenesis of hantavirus infection highlights a close interplay between immune activation and endothelial dysfunction, supporting the development of host-directed therapeutic approaches. Dysregulated inflammatory responses that compromise endothelial integrity appear to

represent a central driver of vascular pathology with important translational relevance. In this context, cytokine-mediated disruption of endothelial barrier function may provide a promising framework for the development of targeted anti-inflammatory and vascular-protective interventions.

### **Conflict of Interests**

The author declares that there is no conflict of interest.

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