

Pathophysiology and Molecular Mechanism of Nipah Virus

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ABSTRACT

Nipah virus (NiV) is a new virus that is a serious threat to public health and global security because it has a high mortality rate and can spread rapidly between people. In this paper, we will summarize our current knowledge of NiV virology, including how NiV enters human hosts, replicates, evades the immune response, and causes disease. A primary focus will be placed on the unique molecular basis for NiV's clinical manifestations, which include the specificity of NiV infection to endothelial and neuronal cells, the dysregulated immune response of the human host, the presence of virulence factors that are unique to each strain of NiV, and the failure of the host immune system to generate an effective immune response to eliminate NiV from the human body. Furthermore, recognizing the global public health threat of NiV infection and its implications for global health security emphasizes the need for innovative and proactive surveillance strategies to reduce the hazards associated with this zoonotic viral pathogen.

Keywords: Nipah virus; Zoonotic infection; Molecular pathophysiology; Immune evasion; Neuroinvasion; Pandemic preparedness

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Introduction

The Nipah virus is a novel virus belonging to the Paramyxoviridae family responsible for causing illness in humans. The Nipah virus was first identified during an outbreak in Malaysia from 1998 to 1999. Bats are the natural reservoir of Nipah virus; transmission may occur via ingestion of infected foodstuffs or through direct contact with infected animal(s) and from person to person (1). After initial outbreaks in Malaysia and Singapore, outbreaks due to Nipah virus have occurred throughout South Asia and Southeast Asia, particularly in Bangladesh and India. Mortality rates for Nipah virus infections are very high, ranging from 40% to over 75%. The Nipah virus represents a significant threat to global health and reflects an urgent need to know more about how the Nipah virus interacts with the body and why it causes severe damage to endothelial and neuronal cells. Due to the high fatality rate, there are currently no approved vaccines or antiviral therapies for Nipah virus infections, and human-to-human transmission is possible. As such, the Nipah virus is a significant concern as both a global public health issue and a global security concern that requires attention before any potential outbreak or pandemic.

Virology of Nipah Virus

Structural and Genomic Features:

The Nipah virus is an enveloped virus with a single-stranded, negative-sense RNA genome of approximately 18.2 kb. The genome encodes six major structural proteins. The nucleo-capsid (N) protein of the Nipah virus packages the viral RNA, while the phosphoprotein (P) and large polymerase (L) form the RNA-dependent RNA polymerase complex necessary for viral transcription and replication. The matrix (M) protein is involved in the assembly of the viral particles. The G glycoprotein and F glycoprotein are both on the surface of the virus, playing important roles in attaching to host cells and triggering membrane fusion between the host cell and the viral envelope, facilitating entry into the host cell (2).

Taxonomy and Classification:

The Nipah Virus is a member of the Paramyxoviridae family, Orthoparamyxovirinae subfamily, and Henipavirus genus. As a member of this genus, the Nipah Virus can infect a wide variety of hosts, has many pathogenic properties, and can be transmitted from animal to man. Nipah Virus was first identified during the 1998-1999 epidemic of Nipah virus and Hendra virus infection, which resulted in many cases of severe illness in humans. Notably, the Nipah virus and Hendra virus are highly virulent paramyxoviruses that can cause severe illness in both the respiratory and central nervous systems.

The Entry and Replication of Nipah Virus: Role of the F and V Proteins

The Nipah virus has two consist receptor proteins, the Ephrin-B2 and the Ephrin-B3, that are employed to invade and hijack mammalian cells. All mammals have these receptors, and they are expressed broadly in endothelial cells, neurons and other types of epithelial cells in the

respiratory tract, which accounts for why the virus has a strong impact on vascular, neuronal and pulmonary tissues." These receptors in multiple mammalian species together facilitate the wide host range and zoonotic potential of Nipah virus. The G glycoprotein binds to one of the two receptor proteins (Ephrin B2 or Ephrin B3), promoting a conformational rearrangement of the F glycoprotein which ultimately results in fusion of Nipah virus membrane with host cell membrane. This leads to fusion of infected cells with neighboring cells and the subsequent creation of multinucleated giant cells (syncytia) that are characteristic of Nipah virus infections. T Once inside the host cell, the RNA-dependent RNA polymerase complex containing L and P proteins transcribes and replicates T the viral RNA. Viral gene expression is closely regulated to allow efficient virus replication, and the viruses escape immune surveillance of their host (3).

Pathophysiological conditions associated with Nipah Virus

Infection of Endothelial Cells and Damage to blood vessels

The nipah virus has a strong affinity for infecting our endothelial cells due to their high expression levels of ephrin-B2 and ephrin-B3 receptors. The ability of the nipah virus to reproduce within these endothelial cells leads to severe damage to the endothelial cells. Damaged endothelial cells then result in vasculitis (inflammation of blood vessels), thrombosis (formation of blood clots), and increased permeability of the endothelial cells, leading to the leakage of fluids out of the blood vessel lumen; therefore, higher incidence of bleeding, increased incident of edema (swelling caused by accumulation of fluid), and decreased blood supply to the organs. Thus, the damage to the endothelium is directly associated with the severity of the nipah virus disease (4).

Neuro-involvement and the Pathology of the CNS

The Nipah virus enters the CNS by breaching the blood-brain barrier through physical disruption caused by damaged endothelial cells as well as through inflammatory mediators. Once this virus has breached the blood-brain barrier and gained access to the CNS, the Nipah virus infects neurons and glial cells (supporting cells within the CNS), resulting in acute encephalitis with widespread necrosis of affected neurons as well as inflammation and microvascular (small blood vessel) injury within the CNS.

Involvement of the Respiratory Tract

Infection of the respiratory tract by the Nipah Virus causes injury to the epithelial cells lining the airways and to the alveolar (air exchange sites in the lungs) epithelial cells surrounding the alveoli. The resultant nasal damage leads to diffuse alveolar injury and the subsequent development of acute respiratory failure due to pulmonary edema and pneumonia, which has a potential for a high rate of mortality.

Host Immune Response and Immune Evasion

Recognition of Host's Innate Immune Response

Innate immunity is the initial defence against Nipah Virus (NiV) infection for the host. Host cells detect the viral RNA upon entry of the virus using some Pattern Recognition Receptors (PRRs), such as Retinoic Acid-Inducible Gene I (RIG-I) and Melanoma Differentiation Associated Protein 5 (MDA5). These PRRs are cytosolic PRRs that recognize intermediates produced during viral RNA replication, triggering multiple downstream signalling pathways, including Mitochondrial Antiviral Signalling Protein (MAVS). Once MAVS is activated, it initiates the activation of various transcription factors such as IRF-3, IRF-7, and NF- κ B, which promote the synthesis of the two Type I Interferons (IFNs) (IFN- α or IFN- β) released by the host cells. Once the IFNs have been released into the surrounding tissue, they can bind to surrounding cells through both autocrine and paracrine means to stimulate the transcription of a multitude of Interferon-Stimulated Genes (ISGs). The binding of the IFNs to their downstream receptors induces the establishment of an antiviral state that prevents early replication of the virus and spread of the virus.

Varying Mechanisms of Immune Suppression by Nipah Virus

The Nipah virus can evade the body's immune response through the use of various mechanisms, even though there is an initial innate immune response to the virus. Interferon-alpha (IFN-alpha) is one of the most important parts of the body's natural defense against viral infections. The Nipah virus has developed a variety of accessory proteins derived from the P gene, including P, V, and W proteins, which interfere with and suppress the immune response of the host. Interferon receptor signaling is mediated by the Janus Kinase (JAK)/Signal Transducer & Activator of Transcription (STAT) signaling pathway; thus, these accessory proteins of the Nipah virus directly block JAK/STAT signaling in three ways.

Blockage of Phosphorylation of STAT1 and STAT2 - The P, V, and W proteins directly bind to STAT1 and STAT2 and prevent their phosphorylation.

Blockage of Nucleus Translocation of Phosphorylated STAT1 and STAT2 - The P, V, and W proteins enter the nucleus and bind to STAT1 and STAT2, making them unavailable to the genome for transcription of Interferon-stimulated genes (ISGs) and other genes.

Suppressing the Host Immune System - The absence of ISGs permits the Nipah virus to replicate unimpeded by immune cells of the host. Since immunosuppression has allowed the Nipah virus to establish a persistent infection and to cause severe disease in the infected host, this is a significant difference from most viruses that infect their host(5).

Immunopathology and Regulation of Cytokines

Immune-pathological responses accompany severe Nipah virus infections and result in dysregulated, excessive amounts of cytokines produced in response to the infection. Uncontrolled release of pro-inflammatory cytokines creates a cytokine storm, leading to significant endothelial damage, increased vascular permeability, and increased inflammation of tissue. This pathological process is responsible for developing encephalitis, respiratory failure, and multi-organ failure, all of which are characteristics of patients who die from severe Nipah virus infection. Therefore, the severity of the symptoms and mortality of Nipah virus infections is

determined by the interplay between the level of viral replication and host-mediated damage to the immune system.

Implications for Therapeutics and Vaccine Development

New discoveries in understanding the molecular pathogenesis of viruses have revealed multiple potentially effective antiviral targets. One type of target is viral entry inhibitors that prevent virus entry into the host cell by blocking interactions between the viral surface proteins and the host cell receptors during the initial entry of the virus into the host cell. Another potential target is the viral polymerase(s), which would have an impact on the replication and transcription of the viral genome, as polymerases are essential and conserved in all viruses and therefore make attractive antiviral targets. Lastly, fusion proteins involved in the fusion of viral and host cell membranes represent an additional potential target, as these proteins can be inhibited to prevent the entry of the virus and spreading of the virus through cells. The development of subunit and vector-based vaccines has been guided by our understanding of molecular pathogenesis. These vaccines target immune-dominant viral proteins and induce protection. The advantages of subunit vaccines include increased safety, and the benefit of vector-based vaccine platforms are to increase their ability to be immunogenic. There are also challenges to achieving long-term immunity due to many factors, including the rapid mutation of the viruses, their strategies to evade the immune response, and the decreasing strength of immune memory over time. Therefore, additional/booster strategies will need to be considered and/or developed in order to acquire long-term immunity and improve the likelihood of developing broadly protective vaccines.

Conclusion

Nipah is an emerging zoonosis with a potentially huge impact due to high fatality rates, availability of a wide range of susceptible hosts, and capacity to transmit human-to-human via contact. The patterns of interaction between the viral surface glycoproteins of the Nipah virus and host cell receptors serve to facilitate the entry of the Nipah virus into all three major cell types targeted by the virus: endothelial cells, nervous system (neuronal) cells, and epithelial cells lining the respiratory tract. After entry into the target cell type, the Nipah virus replicates and uses multiple mechanisms to evade the host immune response, resulting in significant vascular injury, neuro-inflammation, and severe pathology of the lungs in patients with Nipah virus infection. Both disruption of host cell type interferon signaling and the development of a hyper-inflammatory response (i.e., an increase in pro-inflammatory cytokines that leads to an appropriately increased level of inflammation) will serve to establish the degree of illness and clinical outcome for individuals infected with the Nipah virus.

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