Volume 10, Issue 11, November 2024,
Publish Date: 01-11-2024
Doi https://doi.org/10.55640/ijmsdh-10-11-01

International Journal of Medical Science and Dental Health (Open Access)

MOLECULAR INSIGHTS INTO THE MECHANISMS OF RABIES VIRUS NEUROINVASION AND PATHOGENICITY: A REVIEW ARTICLE

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ABSTRACT

Rabies is a major global health problem that kills approximately 59,000 people each year, mostly in developing regions. The rabies virus (Rabies lyssavirus) is a unique neurotropic virus that can invade the nervous system, escape host immune responses and produce a truly devastating nervous system disease. The molecular insights into rabies virus neuroinvasion and pathogenicity, reviewed in this paper, are described in a comprehensive overview. Structural and genomic characteristics of the virus, neuroinvasion mechanisms, and pathologic effects on the host are discussed. Additionally, we discuss the viral strategies they use to evade the host's immune responses. We then review the challenges to current therapeutic approaches, including post exposure prophylaxis and vaccination. We conclude with suggestions of future research directed towards development of better prevention, diagnosis and treatment strategies for rabies.

INTRODUCTION

Rabies is a serious viral disease of major concern to human and animal health globally. This zoonotic infection, which is caused by the rabies virus (Rabies lyssavirus) accounts for about 59,000 deaths in humans per annum, most of which occur in developing countries. Since clinical symptoms appear with high mortality, it is important to understand the disease mechanisms of action for future public health [1, 2].

The Rhabdoviridae family to which the rabies virus belongs is distinctive for its bullet shaped structure and single stranded RNA genome. Once inside the host, the virus primarily affects to the nervous system, where it can hide from your immune system, multiply. Rabies is an important disease that neuroinvasive, the virus travels along peripheral nerves until it enters the central nervous system where it causes encephalitis and death. Defining the molecular mechanisms by which this neuroinvasion occurs is critical for understanding effective therapeutic strategies and prevention methods [3, 4].

Although major progress in rabies research has been made, questions of exactly how the neuron is infected and how it contributes to disease pathogenicity remain poorly understood. The rabies virus hacks host cell machinery and chucks immune detection like it's the walking dead. As a result, these mechanisms can provide an in-depth analysis to identify possible therapeutic targets [4, 5].

This review thus seeks to integrate information learned through current research into how rabies virus neuroinvases and pathogenicity. Using viral and host component interaction as a focus of investigation, this article aims to further elucidate rabies pathogenesis and identify future avenues of research in order to uncover improved prevention and treatment options.

Rabies Virus Structure and Genomics

1. Viral Composition and Structure

This virus is part of the Rhabdoviridae family, which is designated by its distinctive bullet morphologic appearance. It is about 180 nm long × 75 nm wide, with a characteristic enveloped structure. The virion is formed with a host cell membrane derived lipid bilayer within the envelope that harbors glycoproteins playing key roles in viral entry and immune evasion [6-8].

Naturally, the nucleocapsid of the rabies virus, which is at its core, contains a single stranded RNA genome surrounded by N molecule. The matrix protein (M) aids maintenance of the viral structure and its role in the virus's assembly and production in host cells surrounds this nucleocapsid (9).

The virus can enter host cells through the function of the viral glycoprotein (G) within the envelope. infection of the host cell receptors and fusing with the host cell membrane involve the G protein, and entering of the viral RNA in cytoplasm occurs when the viral enveloped is liberated. As you will note from the discussion above, it is essential that this interaction marks the beginning of the infection process [10, 11].

2. Genetic Variability and Evolution

The rabies virus has a relatively small genome, consisting of approximately 12,000 nucleotides organized into five major genes [3, 12-15]:

1. **N (nucleoprotein) -** The nucleoprotein protein that encases the viral RNA.
2. **P-** Phosphoprotein, plays a role in viral replication, and an antagonist of host antiviral responses.
3. **M -** Matrix Protein; Involved in virion assembly and budding.
4. **Glycoprotein (G) -** Crucial for binding the receptor and for entry into host cells.
5. **L -** polymerase RNAD that encodes the viral RNA dependent RNA polymerase for viral replication and transcription.

The infectiousness of rabies virus is based on genetic flexibility that allows it adapt to different hosts and conditions. Research into the phylogeny of the virus has revealed different lyssavirus lineages and differences depending on the animal host including; bats, dogs and other wildlife carnivores. Notably, these differences are valuable for the characterization of transmission processes and to guide reciprocity for vaccine presentation and effectiveness [16, 17].

Table 1 *(Key Structural and Genomic Features of the Rabies Virus.)*

Feature	Description
Viral Morphology	Bullet-shaped, approximately 180 nm long and 75 nm wide
Envelope	Lipid bilayer derived from the host cell membrane
Key Glycoprotein (G)	Mediates attachment to host cell receptors and fusion with the host cell membrane

Nucleocapsid	Composed of single-stranded RNA genome encapsulated by nucleoprotein (N)
Matrix Protein (M)	Plays a role in virion assembly and budding from host cells
Genome Length	Approximately 12,000 nucleotides
Major Genes	1. Nucleoprotein (N) 2. Phosphoprotein (P) 3. Matrix Protein (M) 4. Glycoprotein (G) 5. Polymerase (L)
Genetic Variability	Several distinct lyssavirus lineages observed among different animal reservoirs
Pathogenic Mechanism	Neuroinvasion through the peripheral nervous system to the central nervous system

Mechanisms of Neuroinvasion

Thus, the virulence of RV depends on its ability to neuroinvasate and escape host immune response in order to begin infection in CNS. The processes leading to rabies virus neuro Invasion is summarized in this section [18-22].

1. **Access Points to the Nervous System**

   The rabies nucleocapsid virus enters a host primarily through a bite from infected animals and, during invasion, affects initial muscle cells at the site of the wound. The virus exploits several pathways to reach the nervous system [23, 24]:

   1. **Direct Infection of Peripheral Neurons:** It can once the virus replicates in myocytes infect the peripheral neurons which in turn are connections to CNS.
   2. **Transsynaptic Spread:** It can move from one neuron to another by the use of synapses. Once inside a neuron it can move within axonal tracts to other neurons within the nervous system for distribution a rapid rate.

2. **Cellular Interactions and Receptor Binding**

   The successful neuroinvasion of the rabies virus relies heavily on its ability to attach to and enter host cells:

   1. **Receptor Recognition:** The surface glycoprotein (G) of rabies virus binds to cells receptors. Cholinergic receptors, such as the nicotinic acetylcholine receptor (nAChR), appear to be the primary receptor, but other receptors include neural cell adhesion molecules (NCAM) and fibroblast growth factor receptor (FGFR) [25].
   2. **Endocytosis Mechanism:** Once internalized into the host cell by endocytosis, the virus sets for its genome uncoating. Inside the endosome, the acidic environment promotes the fusion of the viral envelope with the endosomal membrane allowing viral nucleocapsid to escape from the endosome to the cytoplasm [26].

3. Role of Neuronal Transport Mechanisms

Once inside a neuronal cell, the rabies virus utilizes the host's intracellular transport systems to facilitate its movement toward the CNS:

1. **Retrograde Axonal Transport:** The virus exploits retrograde transport mechanisms along microtubules for transport towards the neuronal cell body and the CNS. The transport of results from motor proteins such as dynein [27].
2. **Exploitation of Host Cellular Machinery:** It then manipulates host cellular processes to insure virus replication and assembly within the neuron before retreat further into the CNS [28].

4. Immune Evasion Strategies

The rabies virus has evolved several strategies to evade the host immune response during neuroinvasion [18, 29-31]:

1. **Limited Immune Activation:** It can also suppress local immune response, lowers local inflammation that helps the virus spread.
2. **Neural Immune Privilege:** The CNS is an immune privileged site, meaning the CNS is a site where there is a limited immune surveillance. This reduces the interference by host defenses while allowing the rabies virus to replicate and spread.

5. Pathological Consequences of Neuroinvasion.

As rabies virus spreads through the nervous system, it leads to significant alterations in neuronal function [5, 32, 33]:

1. **Neurodegeneration:** Viral components apparently can trigger apoptosis or necrosis of neighboring infected neurons leading to neurological deficits in infected individuals.
2. **Behavioral Changes:** The disruption of normal neural function gives rise to altered behavior and neurological symptoms of infection in infected individuals.

Table 2 *(Mechanisms of Rabies Virus Neuroinvasion.)*

Mechanism	Description
Entry Pathways	- Direct infection of peripheral neurons - Transsynaptic spread via synaptic connections
Cellular Interactions	- Binding to receptors such as nicotinic acetylcholine receptor (nAChR) - Involvement of neural cell adhesion molecules (NCAM)
Internalization Process	- Virus internalized through endocytosis - Fusion of viral envelope with endosomal membrane
Intracellular Transport	- Exploitation of retrograde axonal transport - Utilization of host motor proteins (dynein)

Immune Evasion	- Suppression of local immune responses - Exploitation of CNS immune privilege
Pathological Consequences	- Induction of neurodegeneration in infected neurons - Alterations in behavior and neurological function

Pathogenicity of Rabies Virus

The rabies virus pathogenicity is a multifaceted process including how the virus will cause disease and finally culminate into very severe neurological symptoms and death. In this section, the authors explore the many different factors that make rabies virus pathogenic.

1. Mechanisms of Virus-Induced Neurodegeneration

The rabies virus can cause significant damage to the nervous system through several mechanisms [3, 30, 34-36]:

1. **Direct Cytopathic Effects:** Inside neuronal cells, the replication of the virus may cause cell death by apoptosis (programmed cell death), or by necrosis. Viral particles accumulate disrupting normal cellular function and neuronal degeneration results.
2. **Inflammation:** The rabies virus can very well dodge the immune system but there is still potential for the virus to lead to a mild inflammatory response. Inflammation can aid in neuronal damage and assist in advancing the disease.

2. Immune Evasion Strategies

One of the hallmarks of rabies virus pathogenicity is its ability to evade the host immune response [34, 37]:

1. **Limited Antigen Presentation:** Rabies virus can block expression of major histocompatibility complex (MHC) by infected cells making them unrecognizable to cytotoxic T lymphocytes and damaging adaptive immunity.
2. **Interference with Cytokine Signaling:** Cytokines that the virus can alter change three things: cytokine production and production of pro-inflammatory and anti-inflammatory cytokines — and an imbalance of pro-inflammatory and anti-inflammatory signals that complicates the immune response even further.

3. Impact on Neural Function and Behavior

The invasion of the rabies virus into the CNS has profound effects on both neural function and behavior [3, 33]:

1. **Neurological Symptoms:** Infections may have wide variety of neurological symptoms such as agitation, confusion, hallucinations, paralysis and hydrophobia. The direct result includes these symptoms, as it is viral replication in very important brain areas regulating behavior and autonomic functions.
2. **Behavioral Changes:** Infected animals often show changes in behavior, which have been caused by the rabies virus. These changes can include aggression, increased vocalization, and abnormal feeding behaviour all of which accelerate further transmission of this virus.

4. Regional Specificity of Infection

The pathogenic effects of rabies virus are also influenced by its regional specificity within the CNS [3, 38, 39]:

1. **Targeting Specific Brain Regions:** The virus prefers attacking parts of the brain such as the hippocampus, brainstem and spinal cord. Symptoms and progression of disease are correlated to infection in these regions.
2. **Neurotropism:** This property of rabies virus, to infect only neuronal cells and thus spread efficiently, with minimal exposure to immune surveillance of non-neuronal tissues, facilitates its high transmission efficiency.

5. Clinical Manifestations and Disease Progression

The clinical manifestations of rabies infection typically follow a predictable progression [40]:

1. **Incubation Period:** Duration of time that may pass between exposure to symptoms varies but is commonly one to three months in duration, depending on site of entry and viral load.
2. **Acute Neurological Phase:** On the other hand, after the incubation period patients develop an acute phase characterized by neurological symptoms that will progress to paralysis, coma and death.

Table 3 *(Pathogenicity Factors of the Rabies Virus.)*

Pathogenicity Factor	Description
Virus-Induced Neurodegeneration	- Direct cytopathic effects leading to apoptosis and necrosis of infected neurons - Mild inflammatory responses contributing to neuronal damage
Immune Evasion Strategies	- Inhibition of MHC molecule expression, reducing T cell recognition - Alteration of cytokine production, disrupting immune signaling
Impact on Neural Function	- Neurological symptoms such as agitation, confusion, and paralysis - Behavioral changes including aggression and altered feeding habits
Regional Specificity of Infection	- Targeting specific brain regions (hippocampus, brainstem, spinal cord) linked to symptom severity - Neurotropism allowing efficient spread within the CNS
Clinical Manifestations	- Variability in incubation periods (typically 1-3 months) - Acute phase characterized by severe neurological symptoms leading to coma and death

Molecular Interactions and Host Responses

The process of rabies virus-host interaction is multistep and consists of several molecular events. These interactions are important to know towards explaining how the virus gets to infect, avoid being eliminated and in the process causes disease. Here, we discuss several possible interactions of the rabies virus and its target cells and the related host reaction.

1. The Function of Viral Proteins

The rabies virus encodes several proteins that play critical roles in its lifecycle and interactions with host cells [41-44]:

1. **Glycoprotein (G):** But this protein is required for the virus to enter within the host cells. It transmits attachments with cellular receptors and the fusion of cells with the help of arrows into the host cell membrane. It also suppresses the host's immune response.
2. **Nucleoprotein (N):** N protein surrounds the viral RNA genome and also plays a role in viral replication. In addition, the viral RNA hides from host's immune system from detection.
3. **Phosphoprotein (P):** It is a cofactor with the viral polymerase and enhances the rate of synthesis of RNA. Besides, it confines host antiviral signaling pathways, helping in escape from the immune response.
4. **Matrix Protein (M):** The M protein plays an important role in virion assembly as well as in budding of new virions from affected cells. It also engages with host cell structures for the purpose of virus replication.
5. **Polymerase (L):** Replication of the viral RNA genome and transcription of mRNA to generate viral proteins are done by the L protein.

2. Host Cellular Responses to Infection

The host's immune system responds to rabies virus infection through a variety of mechanisms aimed at controlling and eliminating the virus [18, 33, 45, 46]:

1. Innate Immune Response: On infection, host pattern recognition receptors (PRR) sense viral components leading to type I IFN and another cytokine release. These molecules cause a neighboring cell to enter into an antiviral state, and to activate immune cells.
2. Adaptive Immune Response: This also allows the rabies virus to escape from the immune response for many aspects of the adaptive immune response, but it can still provoke antibody response to G protein. If produced early in the course of exposure, antibodies will help neutralize a further infection.
3. Cellular Immune Response: However, infected neurons can be targeted and killed by Cytotoxic T lymphocytes (CTLs), albeit lacklusterly, because the virus can inhibit MHC expression on infected cells.

3. Cytokine and Chemokine Profiles During Infection

The profile of cytokines and chemokines produced during rabies virus infection can significantly influence disease outcomes [47-50]:

1. **Pro-inflammatory Cytokines:** In most cases the initial immune response involves pro-inflammatory cytokines like IL6 and TNFα that have the ability to stimulate inflammation but can lead to such damage to the tissue if allowed to run unchecked.

2. **Anti-inflammatory Signals:** They observe that infected neurons might even produce anti-inflammatory cytokines like IL-10 that can help to dampen the immune response and allow the virus to persist within the CNS.

4. Interference with Host Immune Signaling

The rabies virus has developed strategies to interfere with host immune signaling pathways [51, 52]:

1. **Inhibition of Interferon Signaling:** Rabies virus P protein blocks the activity of the Janus kinase signal transducer and activator of transcription (JAK STAT) signaling pathway, thus impairing interferon responses that normally limit viral replication.
2. **Modulation of Apoptosis:** The virus tricks apoptosis pathways into prolonging infected neurons so that there is continued viral replication within those neurons.

Table 4 *(Molecular Interactions and Host Responses to Rabies Virus Infection.)*

Interaction/Response	Description
Viral Proteins	- **Glycoprotein (G)**: Mediates cell attachment and entry; modulates immune response. - **Nucleoprotein (N)**: Encapsulates viral RNA; evades immune detection. - **Phosphoprotein (P)**: Enhances RNA synthesis; interferes with host antiviral signaling. - **Matrix Protein (M)**: Facilitates viral assembly and budding; interacts with host components. - **Polymerase (L)**: Responsible for RNA replication and transcription.
Innate Immune Response	- Activation of pattern recognition receptors (PRRs) leads to type I interferon (IFN) production, establishing an antiviral state in neighboring cells.
Adaptive Immune Response	- Antibody production against the glycoprotein (G) can neutralize the virus; however, the response may be limited due to immune evasion.
Cytokine and Chemokine Profiles	- Pro-inflammatory cytokines (e.g., IL-6, TNF-α) promote inflammation but can lead to tissue damage. - Anti-inflammatory cytokines (e.g., IL-10) help dampen immune responses, allowing viral persistence.
Interference with Immune Signaling	- **Inhibition of Interferon Signaling**: P protein inhibits JAK-STAT pathway, reducing antiviral effectiveness. - **Modulation of Apoptosis**: Virus manipulates apoptotic pathways to prolong neuron survival, allowing continued replication.

Table 5 *(Therapeutic Approaches and Challenges in Rabies Virus Management.)*

Therapeutic Approach	Description	Challenges
Post-Exposure Prophylaxis (PEP)	- Administration of rabies vaccine and rabies immune globulin (RIG) after potential exposure.	- Must be administered promptly; effectiveness diminishes after onset of symptoms.
Vaccination	- Use of inactivated or live attenuated vaccines for prevention in high-risk populations.	- Vaccine coverage may be inadequate in endemic regions; public awareness is crucial.
Antiviral Drug Development	- Investigation of potential antiviral agents targeting viral replication and entry mechanisms.	- Limited clinical efficacy due to the advanced stage of infection at the time of treatment initiation.
Gene Therapy	- Exploring the use of gene editing technologies to modify host cell responses or target viral genes.	- Ethical concerns and technical challenges in delivering gene therapies effectively.
Immunomodulation	- Enhancing host immune responses through adjuvants or immune checkpoint inhibitors.	- Risk of exacerbating inflammation or causing autoimmune reactions.
Monoclonal Antibodies	- Development of monoclonal antibodies targeting rabies virus proteins for therapeutic use.	- High production costs and potential for limited availability in resource-poor settings.

Table 6 *(Future Directions in Rabies Research.)*

Future Research Direction	Description
Improved Vaccine Formulations	- Development of more effective vaccines with longer-lasting immunity and fewer side effects.
Novel Antiviral Agents	- Exploration of small molecules or compounds that can inhibit rabies virus replication.
Understanding Viral Pathogenesis	- Further studies on the molecular mechanisms of neuroinvasion and immune evasion to identify new targets for therapy.
Enhanced Diagnostic Tools	- Development of rapid and accurate diagnostic methods for early detection of rabies infection.

Community Education and Outreach	- Strategies to increase awareness and education about rabies prevention and control measures, especially in endemic areas.

CONCLUSION

Excellent progress in understanding the molecular mechanisms of rabies virus neuroinvasion has been made that is important for the development of interventions against this deadly disease. Although, current strategies such as vaccination and post exposure prophylaxis are effective, they pose a challenge in the administration of the drugs timely. Future research will include better vaccines and better diagnostics as well as novel antivirals to better fight rabies and reduce its global health impact.

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