Chapter 2

Rabies Virus : Pathogenesis, Complications, Vaccine Development, and Therapeutic Approaches

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Abstract

Rabies is a fatal viral zoonotic disease caused by the rabies virus, which primarily affects the central nervous system of humans and other mammals. The virus is mainly transmitted through the bite or saliva of infected animals, particularly dogs. Rabies is a fatal viral disease that affects the central nervous system of humans and animals. It is caused by the rabies virus and is mainly transmitted through the bite or saliva of infected animals. After entering the body, the virus spreads through peripheral nerves to the brain, leading to severe neurological damage. The infection can cause complications such as encephalitis, paralysis, and respiratory failure. Since rabies is almost always fatal once clinical symptoms appear, early prevention is essential. Current preventive measures include effective vaccines and post-exposure prophylaxis. Therapeutic approaches mainly involve proper wound care, administration of rabies immunoglobulin, and vaccination. Continuous advancements in

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vaccine development and treatment strategies are important for controlling rabies and reducing its global impact.

Keywords: Rabies virus, Pathogenesis, Complications, Rabies vaccine, Therapeutic approaches.

1. Introduction

The family Rhabdoviridae consists of more than 100 single-stranded, negative-sense, nonsegmented viruses that infect a wide variety of hosts, including vertebrates, invertebrates, and plants. Human pathogens of medical importance are found in the genera Only the rabies virus, medically the most significant member of the genus *Lyssavirus.* The rabies virus causes acute infection of the central nervous system [1]. Rabies is a zoonotic disease caused by the rabies virus [13]. All rhabdoviruses encode five structural proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and an RNA-directed RNA polymerase (L) (Figure 1). The N protein encapsulates the RNA genome, forming a tightly wound N-RNA complex known as a ribonucleoprotein (RNP) [3]. The majority of lyssavirus species have been detected in various bat species and, as such, are speculated to have originated in bats [4]. This virus has been largely eliminated throughout Western Europe in both domestic and wild terrestrial carnivore species [4]. The major element of transcriptional regulation in nonsegmented negative-strand RNA viruses (*Mononegavirales*), which include the families *Filoviridae*, *Paramyxoviridae*, *Rhabdoviridae* and *Bornaviridae*, is the gene order [5]. To date, all rabies virus (RABV) studies in bats have been performed in wild-caught animals [6]. Rabies has the highest case fatality rate of any conventional infectious disease [8]. The rabies virus (RABV) is a highly neurotropic

pathogen that typically leads to mortality of infected animals and humans [10]. Rabies virus infection of dorsal root ganglia (DRG) was studied *in vitro* with cultured adult mouse DRG neurons [11].

The RABV transcription and replication strategy. The negative-sense genomic RNA (in orange) is the template for the L-P polymerase complex. A) During transcription, five 5′ end-capped (C) and polyadenylated (A) mRNAs (in green) encode the viral proteins. The polymerase complex disassociates from the template at each termination signal (STOP). The polymerase does not always re-engage successfully, leading to a negative transcription gradient from 3′ to 5′**.** B) During replication, the negative-sense genome is transcribed into a positive-sense antigenomic RNA intermediate (in green) by a more processive form of the viral polymerase. The anti-genome is then transcribed back into a negative-sense RNA to complete replication.

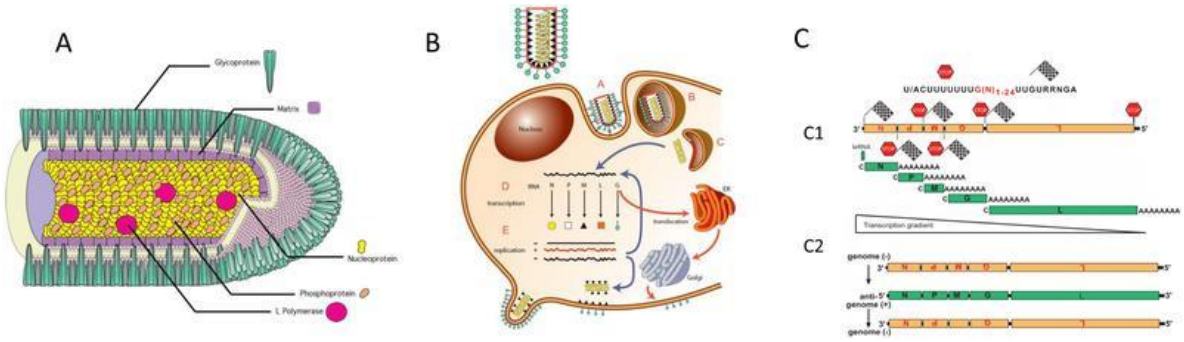

Figure 1: The RABV transcription and replication strategy

1.1 Pathogenesis

After inoculation, rabies virus may enter the peripheral nervous system directly and migrate to the brain or may replicate in muscle tissue, remaining sequestered at or near the entry site during incubation, prior to central nervous system invasion and replication. It then spreads centrifugally to numerous other organs. The case-fatality ratio approaches unity, but exact pathogenic mechanisms are

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not fully understood [1]. From a peripheral site of exposure, neurotropic pathogens such as RABV must enter the CNS to spread and cause disease. However, the mammalian CNS has several anatomical and biochemical barriers that separate it from the rest of the body. Among the most widely studied natural defense barriers is the blood-brain barrier (BBB), the highly selective permeability barrier of the neurovascular epithelium, made up of tight junctions between the epithelial cells [3].

1.2 Etiology

The RABV most likely came from a bat ancestor and evolved through multiple host-switching events in dogs, bats, and other animals. Seven main lineages of RABV exist worldwide, each with many variants associated with specific animals and geographies. The most widespread lineage occurs in dogs and wildlife species such as foxes, jackals, and skunks in Europe, Africa, the Americas, and Asia. Many bat-associated lineages in Latin America continue to cause rabies in humans and domestic livestock. Continued genetic diversification of RABV and other *lyssaviruses* raises concerns that the existing HRIG and rabies vaccines may cease to be effective for human rabies prevention [12].

1.3 Complications

- Seizures
- Fasciculations
- Psychosis
- Aphasia
- Autonomic instability
- Paralysis
- Coma
- Death [12].

2. Clinical Treatment

Treatment for clinical rabies caused by RABV and related *lyssaviruses* is largely supportive, focusing on minimizing patient suffering.

- Mouth care, provision of high-water-content foods, and intravenous fluids for hydrophobia
- Antipyretics, often administered rectally for fever
- Benzodiazepines for the management of agitation, anxiety, and seizures
- Anticholinergics for the management of hypersecretion and disordered swallowing
- Opioids for pain management [12]

3. Current Rabies Vaccines

3.1 Modified live vaccine (MLV)

Non-pathogenic in animals, ability to propagate high virus titers in cells, ability to induce protective immunity after administration, and thermal and genetic stability. To ensure the safety of candidate vaccines, most researchers modified the virus by serial passage in various cells. This technique has led to the development of attenuated live vaccines for controlling the infectious disease [14].

3.2 Inactivated rabies vaccine

Inactivated rabies vaccines require that high RABV titers be produced in tissues or cells. RABV can be grown in brain tissue, and nerve tissue vaccines (NTVs) consisting of inactivated rabies vaccine produced from RABV-infected brain tissue of sheep, goats, and mice were developed about 100 years ago and have been used in some Asian and African countries [14].

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3.3 Dna-Based Vaccines

One approach for developing new-generation rabies vaccines is to use a DNA-based or plasmid vaccine encoding the rabies glycoprotein gene. Advanced recombinant DNA technology has made it possible to generate a variety of DNA vaccines against infectious agents. DNA-based vaccines developed to induce a broad-spectrum immune response when delivered to the host have several advantages, such as action in the presence of maternal antibodies, strong stability, mass production, and cost effectiveness. DNA-based vaccines should provide efficient ways to induce a cell-mediated cytolytic $CD8^+$ T cell response, $CD4^+$ T cells, and VNA [14].

4. History

The study of rabies virus infection in bats can be challenging due to quarantine requirements, husbandry concerns, genetic differences among animals, and lack of medical history [6]. Worldwide, more than 70,000 people die of rabies every year in undeveloped and developing nations; 95% of all human rabies deaths are the result of infection with a canine rabies variant [6]. Although rabies has been the subject of large-scale public health interventions, chiefly through vaccination efforts, the disease continues to take the lives of about 40,000-70,000 people per year, roughly 40% of whom are children [3]. Rabies remains an important public health problem, with more than 95% of all human rabies cases caused by exposure to rabid dogs in areas where effective, inexpensive vaccines are unavailable. Rabies causes an estimated 55,000 human deaths globally each year, 23,750 of which occur in Africa. Moreover, 11 million people undergo rabies postexposure prophylaxis (PEP) worldwide each year. Rabies is a zoonotic disease, with dogs remaining the principal host in Asia, parts

of the Americas, and large parts of Africa, and rabid dogs are the cause of most human rabies. Between 30% and 60% of the victims of dog bites are children under the age of 15. Inappropriate dog vaccination programs, limited access to vaccination, and postexposure treatment of individuals that have been exposed to rabid dogs are major problems in developing countries [2]. Rabies is an ancient disease, and its history can be traced back more than 5000 years [9].

5. Differential Diagnosis

- Guillain–Barré syndrome
- Psychosis
- Seizures
- Poisoning with belladonna alkaloids
- Cerebral malaria
- Meningitis
- Acute encephalitis from any other infectious or noninfectious causes
- Poliomyelitis
- Poisoning
- Metabolic causes such as hypoglycemia and thiamine deficiency
- Cerebrovascular accident
- Creutzfeldt–Jakob disease
- Brain tumor
- Neurosyphilis
- Tetanus
- Autoimmune encephalitis [12]

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