General Internal Medicine and Clinical Innovations

Review Article

A review of three members of the rhabdovirus group

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Abstract

Rhabdoviruses are a group of intracellular parasites that are ubiquitous in nature. The group contains such organisms as vesicular stomatitis virus, rabies, and infectious hematopoietic necrosis virus which causes hemorrhage and necrosis primarily in salmonid fish such as salmon and trout. It is a disease of extreme economic importance. This disease group represents threats to human health, as well as health and economic risk to a wide range of plants and animals. Although not as "popular" as some other disease groups, Rhabdovisuses remain a major disease issue worldwide.

Introduction

The *Rhabdoviridae* are a family of viruses (Group V) that have negative sense, single stranded RNA as their genetic core and affect plants and animals of all types. Structurally they resemble a bullet with one end of the virus being rounded and the other end flat. They are composed of five proteins, Glycoprotein (G), which form trimers that make up attachment structures so the virus may enter a cell, Polymerase protein (L), which is the RNA dependent RNA polymerase, Phosphoprotein (P) component of the viral polymerase, nucleocapsid protein (N), the major component of the viral nucleocapsid and Matrix protein (M), which assists with viral the budding of new virus from a cell [1]. The P, L and N protein comprise the nucleocapsid. There are more than 50 members of the family. The glycoprotein envelope provides both protection against environmental stresses and aides in cellular infection. The virus group on average are about 180 nm long and 75 nm wide. Two of the genera in this family of viruses are *Lyssavirus* and *Vesiculovirus*. This paper reviews viruses of these two genera, vesicular stomatitis virus (VSIV or VSV) the type strain, infectious hematopoietic necrosis virus (IHNV), a devastating disease of fish, and rabies, which made the group famous, and feared around the world [2,3].

Rhabdovirus replication

The life cycle of this group is essentially cytoplasmic. Viral replication of *Rhabdoviruses* begins when spikes on the G protein connected to the outer viral envelope attach to cellular receptors. The receptors for rhabdoviruses have yet to be definitively identified but some experiments point to phospholipids, particularly phosphatidyl serine, as the cell surface receptor molecule [1]. What follows is a pH facilitated fusion of the viral and cellular membranes, releasing viral nucleic acid into the cellular cytoplasm [1,2,4]. The G (66K MW) protein performs two functions, receptor binding and membrane fusion. Since intracellular pH tends to be low, this enhances the membrane fusion process, thus releasing the viral RNA. G protein is directly involved in the pH dependency. Once released, viral RNA is free in the cytoplasm of the cell. Ribonucleoprotein is the template for viral genetic transcription. The nucleic acid is negative sense. Transcription occurs in the 3` to 5` direction where the only promotor on the genome is located. The ribonuclease attaches at this promotor site and will stop and start at the end of a viral gene. A limited amount of polymerase continues past each terminal area to continue the transcription process. This process of interrupted or stuttering transcription results in larger amounts of mRNA from genes located closer to the 3' end of the genome. The N protein is transcribed first as it coats replicated genome sequences. The order of transcription is N (Nucleoprotein), P (Phosphoprotein), M (Matrix), G (Glycoprotein), L (polymerase). The L (RNA polymerase) protein is transcribed last and requires lessor quantities of compound for reproduction. Viral RNA polymerase is comprised by the complex formation of proteins L and P. Rhabdovirus RNA is negative sense so transcription begins essentially with the formation of a positive strand of mRNA. It is unmodified in that this positive strand is uncapped and not poly-adenylated. The switch between transcription of mRNAs and replication of genomic RNAs seems to be controlled by the level of N protein.

The leader strand (+ sense RNA) has no cap and is not poly-adenylated. Also synthesized are the 5 mRNAs representing the five structural proteins. These are capped and poly-adenylated. At a defined point the viral proteins are translated on loose or free ribosomes but the G protein is translated on rough endoplasmic reticulum, where it is also glycosylated [2,3].

Assembly

The G protein mRNA is translated in association with the endoplasmic reticulum and transported via the Golgi body to the cell surface. Here, it forms patches with which the M protein associates. The genomic length negative strand RNA molecules associate with N, L and P proteins forming the core nucleocapsids. This, in turn, associates with the M protein at the inner surface of the plasma membrane or perhaps in the cytoplasm. The interaction between nucleocapsid and M protein causes the former to change configuration so that it appears

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more condensed. The nucleocapsid then buds through the cellular membrane completing the life cycle and may be transmitted as an infectious agent [3].

Pathology

Pathology of VSV, a member of the *Vesiculovirus* genus occurs essentially by ingestion of the virus from the environment or from infected insects. Grazing cattle in a field will become infected by eating grass that has been inoculated from the drool of other sick cattle [5]. Once infected, blisters and lesions form on the tongue and mouth making it difficult or impossible for the animal to consume the quantities of vegetation necessary for survival. Anorexia and lethargy will develop as the animals grow weaker [2,5]. The disease may also develop around the udder, which then aides in disease transmission to healthy stock as young cattle nurse. Humans may become infected in a similar fashion by indirect exposure to contaminated dust or grass via the oral cavity [5]. Once infected, one side of the mouth and tongue develop lesions which resolve over the next 14 days. Since the virus is transmitted along nerves, the other side of the mouth develops ulcers, again making it difficult to eat or swallow. The disease is thus prolonged, with the same symptomology. Recombinant vaccine is used to treat the disease. But the disease is largely self-limiting [6].

In contrast IHNV is water bourn [7-9]. The pathology of IHNV (a member of the *Lyssavirus* genus) occurs by inoculation of Salmonid fish through gills or the digestive tract. It has also been suggested that IHNV may enter at the base of the fins. This agent like all of the lyssavirus subgroup are poor immunogens. Vertical transmission through sexual fluids may also occur. It has been shown that the virus can survive in water for up to one month. Regardless of the route of inoculation water is the medium by which the virus infects fish. Optimal water temperature of transmission is between 8C and 15C. Mass infections usually occur in the spring or early summer just after the water warms. Clinical signs of the disease include abdominal distension, bulging eyes, dark skin and light or pale gills, with overt abnormal activity possible. There is a high mortality rate in fry >90% (young fish). Mortality rates decrease in fish two months old, or older [10]. Necrosis is common in the kidney, liver and spleen of infected fish thus providing the name for the disease. The virus is prevalent in the US Pacific Northwest, Japan and Europe. Control of IHNV is primarily by adjustments in water temperature in hatcheries, cleaning of tanks holding fry and culling of infected fish. Infection can also be controlled by low levels of iodine, 0.1 mg/liter. This effect decreased above pH 7.5 [8,11,12].

Rabies is one of the most famous, and most feared of all human diseases and like IHNV is a member of the *Lyssavirus* genus. Rabies is found globally, and is responsible for as many as 50,000 deaths a year. Infection occurs by puncture from an infected animal [3]. Most famously bats are the culprit but any animal can transmit the disease via bite or another puncture. Animals without salivary glands do not as a rule spread the disease. They can however become infected. Once an animal is bitten, the rabies virus travels by the neural network to the central nervous system [1,2]. This takes anywhere from 30-90 days before symptoms are noticed. Symptom development is somewhat dependent on where the person or animal is bitten, with neck wounds typically having shorter incubation periods as the virus has a shorter transport route to the central nervous system. The P structural protein acts as an interferon antagonist which effectively prevents the immune system from modulating virus spread. Once in the CNS, the virus will spread to other organs especially the mouth. Upon viral entry the body will produce neutralizing antibody against the G protein [4]. Regions of the G protein II and III are mostly targeted.

Once the virus reaches the central nervous system, there is 100% chance off fatality [1,3,13]. Rabies infection causes horrific symptoms. First, individuals who are infected with rabies experience 2-7 days of a non-specific, flu-like prodrome [1,3,4]. The prodrome is followed by behavioral abnormalities such as anxiety, depression, hyperactivity, and aggression [12]. Next, the unusual symptoms of intolerance of tactile, auditory, and visual stimuli begin. This is sometimes referred to as "hydrophobia" because patients are highly averse to the sensation of water in their mouths and on their skin. Insomnia and hallucinations eventually develop as well. The progression of rabies symptoms has been divided into two general tracts: 'furious rabies' and 'dumb rabies.' Symptoms of aggression and hyperactivity are generally more prominent in the case of furious rabies, while the symptom of paralysis is more prominent in the case of dumb rabies. Negri body development in the brain is a common diagnostic sign for the disease as is the aversion to the sight of water and disorientation and photophobia [13]. They are eosinophilic inclusion bodies found in nerve cells, especially Ammon's Horn in the hippocampus of the brain. The stain used is commonly for this purpose is hematoxylin and eosin (H & E) staining of sectioned brain tissue.

Pre-exposure and post-exposure immunizations are available and have a high success rate. Additionally, passive immunization is sometimes used to control the disease [13].

Summary

Rhabdoviruses continue to be an important group of pathogens for human and animal health, and economic reasons. The group is complex in its varied pathologies and variety of symptoms, suggesting an ancient origin to the disease. Most forms are self-limiting, with rabies being the notable exception. This disease like some others brings on visions of abject terror, which given the use of modern therapy are no longer warranted.

Rabies and IHNV are considered slow replicators as compared to VSV. The pathology is less cytotoxic which tends to not provoke as significant an immune response.

Fluorescence microscopy, enzyme linked immunosorbent assay (ELISA), and RT PCR are also used to diagnose these diseases. Research continues to create and improve treatments for all members of this group of pathogens.

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