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An Overview of Ranavirus Infections and Its Impact

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Abstract: Ranaviruses have been causing widespread infections in fish, reptiles, and amphibians, leading to mass deaths globally since the early 1990s. These viruses infect a variety of hosts, particularly amphibians, during their vulnerable life periods. Notable ranavirus species include Frog virus 3 and Chimeric ranaviruses, impacting various amphibian species with severe symptoms such as skin lesions, internal hemorrhaging, and mass die-offs. Indirect transmission through water and direct transmission from consuming infected individuals have been noted. Ranaviruses, with significant impacts on amphibian populations across continents, have raised concerns in the scientific community. The spread of ranaviruses is facilitated by global trade, posing risks to native species. Controlling ranavirus disease involves strict biosecurity measures and preventive strategies, especially in captive settings. Understanding the genetic evolution, host interactions, and transmission dynamics of ranaviruses is crucial to combat their detrimental effects on wildlife and ecosystems. International cooperation and research efforts are essential to develop effective management and conservation strategies for combating ranaviruses and preserving biodiversity.

Introduction

Ranaviruses are widespread infections that seem to be on the rise in the populations of fish, reptiles, and amphibians. At least 177 amphibian species (25 families), 49 fish species (25 families), and 37 reptilian species (17 families) have been found to have ranavirus infection or illness. Since at least the early 1990s, viral infections belonging to the genus Ranavirus and family Iridoviridae have caused mass death in amphibians worldwide. The disease may persist in herpetofaunal and osteichthyan reservoirs and infects a variety of amphibian hosts, including larval and adult cohorts. The icosahedral virions of these double-stranded DNA viruses have a diameter of 120 to 200 nm and occasionally have an envelope made of the cytoplasmic membrane of the host cell. Highly severe ranavirus species and strains have been known to infect caudates and anurans; however virulence is often host specific. Pre or perimetamorphic life periods are typically the most vulnerable. Rarely are ranaviruses recovered from clinically normal humans, but they are often linked to die-offs and sharp population decreases in wild amphibians.

On five continents, across all latitudes and elevations, ranavirus-associated mortality has been documented. Researchers have been studying the pathogen's genetics, ecology, and pathology since the early 1990s, when it was discovered that ranaviruses were an etiologic agent in amphibian die-offs. The goal is to identify potential contributing elements to the pathogen's rise. There have been reports of widespread ranavirus-induced amphibian death in Asia, Europe, and the Americas. North America has the highest number of recorded die-offs, with ranaviruses causing amphibian mortality episodes in more than 20 US states and three Canadian provinces. Although the virus has also been reported in Australia, nothing is known about how it affects the wild environment. Some of the impacted species are economically significant (like bullfrogs, rainbow trout, and soft-shelled turtles), but others are of conservation

concern (like Chinese giant salamanders, box turtles, and dusky gopher frogs).

Virus Characteristics

Different members of Ranaviruses that are known to cause diseases are

1. Epizootic hematopoietic necrosis virus (Ranavirus perca1)
2. Frog virus 3 (Ranavirus rana1)
3. Ambystoma tigrinum virus (Ranavirus ambystoma1)
4. Common midwife toad virus (Ranavirus alytes1)
5. Chimeric ranaviruses
6. Santee-Cooper ranavirus (Ranavirus micropterus1)

Replication cycle Ranaviruses have been extensively studied using Frog virus 3 (FV3), the type species of the genus. Replication of FV3 viruses occurs between:

12 °C and 32 °C, during which viral protein synthesis takes place several hours after cell infection. Cell death can occur within hours of infection, either by necrosis or apoptosis. Major capsid proteins (MCPs) represent about half of the virion weight. This protein is very conservative. A 500 bp long region at the 5' end of the MCP gene is commonly sequenced to characterize ranavirus species. The major capsid protein (MCP) makes up about half the weight of the virion. This protein is highly conserved among ranavirus species and antibodies produced often cross-react with the MCP of the same species. Other members of the clan. A 500-bp region at the 5′ end of the MCP gene is usually sequenced to characterize ranavirus species. Assignment of Ranavirus species should be based on multiple criteria, including host range, sequencing, RFLP and protein profile.

TRANSMISSION

Indirect transmission: Amphibians can become infected with pathogens circulating in the environment. Water and sediment can be effective routes of pathogen transmission, especially for amphibians that use ponds as larvae or adults. The persistence of ranaviruses outside the amphibian host is poorly understood, but fundamental to indirect transmission dynamics. Virions of ATV might persist in the environment for up to 2 weeks. Direct transmission: The direct spread of ranaviruses is very effective among amphibians. It is common for them to consume sick or deceased individuals that are infected with ranavirus. Numerous amphibian species eat embryos that may be infected with ranavirus, and certain larval species (such as *Ambystoma tigrinum* and *Spea multiplicata*) exhibit cannibalistic traits. Ingestion of animal tissue infected with the ranavirus can result in infection, according to several studies.

Transmission of the virus through direct skin contact has been demonstrated. In a study it was found that 1s of skin contact between healthy and diseased salamander is enough for the transmission of virus.

Vertical transmission is not documented and sperms or ova may be contaminated while passing through the cloaca.

Clinical Signs

Outbreaks of ranavirosis can manifest as a multitude of deceased and/or ailing amphibians, often visible in or around aquatic environments, or as the observation of solitary ill animals. Adult amphibians affected by the disease may exhibit skin reddening, skin lesions, bloody mucus in the oral cavity, and may also expel blood from the rectum; internal hemorrhaging is frequently identified during post-mortem examinations. Typically, individual sick animals show signs of lethargy, alongside skin lesions or loss of digits (toes and fingers), which can occasionally lead to the complete loss of feet. Diseased larval amphibians commonly display swollen bodies and indicators of internal bleeding, such as red patches across the tail or body. It is also one of the possible causes of red leg syndrome in amphibian species. There is also erratic swimming patterns, loss of equilibrium, lordosis, skin petechiation and swelling of the entire body.

The majority of outbreaks of ranavirosis happen during the warmer summer months, though it can happen at any time of year when amphibians are active. It has been demonstrated that higher ambient temperatures are linked to more frequent and severe ranavirosis outbreaks. The severity of ranavirosis outbreaks is expected to rise if climate change and warming continue.

Pathological Findings

Intracoelomic lesions, which include petechial or ecchymotic hemorrhages of the internal organs (particularly the liver, reproductive organs, and mesonephros [kidneys]), as well as pale, enlarged livers, may be seen in fatal cases of larvae and adults. Due to anorexia the gall bladder and GIT may be empty. There have been reports cases in adults of erythema of the legs and ventrum, skin ulceration, and erythema close to the vent or

plantar surfaces of the feet. Histological changes may be negligible or nonexistent in subclinically infected individuals, much like gross changes.

Non-specific histological alterations in ranavirus-positive individuals, such as mild to moderate lymphocytolysis, lymphoid depletion, and mild vacuolation of hepatocytes and renal tubular epithelium Tadpoles *of Lithobates catesbeianus* and *L. clamitans*. More severely impacted cells may exhibit varying degrees of vacuolation and necrosis, indicating attenuation of the renal tubular epithelium. Areas of myofibril disarray, fragmentation, and loss of cross striations are characteristics of skeletal muscle degeneration, which has only been documented in adults but most likely also happens in larvae. Numerous cell types, such as erythrocytes, macrophages, lymphocytes, leukocytes, hepatocytes, epithelial cells, and fibroblasts, can have intracytoplasmic inclusions.

Impacts On Trade

Since their host and geographic ranges seem to be growing, ranaviruses are categorized as emerging pathogens. It is becoming clear that the regional and global animal trade is a common way for ranaviruses to spread. For instance, in the southwestern United States, larvae of the barred tiger salamander (*Ambystoma mavortium*) are sold as fishing bait, and it has been demonstrated that up to 100% of them are infected with ATV. Amphibian ranaviruses have been discovered in animals that are traded internationally for a number of purposes, such as the pet trade and human consumption. The spread, variety, and accumulation of ranaviruses have been facilitated by invasive species and international trade. Because of its resistance to ranaviruses, the African clawed frog (*Xenopus laevis*), an invasive species in Chile, is believed to be a reservoir of infection. There are worries that this invasive species could aid in the spread of ranavirus and the subsequent decline of native amphibian species. Since exposure to genetically diverse viruses from geographically distant locations is likely to drive naturally recombinant viruses, it is believed that the genetic diversity of ranaviruses results from the transportation of animals in close proximity, which promotes co-infections and interclass transmission. For instance, genes belonging to the FV3 and CMTV clades were found in a ranavirus isolated from an Egyptian tortoise, which was determined to be a probable mosaic of two parent ranaviruses. It's interesting to note that the majority of the legal international trade in reptiles, including both wild-caught and captive-bred species passes through Europe. Most cases of genetically diverse ranavirus infections in reptiles have also been documented in Europe, frequently with a link to the pet trade.

The World Organization for Animal Health's (OIE) Aquatic Animal Health Code now lists ranavirus in amphibians as a disease that requires notification. The World Organization for Animal Health (OIE) created the World Animal Health Information System (WAHIS), which mandates that member states update their national and regional laws pertaining to diseases like ranavirus on a regular basis. This reporting database helps to prevent pathogen pollution and lower the risk of new disease outbreaks by facilitating risk analysis pertaining to international trade in animal products and sanitary practices in the global food trade, including amphibians.

Impacts on Amphibians and Other Species

Global amphibian populations have been severely impacted by ranaviruses, which have played a major role in the extinction of numerous species, including those that are already endangered. These pathogens primarily affect larval and juvenile amphibians, causing severe disease outbreaks with high mortality rates. Mass die-offs brought on by the high virulence and quick spread of ranaviruses have seriously disrupted local ecosystems and populations. Stress from captivity probably makes ranaculture and aquaculture operations, which usually concentrate on single-species production, more vulnerable to ranavirus infections.

Disease in amphibians can be caused by ranaviruses that infect fish, indicating host switching have taken place. Without taking the right precautions, bringing fish species to new locations can seriously endanger native amphibians with disease.

Country	Year	Species affected
UK	1991-1999	*Rana temporaria*
Australia	1992	*Limnodynastes ornatus*
Canada (Saskatchewan)	1997	*Ambystoma tigrinum diaboli*
USA(Dakota)	1998	*Ambystoma trigrinum*

USA(Arizona)	1998	*Ambystoma tigrinum stebbinsi*
Canada (Ontario)	2002	*Rana sylvatica, Rana pipiens*
Spain	2008	*Mesotriton alpestris cyreni, Alytes obstetricans*
Netherlands	2010	*Pelophylax spp., Lissotriton vulgaris*

Table 1: Showing the mass death of Amphibian species in various regions of the world due to ranaviruses.

In addition to short-term population reductions, Ranavirus has long-term ecological effects on amphibians. Because amphibians are essential for nutrient cycling, pest control, and serving as prey for other wildlife, their decline could have a negative impact on local ecosystems. Moreover, ecosystem resilience may be weakened by the loss of amphibian biodiversity, leaving habitats more susceptible to other environmental stresses.

Prevention And Control

Because ranaviruses can endure for long periods of time outside of their hosts, they can spread through fomites, recreational gear, and sampling equipment. To stop infection, any infected animals should be placed in quarantine. Before and after working at a field site, wildlife biologists, veterinarians, rehabilitators, and anybody else engaged in amphibian or reptilian fieldwork should follow stringent biosecurity procedures and wash and disinfect all clothing and equipment. Regulations should require testing amphibians raised in captivity for commercial purposes in accordance with the World Organization for Animal Health's (OIE) guidelines, particularly those that may be released or escape into wild populations. Regulations pertaining to amphibians traded as bait should either completely forbid their use or limit it to the watershed in which they were caught. It is easier to control ranavirus disease in captivity than it is in the wild. Isolating infected people, cleaning enclosures, lowering stress levels, and adhering to stringent biosafety guidelines are important measures to avoid cross-contamination. Low host densities and warm, regularly filtered water can help stop ranavirus outbreaks in captivity.

Conclusions

The world's biodiversity is seriously threatened by newly emerging infectious diseases. Despite being historically disregarded, over the past 20 years, a group of Iridoviruses in the genus Ranavirus have caused die-offs in fish, amphibian, and reptile populations both in the wild and in captivity. The First International Symposium on Ranaviruses was held in July 2011 in Minneapolis, Minnesota, USA, to exchange current knowledge about ranaviruses and determine important research avenues. The ecology and evolution of ranavirus–host interactions, possible reservoirs, transmission dynamics, and immunological and histopathological reactions to infection were all studied by 23 scientists and veterinarians from nine different nations. Speakers also covered conservation tactics to contain outbreaks and potential die-off mechanisms. A major contributing factor to the worldwide spread of ranaviruses and the interclass transmission of the pathogen is probably the commercial trade in ranavirus hosts. It is essential to comprehend how viruses evolve and adapt, especially the genetic alterations that affect their virulence and host range. It is still unknown what genetic factors contribute to host susceptibility or resistance, and finding particular genetic markers may help with conservation. Furthermore, research is required to understand how the ranavirus interacts with other pathogens in co-infected hosts in order to guide disease management. Lastly, although the fundamental immune responses are understood, more research is needed to create efficient treatment strategies due to the intricate molecular mechanisms of host immunity and viral evasion tactics. Future developments in ranavirus genomics may be utilized to protect wild populations while also creating vaccines and limiting transmission in facilities that house captives.

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