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Herpesviruses of Fish, Amphibians and Invertebrates

Steven van Beurden and Marc Engelsma
Central Veterinary Institute, part of Wageningen UR
Faculty of Veterinary Medicine, Utrecht University
The Netherlands

1. Introduction

Herpesviruses are large and complex DNA viruses which infect a wide range of vertebrates and invertebrates, including humans and domestic animals (Davison et al., 2005a). Severe infections are usually only observed in foetuses and very young or immunocompromised individuals, but economic consequences for livestock can be significant. Certain herpesviruses may also cause serious disease in non-reservoir host species - for example, Bovine malignant catharral fever. Prevention and treatment are complicated due to the ability of herpesviruses to persist as a latent infection.

In general, the occurrence of herpesviruses is host-specific (Davison, 2002). Most herpesviruses have evolved with their hosts over long periods of time and are well adapted to them. This view is supported by molecular phylogenetic data, and consistent with the generally modest pathogenicity of these viruses. In order to understand the evolutionary origin and consequences of herpesviruses infecting higher vertebrates, a profound understanding of the taxonomy of lower vertebrate and invertebrate herpesviruses is needed.

In many of the major aquaculture species, such as carp, salmon, catfish, eel, sturgeon and oyster, herpesviruses have been identified (Table 1). These herpesviruses merely represent the focus of current fish disease research, and it is expected that many other herpesviruses of lower vertebrates exist. The herpesviruses infecting fish, amphibians, and invertebrates make up two families, which are only distantly related to the well-known family of herpesviruses of mammals, birds, and reptiles (Davison et al., 2009).

In the last decades several mass mortality outbreaks in fish and oysters were found to be associated with herpesvirus infections. Management strategies are taken at fish farms to reduce the production losses due to these viruses. Several less-pathogenic fish herpesviruses are known to induce skin tumours and tumour-like proliferations (Anders & Yoshimizu, 1994), and one amphibian herpesvirus causes renal adenocarcinoma (McKinnell & Carlson, 1997). Experimental studies on these spontaneously-occurring viral tumours may serve as a model for viral carcinogenesis in humans. Interestingly, the course of infection of both the high pathogenic and tumour-inducing alloherpesviruses seems to be dependent on host age and ambient water temperature.

Genus	Virus name	Common name	Natural host(s)	Key reference for taxonomy
Batrachovirus	*Ranid herpesvirus 1*	Lucké tumour herpesvirus	Leopard frog (*R. pipiens*)	(Davison et al., 2006)
	Ranid herpesvirus 2	Frog virus 4	Leopard frog (*R. pipiens*)	(Davison et al., 2006)
Cyprinivirus	*Cyprinid herpesvirus 1*	Carp pox	Common carp (*C. carpio*)	(Waltzek et al., 2005)
	Cyprinid herpesvirus 2	Goldfish hematopoietic necrosis virus	Goldfish (*C. auratus*)	(Waltzek et al., 2005)
	Cyprinid herpesvirus 3	Koi herpesvirus	Common carp (*C. carpio carpio*) & Koi (*C. carpio koi*)	(Waltzek et al., 2005)
Ictalurivirus	*Acipenserid herpesvirus 2*	White sturgeon herpesvirus 2	White sturgeon (*A. ransmontatus*)	(Kurobe et al., 2008)
	Ictalurid herpesvirus 1	Channel catfish virus	Channel catfish (*I. punctatus*)	(Davison, 1992)
	Ictalurid herpesvirus 2	Ictalurus melas herpesvirus	Black bullhead (*A. melas*) & Channel catfish (*I. punctatus*)	(Doszpoly et al., 2008)
Salmonivirus	*Salmonid herpesvirus 1*	Herpesvirus salmonis	Rainbow trout (*O. mykiss*)	(Waltzek et al., 2009)
	Salmonid herpesvirus 2	Coho salmon herpesvirus	Salmon spp. (*Oncorhynchus* spp.)	(Waltzek et al., 2009)
	Salmonid herpesvirus 3	Epizootic epitheliotrophic disease virus	Lake trout (*S. namaycush*)	(Waltzek et al., 2009)
Unclassified alloherpesviruses	*Acipenserid herpesvirus 1*	White sturgeon herpesvirus 1	Sturgeon spp. (*Acipenser* spp.)	(Kurobe et al., 2008)
	Anguillid herpesvirus 1	Eel herpesvirus	European eel (*A. anguilla*) & Japanese eel (*A. japonica*)	(van Beurden et al., 2010)
	-	Pilchard herpesvirus	Pacific sardine (*S. sagax*)	(Doszpoly et al., 2011a)
Uncharacterized alloherpesviruses	Esocid herpesvirus 1	Blue spot disease virus	Northern pike (*E. Lucius*) & muskellunge (*E. masquinongy*)	-
	Percid herpesvirus 1	Herpesvirus vitreum	Walleye (*S. vitreum*)	-
	Pleuronectid herpesvirus 1	Herpesvirus scopthalami	Turbot (*S. maximua*)	-
		Atlantic salmon papillomatosis virus	Atlantic salmon (*S. salar*)	-
		Herpesvirus of osmerus eperlanus 1	European smelt (*O. eperlanus*) & rainbow smelt (*O. mordax*)	-
		Tilapia larvae encephalitis virus	Tilapia (*Oreochromis* spp.)	-
		Viral epidermal hyperplasia/necrosis	Japanese flounder (*P. esus*)	-
		-	Angelfish (*P. altum*)	-
		-	Golden ide (*L. ide*)	-
		-	Red striped rockfish (*S. proriger*)	-
		-	Smooth dogfish (*M. canis*)	-
Ostreavirus	*Ostreid herpesvirus 1*	Oyster herpesvirus	Japanese oyster (*C. gigas*) & other bivalves	(Davison et al., 2005b)
Unclassified malacoherpesvirus	*Abalone herpesvirus 1*	Abalone herpesvirus	Abalone (*H. diversicolor supertexta*)	(Savin et al., 2010)

Table 1. Classified, characterized and uncharacterized fish and amphibian herpesviruses of the family *Alloherpesviridae*, and invertebrate herpesviruses of the family *Malacoherpesviridae*

Herpesviruses of fish, amphibians and invertebrates form an important and potentially large group of many yet-undiscovered pathogens. Although the fundamental characteristics of herpesviruses of humans and several other mammals have been thoroughly studied, there is still little knowledge of the herpesviruses of lower vertebrates and invertebrates. This lack of knowledge hampers the development of therapeutic and preventive strategies.
This book chapter describes the fundamentals of herpesviruses infecting fish, amphibians and invertebrates, including their biology, classification and taxonomy, capsid structure and structural proteins, and genome organization and gene conservation. Where possible, a comparison with herpesviruses infecting higher vertebrates is made. An overview of the current knowledge on gene expression, latency and virulence factors of alloherpesviruses, as well as the characterization of specific genes and the development of vaccines, is given at the end of this chapter.

2. Biology of fish, amphibian and invertebrate herpesviruses

2.1 Frog herpesviruses

The North American leopard frog (*Rana pipiens*) is occasionally affected with a renal adenocarcinoma known as the Lucké tumour. A viral aetiology was proposed based on the presence of acidophilic inclusions in tumour cell nuclei, and transmission experiments (Lucké, 1934; 1938). Viral particles were observed by electron microscopy (EM) about 20 years later (Fawcett, 1956). Yet another decade later, the virus was characterized as a herpes-type virus (Lunger, 1964), later designated *Ranid herpesvirus 1* (RaHV-1). Tumour formation could be induced by injection with purified RaHV-1 (Mizell et al., 1969), and Koch-Henle's postulates were fulfilled (Naegele et al., 1974). Virus replication is promoted by low temperature (Granoff, 1999), whereas induction of metastasis is promoted by high temperature (Lucké & Schlumberger, 1949; McKinnell & Tarin, 1984). Although RaHV-1 cannot be cultured in cell lines, it was the first amphibian herpesvirus subjected to extensive genomic studies (Davison et al., 1999).
During an attempt to isolate the causative agent of the Lucké tumour from pooled urine of tumour-bearing frogs, another virus – designated frog virus 4 – was isolated using a frog embryo cell line (Rafferty, 1965). The virus was shown to possess the morphological characteristics of a herpesvirus (Gravell et al., 1968), but appeared to be clearly distinctive from the Lucké tumour herpesvirus with regard to the possibility of *in vitro* propagation and genomic properties (Gravell, 1971). In addition, frog virus 4 has no oncogenic potential, although it infects leopard frog embryos and larvae effectively (Granoff, 1999). Frog virus 4 was later designated *Ranid herpesvirus 2* (RaHV-2).

2.2 Catfish herpesviruses

In the United States, during the rapid expansion of the pond-cultured channel catfish (*Ictalurus punctatus*) industry in the late 1960s, high mortalities were reported in fingerlings and fry shortly after transfer from the hatchery to the fry ponds (Wolf, 1988). Moribund fish showed behavioural changes (swimming in spirals and hanging vertically with the head at the water surface), exophthalmus, pale or haemorrhagic gills, external and internal haemorrhages, and distension of abdomen (ascites and oedema) and stomach (Fijan et al., 1971). In 1968 a virus was isolated from various fish farms, designated channel catfish virus. A year later the virus was shown to be a herpesvirus which replicated best at 25-33 °C (Wolf

& Darlington, 1971), later designated *Ictalurid herpesvirus 1* (IcHV-1). Although mortality among young channel catfish may be very high, the effects of the disease can be minimized through management practices (Wolf, 1988). IcHV-1 has been studied extensively ever since (Kucuktas & Brady, 1999), starting with the biological properties (including pathogenicity and diagnostic possibilities), followed by molecular and structural studies, as well as vaccine development. IcHV-1 was the first fish herpesvirus for which the genome sequence became available (Davison, 1992), which had a significant impact on herpesvirus taxonomy.
In the summer of 1994 another catfish herpesvirus was isolated from adult black bullhead (*Ameiurus melas*) from two different farms in Italy (Alborali et al., 1996). Morbidity and mortality were very high (80-90%), with clinical signs being unexpected spiral movements, swimming in a vertical position and death. Internal findings included haemorrhages on skin, spleen and liver. This catfish herpesvirus was shown to be different from IcHV-1, but appeared to be highly virulent for channel catfish fry and juveniles (Hedrick et al., 2003). Hence, the virus was later designated *Ictalurid herpesvirus 2* (Waltzek et al., 2009).

2.3 Carp herpesviruses

Pox disease of carp was described as early as 1563 by Conrad Gessner. Four hundred years later, herpesvirus-like particles were found to be associated with the pox-like lesions in carp (Schubert, 1966). The agent was eventually isolated in Japan, and designated *Cyprinid herpesvirus 1* (CyHV-1) (Sano et al., 1985a; Sano et al., 1985b). Infection trials showed that the virus was highly pathogenic for carp-fry, but not for older carp (Sano et al., 1990b; Sano et al., 1991). The majority of surviving carp-fry and a number of older carp developed papillomas several months after infection. Mortality and regression of the papillomas appeared to be temperature dependent (Sano et al., 1993).
The causative agent of herpesviral haematopoietic necrosis of goldfish was first identified in the early 1990s in Japan (Jung & Miyazaki, 1995), and later designated *Cyprinid herpesvirus 2* (CyHV-2). This virus may cause severe mortality especially among juvenile goldfish (Chang et al., 1999; Groff et al., 1998; Jeffery et al., 2007; Jung & Miyazaki, 1995), at water temperatures between 15 and 25 °C (Jeffery et al., 2007). Clinical signs include lethargy, anorexia and inappetence. Gross pathology includes pale gills, and swollen spleen and kidney (Jeffery et al., 2007). The disease has been reported in the USA (Goodwin et al., 2006; Goodwin et al., 2009; Groff et al., 1998), Taiwan (Chang et al., 1999), Australia (Stephens et al., 2004), UK (Jeffery et al., 2007), and Hungary (Doszpoly et al., 2011b). CyHV-2 seems to be widespread on commercial goldfish farms, with outbreaks occurring when fish are subjected to stress during permissive temperatures (Goodwin et al., 2009).
In the late 1990s, mass mortalities associated with gill and skin disease occurred in the koi and common carp (*Cyprinus carpio* spp.) industries worldwide (Haenen et al., 2004). Affected fish were lethargic, anorexic and showed increased respiratory movements (Bretzinger et al., 1999; Walster, 1999). The disease is characterized by epidermal lesions, extensive gill necrosis, and an enlarged anterior kidney showing moderate damage histologically. The course is acute or peracute in most cases, with high morbidity and mortality, depending on the water temperature (15-28 °C). EM analyses revealed the presence of herpesvirus-like particles in respiratory epithelial cells of gills of affected koi carp (Bretzinger et al., 1999), and River's postulates were fulfilled subsequently (Hedrick et al., 2000). The etiological agent koi herpesvirus was shown to differ from CyHV-1 (Gilad et al., 2002), and later designated *Cyprinid herpesvirus 3* (CyHV-3) (Waltzek et al., 2005). Common and koi carp are

among the most economically important aquaculture species worldwide, with CyHV-3 still being one of the most significant threats (Michel et al., 2010). CyHV-3 has therefore been the subject of advanced fundamental and applied research in the past decade.

2.4 Salmon herpesviruses

During the early 1970s a herpesvirus was isolated from a rainbow trout (*Oncorhynchus mykiss*) hatchery in the USA, which had increased post spawning mortalities (30-50%) for several years (Wolf, 1976). The virus could only be propagated in cell cultures of salmonid origin at low temperatures (10°C) (Wolf et al., 1978). General characteristics of a herpesvirus were demonstrated by EM. Rainbow trout fry could be infected with this virus, with mortality ranging from 50-100%, but related salmonid species could not (Wolf, 1976). Symptoms observed included inappetence, lethargy, dark pigmentation, pale gills, and sometimes haemorrhagic exophthalmia (Wolf & Smith, 1981). Visceral organs and the heart showed major pathological changes, with the liver and kidneys being prime targets for the virus. The disease failed to spread by cohabitation. The etiological agent was later designated *Salmonid herpesvirus 1* (SalHV-1).

In the same period a number of herpesviruses was isolated in Japan from different salmonid species, such as kokanee salmon (*Oncorhynchus nerka*) (Sano, 1976), masu salmon (*Oncorhynchus masou*) (Hayashi et al., 1986; Kimura et al., 1981b), yamame (*Oncorhynchus masou*) (Sano et al., 1983), coho salmon (*Oncorhynchus kisutch*) (Kumagai et al., 1994), and rainbow trout (Yoshimizu et al., 1995). The viruses appeared to be highly pathogenic particularly for young fry of different salmonid species (Kimura et al., 1983; Yoshimizu et al., 1995). The liver and kidney were the primary target organs, characterized by necrosis (Tanaka et al., 1984). Interestingly, surviving fish developed epithelial tumours around the mouth (Kimura et al., 1981a; Sano et al., 1983; Yoshimizu et al., 1987). Subsequent serological and DNA restriction endonuclease cleavage analysis demonstrated that all isolates could be considered as a single virus species, designated *Salmonid herpesvirus 2* (SalHV-2) (Hayashi et al., 1986; Hayashi et al., 1989; Hedrick et al., 1987; Yoshimizu et al., 1995).

A third salmonid herpesvirus caused high mortalities among hatchery-reared juvenile lake trout (*Salvelinus namaycush*) in the Great Lakes Region of the USA for several subsequent springs and falls (6-15°C) during the mid-1980s (Kurobe et al., 2009). Epidemics were characterized by the rapid onset of mortality, followed by a number of nonspecific clinical signs, including corkscrew swimming, lethargy, and periods of hyperexcitability (Bradley et al., 1989). External symptoms included haemorrhages in the eyes, fin and skin degeneration, and secondary fungus infections (Bradley et al., 1989; McAllister & Herman, 1989). Mortality could be as much as 100%, with fry being more susceptible than fingerlings. In the late 1980s herpesvirus-like particles were associated with the disease. Transmission experiments demonstrated that *Salmonid herpesvirus 3* (SalHV-3) was the etiologic agent of the epizootic epitheliotrophic disease restricted to lake trout. Propagation of the virus in cell culture is still impossible, which hampered detection until very recently (Kurobe et al., 2009).

A fourth salmonid herpesvirus has been described, but not yet characterized. In the late 1970s benign proliferative epidermal papillomatous lesions of cultured Atlantic salmon (*Salmo salar*) in Scandinavia and the UK were investigated (Bylund et al., 1980; Carlisle & Roberts, 1977). Papillomas developed in July and August, after which they sloughed, and in December nearly all were gone. The papillomas appeared as white plaques which raised several millimetres and were up to several centimetres in diameter. They were frequently

multiple and found anywhere on the skin and fins posterior to the head. Morbidity and mortality were generally low. Virus-like particles were observed using EM in samples from papillomatous tissue (Carlisle, 1977), later characterized as a herpesvirus in Atlantic salmon from Russia (Shchelkunov et al., 1992). Attempts to isolate the observed virus in cell culture failed (Carlisle, 1977; Shchelkunov et al., 1992).

2.5 Sturgeon herpesviruses

In 1991 a herpesvirus was isolated from juvenile white sturgeon (*Acipenser transmontanus*) from a commercial farm in California, USA (Hedrick et al., 1991). The white sturgeon herpesvirus 1, later designated *Acipenserid herpesvirus 1* (AciHV-1), was associated with infections of the tegument and oropharyngeal mucosa, and mortality among the juvenile white sturgeons. Experimentally induced infections also resulted in mortality. AciHV-1 was later isolated from other farmed white sturgeons in California and Italy (Kelley et al., 2005; Kurobe et al., 2008).

Few years later another herpesvirus called white sturgeon herpesvirus 2, or *Acipenserid herpesvirus 2* (AciHV-2), was isolated from dermal lesions of subadult white sturgeon and ovarian fluids of a mature white sturgeon (Watson et al., 1995). Mortality among experimentally infected juvenile white sturgeons reached a cumulative total of 80%. AciHV-2 has since been isolated from wild white sturgeon in Idaho and Oregon (USA), from farmed shortnose sturgeon (*Acipenser brevirostrum*) from Canada, and from Siberian sturgeon (*Acipenser baeri*) in Russia (Doszpoly & Shchelkunov, 2010; Kelley et al., 2005; Kurobe et al., 2008; Shchelkunov et al., 2009).

2.6 Eel herpesvirus

Herpesvirus-like particles in wild European eels (*Anguilla anguilla*) were described for the first time in 1986 (Békési et al., 1986). A herpesvirus was later isolated from cultured European eels and Japanese eels (*A. japonica*) in Japan (Sano et al., 1990a). Serological, molecular, and sequence data indicated that Asian and European eel herpesvirus isolates can be considered as a single virus species (Chang et al., 2002; Lee et al., 1999; Rijsewijk et al., 2005; Sano et al., 1990a; Ueno et al., 1992; Ueno et al., 1996; Waltzek et al., 2009), designated *Anguillid herpesvirus 1* (AngHV-1). Clinical and pathological findings of the infection varied among and within outbreaks, and were predominantly apathy, haemorrhages and ulcerative lesions in skin and fins, haemorrhagic or pale and congested gills, a pale spleen, a pale and haemorrhagic liver, a distended gall bladder, and ascites (Chang et al., 2002; Davidse et al., 1999; Haenen et al., 2002; Lee et al., 1999; Sano et al., 1990a). AngHV-1 infection in cultured eels resulted in decreased growth rates and an increased mortality (Haenen et al., 2002). The virus is also frequently observed in wild European eels (Haenen et al., 2010; Jørgensen et al., 1994; van Ginneken et al., 2004).

2.7 Pilchard herpesvirus

In 1995, a massive epizootic occurred in adult Australasian pilchards (*Sardinops sagax neopilchardus*) in south Australia (O'Neill, 1995). In several months it spread thousands of kilometres bidirectionally along the Australian coastline, and then to New Zealand (Whittington et al., 1997). A similar event occurred a few years later in 1998/1999 (Murray et al., 2003). Affected pilchards showed progressive gill inflammation followed by epithelial hypertrophy and hyperplasia (Whittington et al., 1997). Consequent clinical symptoms

included hypoxaemia and hypercapnea, resulting in an estimated mortality of at least 10%. Involvement of an infectious agent was suggested, and PCR analysis revealed the putative involvement of a herpesvirus (Tham & Moon, 1996), which was soon confirmed by EM (Hyatt et al., 1997). Diagnostic tools for detection of the pilchard herpesvirus have been developed (Crockford et al., 2005; Crockford et al., 2008), revealing that the virus is now endemic in Australian pilchard populations (Whittington et al., 2008). Although the pilchard herpesvirus has not yet been isolated in cell culture, hampering further studies, limited phylogenetic analysis showed its relation to other fish and frog herpesviruses (Doszpoly et al., 2011a).

2.8 Other fish herpesviruses

Several other herpesvirus-like particles have been observed and found to be associated with disease in other fish species. Many of these viruses have not been isolated yet, however, and limited sequence availability hampers official classification.

In the late 1970s a herpes-type viral infection of the epithelia of the skin and gills of turbot (*Scophthalmus maximus*) was found, presumably associated with heavy mortalities among farmed turbot (Buchanan & Madeley, 1978; Buchanan et al., 1978). Although the virus could not be isolated in cell culture, EM observations clearly demonstrated herpesvirus characteristics. The virus was tentatively named herpesvirus scophthalmi, later referred to as pleuronectid herpesvirus 1 (PlHV-1).

Few years later a herpesvirus was isolated from hyperplastic epidermal tissue from a walleye *(Stiozostedion vitreum vitreum*) taken in Saskatchewan, Canada (Kelly et al., 1983). The virus was isolated in a walleye ovarian cell line and identified as a herpesvirus based on size, morphology, and apparent pattern of replication. The virus was initially called herpesvirus vitreum, but later designated percid herpesvirus 1 (PeHV-1).

A year later the same research group observed typical herpesvirus particles in epidermal hyperplasia or blue spot disease of northern pike (*Esox lucius*) in several waters of central Canada (Yamamoto et al., 1984). The virus, tentatively designated esocid herpesvirus 1 (EsHV-1), could not be isolated in cell culture, however. EsHV-1 was later also observed in northern pike and muskellunge (*Esox masquinongy*) in the USA, with clinical signs present only for a short period when water temperatures were between 2 and 13 °C (Margenau et al., 1995), and in northern pike in Ireland (Graham et al., 2004).

In the early 1980s, in a quarantined population of golden ide (*Leuciscus idus*) imported from Germany to the USA, 5% of the fish developed carp pox-like lesions (McAllister et al., 1985). EM analysis showed herpesvirus-like particles associated with the lesions, but the virus could not be isolated in cell culture.

In 1985 herpesvirus-like particles were observed in so-called spawning papillomas on the skin and fins of smelt (*Osmerus eperlanus*) in Germany (Anders & Möller, 1985). Herpesvirus-like particles were also observed in similar epidermal tumours of rainbow smelt (*O. mordax*) during spawning-time in Canada and the USA (Herman et al., 1997; Morrison et al., 1996). Isolation and genomic analysis of the herpesvirus of smelt have failed so far (Jakob et al., 2010).

In the same year a viral dermatitis was observed in a small percentage of wild and captive smooth dogfish (*Mustelus canis*) (Leibovitz & Lebouitz, 1985). Most skin eruptions were found on the tail and fins, often exceeding 1 cm in diameter, and histologically characterized by epidermal cell degeneration. EM revealed the progressive development of cellular

pathology associated with a specific epidermal viral infection, and viral particles showed the characteristics of a herpesvirus.

In the mid-1980s a new disease characterized by skin and fin opacity, and associated with high mortality occurred in larvae and juveniles of Japanese flounder (*Paralichthys olivaceus*) hatcheries in Japan (Iida et al., 1989; Miyazaki et al., 1989). Microscopically, epidermal cells at the surface were rounded, and histopathologically the epidermis appeared to be hyperplastic and necrotic (Iida et al., 1991; Miyazaki, 2005). Although the causative agent could not be isolated, herpesvirus-like particles were observed by EM. Infection trials showed that especially larvae <10 mm were susceptible, at water temperatures around 20 °C (Masumura et al., 1989).

After a stress-trigger, all three angelfish (*Pterophyllum altum*) in a fish tank showed loss of equilibrium and hung apathetic at the water surface (Mellergaard & Bloch, 1988). The fish had skin haemorrhages, pale gills and distended liver and spleen. Histopathological findings of the spleen were all suggestive of severe haemolytic anaemia. Herpesvirus-like particles were observed by EM in the nuclei of spleen macrophages and monocytes.

A wild redstriped rockfish (*Sebastes proriger*) demonstrated hepatic lesions, which were histologically suggestive of a herpesvirus-type infection (Kent & Myers, 2000). EM analysis of suboptimally preserved liver tissue revealed the presence of intranuclear particles, consistent in size and shape with herpesvirus capsids.

Recently, an outbreak of a novel disease characterized by a whirling syndrome and high mortality rates occurred in laboratory-reared tilapia larvae (*Oreochromis* spp.) (Shlapobersky et al., 2010). The disease was designated viral encephalitis of tilapia larvae. The morphological characteristics of virus particles found in the brains of diseased larvae as observed by EM were comparable to those of a herpesvirus.

2.9 Oyster herpesvirus

The first description of a herpesvirus-like virus in oysters originates from the United States (Farley et al., 1972). As for the fish and amphibian herpesviruses, it was only the virus morphology that identified this oyster virus as a herpesvirus. The principle susceptible species is the Japanese oyster (*Crassostrea gigas*), and the virus was designated *Ostreid herpesvirus 1* (OsHV-1). In Europe, where the virus was found for the first time in the early 1990s, OsHV-1 has been associated with high mortalities in oyster seedlings (Garcia et al., 2011). Herpesvirus-like particles – later confirmed to be OsHV-1 by molecular analyses – have also been observed in various other bivalve species, associated with mortalities (Arzul et al., 2001; Burge et al., 2011). Recently, an OsHV-1 variant, designated OsHV-1 µvar, was identified as the causative agent of high mortalities in juvenile oysters (Segarra et al., 2010).

2.10 Abalone herpesvirus

A second herpesvirus with an invertebrate host has been identified by EM in cultured abalone (*Haliotis diversicolor supertexta*) in Taiwan in early 2003 and in Australia in late 2005 (Chang et al., 2005; Tan et al., 2008). Abalones of all ages suffered from the disease, which was characterized by mantle recession and muscle stiffness, followed by high mortality within a few days. Histologically the nerve system appeared to be the primary target tissue, characterized by tissue necrosis with infiltration of haemocytes. The virus has been designated *Abalone herpesvirus 1* (AbHV-1).

3. Classification and taxonomy of the order *Herpesvirales*

Herpesviruses are large and complex DNA viruses with a distinctive virion morphology, which consists of four distinct structures: the core, capsid, tegument, and envelope (Davison et al., 2005a). The order *Herpesvirales* is subdivided into three families (Davison et al., 2009), which separated about 500 million years ago (McGeoch et al., 2006). The family *Herpesviridae* comprises the herpesviruses with mammalian, avian and reptilian hosts, and is further subdivided into the subfamilies *Alpha-*, *Beta-* and *Gammaherpesvirinae*, which fall into genera.

The family *Alloherpesviridae* comprises the piscine and amphibian herpesviruses (Waltzek et al., 2009). The criteria for the establishment of genera within the family *Alloherpesviridae* have not been defined yet, nor have rules been formulated for deciding whether species should belong to a particular genus. Currently, genera and their respective species are assigned largely based on available phylogenetic analyses, with phylogenetically closely related species assigned to the same genus. To date, four genera in the family *Alloherpesviridae* have been established: *Batrachovirus, Cyprinivirus, Ictalurivirus* and *Salmonivirus*, comprising a total of 11 different species (Table 1, Fig. 1). In the majority of the cases the classification follows the grouping of alloherpesviruses infecting the same host. At least another 14 herpesviruses infecting fish have been described, but not yet characterized sufficiently to allow classification.

The oyster herpesvirus OsHV-1 has been assigned to the genus *Ostreavirus* of the third herpesvirus family *Malacoherpesviridae*, which comprises the invertebrate herpesviruses (Davison et al., 2009; Davison et al., 2005b). The other invertebrate herpesvirus infecting abalone AbHV-1 has been shown to be related to OsHV-1 (Savin et al., 2010). Despite the similarities in capsid structure between the herpesviruses of mammals, birds and reptiles, fish and amphibians, and invertebrates, the three families are highly divergent. Only a single gene, encoding a DNA packaging enzyme complex distantly related to the ATPase subunit of bacteriophage T4 terminase, is convincingly conserved among all herpesviruses (Davison, 1992; 2002).

4. Conservation of herpesvirus capsid architecture & structural proteins

4.1 Capsid architecture of herpesviruses

Despite their diversity by genes, host range, and genome size, herpesvirus structure is conserved throughout the entire order *Herpesvirales*. Herpesvirus virions invariably consist of a large (diameter >100 nm) thick-walled icosahedral nucleocapsid (T=16), surrounded by a host-derived envelope with a diameter of about 200 nm, with an intervening proteinaceous layer called the tegument (Booy et al., 1996). This appearance is distinctively different from that of any other animal virus. Key to this morphological conservatism is the icosahedral nucleocapsid made up of hollow capsomers. The functionality of the genes involved in capsid assembly is largely conserved.

The capsid structures of alloherpesvirus IcHV-1 and malacoherpesvirus OsHV-1 have been studied by cryoelectron microscopy and three-dimensional image reconstruction (Booy et al., 1996; Davison et al., 2005b). Both viruses have capsids with diameters of approximately 116 nm, which is slightly smaller than the capsids of the human model herpesvirus, Herpes simplex virus type 1 (HSV-1, diameter 125 nm). The capsids of IcHV-1 and OsHV-1 are roughly hexagonal in outline and reconstruction revealed an icosahedral structure with a

triangulation number of *T*=16. The icosahedral facets of IcHV-1 appeared to be flatter, and the shell is about 20% thinner (12.4 nm vs. 15 nm) than that of HSV-1, consistent with the smaller size of its major capsid protein. The hexons and pentons showed protrusions with an axial channel through each capsomer. The outer surface is composed of heterotrimeric complexes or triplexes at the sites of local threefold symmetry, and the inner surface has a relatively flat and featureless appearance. IcHV-1 and OsHV-1 capsids are therefore similar in overall appearance to those of all other herpesviruses studied to date.

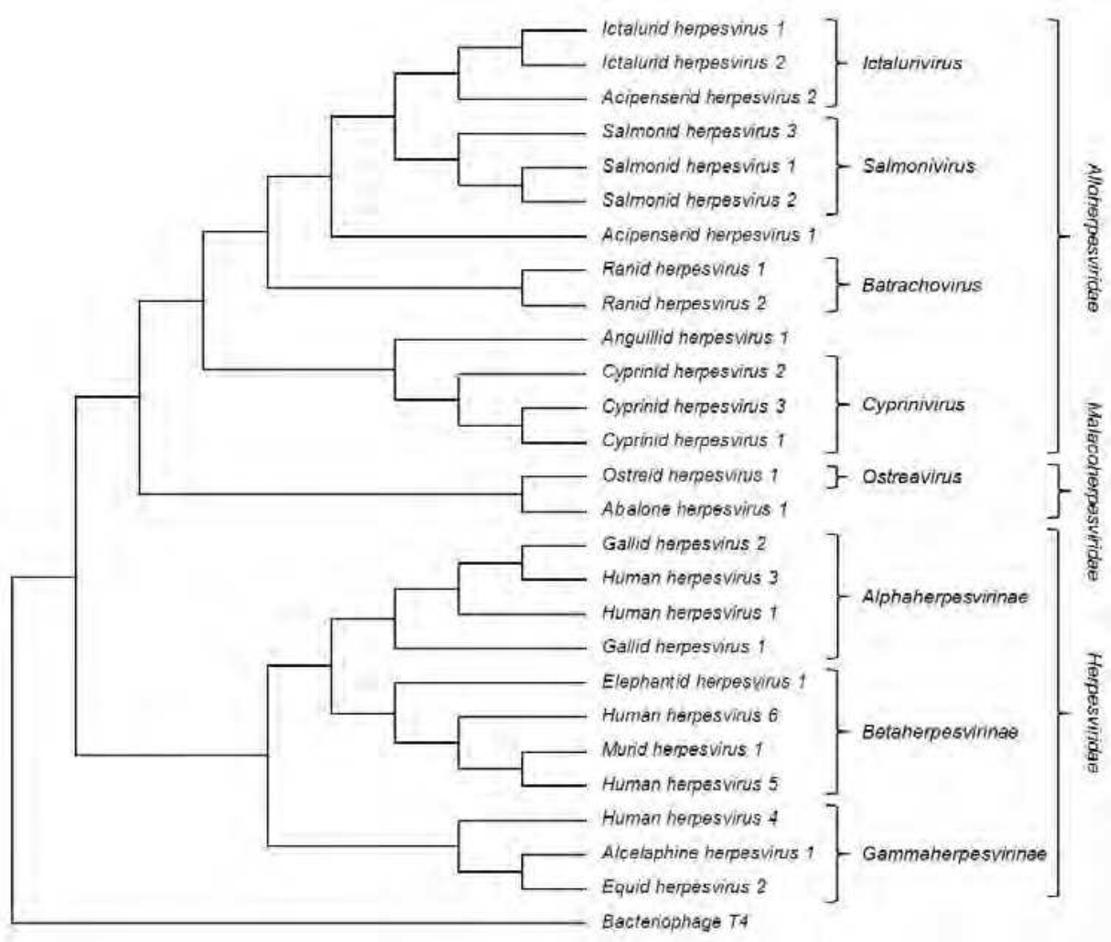

Fig. 1. Phylogenetic tree depicting the relationships (topology only) among viruses in the order *Herpesvirales*, based on partially deduced amino acid sequence of the terminase gene (107 residues, including gaps), analysed with the maximum likelihood method, using the JTT matrix (1,000 replicates), and rooted with bacteriophage T4

4.2 Structural proteins of *Alloherpesviridae*

Complete herpesvirus virions are made up of about 40 viral proteins. Recent mass spectrometry (MS) analyses showed that HSV-1 virions comprise at least 8 viral capsid proteins, 13 viral glycoproteins, 23 potential viral teguments, and 49 host proteins (Loret et al., 2008). When in 1995 the structural proteins of IcHV-1 were identified by MS (Davison & Davison, 1995), a total of 11 genes encoding 15 virion proteins was identified. Based on

analyses of capsid, capsid-tegument, and envelope fractions, the proteins could be assigned to the different compartments of the virion.

More recent studies on the structural proteins of CyHV-3 and AngHV-1 used liquid chromatography tandem MS-based proteomic approaches. For CyHV-3 a total of 40 structural proteins was identified, which were classified based on homology and bioinformatic analyses as capsid (3), envelope (13), tegument (2) and unclassified (22) structural proteins (Michel et al., 2010). For AngHV-1, by analysing separately prepared fractions of capsid, tegument, and envelope, the identified proteins could also be functionally characterized. A total of 40 structural proteins was identified, of which 7 could be assigned to the capsid, 11 to the envelope, and 22 to the tegument (van Beurden et al., 2011).

The protein composition of fish herpesvirus capsids generally mirrors that of mammalian herpesvirus capsids. MS analyses of purified alloherpesvirus capsids demonstrated the presence of the major capsid protein, the capsid triplex protein 2, and, presumably, the capsid triplex protein 1 (Davison & Davison, 1995; van Beurden et al., 2011). The protease-and-scaffolding protein is only abundantly present in premature capsids, and later replaced by viral DNA during maturation. The small protein which forms the hexon tips in mammalian herpesviruses has not been found in alloherpesvirus capsids.

Conservation of tegument and envelope proteins among fish herpesviruses is rather limited (van Beurden et al., 2011). A large tegument protein was found to be partially conserved, and two envelope proteins might be conserved. The higher conservation of structural proteins between members of the family *Herpesviridae* resembles the greater evolutionary distance of the family *Alloherpesviridae*.

5. Genome organization and gene conservation

5.1 Genome properties

The single linear double stranded DNA genomes of herpesviruses vary greatly in size, ranging from 124 kbp for Simian varicella virus, to more than 250 kbp. This enormous variation is also present within the family *Alloherpesviridae*, in which IcHV-1 has the smallest genome of 134 kbp, and AngHV-1 and CyHV-3 represent the largest herpesvirus genomes known of 249 and 295 kbp, respectively (Table 2). G+C content varies from 32 to 75% within the family *Herpesviridae* (McGeoch et al., 2006), but seems to be more restricted among members of the family *Alloherpesviridae* (52.8 to 59.2%), and is rather low for OsHV-1 (38.7%).

5.2 Genome organization

Herpesvirus genomes characteristically contain one or two regions of unique sequence flanked by direct or inverted repeats (McGeoch et al., 2006). To date, six different classes of genome organization have been identified (Davison, 2007). The genome organization of six alloherpesviruses has been determined. The genomes of AngHV-1, CyHV-3, IcHV-1, RaHV-1 and RaHV-2 all consist of one long unique region (U) flanked by two short direct repeat regions (TR) at the termini (Fig. 2).This genome structure (A) is also represented among the *Betaherpesvirinae* (Davison, 2007). Interestingly, the terminal repeats of the ranid herpesviruses are considerably shorter (<1-kbp) than those of the fish herpesviruses (>10-kbp). Genome organization A does not seem to be a general feature of the *Alloherpesviridae*,

since SalHV-1 is known to have a long unique region (U_L) linked to a short unique region (U_S) flanked by an inverted repeat (IR_S and TR_S) (Davison, 1998). This genome structure (D) is characteristic of *Alphaherpesvirinae* in the *Varicellovirus* genus (Davison, 2007).

Name	Genome length	Terminal repeat length	G+C content	Number of ORFs	ORF density per kpb	Refseq accession	Key reference
Anguillid herpesvirus 1	248,531 bp	10,634 bp	53.0%	136	0.57	NC_013668	(van Beurden et al., 2010)
Cyprinid herpesvirus 3	295,146 bp	22,469 bp	59.2%	156	0.57	NC_009127	(Aoki et al., 2007)
Ictalurid herpesvirus 1	134,226 bp	18,556 bp	56.2%	77	0.67	NC_001493	(Davison, 1992)
Ranid herpesvirus 1	220,859 bp	636 bp	54.6%	132	0.60	NC_008211	(Davison et al., 2006)
Ranid herpesvirus 2	231,801 bp	912 bp	52.8%	147	0.64	NC_008210	(Davison et al., 2006)
Ostreid herpesvirus 1	207,439 bp	7584 bp 9774 bp	38.7%	124	0.65	NC_005881	(Davison et al., 2005b)

Table 2. Genome characteristics of completely sequenced members of the families *Alloherpesviridae* and *Malacoherpesviridae*

Genome structure E is the most complex genome structure and characteristic of *Alphaherpesvirinae* in the *Simplexvirus* genus, and certain members of the genus *Cytomegalovirus* of the *Betaherpesvirinae* (Davison, 2007). The gross genome organization of OsHV-1 is a combination of class D and E genomes, consisting of two invertible unique regions (U_L & U_S), each flanked by inverted repeats (TR_L & IR_L and IR_S & TR_S), with an additional short unique sequence (X) between the inverted repeats (Davison et al., 2005b).

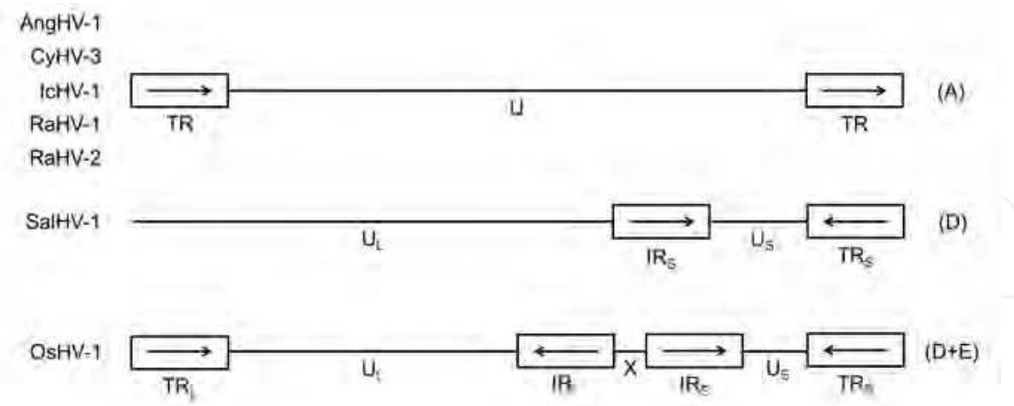

Fig. 2. Schematic representation of the genome organization of selected members of the families *Alloherpesviridae* and *Malacoherpesviridae*

5.3 Gene conservation

Herpesvirus genomes show a wide range in number of genes, ranging from about 70 (Varicella zoster virus) to more than 200 (Human cytomegalovirus) genes (Davison, 2007; McGeoch et al., 2006). Herpesvirus genes are divided into core genes and non-core genes.

The core genes are inherited from a common ancestor and fundamental to replication, being involved in capsid assembly and structure, DNA replication machinery, processing and packaging of DNA, egress of capsids from the nucleus, and control and modulation. The non-core genes represent accessory systems that developed more recently and fit a virus to a particular biological niche. These genes are involved in cellular tropisms, control of cellular processes, manipulation or evasion from the host immune system, and latency. Among the *Herpesviridae*, there is a subset of 43 core genes (McGeoch & Davison, 1999).

Only 13 genes are convincingly conserved among all members of the family *Alloherpesviridae* (Aoki et al., 2007). These genes encode proteins putatively involved in capsid morphogenesis, DNA replication and DNA packaging (Table 3). Five of the identified conserved genes encode proteins with unknown functions. With only 13 genes conserved among all family members, the family *Alloherpesviridae* appears to be considerably more divergent than the family *Herpesviridae*, reflecting the greater divergence of its host species.

Function	**AngHV-1**	**CyHV-3**	**IcHV-1**	**RaHV-1**	**RaHV-2**
ATPase subunit of terminase	ORF10	ORF33	ORF62	ORF42	ORF68
Primase	ORF21	ORF46	ORF63	ORF87	ORF121
Unknown	ORF22	ORF47	ORF64	ORF88	ORF122
Capsid triplex protein 2	ORF36	ORF72	ORF27	ORF95	ORF131
DNA helicase	ORF37	ORF71	ORF25	ORF93	ORF129
Unknown	ORF52	ORF80	ORF60	ORF84	ORF118
DNA polymerase	ORF55	ORF79	ORF57	ORF72	ORF110
Capsid protease and scaffolding protein	ORF57	ORF78	ORF28	ORF63	ORF88
Large envelope glycoprotein	ORF67	ORF99	ORF46	ORF46	ORF72
Unknown	ORF82	ORF61	ORF54	ORF75	ORF113
Unknown	ORF98	ORF107	ORF56	ORF73	ORF111
Unknown	ORF100	ORF90	ORF37	ORF52	ORF78
Major capsid protein	ORF104	ORF92	ORF39	ORF54	ORF80

Table 3. Conserved genes of the family *Alloherpesviridae*

The arrangement of homologous genes in AngHV-1 and CyHV-3 appears to be conserved in clusters (van Beurden et al., 2010). Several conserved gene blocks can be identified, either in the same or in inverse orientation. At the *Alloherpesviridae* family level, the 13 conserved genes seem to be conserved within the same clusters, which was previously shown also for IcHV-1 and SalHV-1 (Davison, 1998), and appears to apply for all completely sequenced *Alloherpesviridae* (Fig. 3). This resembles the seven blocks of core genes that are typically arranged throughout the family *Herpesviridae* (McGeoch et al., 2006).

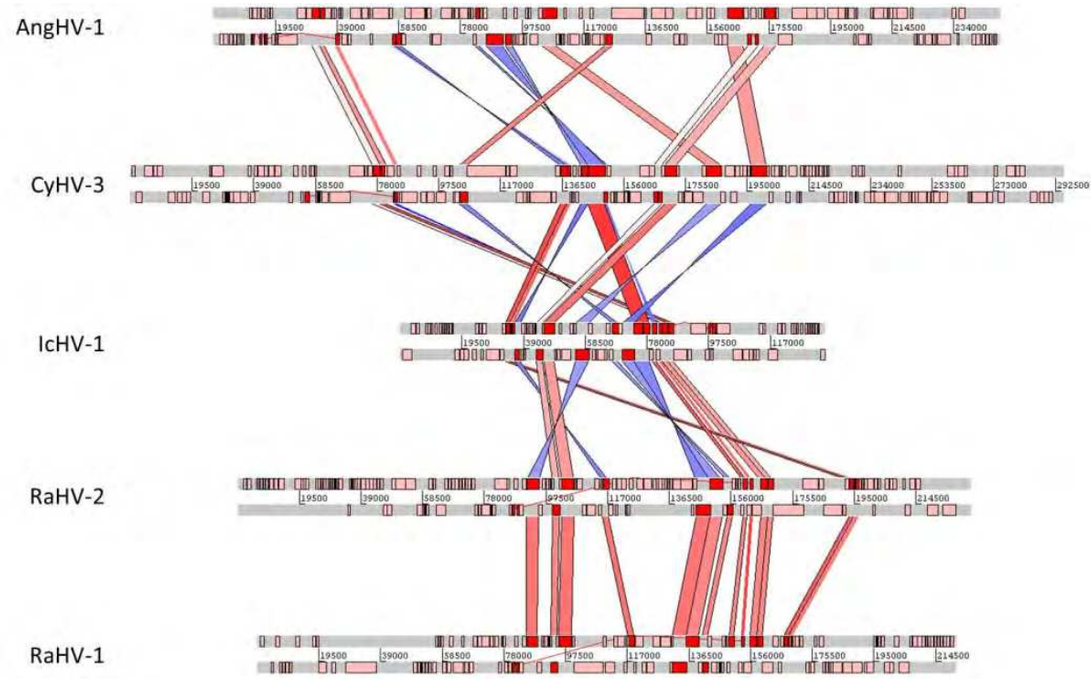

Fig. 3. Geneblock conservation throughout the family *Alloherpesviridae*: conserved genes are coloured red and connected through the genomes by coloured bars; red bars indicate similar and reading frame direction, blue bars indicate reversed reading frame direction; percentage sequence identity at amino acid level is indicated by bar colour intensity

6. Extended characterization of *Alloherpesviridae*

6.1 Gene expression

Gene expression of herpesviruses is regulated in a temporal fashion, with genes being classified on the basis of their expression kinetics as immediate early, early, and late genes (McGeoch et al., 2006). Temporal gene expression has been suggested for IcHV-1 based on polypeptide analyses of *in vitro* infection experiments (Dixon & Farber, 1980). Transcription studies of selected ORFs, especially of the terminal repeat region of IcHV-1, confirmed the temporal expression of these genes (Huang & Hanson, 1998; Silverstein et al., 1995; Silverstein et al., 1998; Stingley & Gray, 2000). Expression of certain ORFs of CyHV-3 at lower and higher temperatures *in vitro* has been studied using RT-PCR (Dishon et al., 2007). Initial experiments to determine the complete transcription profile of AngHV-1 by quantitative RT-PCR showed similar temporal expression kinetics as have been determined for members of the family *Herpesviridae* (van Beurden et al., unpublished results).

6.2 Latency

The ability to establish a latent infection is one of the hallmarks of herpesviruses. Latent infections are characterized by the absence of infectious virus particles and regular viral transcription and replication, but the presence of intact viral genomic DNA and transcription of latency associated transcripts. Accordingly, the presence of viral DNA (and not infectious virus) has been demonstrated in fish surviving infections with IcHV-1 and CyHV-3 (Eide et al., 2011a; Gray et al., 1999), whereas viral replication was absent in such

fish (Eide et al., 2011b; Stingley et al., 2003). It has been shown *in vitro* that CyHV-3 is able to persist in cultured cells at a nonpermissive temperature, with viral propagation and viral gene transcription being turned off, and reactivated upon return to the permissive temperature (Dishon et al., 2007). Reactivation of fish herpesviruses *in vivo* has been demonstrated for AngHV-1 following dexamethasone treatment (van Nieuwstadt et al., 2001), and for CyHV-3 following temperature stress (Eide et al., 2011b; St-Hilaire et al., 2005).

6.3 Gene characterization

Identification and characterization of most alloherpesvirus ORFs is based on sequence homology and bioinformatics. Recent probabilistic mapping of IcHV-1 (Kunec et al., 2009), and complete transcriptome analysis of AngHV-1 (van Beurden et al., unpublished results), show, however, that there might still be a large discrepancy between the predicted and actual numbers of ORFs.

MS analysis of purified capsids resulted in the identification of the structural proteins of IcHV-1, CyHV-3 and AngHV-1 (Davison & Davison, 1995; Michel et al., 2010; van Beurden et al., 2011). Based on the localization of the structural proteins in the different virion compartments, several of these proteins could be functionally characterized. Two alloherpesvirus proteins have been characterized in more detail: IcHV-1 ORF50 has been shown to encode a secreted mucin-like glycoprotein (Vanderheijden et al., 1999), and CyHV-3 ORF81 has been identified as an envelope protein (Rosenkranz et al., 2008).

6.4 Virulence factors and vaccine development

In many herpesviruses the homologues of cellular enzymes are nonessential for virus replication *in vitro*, but relevant for virulence *in vivo*. Attenuated IcHV-1 and CyHV-3 strains with specific gene deletions have been developed and tested for virulence. Thymidine kinase-negative mutants of IcHV-1 resembled wild type IcHV-1 *in vitro*, but appeared to be much less pathogenic *in vivo* (Zhang & Hanson, 1995). Similarly, CyHV-3 recombinants possessing deletions within the viral ribonucleotide reductase, thymidine kinase and dUTPase genes were developed and tested for attenuation (Fuchs et al., 2011). The use of the attenuated strains as modern live vaccines in challenges with wild-type virus showed promising results.

Several other attempts of vaccine development have been undertaken for IcHV-1 and CyHV-3. For CyHV-3, immunization with wild type and attenuated virus has been tested in relation to different water temperatures (Ronen et al., 2003). For IcHV-1, experimental subunit and attenuated vaccines were developed and tested (Dixon, 1997). Also, DNA vaccination with several different ORFs has been tested for IcHV-1 (Nusbaum et al., 2002). Later, an overlapping and a full BAC have been developed for IcHV-1 (Kunec et al., 2008) and CyHV-3 (Costes et al., 2008), respectively. The latter was used to test attenuation after disruption of the thymidine kinase locus and deletion of ORF16. To date no satisfying vaccine has been developed nor registered for any of the fish herpesviruses.

7. Conclusions

In conclusion, herpesviruses of fish, amphibians and invertebrates form a potentially large group of important pathogens. Understanding the origins of the distantly related families

Alloherpesviridae and *Malacoherpesviridae* provides insights into the evolution of the family *Herpesviridae*. The association of many fish herpesviruses with severe diseases in important aquaculture species has stimulated fundamental and applied research. For a selected number of alloherpesviruses, complete genome sequences and structural analyses of the virus particles are now available and have revealed similarity to the basic composition of higher vertebrate herpesviruses. Extended characterization of gene expression, latency, the function of specific genes and virulence factors as well as vaccine development is currently ongoing. These studies will add to the control and prevention of fish herpesvirus associated diseases, and might serve as models for research on human and domestic animal herpesviruses.

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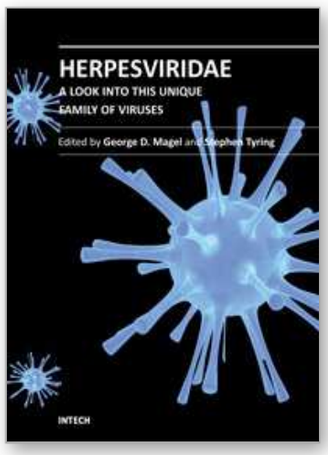

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In order to fully understand the nature of viruses, it is important to look at them from both, their basic science and clinical, standpoints. Our goal with this book was to dissect Herpesviridae into its biological properties and clinical significance in order to provide a logical, as well as practical, approach to understanding and treating the various conditions caused by this unique family of viruses. In addition to their up-to-date and extensive text, each chapter is laced with a variety of diagrams, tables, charts, and images, aimed at helping us achieve our goal. We hope that this book will serve as a reference tool for clinicians of various specialties worldwide.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

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INTECH
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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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