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Review

# Aquatic viruses induce host cell death pathways and its application

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ABSTRACT

Virus infections of mammalian and animal cells consist of a series of events. As intracellular parasites, viruses rely on the use of host cellular machinery. Through the use of cell culture and molecular approaches over the past decade, our knowledge of the biology of aquatic viruses has grown exponentially. The increase in aquaculture operations worldwide has provided new approaches for the transmission of aquatic viruses that include RNA and DNA viruses. Therefore, the struggle between the virus and the host for control of the cell's death machinery is crucial for survival. Viruses are obligatory intracellular parasites and, as such, must modulate apoptotic pathways to control the lifespan of their host to complete their replication cycle. This paper updates the discussion on the detailed mechanisms of action that various aquatic viruses use to induce cell death pathways in the host, such as Bad-mediated, mitochondria-mediated, ROS-mediated and Fas-mediated cell death circuits. Understanding how viruses exploit the apoptotic pathways of their hosts may provide great opportunities for the development of future potential therapeutic strategies and pathogenic insights into different aquatic viral diseases.


**Contents**



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## 1. Introduction

The farming of fish and other aquatic animals is an ancient practice. However, despite its ancient origins, aquaculture remained largely a low-level, subsistence farming activity until the mid-twentieth century when experimental husbandry practices for salmon, trout and an array of tropical fish and shrimp species were developed and adopted. Aquaculture has expanded rapidly over the past three decades to become a major economic and the most efficient agricultural production industry in the world (Biacchesi, 2011). However, disease is a major obstacle to global aquaculture production. The aquaculture industry has been plagued by a number of aquatic animal diseases caused by bacteria, fungi, viruses and other parasites, with new pathogens being identified every year (Murray and Peeler, 2005). Primarily, viral diseases, which have been frequently reported in aquaculture animals, have hampered aquaculture development (Daszak et al., 2000; Walker and Winton, 2010; Collins and Crump, 2009). The prevention and treatment of viral infections is particularly challenging because viruses use the host cell machinery to replicate, and interrupting viral replication without damaging host cell structures or processes presents a puzzle. Typically, virus infections start with local invasion and result in the infection of the target organ. Following their entry into the cell, viruses then face a variety of hurdles that constitute the cellular host's defense, which is designed to protect the organism and eradicate the infecting agent. To help resolve these problems, researchers have looked for and identified a large number of diverse pathogenic viruses in aquaculture and natural aquatic animals including iridoviruses, orthomyxovirus, reoviruses, nodavirus and aquabirnavirus. These pathogenic aquatic viruses have been found to be the cause of epizootic diseases in aquaculture animals and the global decline of amphibian populations (Chinchar et al., 2009; Une et al., 2009; Hyatt et al., 2000; Kik et al., 2012).

Apoptosis, the natural, genetically highly regulated cell death process of removing unneeded or damaged cells, plays a central role in the normal development and homeostasis of multicellular organisms (Ameisen, 2002). Apoptosis may be used by the host both to limit the production of viruses and to disseminate them (Münz, 2007; Benedict et al., 2002; Vanlandschoot and Leroux-Roels, 2003; Deretic and Levine, 2009). However, viruses use the apoptosis process to produce sufficient virus progeny or facilitate virus release (Benedict et al., 2002; Orvedahl et al., 2007). The process of programmed cell death (PCD) is controlled by a different range of cell signaling pathways originating either from the external environment of a cell (extrinsic) or from within the cell itself (intrinsic) (Kumar, 2006). The common event at the end-point of both the intrinsic and extrinsic pathways is the activation of a set of cysteine proteases (caspases) (Liu et al., 2005). The extrinsic pathway originates at the plasma membrane following the engagement of a family of cytokine receptors, such as tumor necrosis factor receptor-1 (TNF-R1) by their cognate ligands (TNF-α). Ligand/receptor binding induces the recruitment of several adapter proteins and proenzymes, which in turn activate caspases (caspase-8 and -10), and finally results in apoptosis and cell death (Ashkenazi and Dixit, 1998). The intrinsic pathway is triggered by different extracellular or intracellular signals, such as oxidative stress, that results in activation of the initiator caspase-9. Caspase-9, in turn, activates caspase-3, a major effector caspase responsible for the degradation of cellular substrates (Allen et al., 1997). The PCD induced by virus infection has often been defined as typical apoptosis (Mao et al., 2009; Pearce and Lyles, 2009; Huang et al., 2007, 2009). However, recent studies disclosed that non-apoptotic forms of PCD are important for the pathogenesis of certain RNA viruses, including the JC virus, hepatitis C virus, coxsackievirus B3, Enterovirus and dengue virus (Seth et al., 2004; Sir et al., 2008; Wong et al., 2008; Lee et al., 2008; Orvedahl and Levine, 2009). The mechanism of DNA virus-induced non-apoptotic cell death is not well known. Although not all signals initiating the apoptosis pathway are understood, in many but not all, cases, and the tumor suppressor protein p53 is required to propagate the signal to commit suicide (Levine, 1997). The fate of the cell to undergo apoptosis mainly depends on the dynamic balance between the Bcl-2 family sensor proteins, which both promote and inhibit apoptosis (Fig. 1) (Rao and White, 1997; Clem and Duckett, 1997). Members of the Bcl-2 family sensor proteins represent a major key point in the apoptotic pathways. They appear to sit at a node in the apoptotic pathway at a point of integration for stimuli that provoke apoptosis and, in many but not all cases, they appear to influence the activation of caspase family members (proteases), which perform the "execution" phase of apoptosis, by cleaving a number of cellular proteins to bring about the destruction of cellular structures (Nagata, 1997; White, 1996). Virus-induced pathogenesis is associated not only with apoptosis but also with oxidative damage (Valyi-Nagy and Dermody, 2005). Oxidative stress, primarily due to increased generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), is a feature of many viral infections (Valyi-Nagy and Dermody, 2005; Li et al., 2010). The ROS and RNS deplete intracellular antioxidant compounds and consequently lead to cell death (Edens et al., 2008). The role of oxidative stress in the pathogenicity of viruses is indicated by the finding that virus infections increase the levels of ROS (Reshi et al., 2014a,b; Lin et al., 2011). However, the role of ROS in viral diseases is more complex because it includes metabolic regulations for both host metabolisms and viral replication. The purpose of this review is to summarize the death signaling network induced by aquatic viruses *in vitro* and *in vivo*.

## 2. Aquabirnavirus

### 2.1. Infectious pancreatic necrosis virus (IPNV)

Infectious pancreatic necrosis virus (IPNV) is a member of the genus *Aquabirnavirus* in the family Birnaviridae. Until recently, the virus has remained one of the most intensely studied viruses of fish and was the first fish virus isolated in cell culture (Wolf et al., 1960). The non-enveloped icosahedral capsid has a diameter of 60 nm and contains two genome segments (A and B) of double-stranded RNA (Dobos, 1995). The smaller segment B encodes the virus polymerase VP1 (Duncan et al., 1991). Segment A contains a large open reading frame (ORF) encoding a 107-kDa polyprotein that is processed into the major structural proteins VP2 and VP3 by the viral protease VP4 (Duncan et al., 1987; Macdonald and Dobos, 1981; Petit et al., 2000). A second ORF, overlapping the N-terminal region of VP2, encodes the small non-structural protein VP5 (Håvarstein et al., 1990; Magyar and Dobos, 1994). Replication of IPNV takes place in the cytoplasm of susceptible cells, and within