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Aquatic animal viruses mediated immune evasion in their host

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ABSTRACT

Viruses are important and lethal pathogens that hamper aquatic animals. The result of the battle between host and virus would determine the occurrence of diseases. The host will fight against virus infection with various responses such as innate immunity, adaptive immunity, apoptosis, and so on. On the other hand, the virus also develops numerous strategies such as immune evasion to antagonize host antiviral responses. Here, We review the research advances on virus mediated immune evasions to host responses containing interferon response, NF-κB signaling, apoptosis, and adaptive response, which are executed by viral genes, proteins, and miRNAs from different aquatic animal viruses including *Alloherpesviridae*, *Iridoviridae*, *Nimaviridae*, *Birnaviridae*, *Reoviridae*, and *Rhabdoviridae*. Thus, it will facilitate the understanding of aquatic animal virus mediated immune evasion and potentially benefit the development of novel antiviral applications.

1. Introduction

Aquatic viruses have been an essential part of the biosphere, and also a part of human and aquatic animal lives. The virus-host interactions are ubiquitous on earth [1]. There are many aquatic animals with more aquatic animal viruses, which have caused enormous harms to the aquaculture development and water environment, and threaten global food security [2–4]. Although several methods have been used in the virus prevention and control, it is still difficult in treatment of these diseases [5]. Battles between host and virus determine whether or not the disease occurs. Host can fight against virus with its immune system. The virus could resist or escape from host immune system [6,7]. If the latter occurs, the disease would happen. Compared with higher animals, the aquatic animals have relative lower evolved immune system, which would benefit the virus invading. Information about virus-host interactions may give us inspiration in virus treatment, which has attracted more and more attentions.

The host recognize viral components which is called pathogen-associated molecular patterns (PAMPs) with pattern recognition receptors (PRRs). After recognition of PAMPs, several signal cascades in host will be activated [8–10]. Ultimately, a lot of antiviral responses such as inflammatory responses, interferon (IFN) responses, regulated cell death, and adaptive immune responses will be induced. Although these responses have been defined in mammals, researches on the antiviral responses of several important aquatic animals such as Atlantic salmon, common carp, gibel carp, grass carp, grouper, rainbow trout, and shrimp have been carried out in past several years [11–18].

Various antiviral responses have been revealed [19–22]. How they are overcome by different viruses? Here, we select twenty three strains of aquatic animal viruses which represent great harms to aquatic animals. The viruses belong to six families including three kinds of DNA viruses and three kinds of RNA viruses. They could utilize viral elements including their genes, gene products, and miRNAs to resist and escape from host immune systems (Table 1), which were known as immune evasion strategies. We focus on the viral elements and their targeted host molecular or pathways.

The three kinds of DNA viruses are briefly introduced as follows: (i) The herpesviruses (family *Alloherpesviridae*), such as cyprinid herpesvirus 1 (CyHV-1), cyprinid herpesvirus 2 (CyHV-2), and cyprinid herpesvirus 3 (CyHV-3, also known as Koi herpesvirus, KHV), which infect fish have gained more and more research interest in the past decade [23,24]. Although host responses including innate and adaptive immune responses have been reported in herpesvirus infected fish [12,25,26], knowledge on the herpesvirus mediated immune evasion is limited and mainly focus on the virus encoded host homologous proteins (Table 1). (ii) Members of the family *Iridoviridae* have been reported to cause high mortalities and threats in aquaculture or wild animals [27–29]. The molecular and immunological events in ranavirus (genus *Ranavirus*, family *Iridoviridae*) replication have been reported by researchers [30]. It is a remarkable fact that the interspecies infection or transmission have occurred in ranaviruses [31–33]. Recent study on the transcriptomic responses of Chinese giant salamander under different ranaviruses infection revealed the divergent host responses and virus yields [34], which hinted the importance of virus mediated

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Table 1
Potential viral genes, proteins, and miRNAs that involved in virus mediated immune evasion in aquatic animals.

	Family	genus	Virus strains	*Gene*;Protein; miRNAs	Homology	Potential or proved function	References
DNA virus	*Alloherpesviridae*	*Cyprinivirus*	KHV (Koi herpesvirus)	*134*	IL-10	Deactivate the inflammatory activities of carp macrophage; promote the proliferation of Igm^+ B cells and memory T cells	[177,178]
			CyHV-3 (Cyprinid herpesvirus 3)	*112*	PKZ	Paralog of PKR; inhibitor of interferon response	[114,115]
				12	TNFR	Delay behavioral fever in carp	[182,183]
			CaHV (Crucian carp herpesvirus)	*25L*	GPCR	Paralog of host GPCR	[133]
	Iridoviridae	*Ranavirus*	ATV (*Ambystoma tigrinum* virus)	*57R*	eIF2α	Inhibition of eIF2α phosphorylation	[106–108]
				25R	RNase III	Reduce the phosphorylation of eIF2α	[112]
			FV3 (Frog virus 3)	*26R*	eIF2α	Virus against IFN-mediated immunity	[110]
				64R	CARD	Virus against IFN-mediated immunity	[110]
				52L	β-HSD	Immune evasion	[184]
			RGV (*Rana grylio* virus)	*28R*	eIF2α	Potential inhibitor of IFN response	[109]
				52L	3β-HSD	Inhibit virus induced cytopathic effect	[185]
				68R	CARD	Potential inhibitor of IFN response	[109]
			GIV (Grouper iridovirus)	*27L*	CARD	Inhibit apoptosis	[152]
				GIV66	Bcl-2	Bind to cellular Bim to inhibit apoptosis	[137,138]
			SGIV (Singapore grouper iridovirus)	*155R*	Semaphoring	Inhibit cellular immune response	[181]
				51L; *096R*	TNFR	Enhance cell proliferation; inhibit apoptosis	[130,131]
		Lymphocystivirus	LCDV-C (Lymphocystis disease virus isolated in China)	*124R*	GPCR	Inhibit apoptosis	[134]
		Megalocytivirus	RBIV (Rock bream iridovirus)	*83R*	RNase III	Cleave dsRNA *in vitro*	[111]
			ISKNV (Infectious spleen and kidney necrosis virus)	*124L*	ANK repeat	Inhibit the TNF-α induced NF-κB signaling	[123]
	Nimaviridae	*Whispovirus*	WSSV (White spot syndrome virus)	*ie1* (IE1)		Interact with host transcription factors	[161–163,186]
				WSSV449		Activate host NF-κB pathway	[164]
				WSSV249/403	E3 ubiquitin ligase	Function as E3 ligase	[153,154]
				VP38/41B		Regulate shrimp *PjCaspase* promoter activity	[145]
				WSSV134/322		Anti-apoptotic activity	[146,147]
				WSSV222	E3 ubiquitin ligase	Lead to the degradation of TSL; anti-apoptotic	[155,156]
				PK1	Protein kinase 1	Regulate cell's iron-withholding defense	[175]
				miR-N24		Anti-apoptosis	[148]
				miR-N13/N23		Suppress the Spz-Toll-Dorsal-ALF signaling pathway	[171]
				miR-22		Target host STAT	[169]
RNA virus	*Birnaviridae*	*Aquabirnavirus*	IPNV (Infectious pancreatic necrosis virus)	VP4; VP5		Inhibit IFN-induced Mx expression	[118]
				VP5	Bcl-2	Anti-apoptosis	[142]
			POBV (*Paralichthys olivaceus* birnavirus)	VP5	Bcl-2	Potential inhibitor of apoptosis	[37]
	Reoviridae	*Aquareovirus*	GCRV (Grass carp reovirus) 106	VP41		Suppress the phosphorylation of MITA and inhibit IFN response	[102]
			GCRV JX-01	NS26		Interact with cellular LITAF	[129]
			GCRV 109	VP33		Possessing immunogenic properties	[46]
	Rhabdoviridae	*Novirhabdovirus*	IHNV (Infectious hematopoietic necrosis virus); VHSV (Viral hemorrhagic septicemia virus)	NV		Inhibitit TBK1-IFN response; Anti-apoptosis; Inhibit NF-κB pathway	[96,97,120,121,187]
			SHRV (Snakehead rhabdovirus)				[188]
			PORV (*Paralichthys olivaceus* rhabdovirus)				[52]
			VHSV (Viral hemorrhagic septicemia virus)	M		Suppress MAVS-IFN response	[101]
		Sprivivirus	SVCV (Spring viremia carp virus)	P		Interact with TBK1 and inhibit IFN response	[99]
				N		Degrade MAVS and inhibit IFN response	[100]

AbbreviationsIFN, interferon; eIF2α, alpha subunit of eukaryotic initiation factor 2; CARD, caspase recruitment domain; β-HSD, beta-hydroxysteroid dehydrogenase; Bcl-2, B-cell lymphoma 2; TNFR, tumor necrosis factor receptor; GPCR, G protein-coupled receptor; ANK, ankyrin; IL-10, interleukin 10; PKZ, Z-DNA-dependent protein kinase; TSL, tumor suppressor-like; MITA, mediator of IFN regulatory factor 3 (IRF3) activation; TBK1, Traf family member-associated NF-κB activator (TANK)-binding kinase 1; MAVS, mitochondrial antiviral signaling protein.

immune evasion. (iii) Viruses in the family *Nimaviridae* have been isolated only from invertebrates. The type species is White spot syndrome virus (WSSV), which has caused massive mortality and great loss in the shrimp cultivation industry [35]. Recently, a nimavirus *Procambarus clarkii* virus (PCV) was isolated from spontaneously infected crayfish (Genbank accession number: MH663976). Based on the genomic comparison, the PCV *96R* is predicted to encode a protein with high homologue to WSSV VP38, which has anti-apoptosis activity. Several viral elements including gene, protein, and miRNA are utilized by WSSV to modulate the shrimp antiviral responses.

The other three kinds of RNA viruses are as follows: (i) Birnaviruses from fish, molluscs, and crustaceans are belonged to the genus *Aquabirnavirus* (*Birnaviridae*) and have double-stranded RNA (dsRNA) genome with two linear segments [36,37]. Anti-IFN induced responses and anti-apoptosis have been reported in aquabirnaviruses. (ii) Another aquatic animal virus containing dsRNA genome belongs to the *Reoviridae*, which contain 9 to 12 segments of linear dsRNA segments [38]. Aquareoviruses constitute the genus *Aquareovirus*, which have been isolated from a wide variety of aquatic animals [38–42]. Recently, the most noticed virus in *Aquareovirus* is the grass carp reovirus (GCRV), which caused pandemic grass carp hemorrhagic disease in China and East Asia. Although the virus-induced responses of grass carp from gene level to transcriptome level, immunoprotection, and the immunogenicity of its proteins have been reported by several researchers [43–48], the immune evasion mechanisms of GCRV is still limited. (iii) Genome of rhabdoviruses (family *Rhabdoviridae*) are negative-sense, single-stranded RNA (ssRNA), which encodes five structural proteins (N, P, M, G, and L) [49,50]. Some rhabdoviruses including *Scophthalmus maximus* rhabdovirus (SMRV) and *Paralichthys olivaceus* rhabdovirus also encode other proteins [51,52]. It has been reported that infection of rhabdovirus such as Infectious hematopoietic necrosis virus (IHNV) and SMRV induced host antiviral responses including immune signaling and apoptosis [53–56]. However, viral proteins have important functions in rhabdovirus mediated immune evasions. In addition, antibodies or vaccines with gene or protein have showed significant protection effect against rhabdovirus infection [57–59], which revealed the immunogenicity of the proteins.

Above mentioned viruses possess various interactions between viral elements and their targets to escape from host antiviral responses (Table 1). The main representative immune evasion strategies are described. It is a comprehensive summary on immune evasion around multiple groups of viruses based on research advances of recent years.

2. Virus recognition and signal transduction

2.1. Virus recognition by innate immune system

Upon virus infection, the host recognize the non-natural components and develop a series of responses such as type I (IFN) response and regulated cell death to fight against the invader. The first defense line of host is the innate immunity [8,9], which recognizes the PAMPs with PRRs. PAMPs of virus include viral proteins, dsRNA, ssRNA, and double-stranded DNA (dsDNA). Among them, nucleic acids have been considered as the major object for innate immune recognition [9]. Currently known PRRs that recognize viral nucleic acids and are involved in the present review contain Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I) -like receptors (RLRs), and cytosolic DNA sensors.

TLRs are a large family of proteins with an extracellular leucine-rich-repeat domain, a transmembrane domain, and a cytosolic Toll-IL1R domain [60]. At least 20 TLRs have been identified in several fishes [61–63]. Among them, TLR3, 7/8, and 9 localize on endosome membrane and could recognize dsRNA, ssRNA, and unmethylated CpG DNA respectively. Several viruses could enter into cells by endocytosis and the extracellular nucleic acids could also be brought into cells by this pathway, which made the endosomal TLRs become important PRRs. After recognizing PAMPs, TLRs are activated and further activate downstream signaling molecules. For example, TLR3 transmits signals to adaptor molecule toll/interleukin-1 receptor (TIR) domain containing adapter inducing IFN-β (TRIF) and TLR 7/8/9 activate myeloid differentiation factor 88 (MyD88). Several molecules participate in the TLR induced signal cascades. It has been reported that zebrafish TRIF interacts with Traf family member-associated NF-κB activator (TANK)-binding kinase 1 (TBK1) and receptor-interacting protein 1 (RIP1), and then activate interferon regulatory factor (IRF) 3/7 and nuclear factor kappa-B (NF-κB) respectively [64,65]. The activated IRF3/7 and NF-κB would translocate into nucleus, inducing the expression of IFN, IFN-stimulated genes (ISGs), and proinflammatory cytokines [66,67].

Cytosolic RNAs are usually recognized by three members of RLRs: RIG-I, melanoma differentiation associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2), which are a family of DExD/H RNA helicases [68–70]. There could be three domains in the three proteins: two tandem N-terminal caspase-recruitment domain (CARD) which are found in RIG-I and MDA5 but not in LGP2, a central DExD box helicase/ATPase domain (DExD/H), a C-terminal domain (CTD). RLRs have been identified in fishes including zebrafish, common carp, crucian carp, grass carp, atlantic salmon, channel catfish, rainbow trout, Japanese flounder, and so on [71]. After activated by PAMPs, RIG-I or MDA5 bind to their adaptor protein mitochondrial antiviral-signaling protein (MAVS, also known as IPS-1, VISA, or Cardif) which localizes in mitochondria. Activated MAVS could further recruit and activate TBK1 and IκB kinase complex (IKKα/β/γ), and then induce the downstream IRF and NF-κB activity. In addition, the other adaptor molecule, mediator of IRF3 activation (MITA, also known as STING, ERIS, and MYPS), which localizes in endoplasmic reticulum could transmit signals from RIG-I and MDA5 through MITA-TBK1-IRF3/7 pathway [72].

The best known cytosolic DNA-sensing pathway is the cyclic GMP-AMP synthase (cGAS) - STING pathway. Cytosolic DNA binds and leads to the activation of cGAS, which synthesizes 2'3'-cGAMP as second messenger. cGAMP further binds and activates STING, which then activates TBK1 and IKK complex, leading to the activation of IRF3 and NF-κB [73].

2.2. Virus recognition by cell death receptors

Regulated cell death is the other important host response to fight against virus infection. Different cell deaths including apoptosis, necroptosis, pyroptosis, and autophagy have been reported in aquatic virus infection. For example, an extrinsic apoptosis pathway has been revealed by transcriptomic analysis of channel catfish virus (*Alloherpesviridae*) infected channel catfish ovary cells [74]. The mitochondrion-mediated or caspase-dependent apoptosis has been reported in iridoviruses including *Rana grylio* virus (RGV), Epizootic hematopoietic necrosis virus (EHNV), Singapore grouper iridovirus (SGIV), Grouper iridovirus (GIV), and Giant seaperch iridovirus (GSIV) [75–80]. Analysis of the autophagy and apoptosis induced by Chinese giant salamander iridovirus (CGSIV) revealed that autophagy occurred during early infection, followed by innate immune response and apoptosis [81]. The type of cell death induced by some iridoviruses is cell- or virus-dependent. SGIV induce nonapoptotic programmed cell death in host cells, but induce typical apoptosis in non-host cells [78]. GIV and LMBV (Largemouth bass virus) but not ISKNV (Infection spleen and kidney necrosis virus), TFV (Tiger frog virus), and CGSIV induce antiviral autophagic effects in mandarin fish fry (MFF-1) cell [82]. Apoptosis has been also involved in RNA virus infection such as GCRV [83,84], infectious pancreatic necrosis virus (IPNV, *Birnaviridae*) [85], SMRV [55], and *Micropterus salmoides* rhabdovirus (MSRV, *Rhabdoviridae*) [86]. Viral haemorrhagic septicemia virus (VHSV) and spring viremia of carp virus (SVCV, *Rhabdoviridae*) both induce autophagy in cells and zebrafish [87]. Among the different pathways of regulated cell death, apoptosis related pathways are discussed in the present review.

Apoptosis could be induced by cell extrinsic and intrinsic pathways. The extrinsic pathway initiates from the cell surface receptors, such as tumor necrosis factor receptor (TNFR) and FAS-ligand (FASL) receptor [88]. By binding of specific extracellular ligands, the receptors could activate intracellular protease caspase-8, which cleaves the effector caspase-3 and -7, and then induces apoptotic cell death. The intrinsic pathway begins with the activation of proteins BAX or BAK by intracellular stresses. Activation of BAX or BAK leads to mitochondrial outer membrane permeabilization, which causes the release of cytochrome *c* and further the formation of apoptosome. Apoptosome recruits caspase-9 which could cleave caspase-3 and -7. Several studies have also reported the closely relationship between innate immune system and cell death pathways [89].

3. Virus mediated evasion to type I IFN responses

It has been reported that IFN responses were induced by several aquatic viruses. For example, frog virus 3 (FV3, *Iridoviridae*) infection induces different IFN responses (type III responses for tadpoles, type I for adults) in *Xenopus laevis* tadpoles and adult frogs [90]. Immune signaling including IFN and MHC responses have been revealed in Chinese giant salamander under *Andrias davidianus* ranavirus (ADRV, *Iridoviridae*) infection [91,92]. However, Viruses have evolved to antagonize IFN responses by targeting different parts of the signaling pathway. Researches on the virus mediated evasion to IFN responses mainly focus on the type I IFN responses.

3.1. Suppressing the signal cascades

Reports on the virus mediated antagonism to the innate immune signal cascades related to type I IFN response are mainly come from rhabdoviruses and aquareovirus. Several fish rhabdovirus including (IHNV), VHSV, and snakehead rhabdovirus (SHRV) in the genus *Novirhabdovirus* encode a nonvirion (NV) protein. The NV protein is essential for efficient growth and pathogenicity of IHNV and VHSV [93–95]. Deletion of NV or its nuclear localization residues increased IHNV sensitivity to poly I:C treatment, indicating its function in inhibition of the IFN system [96]. Infection of NV gene knock-out recombinant VHSV *in vitro* and *in vivo* also showed its function in inhibition the IFN responses [97]. A recent study showed that NV can recruit protein phosphatase Mg^{2+}/Mn^{2+}-dependent 1Bb (PPM1Bb) in the close vicinity of mitochondria in *epithelioma papulosum* cyprinid (EPC) cells, which then reduced the phosphorylation of TBK1 and led to the inhibition of IFN and ISGs production [98].

For the functions of structural proteins of rhabdoviruses in regulation of IFN response, SVCV P protein can interact with TBK1 and inhibit IRF3 phosphorylation competitively, and then prevent IFN production [99]. Its N protein can degrade fish MAVS through the ubiquitin-proteasome pathway, and then inhibit IFNφ1 production [100]. M protein of VHSV could suppress host transcription including MAVS and type I IFN-induced gene expression. It also regulate cytotoxicity caused by virus [101].

A structural protein VP41 (encoded by S8 genome segment) of GCRV 106 (*Aquareovirus*) has been reported to suppress the phosphorylation of MITA and then inhibit IFN production [102] (Table 2).

3.2. Suppressing IFN-stimulated genes

IFN will induce a series of ISGs to establish an antiviral state [103], which is an important anti-virus strategy in lower vertebrates. One of the ISGs is the dsRNA-activated protein kinase R (PKR), which is a serine/threonine kinase that could lead to the phosphorylation of the alpha subunit of eukaryotic initiation factor 2 (eIF2α) [104]. Phosphorylation of eIF2α results in the inhibition of translation initiation complex formation and then the global inhibition of protein translation. PKR and its conserved function in fish was first investigated in *Paralichthys olivaceus* [105]. Interestingly, homologues of the components of the dsRNA-PKR-eIF2α pathway are found in aquatic animal viruses including iridovirus and herpesvirus. *Ambystoma tigrinum* virus (ATV, *Iridoviridae*) ORF 57R encodes a homologue of eIF2α (vIF2αH) [106,107]. The recombinant virus ATVΔ57R in which the vIF2αH was replaced by neomycin selection marker leads to host eIF2α phosphorylation. It is more sensitive to interferon than wild type ATV. The ATV vIF2αH could partially replace the vaccinia virus PKR inhibitor E3L and cause the degradation of PKR in infected cells by using recombinant vaccinia virus [108]. Interestingly, a truncated homologue of eIF2α was found in some ranaviruses, such as FV3 and RGV [109]. It has been proved that the truncated vIF2α of FV3 contributes to the virus against IFN-mediated immunity in tadpoles [110].

The other protein used by iridovirus to counteract the dsRNA mediated antiviral pathway is an RNase III homologue. ORF encoding this homologue has been found in all sequenced iridoviruses. Recombinant RNase III homologue protein of Rock bream iridovirus (RBIV) could cleave dsRNA *in vitro* [111]. Overexpression of ATV RNase III homologue (ORF 25R) could reduce the phosphorylation of cellular eIF2α, which may through the reduced activation of PKR. Deletion of this homologue in ATV reduced its pathogenicity in tiger salamanders [112].

CyHV-3 (*Alloherpesviridae*) ORF112 encodes a Z-DNA-dependent protein kinase (PKZ) homologue which contains a Zalpha domain at its C-terminal. The Zalpha domain could bind the left-handed conformer of dsDNA (Z-DNA) and dsRNA (Z-RNA). Thus, host PKZ could function as a paralog of PKR in detecting Z-DNA or Z-RNA and inducing antiviral response [113]. Crystal structure of the CyHV3 ORF112 protein revealed its binding ability to left-handed conformation and the conserved mechanism with poxvirus E3L, which has been proved as potent inhibitor of IFN response. These results revealed the possible function of ORF112 in inhibition of IFN responses [114,115]. Nevertheless, the exact function of ORF112 *in vivo* needs further research.

IPNV is an aquabirnavirus that cause disease with high mortality in salmonid fish. It has been reported that IPNV has the ability in inhibiting the IFN signaling such as Mx activation in Chinook salmon embryo (CHSE-214) and Rainbow trout gonad (RTG-P1) cells [116,117]. Further research showed that IPNV VP4 and VP5 could bind to the Mx promoter and inhibit IFN-induced Mx expression [118]. Interestingly, IPNV infection could induce the phosphorylation of eIF2α and inhibit protein synthesis in CHSE cells, which could be a strategy to evade the host innate antiviral responses [119].

It is noteworthy that the viral proteins modulating cellular dsRNA mediated antiviral response have been proved in DNA virus including iridoviruses. However, DNA virus may induce the dsDNA mediated antiviral response such as cGAS-STING pathway mediated responses [73]. Whether DNA viruses such as iridovirus infection would induce the pathway and the viral proteins that are involved in the pathway need further research.

4. Virus mediated evasion to NF-κB signal

The NV protein of rhabdoviruses also has negative effect on NF-κB signaling. It has been reported that VHSV with NV deletion induced higher NF-κB activity than wild type. Its NV protein could inhibit TNF-α-mediated NF-κB activation in EPC cells [120]. IHNV infection activates NF-κB pathway in fish cells. Its L protein activates but NV inhibits NF-κB signaling pathway. NV can block the degradation of the inhibitor of NF-κB (IκBα) and suppress NF-κB nuclear translocation [121]. The inhibition of NF-κB activation could be the other function of NV in immune evasion. A recent study showed that the ^{32}EGDL^{35} residues of IHNV NV is essential for its inhibition of IFN and NF-κB pathways, and also for virus pathogenicity *in vivo* [122].

ISKNV ORF124L encodes an ankyrin (ANK) repeat protein, which has been reported that could interact with mandarin fish IκB kinase β protein (scIKKβ) and inhibit the TNF-α induced NF-κB signaling [123].

Table 2
Representative viral gene, proteins, and miRNAs that involved in aquatic virus mediated immune evasion. Abbreviations are described in Table 1.

Immune evasion strategies	Virus			Host		References
		strains	*gene* proteins miRNAs	Targets and pathways	Effects	
Anti-IFN response	Rhabdovirus	IHNV VHSV SVCV PORV	$NV_{IHNV/VHSV}$	TBK1 - IFN pathway (TBK)	Inhibit IFN response	[98]
			P_{SVCV}	TBK1 - IFN pathway (IRF-3/7)		[99]
			M_{VHSV}, N_{SVCV}	MAVS - IFN pathway (MAVS)		[100, 101]
	Reovirus	GCRV106	VP41	MITA - IFN pathway (MITA ▶ IRF-3/7)	Inhibit IFN response	[102]
	Iridovirus	ATV FV3 RGV RBIV	vIF2α, vRNase III	PKR mediated pathway (PKR, P, eIF2α)	Resist with host translation inhibition	[106-110, 112]
	Alloherpesvirus	KHV/CyHV-3 CaHV	vPKZ	PKZ mediated pathway (PKZ, P, eIF2α)	Resist with host translation inhibition	[114, 115]
	Birnavirus	IPNV	VP4, VP5	Mx expression (Mx)	Inhibit Mx expression	[118]
Anti-NF-κB signal	Rhabdovirus	IHNV VHSV	$NV_{IHNV/VHSV}$	NF-κB activation (NF-κB)	Inhibit NF-κB signaling	[120-122]
Anti-apoptosis	Iridovirus	GIV SGIV ISKNV LCDV-C	vGPCR, vTNFR	Cytokine receptors (TNFR, GPCR, caspase) → apoptosis	Inhibit apoptosis	[127, 128, 130, 131, 134]
			vBcl-2, vCARD	Caspases-apoptosis	Inhibit apoptosis	[137, 138, 152]
	Birnavirus	IPNV POBV	VP5	Bcl-2-apoptosis (Bcl-2, caspase)	Inhibit apoptosis	[142]
	Nimavirus	WSSV	WSSV222	TSL-apoptosis (TS) → apoptosis	Inhibit apoptosis	[155, 156]
			VP38/41B, WSSV134, miR-N24	Caspases-apoptosis (caspase) → apoptosis	Inhibit apoptosis	[145-148]
Anti-immune signal in shrimps	Nimavirus	WSSV	*ie1*/IE1	Transcription factors	Increase viral gene expression	[160-164, 1861
			miR-22	JAK/STAT pathway	Resist host immune signaling	[169]
			miR-N13/N23	Spz-Toll-Dorsal-ALF pathway		[171]
Iron holding			Protein kinase 1	Cell's iron-withholding defense (iron)	Increase free iron for virus	[175]

5. Virus mediated evasion to apoptosis

Apoptosis at the early stage of infection can hamper the persistent replication of virus. Hence, virus evolved to encode proteins to modulate the process to facilitate its replication. The cell apoptosis/survival regulation needs a series of signaling cascades that contain cooperation of several genes/proteins.

5.1. Viral disturbance to the cell surface receptors

One of important signaling cascade from cell surface is the tumor necrosis factor (TNF) and its receptor TNFR mediated pathway. Members of the TNFR superfamily are transmembrane proteins. Due to the different structure and expression pattern, TNFR could induce several responses including inflammation, tissue regeneration, cell proliferation, apoptosis, necroptosis, and so on [124,125]. The Lipopolysaccharide (LPS) induced TNF-α factor (LITAF) could affect TNF-α expression [126]. Many LITAF homologues have been identified in iridoviruses. Among them, SGIV ORF136 encodes a putative LITAF. Its overexpression could induce apoptosis and increase NF-κB and NFAT activities in fish cells [127], but a microRNA (miR-homoHSV) encoded by the virus could suppress the virus-encoded LITAF expression and apoptosis [128]. NS26 (encoded by S11 genome segment) of GCRV JX-01 (*Reoviridae*) could interact with cellular LITAF [129], but its exact function need further research. Virus also encodes TNFR homologues to mimic host receptors. It has been reported that SGIV ORF51L and ORF096 encode TNFR-like protein respectively. The two proteins all could enhance cell proliferation and inhibit apoptosis for effective virus replication [130,131].

Another important signaling protein is the G protein-coupled receptor (GPCR), which makes up a large and diverse superfamily of transmembrane (TM) proteins, and function in signal transduction across cell membranes [132]. Interestingly, viruses have developed strategies to exploit GPCR signaling to benefit their life cycle. Several putative homologues of GPCR have been found in the viruses [133,134]. It has been reported that lymphocystis disease virus isolated in China (LCDV-C, *Iridoviridae*) contains a putative homologue of cellular GPCRs (LCDV-C GPCR). Overexpression of the LCDV-C GPCR could enhance cell proliferation and inhibit apoptosis [134].

5.2. Suppressing the intracellular signal cascades

A critical regulator family of the mitochondrially mediated apoptotic pathway is the B-cell lymphoma 2 (Bcl-2) protein family [135]. Proteins in the family contain one to four conserved Bcl-2 homology domains and could function as pro-apoptotic or pro-survival factors [136]. Some aquatic viruses encode proteins that contain Bcl-2 domains. For example, GIV (*Iridoviridae*) encodes a Bcl-2 protein (GIV66), which belongs to the immediate-early gene product and could localize on the mitochondria. Overexpression of GIV66 inhibits UV-induced apoptosis in HeLa cells [137]. Further research with the purified GIV66 protein show that it is a single-specificity Bcl-2 protein that bind to cellular Bim to inhibit apoptosis [138]. IPNV (*Birnaviridae*) induced cell death including mitochondria-mediated apoptosis, necrotic cell death, and ER stress-mediated cell death have been reported by several researchers [139–141]. However, its structural protein VP5 contains Bcl-2 homology domains and is capable of enhancing cell viability as anti-apoptosis factor [142].

Caspases (cysteine-aspartic proteases) are a family of proteases playing key roles in apoptosis [143]. Extrinsic and intrinsic signals both should be transmitted by caspase cascades. As described above, Caspase 8 and 9 are key caspases related to extrinsic and intrinsic pathways respectively. They activate the effector caspases, caspase 3 and 7, to induce apoptosis. Silence of the *Pjcaspase* gene from the marine shrimp *Marsupenaeus japonicus* inhibits the WSSV (*Nimaviridae*) induced apoptosis and results in the increase of viral copies in shrimp [144]. Two

envelope proteins of WSSV, VP38 and VP41B, are reported to bind to shrimp *PjCaspase* promoter, and regulate its transcription [145]. Recombinant WSSV134 (VP36A) can inhibit caspase activity of *Penaeus monodon* (PmCasp) *in vitro* [146], and possess anti-apoptotic activity [147]. WSSV also express miRNAs to facilitate its replication. It has been reported that several viral miRNAs were expressed by WSSV [148–150]. Among them, WSSV-miR-N24 could target the shrimp caspase 8 gene and suppress the apoptosis of shrimp hemocytes *in vivo* [148].

The CARD-containing proteins have vital regulatory roles in apoptosis including recruit caspases to apoptosis signaling-complexes [151]. Iridoviruses encode several CARD-containing proteins by sequence analysis. Overexpression of the GIV CARD could inhibit apoptosis induced by mitochondrial and death receptor signaling, which involve the inhibition of caspase-8 and -9 activities [152].

In addition, there are other approaches to fight against apoptosis. For example, viruses have gained the ability to modulate the ubiquitin-dependent proteolysis which is the main protein degradation pathway in eukaryotic cells to affect apoptosis. Four proteins of WSSV, WSSV199/222/249/403, were predicted to contain the RING-H2 motif, which is a conserved motif in E3 ubiquitin protein ligase [153,154]. It has been reported that WSSV222 possesses E3 ligase activity. It can interact with shrimp tumor suppressor-like protein (TSL) which induces apoptosis *in vitro*, and then lead to the ubiquitin-mediated degradation of TSL, and function as an anti-apoptosis protein for efficient replication of WSSV [155,156].

6. Virus mediated evasion to immune signaling in shrimps

As arthropod species, shrimp lacks specific immunity and relies on innate immunity against virus infections [157], which including immune signaling pathways, phagocytosis, RNAi, and apoptosis [16,22,158]. The virus mediated evasions to immune signaling are discussed in this section.

The immediate early (IE) genes of DNA viruses usually encode regulatory proteins. WSSV immediate-early gene *ie1* and its product IE1 can interact with various host factors. For example, The Janus family tyrosine kinase and signal transducer and activator of transcription (JAK/STAT) signaling pathway plays a vital role in innate immunity [159]. It has been reported that *ie1* promoter contains STAT binding motif. The promoter can bind with shrimp *Penaeus monodon* STAT protein, which could increase its promoter activity [160]. IE1 interact with *Litopenaeus vannamei* (*L. vannamei*) STAT (LvSTAT) and promote its transcriptional activation activity. Meanwhile the LvSTAT can bind to the promoters of *ie1* and *wsv051*, and enhance their promoters' activities [161]. It has been reported that *L. vannamei* Shrimp transcription factor NF-κB could bind to *ie1* promoter and upregulate its activity [162]. The *ie1* promoter could bind another transcription factor, *Litopenaeus vannamei* shrimp Yin Yang 1 (LvYY1), and then activates its own expression [163]. In addition, WSSV449 can activate host NF-κB pathway, and then induce the promoter activities of *ie1*, *WSSV303*, and *WSSV371* [164]. It seems like the ie1/IE1 could interact with various host factors and regulate virus replication.

The JAK/STAT, Immune deficiency (IMD), and Toll pathways are regarded as main immune signaling pathways that regulate humoral immune responses in invertebrates including shrimp [159,165]. Activated JAK/STAT upon virus infection can activate the transcription of several immune related genes [166]. It has been reported that the transcription of shrimp STAT was regulated by WSSV infection [167,168]. WSSV replication was increased when the expression of JAK or STAT was knocked down by siRNA. The WSSV-miR-22 was reported to target host STAT gene and promote virus infection [169]. Most of the components of the Toll pathway have been identified in shrimps [18,165]. Dorsal and Dorsal related immunity factor are canonical components of the Toll pathway [170]. Two viral miRNAs, WSSV-miR-N13 and WSSV-miR-N23, can target *Dorsal* gene and suppress the Spz-Toll-Dorsal-ALF signaling pathway in shrimp, which prompts virus infection [171].

7. Virus regulated ionic balance to suppress host defense

Iron is essential for nearly all living organisms. By preventing the accumulation of iron in sensitive sites, organisms can fight against pathogens with iron-withholding defense mechanism [172,173]. Ferritin is the major iron storage protein, which could modulate the cellular labile iron pool (LIP) [174]. WSSV encodes a protein kinase 1 homologue. It can interact with shrimp ferritin and apoferritin. It can prevent apoferrintin from iron loading and increase the cellular LIP levels, which could be a strategy to counteract the host cell's iron-withholding defense mechanism [175].

8. Virus mediated evasion to adaptive immune responses

The innate immune system and adaptive immune system constitute the two main immunity systems in vertebrates. Important components of the adaptive immune system such as B/T cells, major histocompatibility complex (MHC) molecules, and T cell receptors have been identified in bony fish [176]. However, information about the virus mediated immune evasion to adaptive immune responses is rare.

It has been reported that the interleukin-10 (IL-10) homologue (khvIL-10) which is encoded by KHV ORF134 utilizes same receptor with zebrafish IL-10. Expression of khvIL-10 induced similar phenomenon with zebrafish IL-10 in zebrafish embryos including the increase of lysozyme positive cells [177]. However, deletion of the ORF134 does not affect viral replication *in vitro* and virulence in common carp [178]. Further *in vitro* study using recombinant khvIL-10 protein showed that it can deactivate the inflammatory activities of carp macrophages. It can also promote the proliferation of IgM^+ B cells and memory T cells of carp [179]. In addition, It has been reported that KHV infection induced the down-regulation of MHC class I mRNA expression in carp [180]. But its exact mechanism needs further research. Inhibition of MHC expression has been also reported in iridovirus including SGIV and ADRV [34,181]. However, the mechanisms of aquatic virus mediated resistance to adaptive immunity need more concern [189].

9. Conclusion

Present review summarize and analyze the potential immune evasion functions of three representative viral components including genes, proteins, and miRNAs from twenty three strains of aquatic animal viruses in six families, which involve virus mediated resistance to several host responses containing innate immunity, apoptosis, and adaptive immunity, especially virus mediated evasion to IFN and apoptosis responses. Thus it can be seen three main immune evasion strategies that used by aquatic animal viruses have gained more attentions until now. Resistance to IFN responses are more common in aquatic vertebrates. However, resistance to immune signaling such as JAK/STAT and Toll pathway are dominant in aquatic invertebrates. Moreover, resistance to apoptosis which is a widespread manner in antiviral responses of multicellular organisms are found in both aquatic animals above. This context provides an outline of aquatic animal virus mediated immune evasion and could facilitate the research on aquatic virus-host interactions and antiviral applications.

Conflicts of interest

The authors declare no conflicts of interest.

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