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The immune evasion strategies of fish viruses

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ABSTRACT

Viral infection of a host rapidly triggers intracellular signaling events that induce interferon production and a cellular antiviral state. Viral diseases are important concerns in fish aquaculture. The major mechanisms of the fish antiviral immune response are suggested to be similar to those of mammals, although the specific details of the process require further studies. Throughout the process of pathogen–host coevolution, fish viruses have developed a battery of distinct strategies to overcome the biochemical and immunological defenses of the host. Such strategies include signaling interference, effector modulation, and manipulation of host apoptosis. This review provide an overview of the different mechanisms that fish viruses use to evade host immune responses. The basic mechanisms of immune evasion of fish virus are discussed, and some examples are provided to illustrate particular points.

1. Introduction

Viruses are the most abundant life forms on earth, inhabiting nearly every ecosystem including almost all living species [1]. In turn, probably as a result of the constant evolutionary pressure from viral invaders, these organisms possess very sophisticated defense mechanisms designed to effectively counter virus insult to a host. The winner of the battle between a host and a virus depends on the ability of the host to mount a strong immune response or the ability of the virus to use its virulence factors that allow it to replicate fast enough before direct confrontation of host responses and the use of immune evasion mechanisms that allow the virus to replicate in the presence of a host potent immune response. Several mammalian viruses have evolved to acquire mechanisms of antagonizing innate and adaptive immune response [2]. This capacity of viruses to counteract the host immune response can influence the outcome of a disease process by allowing the virus to replicate in the presence of a potent host response.

Fishes represent a transition point in the phylogenetic spectra between species possessing only innate immune (i.e., invertebrates) and species depending heavily on adaptive immune (i.e., mammals) [3]. Antiviral immunity has been studied only in a few fish species, either model species or aquaculture fish. Fish are vertebrates and share with humans and mice most of the key antiviral pathways. However, fish have long and complex genome history and developed a specific adaptation to aquatic environment (and to its pathogens). In recent years, many studies have highlighted the importance of fish virus and host interaction. This review aims to summarize the current knowledge of fish viral evasion mechanisms. An overview of the different mechanisms that fish innate immune responses is provided and the basic mechanisms of immune evasion of fish viruses are discussed, and some examples are provided to illustrate particular points.

2. Fish antiviral innate immune response

Fish are the ancestral vertebrate group that have well-developed immune systems. Their immune systems comprise two distinct but closely interdependent components: innate immune systems and adaptive immune systems. In mammals, the innate immune response is responsible for early detection of invading virus-associated molecular patterns using a set of limited germ line-encoded pattern recognition receptors (PRRs). After the recognition, the downstream signaling molecules for each PRR family become active, which bring about antiviral response, that is, the production of either type I interferons (IFNs) or pro-inflammatory cytokines. The apoptosis and autophagy are also triggered by virus infection and play an important role in the antiviral innate immunity. In fish, the previous studies have suggested

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that the major process of fish innate immune response was similar to that of mammals, although there still is incomplete information about the fish innate immune response, which need further investigated.

2.1. Virus detection by host PRRs

As the first line of host defense, the innate immune system relies on a large family of PRRs to recognize pathogen-associated molecular patterns (PAMPs) derived from various microbial pathogens [4]. In mammals, viral infection is rapidly detected by specialized PRRs, such as Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), cytosolic DNA sensors (CDSs), and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) [5–8]. These cellular sensors of invading virus activate signaling cascades leading to the nuclear factor-kappa B (NF-κB) and IFN response factor (IRF) family transcription factors, thereby leading to the induction of pro-inflammatory cytokines, chemotactic cytokines, and antivirus responses [9,10].

The fish possesses a number of PRRs capable of sensing virus PAMPs (i.e., DNA, dsRNA, and ssRNA), which can be found on the cell surface, in endosomes, or the cytosol [11]. On the cell surface, the fish-specific TLR22, with an expression exclusive to fish, can sense long extracellular dsRNA molecules to recruit and activate the adaptor protein TIR-domain-containing adapter-inducing interferon-β (TRIF) [12]. Surface SR-As bind nucleic acids (i.e., DNA and dsRNA) in the extracellular space and transport these nucleic acids into endosomes [13,14]. Endosomal nucleic acid PRRs include TLR3 and TLR19, which recognizes dsRNA and recruits the adaptor protein TRIF [15–17]. TLR7 and TLR8 are also located in the endosome, where they recognize ssRNA [18,19]; TLR9 and TLR21 are also located in the endosome but recognize DNA [20–22]. TLR7, TLR8, TLR9, and TLR21 recruit myeloid differentiation factor 88 (MyD88) for downstream signaling [20–22]. With respect to cytosolic nucleic acids, the retinoic acid-inducible gene I (RIG-I), mitochondrial antiviral signaling protein (MDA5), and laboratory of genetics and physiology 2 (LGP2) recognize viral dsRNA in the cytosol and activated mitochondrial antiviral-signaling protein (MAVS) for downstream signaling, collectively referred to as RLRs [23]. Recognition of cytosolic DNA appears to involve several intracellular receptors, collectively referred to as CDSs. These receptors include: DNA-dependent activator of IFN-regulatory factors, absent in melanoma 2, RIG-I via RNA polymerase III, leucine-rich repeat (in Flightless I) interacting protein-1, DExD/H-box helicases DDX41, DHX9, and DHX36, cyclic GMP-AMP synthetase (cGAS), and IFI16 (also known as p204) [24]. In fish, DDX41 remains the only CDS described thus far. DDX41 activation leads to the recruitment and activation of the adaptor protein-stimulator of interferon genes (STING) and subsequent activation of the TANK-binding kinase 1 (TBK1). Whether the additional CDSs existing in fish remains a topic of ongoing research [25,26].

2.2. Downstream signaling pathways of PRRs

Once the PRRs are activated, adaptor proteins are recruited to transduce the signal and initiate the downstream signaling pathways. When the TLRs are activated, adaptor proteins are recruited to their cytosolic tails. These adaptor proteins include MyD88 and TRIF, which mediate the inflammatory and type I IFN responses within the cell [8]. MyD88 sequences have been identified in fish species, such as Atlantic salmon (*Salmo salar*), grass carp (*Ctenopharyngodon idella*), Japanese flounder (*Paralichthys olivaceus*), large yellow croaker (*Pseudosciaena crocea*), rainbow trout (*Oncorhynchus mykiss*), and zebrafish (*Danio rerio*) [27–30]. MyD88-binding to an activated PRR leads to activation of NF-κB activation and translocation followed by expression of pro-inflammatory cytokines. Some of the important signaling proteins of the MyD88-activated signaling pathways include IRAK-4 and TRAF6. Overexpression of IRAK-4 or TRAF6 resulted in stimulation of NF-κB in zebrafish cells [31]. In addition to the NF-κB mediated inflammatory response, MyD88 has also been shown to interact with the type I IFN-pathway-associated transcription factors, IRF3 and IRF7 [32]. The majority of TLRs signal through MyD88, while TLR3 and TLR22 signal through TRIF, which has been identified in multiple species, including Channel catfish (*Ictalurus punctatus*), Fugu (*Takifugu rubripes*), and zebrafish (*D. rerio*) [33–35]. TRIF activates the NF-κB response promoter in zebrafish and activates the IRF3- and IRF7-mediated pathways. Fish TRIF appears to have similarities to its mammalian counterpart, such as its activation of specific signaling pathways and IFN production [36,37].

MAVS protein, also known as CARDIF, VISA, or IPS-1, is the most important downstream adaptor protein of RLRs. MAVS is located on mitochondria. Through recognition of PAMPs by RLRs, MAVS was recruited and then became associated with TRAF3, STING (also known as TMEM173, MITA, MPYS, and ERIS), and TBK1, leading to the phosphorylation and activation of IRF3/IRF7 for translocation into the nucleus to the production of type I IFNs [6]. MAVS is also involved in the activation of TRAFs, IκB kinase (IKK)i/IKKε-containing macromolecular complex that signals the activation of NF-κB, leading to pro-inflammation cytokine production [38]. MAVS was cloned from a variety of fish, such as Atlantic salmon (*S. salar*), grass carp (*C. idella*), zebrafish (*D. rerio*), and Japanese flounder (*P. olivaceus*); the function of the fish MAVS is similar to that of mammalian MAVS [39–41]. These results indicated that this pathway also occurs in fish.

STING is regarded as the key adaptor protein for cytosolic DNA sensing. Overexpression of STING enhances type I IFN and IFN-stimulated gene (ISG) expression, whereas STING deficiency inhibits the innate antiviral response, causing increased susceptibility to both RNA and DNA viruses [42]. Moreover, STING has been shown to directly bind self and foreign DNA to stimulate downstream signaling characterized by the activation of antiviral and inflammatory genes, including type I IFN [43]. Once activated by cytosolic DNA signaling, STING undergoes a dramatic relocalization from the endoplasmic reticulum to the Golgi complex and assembles into punctate structures that contain the kinase TBK1. This process may somehow stimulate TBK1, resulting in the phosphorylation of IRF3 [44]. While CDSs themselves have not been well characterized in fish. Fish STING has been identified in many fish, including zebrafish (*D. rerio*), fathead minnow (*Pimephales promelas*), grouper (*Epinephelus coioides*), and black carp (*Mylopharyngodon piceus*), and has been found to function analogously to mammalian STING [45–47]. Downstream of STING has been shown to interact with TBK1, which phosphorylates and activates IRF3 to induce IFN. As such, TBK1 is recognized as the central kinase for DNA recognition. With respect to fish, TBK1 transcripts have been identified in zebrafish (*D. rerio*), crucian carp (*Carassius carassius*), Atlantic cod (*Gadus morhua*), and common carp (*Cyprinus carpio*). Crucian carp TBK1 was shown to enhance type I IFN promoter activity in an IRF3- and IRF7-dependent manner [48–50]. This evidence suggests that fish possesses a functional conserved STING-TBK1-IRF3-IFN pathway, capable of inducing type I IFNs in response to cytosolic nucleic acids. STING was also a key component of the RIG-I pathway of cytosolic RNA recognition in these fish [51].

2.3. IRFs and NF-κB

IRFs and NF-κB are the most important transcription factors that receive signaling from PRRs, expression of IFNs or pro-inflammatory cytokines. The IRFs are a group of transcription factors that initiate the expression IFNs. The IRF3 and IRF7 are regulators of type I IFN expression [9]. Members of the TLRs, RLRs, and CSD families signal through IRF7- or IRF3-mediated pathways in fish. IRF3 and IRF7 have been identified in various fish; both IRF3 and IRF7 were upregulated in response to poly (I:C), as well as recombinant type I and type II IFN [52]. Moreover, fish IRF3 functions as an interferon-stimulated gene (ISG), in addition to an IFN transcription factor, which is not the case for mammalian IRF3 [53].

The NF-κB family is composed of five related transcription factors:

p50, p52, p65, c-Rel, and Rel B. When cellular receptors sense external stimuli, they transmit signals to the IKKs through adaptor proteins, resulting in the phosphorylation of IKKs, degradation of IκB, nuclear transfer of p50/p65, and activation of NF-κB. Active NF-κB can express numerous pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-8, and COX2) [54]. NF-κB was identified in many kinds of fish and the function of NF-κB conserved in fish.

2.4. JAK-STAT signaling pathway

IFN binding to their membrane receptors activates the Janus kinase (JAK) - signal transducer and activator of transcription (STAT) signaling pathway. Type I IFN association to its receptor triggers recruitment and binding of the kinases nonreceptor tyrosine-protein kinase (TYK2) and JAK1 to IFNAR1 and IFNAR2, respectively. Subsequently, these kinases promote the phosphorylation of STAT1 and STAT2 proteins preceding their oligomerization. Conjugation of cytoplasmic IRF9 to the STAT1/2 oligomers generates the complex IFN-stimulated gene factor 3, which induces the transcription of ISGs after binding nuclear IFN-stimulated response elements on their promoter [55]. The constitute class of inducible negative feedback regulators of the JAK/STAT signaling pathway is a suppressor of cytokine signaling (SOCS) proteins; SOCS plays an important role in controlling the JAK-STAT signaling pathway [56]. JAK and STAT family members have been identified from Drosophila to humans, and they play a significant role in cytokine signaling [57]. In fish, the main proteins of this pathway (such as JAK1 and TYK2, STAT1 and STAT2) were also identified, and studies implied that they have similar functions as their mammalian analog, and even have some difference in detail [57].

2.5. Interferon-stimulated genes (ISGs)

Type I IFNs do not possess antiviral activity but interfere with viral infection through induction of a vast repertoire of ISGs through the JAK/STAT pathway. A few hundred ISGs with a rich diversity of molecular functions have been identified in humans [58]. Some ISGs, such as Mx, Viperin/Vig1, ISG15, PKR, and TRIM5, exert a direct antiviral activity. However, the connection of most ISGs to antiviral mechanisms and even their role in the biology of the cell remain unknown. ISGs are intrinsically located downstream of IFN in the antiviral pathways induced by viral infections, a number of them are able to up-regulate type I IFNs and are therefore involved in positive feedback regulatory loops (such as TRIM25, STAT1, IRF7, and Viperin/Vig1), while some also feedback negatively on IFN signaling (such as SOCS1 and SOCS2) [59–61]. Furthermore, the recognition of viral compounds by cellular sensors can directly up-regulate some ISGs, that is, independent of IFN induction; such bypass has been shown for Mx and for Viperin in humans and fish [62–64]. Orthologues of human ISGs involved in IFN amplification have often been retrieved as ISGs in fish, which may indicate that they belong to the primordial IFN pathway: for example, TRIM25, RIG-I, STAT1, IRF7, and Viperin/Vig1 are conserved in fish and are induced by type I IFN in these organisms [65]. In fish, this list also includes IRF3, which is not an ISG in mammals. Although their induction pathways are partly unknown, IFN-independent induction has been observed for some of them. Whether regulatory loops of signaling pathways for type I IFN and ISGs induction are ancestral or have been shaped independently during fish versus tetrapod evolution remains to be clarified.

2.6. Apoptosis

Apoptosis is an active mode of programmed cell death exhibiting a series of morphological and biochemical changes by which it can be distinguished from other cell death subroutines [66]. At a morphological level, these modifications include cell shrinkage, nuclear pyknosis, and nuclear fragmentation. Eventually, dying cells break down into small, discrete bodies known as apoptotic bodies. Apoptosis can be triggered by two fundamentally distinct signaling cascades, namely the extrinsic and intrinsic (or mitochondrial) pathways [67]. The extrinsic pathway is started by the ligand-induced oligomerization of specific cell surface receptors, such as Fas/CD95, and the tumor necrosis factor receptor (TNFR). This induces the intracellular assembly of the death-inducing signaling complex, a molecular platform for the activation of the caspase cascade that emanates from caspase-8 and results in the activation of effector caspase and nucleases [68]. By contrast, the intrinsic pathway is controlled by mitochondria, which collect and integrate pro- and anti-apoptotic signals incoming from other organelles and from the extracellular microenvironment. Notably, pro-apoptotic stimuli as diverse as DNA damage, endoplasmic reticulum stress, lysosomal stress, reactive oxygen species, and calcium (Ca^{2+}) overload are able to activate the intrinsic pathway of apoptosis by favoring mitochondrial membrane permeabilization [69].

Apoptosis, or programmed cell death, can be triggered by a variety of inducers, including ligands of the TNF family, irradiation, cell cycle inhibitors, or infectious agents such as viruses [70]. The elimination of virus infected cells through programmed cell death is one of the most ancestral defense mechanisms against infection. Apoptosis can be considered an innate cellular response to provoking inflammatory responses, limiting viral propagation, and expression of proteins by the viruses [70]. Viruses have acquired the capacity to regulate host cell apoptosis, control inflammatory responses, and evade immune reactions [70]. Although information on the role played by host cell death in the onset of viral infection in fish is scarce, it seems that fish viruses use similar strategies and signaling pathways as their mammalian counterparts to interfere with host cell death [71].

2.7. Autophagy

Autophagy is an evolutionarily conserved cytosolic degradation pathway that maintains cellular homeostasis by regulating the turnover of cytosol, accumulating proteins or protein assemblies and (dysfunctional) organelles by forming double-membrane vesicles around the cargo [72]. Cargo-containing autophagosomes then migrate to the perinuclear region where they fuse with lysosomes to form autolysosomes, resulting in content degradation, which supplies the cell with nutrients during periods of starvation or other types of stress [72]. Autophagy is an important part of cellular innate immunity that targets and degrades incoming pathogens, such as bacteria or viruses [73]. Autophagic degradation threatens the invading pathogen by limiting its replication; Moreover, pathogen degradation through autophagy leads to the production of microbial peptides, which are presented through major histocompatibility complex molecules to initiate an adaptive immune response [74,75]. Autophagy is an evolutionarily conserved pathway largely reported from yeast to mammals, such as mouse, common carp, and yeast [76–79]. A large number of works indicated that autophagy plays an important role in fish immunity [80–82].

3. The immune evasion strategies of fish viruses

The complexity of antiviral signaling pathways reflects the dynamic interactions between viruses and their hosts, and has been shaped by the highly diverse strategies developed by these pathogens to evade antiviral immunity. In mammals, a vast number of strategies that target immunity have been discovered. Fish viruses also exhibit multiple strategies to evade host immune response; however, these strategies remain poorly described. Here, we mainly discuss the strategies of fish viruses evasion from antivirus innate immunity (Fig. 1).

3.1. Evasion strategies of fish viruses for PRR activation

Viral interference with PAMP recognition and PRR activation essentially blinds the host cell from detecting or signaling the presence of

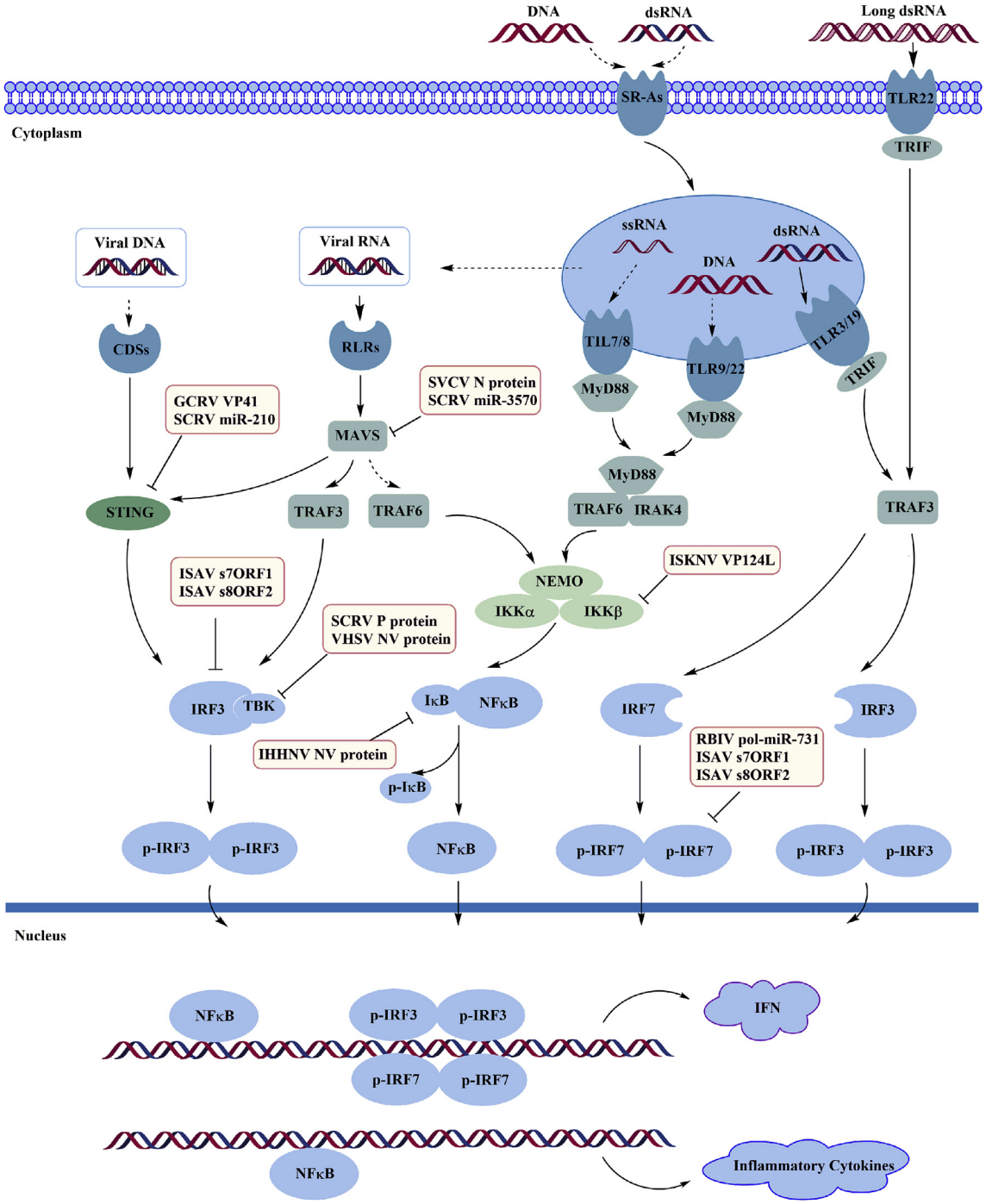

Fig. 1. Immune evasion strategies of fish viruses for PRRs signaling pathways. SVCV N protein and SCRV induced host miR-3570 target MAVS to inhibit the IFN production; GCRV VP41 and SCRV induced host miR-210 target STING to regulate the IFN production. SVCV P protein and fish Novirhabdovirus NV protein target the TBK1 to regulate the IFN production. ISAV proteins s7ORF1, s8ORF2, and RBIV induced pol-miR-731 target IRFs to regulate the IFN production. ISKNV VP124L target IKKβ to regulate NF-κB. IHNV NV protein targeted IκBα and suppressed the NF-κB.

invading viruses. The subsequent attenuation of the host response presents the virus with opportunities to escape and establish successful infection without the limitations imposed by IFN. Generally, the mechanisms of fish viruses escaping host PAMP recognition has not been reported. Here, we mainly focus on the mechanisms of fish viruses evading host PRRs activation (Fig. 1).

Some fish virus evades host innate immunity by targeting MAVS. Spring viraemia of carp virus (SVCV) is an efficient pathogen causing high mortality in the common carp (*C. carpio*). SVCV infection can suppress the poly (I:C)-triggered, RIG-I or MAVS induced the up-regulation of IFNφ1. The mechanism of the above phenomenon is that N protein of SVCV down-regulated MAVS expression at the protein level but not at the mRNA level [83]. The N protein of SVCV targeted MAVS for K48-linked ubiquitination and promoted the degradation of MAVS [83]. *Siniperca chuatsi* rhabdovirus (SCRV), a typical RNA rhabdovirus, greatly threatens the mandarin fish (*S. chuatsi*) aquaculture. SCRV infection significantly up-regulated host miR-3570 expression in miiuy croaker (*Miichthys miiuy*) macrophages. The miR-3570 was found to target and post-transcriptionally down-regulate MAVS [84]. Thus, SCRV induced miR-3570 and negatively modulated RNA virus-

triggered type I IFN, as well as antiviral gene production, finally facilitating virus replication [84].

STING is an important protein disturbed by fish virus. Grass carp reovirus (GCRV), a highly virulent pathogenic agent of fish, has caused severe epidemic outbreaks of hemorrhagic disease and resulted in tremendous mortality in grass carp (*C. idella*). Overexpression of the GCRV VP41 can inhibit the activation of the IFN promoter stimulated by MAVS and STING (also named MITA). GCRV VP41 is colocalized in the cellular endoplasmic reticulum and associated with STING. VP41 significantly decreased the phosphorylation of STING [85]. These findings suggest that GCRV VP41 prevents the fish IFN response by attenuating the phosphorylation of STING for viral evasion [85]. Moreover, miR-210 suppresses type I IFN production by targeting STING in fish. SCRV infection can induce miR-210 expression and negatively regulate virus-triggered type I IFN, as well as inflammatory cytokine production, thereby promoting viral replication [86].

TBK1 is a potential target for fish viruses to negatively regulate IFN response and facilitate viral evasion. SVCV P protein colocalized and interacted with TBK1 [87]. Dominant negative experiments showed that the TBK1 N-terminal kinase domain interacted with SVCV P protein and was essential for P protein and IRF3 phosphorylation. Overexpression of SVCV P protein reduced the IRF3 phosphorylation activated by TBK1 and reduced host cellular IFN transcription [87]. These data demonstrated that the SVCV P protein is a decoy substrate for the host phosphokinase TBK1, preventing IFN production and facilitating SVCV replication [87]. Non virion (NV) protein expression is critical for fish Novirhabdovirus, Viral hemorrhagic septicemia virus (VHSV), and Infectious hematopoietic necrosis virus (IHNV) in *in vivo* pathogenesis. NV proteins specifically interact with a protein phosphatase, Mg^{2+}/Mn^{2+}-dependent 1Bb (PPM1Bb) and recruit it in the close vicinity of the mitochondria [88]. PPM1B proteins belong to the PP2C family of serine/threonine (Ser/Thr) protein phosphatase and have recently been shown to negatively regulate the host antiviral response through dephosphorylation of TBK1 [88]. NV proteins and PPM1Bb counteract RIG-I- and TBK1-dependent IFN and ISG promoter induction in fish cells and, hence, the establishment of an antiviral state. Furthermore, the expression of VHSV NV strongly reduced TBK1 phosphorylation and thus, its activation. These findings provide evidence for VHSV evasion of IFN and antiviral gene production [88].

3.2. Fish virus antagonizes the IRFs and NF-κB

IRFs are the most important downstream transcription factors for IFN expression and are targets for fish virus antagonization (Fig. 1). Infectious salmon anemia virus (ISAV) is an orthomyxovirus that may cause multisystemic disease and high mortality of Atlantic salmon (*S. salar*). ISAV proteins s7ORF1 and s8ORF2 antagonize IFN-I transcription activation mediated by the IRFs of salmon. ISAV s7ORF1 significantly inhibited IRF3- and IRF7-induced IFN promoter activity, while s8ORF2 significantly inhibited IRF1- and IRF3-induced promoter activity [89]. Immunoprecipitation results showed that both s7ORF1 and s8ORF2 could bind to IRF1, IRF3, IRF7A, or IRF7B, respectively, suggesting that both ISAV s7ORF1 and s8ORF2 could antagonize IFN-I transcription activation mediated through the IRFs [89]. Red sea bream iridovirus (RBIV) is a causative agent of high-mortality diseases in a wide array of marine fish. In vivo and in vitro studies revealed that Japanese flounder (*P. olivaceus*) microRNA, pol-miR-731, specifically suppresses the expression of IRF7 [90]. Overexpression of pol-miR-731 can promote RBIV replication and disrupt RBIV-induced type I IFN response through IRF7. RBIV-infected Japanese flounder can induce expression of pol-miR-731, suggesting that a fish virus-induced host miRNA can facilitate viral infection by suppressing antiviral pathways [90].

NF-κB is a key transcriptional regulator of PPRs and one common target for manipulation by many fish viruses. Infectious spleen and kidney necrosis virus (ISKNV) is the type species of the genus *Megalocytivirus* in the family *Iridoviridae* and is a causative agent of epizootics in mandarin fish (*S. chuatsi*). ISKNV encodes a viral ankyrin repeat protein VP124L, and it can interact with IKKβ, which is an active protein of the NF-κB signaling pathway [91]. VP124L attenuated TNF-α- or phorbol myristate acetate-induced activity of NF-κB but did not interfere with the activity of an activator protein 1 (AP-1) using double luciferase reporter assays [91]. Phosphorylation of IκBα and nuclear translocation of NF-κB were also impaired by VP124L [91]. These results indicate that ISKNV VP124L inhibits NF-κB signaling pathway by physic interaction with IKKβ [91]. Another active protein of the NF-κB signaling pathway, IκBα, is also targeted by fish virus. The NV protein of IHNV can block the degradation of the IκBα and suppress the NF-κB nuclear translocation [92]. Activation of NF-κB is a key step in TNF-α-mediated immunomodulatory pathway. Pretreatment with TNF-α showed a strong resistance against VHSV infection in *Epithelioma papulosum cyprini* (EPC) cells, but cells treated with TNF-α after VHSV infection showed no resistance, suggesting that VHSV can inhibit TNF-α-mediated immunomodulatory pathways. Activation of NF-κB by TNF-α exposure was inhibited in EPC cells harboring VHSV NV gene expressing vectors. Furthermore, the NV gene knock-out recombinant VHSV (rVHSV-DNV-EGFP) induced significantly higher NF-κB activity than the wild-type VHSV in EPC cells, suggesting that the latter adopted a strategy to suppress early activation of NF-κB in host cells through the NV gene [93]. Generally, miR-146a is the most reported cellular miRNA, and it participates in the regulation of multiple cellular processes, such as suppressed NF-κB activation. Singapore grouper iridovirus (SGIV) is a high pathogenic double-stranded DNA virus isolated from cultural groupers. It belongs to genus *Ranavirus*, family *Iridoviridae*. The expression of miR-146a, which can suppress the NF-κB activation in fish cells, was increased in the SGIV infected grouper cells. The increase expression of the miR-146a may be responsible for suppression of the SGIV induced NF-κB active [94]. Another important grouper virus is the Red-spotted grouper nervous necrosis virus (RGNNV). The endogenous expression level of miR-146a also significantly increased along with the RGNNV infection time. NF-κB downstream target gene pro-inflammatory cytokines, including TNF-α, IL-8, and IL-1β, were all significantly decreased in miR-146a mimic transfected cells but increased in miR-146a-inhibitor-transfected cells during RGNNV infection. Furthermore, overexpression of miR-146a significantly facilitated viral infection, while knockdown of miR-146a decreased RGNNV replication [95]. These observations indicate that RGNNV suppresses the host NF-κB through miR-146a.

3.3. Fish virus manipulated the JAK-STAT signaling pathway

The JAK-STAT pathway has been shown to contribute positively to innate immune responses against viral infections from Drosophila to vertebrates. Viruses have evolved counter measures that block different components of the JAK-STAT pathway to prevent production of antiviral compounds. For example, the West Nile Virus similarly attenuates IFN signaling by preventing the phosphorylation of IFN-receptor-bound kinases [96]; dengue virus impedes IFN-induced tyrosine phosphorylation and activation of TYK2 [97]; Rubulavirus V protein binds to STATs and directs their poly-ubiquitylation, resulting in STAT degradation within proteasomes [98].

JAK-STAT pathway is also the target of some fish virus to evade the host immunity. The transcriptome analysis results showed that Salmonid alphavirus subtype 3 favor virus (SAV3) could down-regulate the expressions of JAK-STAT pathway downstream genes in SAV3 infected macrophage/dendritic Like TO-cells (derived from Atlantic salmon headkidney leukocytes), such as CRFB1, CRFB2, CRFB, JAK2, TYK2, STAT3, and STAT5. Those results indicated that SAV3 infection inhibited the JAK-STAT signaling pathway. However, there is need for further studies to demonstrate the mechanism of SAV3 escaping the JAK-STAT signaling pathway [99]. Moreover, an important evidence of fish virus evasion of JAK-STAT signaling pathway was confirmed.

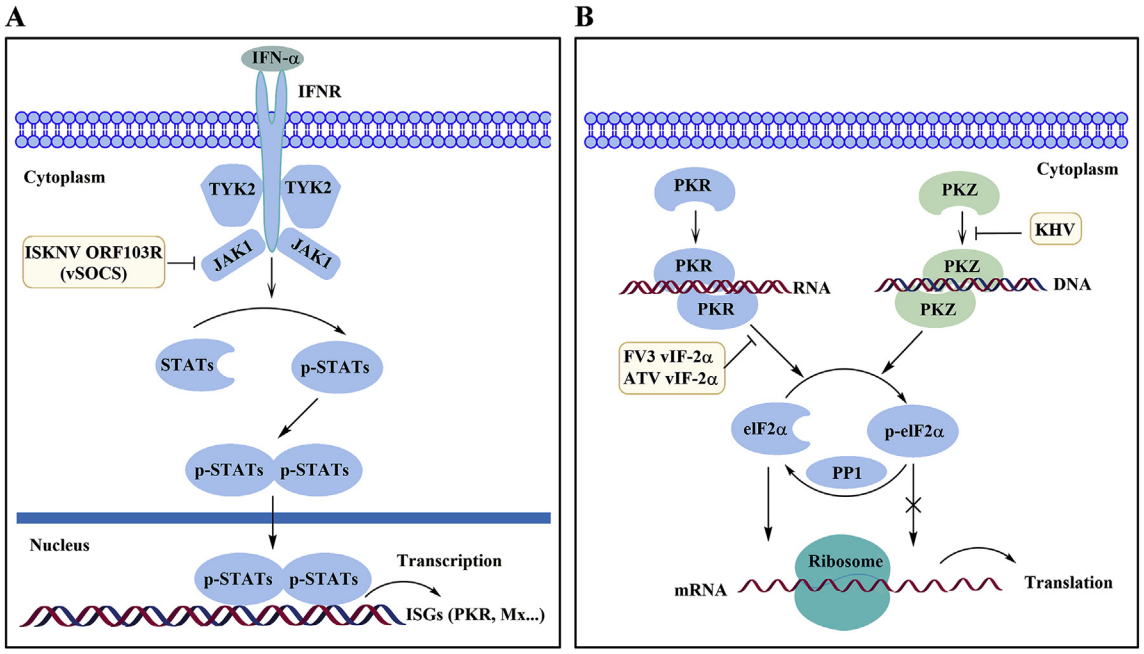

Fig. 2. Fish viruses manipulate the JAK-STAT signaling pathway and inhibit the PKR/Z antiviral responses. (A) ISKNV-vSOCS interacted with JAK1 protein and inhibited the JAK-STAT signaling pathway. (B) Ranavirus (FV3, ATV) vIF-2α inhibited eIF2α phosphorylation, and KHV ORF112 is a viral PKZ, which may inhibit the cellular PKZ.

ISKNV ORF103R encodes a predicted viral SOCS (vSOCS) with high homology to the vertebrate SOCS1 [100]. Overexpression of ISKNV-vSOCS inhibited the activities of IFN-stimulated response element promoter; however, the inhibitions by ISKNV-vSOCS were dose dependent [100]. ISKNV-vSOCS interacted with JAK1 protein and inhibited its tyrosine kinase activity in vitro. ISKNV-vSOCS also impaired the phosphorylation of STAT1 proteins and suppressed their activations [100]. All results reveal that the mechanism of ISKNV escapes the IFN-α response through the ISKNV-vSOCS blockage of the JAK-STAT signaling pathway (Fig. 2A) [100].

3.4. Fish virus evasion of the ISG antiviral responses

The activity of ISGs is subject to viral regulation to affect immune evasion. Viruses have developed strategies that inactivate downstream ISGs. For example, Kaposi's sarcoma-associated herpes virus induces BST2 degradation through the viral ubiquitin ligase K5/MIR2 [101], catalytic activation of 2'-5'-oligoadenylate synthesis is blocked by the influenza A virus NS1 protein and Vaccinia virus E3L protein, the NS1 protein from influenza B virus binds ISG15 and prevents its conjugation to cellular proteins during infection [102]. To cope with ISGs, fish virus is well known for targeting the antiviral responses of protein kinase R/Z (PKR/Z) (Fig. 2B).

PKR was initially identified as a regulator of antiviral responses through protein synthesis studies in cell-free lysates from type I IFN and dsRNA-treated cells. This enzyme is part of a small family of protein kinases that respond to environmental stressors by regulating cellular protein synthesis through the phosphorylation of the alpha subunit of eukaryotic translational initiation factor 2 (eIF2α) [103,104]. Phosphorylation of eIF2α blocks its ability to exchange GDP for GTP and results in the inhibition of protein synthesis at the initiation level [105]. The N-terminal domain of PKR functions as a steric inhibitor, and as a result, PKR is predominantly found as an inactive monomeric state that is unable to phosphorylate eIF2α. However, in response to cellular activation and/or the presence of viral (or synthetic) dsRNA, PKR dimerizes and is activated by autophosphorylation. Activated PKR subsequently phosphorylates eIF-2α, resulting in the inhibition of translation [106]. Given that eIF2α is a key component of cellular translational machinery, its phosphorylation and inactivation establish a state of cellular translation arrest, thereby preventing cell proliferation, as well as synthesis of cellular and viral proteins [107]. In some fish species, another protein kinase, Z-DNA-dependent protein kinase (PKZ), plays a similar role; however, instead of dsRNA-binding domains, PKZ has Zα domains [108]. These domains recognize the left-handed conformer of dsDNA and dsRNA known as Z-DNA/Z-RNA [108].

Many ranaviruses, such as Frog virus 3 (FV3), Epizootic haematopoietic necrosis virus (EHNV), Tiger frog virus (TFV), *Rana catesbeiana* virus (RCV), and *Ambystoma tigrinum* virus (ATV), encode viral homologs of eIF-2α (vIF-2α) [109]. The nucleotide and putative amino acid sequences of these molecules share high identity with cellular eIF2α. To ascertain the function of vIF-2α, virus lacking this gene was generated [109]. The first attempt at determining the function of vIF-2α utilized ATV. The gene ATV encoding vIF-2α (ORF57R) was deleted from ATV genome using homologous recombination and replaced with a selectable marker (ATVΔ57R) [110]. Compared with wild-type ATV, the ATVΔ57R failed to inhibit the phosphorylation of host cell eIF2α. Moreover, the knock out virus was substantially more susceptible to PKR induction by poly (I:C). Furthermore, when fathead minnow (FHM) cells were infected with the wild-type ATV, eIF2α phosphorylation was inhibited, and the promoter PKZ, the fish PKR-related enzyme, was degraded [110]. However, FHM cells infected with ATVΔ57R displayed eIF2α phosphorylation because of the presence of a functional eIF-2α kinase [110]. Moreover, the viral RNase III gene is one of 26 conserved core genes among the iridovirus. ATV RNase III-like gene (ORF25R) can modulate the host innate immune response in fish and human cells [111]. Overexpression of ATV VP25R can decrease levels of cellular eIF2α phosphorylation. ATV deletion of the RNase III gene (ATVΔ25R) led to reduced pathogenicity in tiger salamanders (*Ambystoma tigrinum*) [111]. These observations suggested that ATV ORF25R is a pathogenesis factor that may function to help evade the host's immune response by masking activators of PKR [111]. Moreover, Cyprinid herpes virus 3 (CyHV-3) infects common and koi carp, which have PKZ, and encodes the ORF112 protein that itself bears a Z domain. The crystal structure of ORF112-Z domain in complex with an 18-bp CpG DNA repeat at 1.5 Å were demonstrate. The bound DNA is in the

left-handed conformation and identifies the key interactions for the specificity of ORF112 [112]. These structural characteristic indicate that ORF112 is a putative competitive inhibitor of PKZ.

3.5. Fish viruses have developed strategies for modulating cytokine signaling

Cytokine activity is marshaled early against the initial stages of viral infection and is an essential component of host defense. In the majority of cases, cytokine-mediated responses can account for the complete clearance of viral infection. Most of the damage inflicted on virally infected cells is the result of activities initiated by pro-inflammatory cytokines, such as IFN, interleukin-1 (IL-1), IL-12, IL-18, and TNF-α, as well as a number of chemokines [113]. Not surprisingly, these agents are favored targets for viral subterfuge, and most viruses have developed strategies for modulating cytokine signaling in infected cells. For example, YaBa-like disease virus decoy (Y136) can inhibit human Type III IFNs in addition to Type I IFNs [114]; Kaposi's sarcoma-associated herpesvirus encodes a chemokine antagonist related to CC-chemokines that have been shown to bind to multiple CC chemokine receptors to block function [115]; and poxviruses viral IL-18-binding proteins can effectively inhibit both human and mouse IL-18, which decreased the levels of IFNγ produced in response to viral infection [116].

These common strategies of immune evasion were also used by fish virus. The immune evasion about the IFN production, signal transduction, and ISGs was described above. Here, we exhibit some other cytokines countered by fish virus (Fig. 3). Most fish viruses develop a strategy to encode mimicries of cytokines and cytokine receptors to regulate the host immune response. IL-10 is one of the most important anti-inflammatory cytokines with a key role in the termination of inflammation and restoration of homeostasis [117]. Koi herpesvirus (KHV, a species of CyHV-3) ORF134 was shown to transcribe a spliced transcript encoding an IL-10 homolog (khvIL-10) in koi fin cells [118]. In KHV-infected fish, khvIL-10 transcripts were observed to be highly expressed during the acute and reactivation phases. Injection of khvIL-10 mRNA into zebrafish embryos increased the number of lysozyme-positive cells to a similar degree as in zebrafish IL-10 [118]. Down-regulation of the IL-10 receptor long chain (IL-10R1) abrogated the response to both khvIL-10 and zebrafish IL-10 transcripts, indicating that khvIL-10 functions through IL-10R1. KHV IL-10 can signal through a conserved STAT3 pathway, modulate immune cells, and deactivate phagocytes with a prominent effect on macrophages on the carp similar to that on carp IL-10 [118]. Infectious pancreatic necrosis virus (IPNV) is the agent of a well-characterized acute disease that produces a systemic infection and high mortality in farmed fish species, as well as persistent infection in surviving fish after outbreaks. IPNV infection induces an increase of the IFNa1 and IL-10 mRNA levels in the spleen and head kidney of Atlantic salmon after acute experimental infection, while the levels of the pro-inflammatory cytokines IL-1b and IL-8 did not rise in the spleen [119]. In carrier asymptomatic salmon, cytokine gene expressions of IFNa1 in the spleen and IL-10 in the head kidney were significantly higher than that in noncarrier fish [120]. IPNV always induces up-regulation of the anti-inflammatory cytokine IL-10 in Atlantic salmon. These effects may be part of the viral mechanisms of immune evasion. Given that this is accompanied by a lack of induction of the pro-inflammatory cytokines IL-1b and IL-8, the anti-inflammatory milieu may explain the high frequency, prevalence, and persistence of IPNV in salmon.

The members in TNF induce intracellular pathways through the

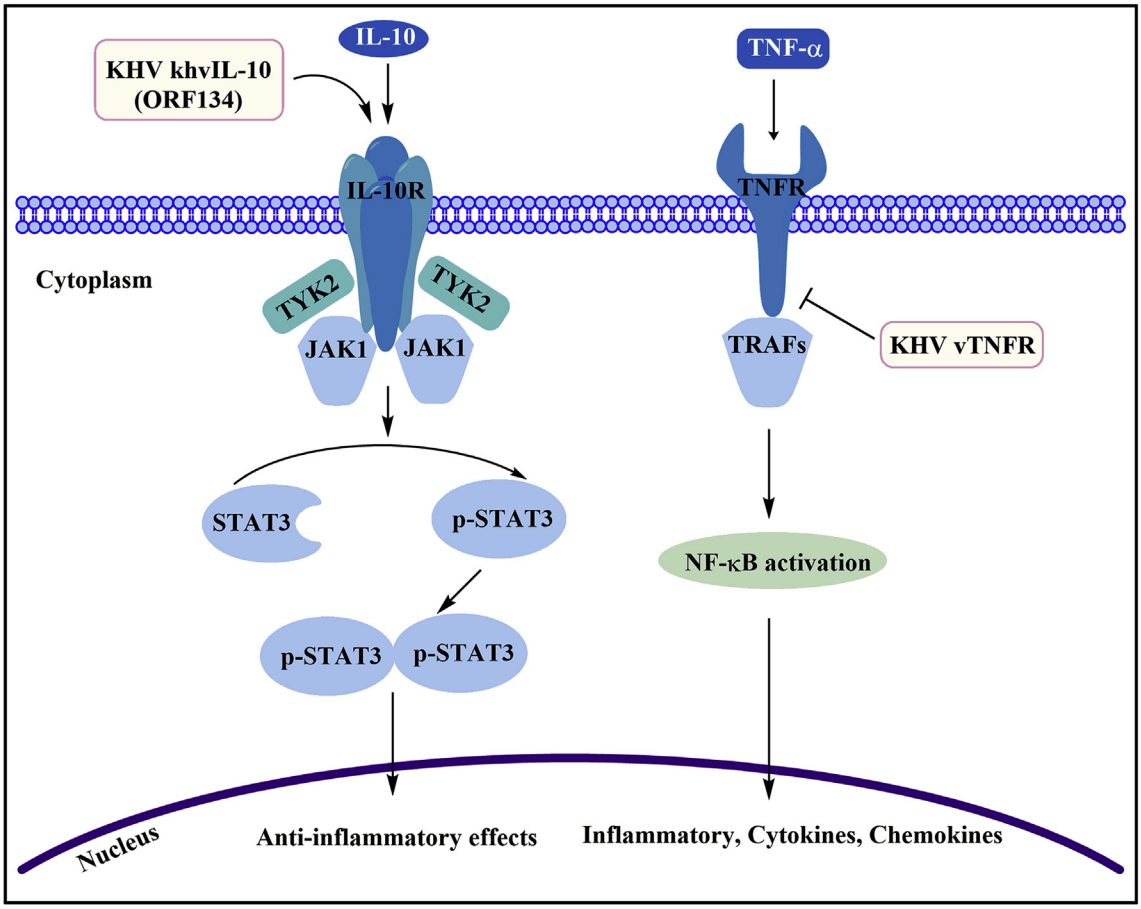

Fig. 3. Fish viruses inhibit TNF-α mediated signal pathway and regulate IL-10 mediated signal pathway. KHV ORF134 encoding an IL-10 homolog (khvIL-10) and have a similar function as host IL-10 that signals through conserved STAT3 pathway, modulating immune cells and deactivating phagocytes. KHV ORF4 and ORF12 encode vTNFR and suppress the TNF-α mediated signal pathway.

cognate TNFR members and exert multiple biological effects, such as survival, differentiation, proliferation, migration, or, on the other hand, apoptosis. Viral infection can stimulate the TNF superfamily (TNFSF)-mediated signaling pathways to regulate the host immune system and activate a series of antiviral activities [113]. Some large DNA viruses, such as herpesvirus and poxvirus, adopt a particular strategy to encode mimicries of TNF and TNFR in order to modulate the host immune response [113]. In fish virus, KHV encodes two novel viral homologues of TNFR (vTNFR), CyHV3-ORF4 and -ORF12. CyHV3-ORF4 was identified as a homologue of Herpesvirus entry mediator (HVEM, also known as TNFRSF14) and CyHV3-ORF12 as a homologue of TNFRSF1 [121]. Overexpression of CyHV3-ORF4 and -ORF12 in zebrafish embryos results in embryonic lethality, morphological defects, and increased apoptosis [121]. Although any interaction between the two vTNFRs and their potential ligands in zebrafish TNFSF failed to be identified by the yeast two-hybrid system, the expressions of some genes in TNF or TNFRF were misregulated in ORF4- or ORF12-overexpressing embryos, especially the death receptor zHDR and its cognate ligand DL1b [121]. These results indicated that two vTNFRs have some influence in TNFSF-mediated signaling pathways, but the concrete mechanism of these two vTNFRs remains unclear. Recent research on CyHV-3-infected carp mode revealed an important function of CyHV-3 ORF12 in the behavioral fever pathways [122]. Both endotherms and ectotherms (e.g., fish) increase their body temperature to limit pathogen infection. Ectotherms do so by moving to warmer places, hence the term “behavioral fever.” The manifestation of behavioral fever in the common carp infected by CyHV-3 (a native carp pathogen) was studied. Carp maintained at 24 °C died from the infection, whereas those housed in multichamber tanks encompassing a 24–32 °C gradient migrated transiently to the warmest compartment and survived as a consequence. Behavioral fever manifested only at advanced stages of infection [122]. Consistent with this result, the expression of CyHV-3 ORF12, encoding a soluble decoy receptor for TNF-α, delayed the manifestation of behavioral fever and promoted CyHV-3 replication in the context of the temperature gradient. Injection of anti-TNF-α neutralizing antibodies suppressed behavioral fever and decreased fish survival in response to infection [122]. These results provide unique examples of how fish viruses have evolved to alter host behavior to increase fitness [122].

Chemokines constitute one of the first secreted immune factors upon an encounter with a pathogen that not only orchestrate immune cell recruitment to the area of inflammation but also condition the immune response that is mounted as they regulate the immune functions of their target cells. VHSV can regulate the chemokine response at the entry site [123]. The fin bases constitute the main portal of rhabdovirus entry into rainbow trout (*O. mykiss*), and replication in this first site strongly conditions the outcome of the infection. The chemokine response was elicited in this area in response to VHSV. Among all the rainbow trout chemokine genes studied, only the transcription levels of chemokine (CK) 10 and CK12 were significantly upregulated in response to VHSV [123]. As the virus was previously shown to elicit a much stronger chemokine response in internal organs, compared with the effect of VHSV on the gills, another mucosal site which does not constitute the main site of viral entry or rhabdoviral replication. In this case, a significantly stronger chemokine response was triggered, with CK1, CK3, CK9, and CK11 being upregulated in response to VHSV, and CK10 and CK12 being down-modulated by the virus [123]. Further experiments are necessary to understand how these different chemokine responses of mucosal tissues can correlate with their capacity to support VHSV replication. No viral replication was detected in the gills, while at the fin bases, only the skin and the muscle actively supported viral replication. Within the skin, viral replication occurred in the dermis, while viral replication was blocked within epidermal cells at some point before protein translation. The different susceptibilities of the different skin layers to VHSV correlated with the effect that VHSV can secrete chemotactic factors [123]. Altogether, these results suggest a VHSV interference mechanism on the early chemokine response at its active replication sites within mucosal tissues, a possible key process that may facilitate viral entry.

Semaphorins are a large, phylogenetically conserved family of proteins that are involved in a wide range of biological processes, including axonal steering, organogenesis, neoplastic transformation, as well as immune responses [124]. A semaphorin homologue gene belonging to the SGIV ORF155R (termed SGIV-sema) was cloned and characterized [125]. SGIV-sema attenuated the cellular immune response through decreased expression of inflammation/immune-related genes, such as IL-8, IL-15, TNF-α and STING, in SGIV-sema-expressing cells before and after SGIV infection [125]. These results suggest that SGIV ORF155R is involved in the evasion of the virus from host inflammation.

3.6. Fish virus manipulates host apoptosis

Many viruses in different families have been found to manipulate apoptosis during their infection cycles. Hosts prevent viral infection by apoptosis, but viruses have also developed a range of strategies to fight against the host response. On the one hand, they use apoptosis during infection to disseminate progeny virus. On the other hand, some viruses have different strategies to inhibit apoptosis in the complete life cycle in host cells.

3.6.1. Induce apoptosis by fish virus

In recent years, many fish viruses of different families (such as *Iridoviruses*, *Nodaviruses, Birnaviruses,* and *Orthomyxoviruses*) have been found to induce apoptosis during their infection cycles (Fig. 4).

ISKNV encodes a viral protein similar to TNF receptor-associated factor (TRAF) that interacts with TNF receptor type 1 associated death domain protein [126]. A recombinant plasmid containing the DNA sequence of ORF111L was microinjected into zebrafish embryos at 1–2 cell stage to overexpress ORF111L in the embryos, which resulted in increased apoptosis. The knockdown of zebrafish caspase-8 expression effectively blocked the apoptosis induced by overexpression of ORF111L [126]. Moreover, overexpression of ORF111L resulted in considerably stronger effect on caspase-8 and caspase-3 up-regulation compared with zebrafish TRAF2. These observations show that ISKNV induce apoptosis throw the extrinsic pathway [126]. Giant seaperch iridovirus (GSIV) genome encoded a serine/threonine kinase (ST kinase) protein [127]. Transient expression of the ST kinase resulted in apoptotic cell features in GF-1 cells. Overexpression of ST kinase can up-regulate the expression of p53 and the pro-apoptotic gene Bax, and then activate caspase-9 and caspase-3 in the downstream. These results suggest that GSIV ST kinase can induce apoptosis through up-regulation of p53 and Bax expression [127]. RGNNV B2 was involved with the host cell death. Transiently expressed B2 in RGGNV-infected grouper liver cells resulted in apoptotic cell features (positive TUNEL assays 28% at 24 h post-transfection) and induced the expression of the pro-apoptotic gene Bax, but not mitochondrial cytochrome c release [128]. Using RNA interference to reduce B2 expression, both B2 and pro-apoptotic Bax expression were down-regulated and RGNNV infected cells were rescued from secondary necrosis [117]. Furthermore, overexpression of anti-apoptotic Bcl-xL and Mcl-1 effectively prevented B2-induced mitochondria-mediated necrotic cell death [117]. Greasy grouper nervous necrosis virus (GGNNV) infection induced apoptosis in sea bass (SB) cells. GGNNV-infected SB cells showed an increased activity of caspase-8-like protease and caspase-3-like proteases, whereas inhibitor of caspase-8 and caspase-3 reduced GGNNV-induced apoptosis [129]. Moreover, protein alpha, the precursor of GGNNV capsid proteins, may serve as an apoptotic inducer in SB and Cos-7 cells [129]. Overexpression of IPNV VP3 induced apoptotic cell death by TUNEL assay. Overexpression of IPNV VP3 up-regulated Bad gene expression in zebrafish liver epithelial cells (ZLE cells) by threefold at 12 h post-transfection. VP3 up-regulation of Bad expression altered mitochondria function,

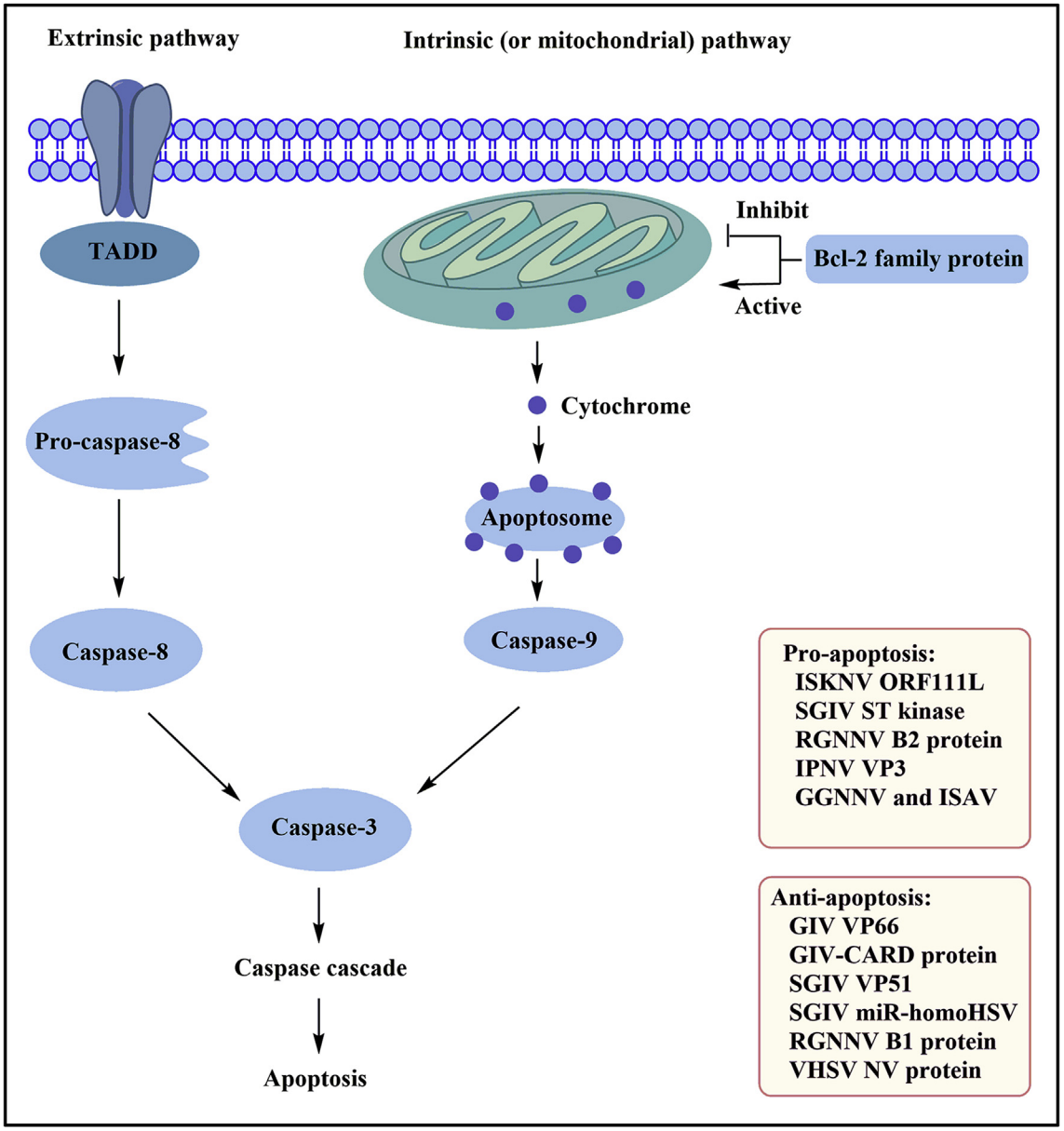

Fig. 4. Fish viruses manipulate the host apoptosis. The GIV vBcl-2 and vCARD proteins, SGIV VP51 and miR-homoHSV, RGNNV B1 protein and VHSV NV protein can inhibit host apoptosis. The ISKNV VP111L, GSIV ST kinase, and RGNNV B2 protein can induce host apoptosis.

inducing mitochondrial membrane potential loss and activating initiator caspase-9 and effector caspase-3 [130]. Overexpression of the anti-apoptotic gene, zebrafish Bcl-xL, reduced VP3-induced apoptotic cell death and caspase-3 activation at 24 h in fish cells. These observations suggest that IPNV VP3 induces apoptosis through up-regulation of Bad expression and mitochondrial disruption [130]. ISAV is a very important fish virus in the Northern hemisphere. Characteristic apoptotic DNA fragmentation was observed only in ISAV-infected salmon head kidney 1 (SHK-1) and Chinook salmon embryonic 214 (CHSE-214) cells [131]. Apoptosis in ISAV-infected SHK-1 cells was confirmed by fragment end-labelling assay. ISAV-infected TO cells did not undergo apoptosis but demonstrated leakage of high-mobility group 1 protein from the nucleus, which is characteristic of cells undergoing necrosis. ISAV-induced apoptosis in the SHK-1 cells was inhibited by a pan-caspase inhibitor, Z-VAD-fmk, indicating a caspase-activation pathway [131]. Moreover, the ISAV putative PB2 protein and proteins encoded by RNA segment 7 bound caspase-8 specifically *in vitro* indicate that these viral proteins may have a role in ISAV-induced apoptosis [132].

3.6.2. Suppress apoptosis by fish virus

Apoptosis can be hired by host cells to defend them from viral infection, but fish viruses have developed a range of strategies to fight apoptosis (Fig. 4).

The genomes of Grouper iridovirus (GIV) contains an antiapoptotic B-cell lymphoma (Bcl)-2-like gene (GIV ORF66). The localization of GIV vp66 on the mitochondrial membrane and overexpression of GIV vp66 were effectively inhibited by apoptosis [133]. Molecular and structural investigations show that GIV vp66 harbors an unusually high level of specificity for pro-apoptotic Bcl-2 and displays affinity only for Bcl-2-like 11 (Bcl2L11 or Bim) [134]. GIV also encodes another anti-apoptotic protein, the caspase recruitment domain (CARD). Knockdown of GIV-CARD in grouper kidney cells infected with GIV reduced GIV infection ability. Overexpression of GIV-CARD protein inhibited apoptosis induced by mitochondrial and death receptor signaling in HeLa cells. Expression of GIV-CARD significantly reduced the activities of caspase-

8 and -9 following apoptosis triggered by anti-Fas antibody in HeLa cells. These results indicate that GIV-CARD can inhibit apoptosis [133]. SGIV VP51 encodes a TNFR-like protein. The expression of SGIV VP51 *in vitro* enhanced cell proliferation and affected cell cycle progression through altering the G1/S transition. Overexpression of SGIV VP51 improved cell viability during SGIV infection through inhibiting virus-induced apoptosis, as evidenced by the reduction of apoptotic bodies and the decrease of caspase-3 activation [135]. Another way of SGIV attenuation of apoptosis is through a miR-homoHSV encoded by SGIV. miR-homoHSV targets SGIV ORF136R, a viral gene that encodes the pro-apoptotic lipopolysaccharide-induced TNF-α (LITAF)-like factor [136]. miR-homoHSV suppressed SGIV LITAF expression, and thus inhibited SGIV LITAF-induced apoptosis. Meanwhile, expression of miR-homoHSV attenuated cell death induced by viral infection [136]. RGNNV B1 has been shown to act as an early protein in nodavirus infection, where it probably inhibited apoptosis. B1 showed a low level of expression in the early replication cycle being detected at 12 h post-infection, while its expression substantially increased at 24 h post-infection in RGNNV-infected grouper liver cells. Overexpression of B1 protected cells against necrotic cell death following RGNNV infection, while knockdown of B1 expression enhanced cell death. However, the molecular mechanism underlying the role of B1 remains unknown [137]. Viral hemorrhagic septicemia virus (VHSV) and Infectious hematopoietic necrosis virus (IHNV) are members of the genus *Novirhabdovirus* within the *Rhabdoviridae* family, which can cause severe hemorrhagic disease in fresh- and saltwater fish worldwide. The non-structural NV protein has been implicated to play a role in apoptosis control. Comparisons of the replication kinetics and markers for virus-induced apoptosis indicate that the NV-deficient and NV knockout mutant viruses induce apoptosis earlier in cell culture than in wild-type VHSV [138]. Furthermore, a created chimeric VHSV, in which the NV gene of VHSV is replaced by the IHNV NV gene, is capable of suppressing apoptosis in cell culture [138].

3.7. Autophagy is manipulated by fish virus

As an important part of cellular innate immunity, not surprisingly, pathogens have evolved mechanisms to control antimicrobial autophagy, such as the Adenovirus (AdV). AdVs limit autophagy by preventing efficient autophagosome maturation even after they have escaped. Some fish viruses can also manipulate host autophagic to benefit themselves.

Spring viraemia of carp virus (SVCV) is a bullet-shaped RNA virus that enters and amplifies in gill epithelium and later spreads to internal organs. Current study observed that autophagy is activated in SVCV-infected EPC cells [139]. The SVCV glycoprotein (SVCV-G protein), rather than viral replication, activates the autophagy pathway. SVCV induces autophagy in EPC cells through the ERK/mTOR signaling pathway to facilitate its own genomic RNA replication. Autophagy promoted the survival of SVCV-infected cells by eliminating damaged mitochondrial DNA generated during viral infection [139]. These observations suggest that a connection between autophagy and SVCV replication exist and propose autophagy suppression as a means to restrict SVCV viral replication.

Autophagy study of iridoviruses, including one megalocytivirus (ISKNV) and four ranaviruses (Chinese giant salamander iridovirus, CGSIV; TFV; GIV; and Largemouth bass virus, LMBV), were investigated. Autophagosome formation in GIV- and LMBV-infected cells were marked but not in ISKNV-, CGSIV-, and TFV-infected mandarin fish fry (MFF-1) cells. Antiviral autophagic effects can be triggered by GIV and LMBV but not by ISKNV, TFV, and CGSIV in a common susceptible cell model. These observations indicate the ISKNV, TFV, and CGSIV may have a potential strategy to escape the antiviral autophagic effects in MFF-1 cells [140].

3.8. Virus-mock basement membrane

Basement membrane (BM), a dense and sheet-like structure, that is always associated with cells, is a very important specialized form of extracellular matrix [141]. BM consists of a layer of laminin polymer, a layer of type IV collagen network, and nidogen protein, which acts as a cross-linker of these two networks [142]. The components of BM can self-assemble and form a sheet-like structure, and laminin is the key molecule in this process [141]. In the ISKNV-infected mandarin fish (*S. chuatsi*), a unique phenomenon in which lymphatic endothelial cells are attached on infected cells, has never been found in other viruses. In order to explain this phenomenon, the virus-mock basement membrane (VMBM), was named. Investigation results showed that ISKNV VP23R was homologous to the laminin γ1 and was expressed on the plasma membrane of the ISKNV-infected cells [143]. ISKNV VP23R can interact with nidogen-1, which was localized on the outer membrane of the ISKNV-infected cells [143]. Furthermore, the ISKNV VP08R functioning as collagen IV was investigated [144]. Research found that ISKNV VP08R was located on the plasma membrane of infected cells and interacted with both VP23R and nidogen-1 [144]. Through these studies, the concept of VMBM was explained. The viral proteins VP23R (viral mimic laminin) and VP08R (viral mimic type IV collagen), as well as the host protein nidogen-1 constitute the VMBM in the outside of the ISKNV-infected host cells, which may segregate the infected cells from the host immune system. This is a unique immune evasion strategy adopted by ISKNV to effectively shield the infected cells from immune attacks.

3.9. Virus inhibit host transcription

Viruses can evade the host response by inhibiting cellular gene expression while simultaneously promoting transcription and translation of viral genes. For example, the influenza A virus NS1 protein inhibits cellular translation processes by blocking nuclear export of mRNAs that contain 3′ poly (A) ends [145]; Vesicular stomatitis virus suppresses host gene expression by inhibiting nuclear export of mRNA through the actions of the matrix protein [146]; and NSs protein encoded by Rift Valley fever virus (RVFV) interacts with the basal transcription factor TFIIH and disrupts TFIIH assembly, thereby inhibiting cellular gene expression [147]. This strategy of inhibiting cellular gene expression has been developed by fish virus.

VHSV infection with fish cells leads to up-regulation of the host's virus detection response, but the virus quickly suppresses IFN production and antiviral gene expression. VHSV genotype IVb (VHSV-IVb) M protein can suppress the constitutively active SV40 promoter and globally decreased cellular RNA levels [148]. Chromatin immunoprecipitation (ChIP) assay showed that M protein inhibited host RNA polymerase II (RNAP II) recruitment to gene promoters and decreased RNAP II phosphorylation during VHSV infection. SGIV encodes a histone H3-binding protein ORF158L [149]. SGIV ORF158L was located in nuclei and was involved in both the regulation and the expression of histone H3 and H3 methylation. Knockdown of SGIV ORF158L resulted in a significant decrease in the virus yielded in grouper embryonic cells [149]. Isothermal titration calorimetry experiments suggested the interactions of SGIV ORF158L with the histone H3/H4 complex and H3 [149]. These observations indicate that SGIV enable ORF158L to control host cellular gene transcription and to facilitate viral replication.

4. Conclusion

Accumulating research evidence has provided considerable information about host-pathogen interactions during fish virus infection. In the review, we outlined the progresses in fish antiviral innate immune response and summarized the major strategies of fish viruses escaped host antiviral innate immune response. A number of multiple

strategies that fish viruses have adopted to evade and inhibit host antiviral innate immune response include the PRRs activation, signaling transduction, the cytokine produced, ISG function, manipulate the apoptosis and autophagy. Especially, formation of a virus-mock basement membrane to evade the immune cell recognizing the virus infection cells was identified in ISKNV, which provides a new strategy for fish virus evasion of host immune surveillance.

Although, we enumerate numerous fish virus immune evasion strategies of fish viruses, they are very rare compared with mammalian virus. The previous studies of main escaping mechanisms of fish viruses focus on the phase of immune signal transduction and transmission, but other phases of antiviral innate immunity were ignored. For example, recognition of the virus by PRRs is the first line of host antiviral defense, which is subverted by a large number of viruses in mammals; however, to our knowledge, fish viruses were still not found to evade this phase. Thus, firstly, further study could emphasize strategies of how fish viruses to evade the other important phase of antiviral innate immunity (such as the immune recognition, ISGs effect and so on). Secondly, the research about the immune evasion of fish viruses concerns not only evasion the innate immunity, but also the evasion strategy about adaptive immunity, which is almost not founded in previous studies. Finally, further study should pay more attention to the fish antiviral immunity to reveal more details of the fish antiviral immunity. Because the virus immune evasion is an important part of virus-host interaction, the best understanding of the antiviral immunity can help to uncover the immune evasion strategies of fish viruses. Based on the sufficient understanding of the immune evasion of fish viruses, we may find rational ways to tip this response for a better advantage for the host, which can lead to the design of novel antivirals drugs and vaccines.

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