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Effects of environmental stress on shrimp innate immunity and white spot syndrome virus infection

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ABSTRACT

The shrimp aquaculture industry is plagued by disease. Due to the lack of deep understanding of the relationship between innate immune mechanism and environmental adaptation mechanism, it is difficult to prevent and control the diseases of shrimp. The shrimp innate immune system has received much recent attention, and the functions of the humoral immune response and the cellular immune response have been preliminarily characterized. The role of environmental stress in shrimp disease has also been investigated recently, attempting to clarify the interactions among the innate immune response, the environmental stress response, and disease. Both the innate immune response and the environmental stress response have a complex relationship with shrimp diseases. Although these systems are important safeguards, allowing shrimp to adapt to adverse environments and resist infection, some pathogens, such as white spot syndrome virus, hijack these host systems. As shrimp lack an adaptive immune system, immunization therapy cannot be used to prevent and control shrimp disease. However, shrimp diseases can be controlled using ecological techniques. These techniques, which are based on the innate immune response and the environmental stress response, significantly reduce the impact of shrimp diseases. The object of this review is to summarize the recent research on shrimp environmental adaptation mechanisms, innate immune response mechanisms, and the relationship between these systems. We also suggest some directions for future research.

1. Introduction

Crustaceans, including shrimp, are poikilothermic animals with open hemolymph systems [1]. In such animals, the hemolymph flows directly into the body cavity, and external substances, such as oxygen and ammonia, are extracted from the surrounding water via the gills [1]. Shrimp are affected by both biological and non-biological factors in the surrounding water. Biological factors include the diverse microorganisms present in natural water; some of these microorganisms are potentially pathogenic, infecting shrimp and causing disease under certain conditions. Non-biological factors include the complex and changeable physical parameters of the surrounding water, which directly affect shrimp physiological processes.

Shrimp, which are globally distributed, have evolved effective strategies to adapt to the multivariate aquatic environment. Organismal responses to non-biological factors are referred to as environmental adaptations. Although responses to biological factors are often considered part of organismal immunity, these responses also fall into the broader category of environmental adaptations. In aquatic systems, biological and non-biological factors regulate each other: physiochemical factors dictate the growth of various microorganismal populations, while the microorganismal populations affect non-biological aquatic factors, such as dissolved oxygen [2]. Therefore, it is not surprising that, in shrimp and other aquatic animals, the environmental stress and immune responses are closely related [3].

Recently, the global shrimp production capacity has exceeded four million tons per year. However, pathogens and environmental factors continue to plague the aquaculture industry. In this integrated review, we aim to assess and synthesize recent studies of environmental stress responses and innate immune responses in shrimp, and to discuss the relationship between these adaptations and shrimp diseases.

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2. Mechanisms of environmental stress adaptation in shrimp

The shell of shrimp acts as a physical barrier, protecting the shrimp from the external environment. And here, we focus on adaptations to non-physical environmental factors. Recently, some signaling pathways involved in the environmental stress response in shrimp have been identified. Among these, the unfolded protein response (UPR) pathway, which is induced by endoplasmic reticulum (ER) stress, has received the most systematic and in-depth study.

2.1. Composition of the shrimp UPR system

Most studies of the UPR and ER-stress studies have focused on mammals, especially humans. Little is known of the UPR system in invertebrates [4]. The UPRs of invertebrates and vertebrates differ significantly. For example, vertebrates generally have two *Cyclic AMP-dependent transcription factor 6* genes (*ATF6α* and *ATF6β*), while invertebrates have only one *ATF6* gene. In addition, two genes important to the UPR (*GADD34* and *CHOP*) are only found in vertebrates [5,6]. Although a recent transcriptional analysis of the *Litopenaeus vannamei* UPR system has provided a general framework for shrimp environmental adaptation mechanisms at the cellular level (Table 1), many of the details remain unclear [7]. Indeed, only a few dozen of the proteins differentially expressed in *L. vannamei* after UPR activation were homologous to vertebrate UPR proteins. Up to 90% of the 1800 unigenes differentially expressed in *L. vannamei* after UPR activation had unknown functions.

2.1.1. The [(inositol-requiring enzyme-1)-(X-box binding protein 1), IRE1-XBP1] signaling pathway

The IRE1-XBP1 signaling pathway is the most highly conserved in the UPR. This pathway is widely distributed in a variety of organisms, including yeast, fruit flies, and mammals [5,8,9]. In the resting state, the alkaline lysine structure domain (BRLZ) of the *XBP1* transcription factor gene encodes two peptides without transcriptionally activity. After ER-stress, the upstream non-folding protein recognition factor IRE1 dimerizes and self-phosphorylates, enhancing endonuclease activity. Then, IRE1 specifically detects the conserved CNG'CNGN motif in the *XBP1* precursor mRNA, and cuts off a particular intron [4]. Once the *XBP1* precursor mRNA is spliced, the two Open reading frames (ORFs) combine to encode an XBP1 with transcriptionally activity: XBP1s. XBP1s moves into the nucleus and initiates the transcription of downstream genes. It has also been reported that peptide encoded by the *XBP1* precursor mRNA has a role in XBP1s inhibition [10]. The key genes in the IRE1-XBP1 signaling pathway (*IRE1* and *XBP1*) have been cloned in shrimp [11]. To date, only a single *IRE1* gene has been identified in shrimp. This gene encodes a protein with relatively high identity to mammalian IRE1α (68%) and human IRE1β (60%).

Table 1
Key UPR genes of shrimp.

UPR gene	Spacise	Stress response	Function	Reference
Bip	*L. vannamei*	WSSV	unfolded or misfolded proteins recognize, WSSV attachment	[11,27]
XBP1	*L. vannamei*	DTT, heat shock	transcription factor	[11,22]
IRE1	*L. vannamei*	/	ER-strss sense, nucleic acid endonuclease	[11]
eIF2a	*L. vannamei*	WSSV	protein translation regulation	[13]
PERK	*L. vannamei*	/	posphorylated eIF2a	[13]
ATF6	*L. vannamei* *M. japonicus*	WSSV, Tm, Tg	ER-strss sense, transcription factor	[28]
ATF4	*L. vannamei*	WSSV	transcription factor	[22]
Calnexin	*M. japonicus*	*V. anguillarum*	chaperones innate immunity	[29]
Calreticulin	*L. vannamei*	osmotic stress	chaperones	[30]
HSP10	*L. vannamei* *P. monodon*	*V.parahaemolyticus*,WSSV, low/high pH challenge	chaperones	[31,32]
HSP21	*P. monodon* *F. chinensis*	WSSV	chaperones	[33,34]
HSP37	*M. rosenbergii*	IHHNV	chaperones	[35]
HSP40	*M. japonicus*	WSSV		[36]
HSP60	*P. monodon* *M.rosenbergii* *L. vannamei* *F.sbrasiffensis*	pH challenge, osmotic stress, heavy metal exposure, MrNV,WSSV, osmotic stress, *S. aureus*, *V. alginolyticus*	chaperones	[32,37–40]
HSP70	*E. carinicauda* *L. vannamei* *M. rosenbergii* *M.japonicus* *P. monodon* *F. brasiffensis* *F. chinensis*	WSSV, *V. anguillarum*, heat shock, ammonia, stocking density, oxidative Stress, metal exposure (Cd and Zn), MrNV, IHNNV, nitrite, osmotic pressure	chaperones	[37,40–49]
HSC70	*L. vannamei* *M. ensis* *F.chinensi*	heat shock, WSSV	chaperones, regulator in Vitellogenin	[50–53]
HSP90	*E. carinicauda* *M.rosenbergii* *F. chinensis* *M. japonicus* *P. monodon* *M. ensis*	WSSV, *V. anguillarum*, MrNV, pH and ammonia-N stresses	chaperones, regulator in Vitellogenin	[37,41,44,54–57]
PD1	*F. chinensis* *P. monodon*	*V. anguillarum*, WSSV	formation and isomerization of disulfide bridges, chaperone	[58,59]

Previously, we identified two *IRE1* isoforms in *L. vannamei* that differed at 42 base positions. The functional differences between these isoforms remain unknowns. The CNG'CNGN motif found in *L. vannamei XBP1* precursor mRNA has also been identified in other species. Interestingly, it was shown that although 75.6% of all *XBP1* precursor mRNAs were spliced at the predicted splicing site, the remaining 24.4% were spliced 6 bp before the predicted site [11]. However, both splice positions removed a 23 bp intron, and the encoded peptides were identical.

2.1.2. The [protein kinase RNA (PKR)-like ER kinase-eIF2α, PERK-eIF2α] signaling pathway

ER-stress is caused by an overabundance of newly-folded peptides in the cell, which leads to the aggregation of misfolded peptides in the ER lumen [4]. Therefore, ER-stress may be effectively alleviated by reducing the synthesis of new peptides. EIF2a is the component of protein translation initiation complex that, when phosphorylated, typically initiates protein translation. After ER-stress, PERK dimerizes and self-phosphorylates, phosphorylating eIF2a. When eIF2a is phosphorylated, the activity of the protein translation initiation complex is greatly reduced, decreasing protein synthesis and diminishing ER stress [4,6]. However, the mRNAs of some genes, including the UPR downstream transcription factor *ATF4*, have special structures in the 5′-untranslated regions (UTRs). These structures increase translation efficiency. Recently, the *PERK*, *eIF2a,* and *ATF4* genes in the shrimp PERK-eIF2a signaling pathway have been identified [11–13]. The proteins PERK and eIF2a from *L. vannamei* are highly homologous to proteins from other species, exhibiting conserved domain structures and distributions.

2.1.3. The ATF6 signaling pathway

The ATF6 signaling pathway is less well conserved than other pathways associated with the UPR. Indeed, this signaling pathway is absent in yeast. In addition, although the fruit fly genome encodes an ATF6 protein, there is no definitive evidence that this protein is involved in the ER-stress response in fruit flies [14]. Most vertebrates have two highly homologous *ATF6* genes: *ATF6α* and *ATF6β*. ATF6α is involved in the ER-stress response. The function of ATF6β is not clear, but some studies have suggested ATF6β may function similarly to ATF6α with weaker transcriptional activity [15]. Under ER-stress, the ATF6 protein in the ER becomes polymorphic, and is transferred from the ER to Golgi. In the Golgi, the proteases site 1 protease (S1P) and S2P cleave ATF6 at specific sites [4]. Next, the amino terminals of the spliced ATF6 proteins move into the nucleus and regulate the transcription of downstream effectors. To date, only a single *ATF6* gene has been cloned from *L. vannamei*. *L. vannamei* ATF6 is slightly more similar to human ATF6α than to ATF6β [12]. A previous study, which treated 293T cells over-expressing *L. vannamei* ATF6 with known UPR activators, showed that *L. vannamei* ATF6 was transferred from cytoplasm to nucleus after thapsigargin treatment. This indicated that, in *L. vannamei,* the ATF6 signaling pathway was involved in the ER-stress response, and should therefore be considered part of the UPR [12]. *S2P* and *S1P* gene fragments have also been identified in *L. vannamei*, providing additional evidence that the ATF6 signaling pathway is present in shrimp.

The UPR relieved ER-stress via downstream effectors, including heat shock protein (HSP), protein disulfide isomerase (PDI), glycosyltransferase, and protease. Signaling transduction molecules link the upstream unfolded protein signaling recognition molecules and the downstream effector genes. In the UPR, this role is played by the BRLZ domain transcription factors, including XBP1, ATF4, and ATF6 [6]. These molecules receive upstream signals and bind to the transcription factor binding elements (e.g., ATF/CREN AP1, ESRE-I, ESRE-II, MARESP-1 and TRE) in the promoters of the target genes to regulate transcription. Although a given transcription factor may strongly affect a given binding element, there is no strict specific correspondence between these transcription factors and their binding sites. Some proteins involved in the shrimp UPR have already been cloned, and additional proteins may be identified through transcriptome analyses. For example, we previously identified 87 novel genes encoding heat shock proteins in *L. vannamei* [7]. This large number of genes may explain why shrimp are highly adaptable to environmental stress. It is believed that, once the shrimp genome has been fully sequenced, additional proteins associated with the UPR will be identified. In addition to the UPR, ER-stress also activates the ER-related protein degradation (ERAD) pathway, the calcium signaling pathway, and other signaling pathways, including the MAPK signaling pathway [16–18]. Although studies of the MAPK signaling pathway in shrimp are available, these studies have focused on the immune functions of this pathway; its roles in the environmental stress response remains unknown [19–21]. The shrimp ERAD and calcium signaling pathways have not yet been investigated.

2.2. The function of the shrimp UPR

The UPR is key to the ER-stress response in invertebrates. In addition, the UPR plays an important role in the response to environmental stress in shrimp (Table 1). In *L. vannamei*, the IRE1-XBP1 pathway is activated in response to DTT treatment, thermal stress, and WSSV infection [11,13]. When *L. vannamei* is subjected to these types of stress, the *XBP1* precursor mRNA is spliced by IRE1 [22]. The ATF6 signaling pathway was shown to be activated both by Thapsigargin and by dsLvBip injection [12]. n both cases, *L. vannamei* ATF6 was over-expressed in 293T cells, ATF6 was then spliced and transferred from the cytoplasm to the nucleus. These results suggested that the ATF6 signaling pathway is part of the shrimp UPR as well as the, shrimp ER-stress response. Few studies of the shrimp PERK-eIF2a pathway are available. To date, it has only been shown that this signaling pathway is activated by WSSV infection [13]. Several transcriptome analyses of shrimp under stress conditions have shown that the UPR is important to the environmental stress response of shrimp. For example, the genes *XBP1s*, *ATFβ,* and *IRE1,* which are associated with the UPR, were upregulated after exposure to ammonia nitrogen [23]; while the *MnSOD* and *PDI* were significantly differentially expressed in response to hypoxia. In addition, UPR effectors, including *calreticulin*, *HSP70,* and *HSC70-5,* were upregulated after WSSV infection [24–26].

2.3. Other environmental response systems in shrimp

2.3.1. The redox state regulation system in shrimp

The normal physiological activities of multicellular organisms require a relatively stable internal redox state. However, various external factors, such as mycotoxin and heavy metal stress, may lead to an internal redox state imbalance, possibly even inducing oxidative stress. Oxidative stress produces reactive oxygen species (ROS) and reactive nitrogen species (RNS) that damage DNA and proteins, inhibiting normal cellular function. Organisms have thus developed a variety of strategies to eliminate such damage. Strategies to eliminate ROS and RNS typically include upstream signaling recognition and signaling transduction molecules, as well as downstream enzymes, including superoxide dismutase (SOD) and glutathione reductase (GR), which eliminate ROS/RNS. Several enzymes related to redox reactions have been studied in shrimp, with SOD being the most well investigated (Table 2). In shrimp, MnSOD and Cu/ZnSOD have been described; FeSOD had not yet been identified [60,61]. These SODs have recently been shown to play a role in the removal of ROS/NOS in shrimp, and to be associated with a reduction in oxidative stress [62]. Adaptations to stress have also been shown to enhance disease resistance in shrimp. For example, Cu/ZnSOD (GenBank accession number: HM371157) is associated with resistance to WSSV and *Vibriones* [63]. Physiologically, maintenance of the redox environment *in vivo* depends on the reduced glutathione (GSH)-oxidized glutathione (GSSG) cycle. GSH contains an active sulfhydryl (SH), which is easily oxidized and dehydrogenated. SH is an important scavenger of free radicals *in vivo*. For example, when

Table 2
Redox state regulation enzymes in shrimp.

Species	Enzymatic	Stress response	Reference
L. vannamei	CMnSOD, MnSOD, CZSOD	Cd exposure, thermal stress, *V. alginolyticus*, WSSV, hypoxia, P-glucan	[70–77]
M. nipponense	mtMnSOD, CZSOD	*A. hydrophila*	[78–80]
C. quadricarinatus	CuZnSOD, cMnSOD	*S. eriocheiris*, *A. hydrophila,* WSSV	[81,82]
M. japonicus	CZSOD, CMnSOD, mtMnSOD	WSSV, *V. penaeicida*, *V. alginolyticus*	[83,84]
P. clarkii	cMnSOD	/	[85]
F. chinensis	MnSOD	WSSV	[86]
M. rosenbergii	mtMnSOD, CZSOD, cMnSOD	Lactococcus garvieae	[87–89]
P. monodon	GSH-px1, GSH-px7	osmotic stress, heavy metal exposure, bacterial infection	[90]
E. carinicauda	GSH-px	*V. anguillarum*, WSSV	[91]
P. clarkii	GSH-px	*V. harveyi*, *S. aureus*, WSSV	[92]
L. vannamei	GSH-px	pH stress, Cd exposure, *V. alginolyticus*	[66,93]
M. ensis	GSH-px	oxidative stress	[94]
M.rosenbergii	GSH-px	/	[95]
F. chinensis	GSH-px	*V. anguillarum*	[96]
P. pugio	GSH-px	fipronil, endosulfan, Cd	[97]
P. monodon	Thioredoxin	/	[98–100]
L. vannamei	Thioredoxin	WSSV, hypoxia	[101,102]
F. chinensis	Thioredoxin	WSSV	[103]
E. carinicauda	Thioredoxin	/	[91]
F. chinensis	Thioredoxin	*V. anguillarum*	[96]
L. vannamei	Peroxidase	WSSV	[104]
P. monodon	Catalase	pH stress	[105]
M. japonicus	Catalase	*V. anguillarum*	[106]
E. carinicauda	Catalase	low salinity stress	[107]
L. vannamei	Catalase	hypoxia, pH stress, *Microcystis aeruginosa*	[108–110]
M. rosenbergii	Catalase	infectious hypodermal and haematopoietic necrosis *virus*	[111]
M. japonicus	NADPH oxidase	*V. penaeicida*, poly(I:C)	[112]
Palinuridae argus	P-450	/	[113]
Astacus astacus	P-450	/	[114]
M. japonicus	Aldehyde oxidase	*V. penaeicida*	[115]

cells produce small amounts of H_2O_2, GSH is reduced to H_2O by glutathione peroxidase (GSH-Px), which self-oxidizes to GSSG. GSSG is reduced to GSH by GR, sustaining the scavenging of free radicals *in vivo* [64]. Shrimp GR and GSH-Px stabilize the redox environment by maintaining the GSH-GSSG cycle *in vivo*. Indeed, glutathione supplementation in shrimp feed reduced antioxidant in *L. vannamei* [65]. Several enzymes, including oxygen and sulfur protein, peroxidase, and catalase, also have been studied in shrimp [66–68].

Although antioxidation in shrimp has been well studied, additional questions remain. For example, the appropriate ROS level required for normal immune function in shrimp is unknown. This is important because superfluous ROS damage the shrimp body. In addition, the mechanisms that maintain balanced ROS production are also unknown. Because the nuclear factor erythroid 2-related factor 2 (NRF2)-Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1 (Keap1) signaling pathway in eukaryotic cells stabilizes the regulation of redox state regulation *in vivo*, we suggest that the NRF2-Keap1 pathway may play an important role in maintaining the redox state in *L. vannamei* [69]. Yet this pathway in shrimp has yet to be investigated. An understanding of the NRF2-Keap1 pathway may be necessary in order to better clarify the mechanisms underlying redox stability in shrimp.

2.3.2. Heavy metal detoxification system of shrimp

Heavy metals are common stressors of shrimp. In shrimp, studies of the effects of heavy metals contamination and the mechanisms of heavy metal resistance have primarily focused on metallothionein (MT). MT is a metal-binding protein rich in cysteine; the sulfhydryl group of MT strongly chelates toxic metals and expels them from the body [116]. It has been shown that cloned *MT* genes play a role in copper detoxification [117]; while MT expression in *L. vannamei* was induced by both calcium and zinc exposures [118]. The mechanisms underlying the expression of *MT* genes have also been investigated: Tian et al. cloned the promoter region of the *Penaeus chinensis MT* gene, and investigated its regulatory activity [119]; *MT* has also been used as a target gene for the selection of stress resistant species [120]. In addition, MT is a strong antioxidant and is an effective scavenger of free radicals. Indeed, MT is a better scavenger of free radicals (·OH) than either SOD or GSH [121]. The relationship between MT and antioxidant stress reduction is presently under investigation [122].

3. The innate immune system in shrimp

Generally speaking, shrimp innate immune system made up of humoral immunes response and cellular immune resposne. And TLR/IMD−NF−κB signaling pathway, JAK-STAT signaling pathway and RNAi signaling pathway are the mainly signaling pathways contribute to shrimp humoral immunes response.

Similar to *D. melanogaster*, the TLR signaling pathway in shrimp is triggered by the extracellular cytokine Spaetzle (Spz), which circulates in bodily fluids and may be spliced upon the induction of foreign microorganisms [123]. The spliced Spz binds to the extracellular region of TLR and alters the conformation of the intracellular region of TLR to recruit MyD88, Tube, and Pelle [124]. Pelle may play a role hydrolase activation and Cactus degradation; Cactus inhibits NF-κB. After Cactus degradation, the NF-κB transcription factor moves into the nucleus and participates in the regulation of antibacterial peptide genes, such as *Penaeus* [123]. However, at least two aspects of the shrimp TLR−NF−κB signaling pathway require further clarification. First, it is unclear how the signaling upstream of the TLR signaling pathway is triggered and transduced. Second, the functional differences among the various TLRs are unknown. With respect to the first question, a number of pathogen-pattern recognition (PPR) molecules, such as lipopolysaccharides and β-1, 3-glucan binding protein (LGBP), have already been identified in shrimp [125]. In addition, more than four *Spz* genes have been identified in *L. vannamei*. However, homologs of several proteins in the *Drosophila* TLR signaling pathway members have not yet been described in shrimp, and only a few novel proteins have been described in the shrimp TLR signaling pathway. Thus, the mechanisms underlying upstream triggers remain unknown. With respect to the second question, the immune functions of several TLRs genes have been studied in shrimp [123,126,127]. It has been shown that *L. vannamei* possesses at least 11 TLRs of unclear function. In comparison, *D. melanogaster* possesses nine TLRs, and one is involved in the immune response.

The composition of the TLR/IMD−NF−κB signaling pathway in shrimp is generally consistent with that of *D. melanogaster* [128,129]. In *D. melanogaster* and other invertebrates, the IMD−NF−κB signaling pathway has various antiviral functions. In shrimp, WSSV infection activates the Relish protein, which affects WSSV gene replication [130]. In contrast to *D. melanogaster*, the IMD−NF−κB and the TLR signaling pathways in shrimp do not seem to be specific for gram-positive and -negative bacteria. In shrimp, the functions of these signaling pathways overlap [131,132].

In shrimp, key members of the JAK-STAT signaling pathway, including JAK, STAT, domeless, and SOCS2, have been studied. It has been shown that the intracellular signal transduction of the JAK-STAT pathway is relatively well conserved across invertebrates [133–136]. However, the JAK-STAT signaling pathway in shrimp differs from that of *Drosophila* in several ways. First, shrimp domeless recognizes different upstream molecules than *Drosophila* domeless: in the *Drosophila* JAK-STAT signaling pathway, domeless recognizes upd1, upd2 and upd3, but homologs of these genes have not been identified in shrimp. Indeed, *L. vannamei* domeless binds lectin and the IFN-like protein Vagos [137]. ② In addition, the JAK-STAT signaling pathway is involved in the transcriptional regulation of the *AMP* genes in shrimp, but not in *Drosophila.* In *P. japonicus,* lectin CTL is associated with the transcriptional regulation of the genes *ALF-A1* (KU213607), *ALF-C1* (KU213608), *ALF-C2* (KU160498), *ALF-D1* (KU160499), *Cru 1* (KU160502), and *Cru I-5* (KU213606) via STAT, but this association has not been reported in *Drosophila* [138,139]. Finally, the JAK-STAT signaling pathway has antibacterial activity in shrimp, while the *Drosophila* JAK-STAT signaling pathway acts as an antiviral. As the JAK-STAT signaling pathway in shrimp regulates the transcription of *AMP* genes, this pathway has both antiviral and antibacterial functions. Indeed, the JAK-STAT signaling pathway was associated with resistance to *Vibrio anguillarum* function [139,140].

The JAK-STAT signaling pathway in shrimp may also be regulated by miRNAs. In *P. clarkii*, miR-9041 and miR-9850 inhibited the expression of STAT in the gill, increasing WSSV replication; WSSV miRNA also inhibited the expression of host STAT or JAK [141,142]. It is debated whether the JAK-STAT signaling pathway benefits WSSV infection. Studies by different research teams obtained different results, even using the same species of shrimp. Further clarification is needed to determine whether these differences were due to different experimental methods, individual differences among shrimp, or distinct viral strains.

Shrimp at least have two Dicer proteins: Dicer 1 and Dicer 2, and their are associated with the miRNA and siRNA signaling pathways, respectively [143]. Here, we focus on the siRNA signaling pathway, which is important to shrimp innate immune response. In *L. vannamei,* dsRNA induced an antiviral immune response [144]. Wu et al. used RNAi technology based on shrimp siRNA to demonstrate that the WSSV *thymidylate kinase gene* (*tk-tmk*) effectively inhibited WSSV [145]. It was later shown that the non-specific antiviral effects of dsRNA in shrimp were correlated with ~200–600 bp dsRNAs, and that these non-specific antiviral functions and the RNAi effects were realized through the same pathway [144,146]. Dicer2 in the shrimp RNAi signaling pathway has been shown to play an anti-WSSV role via the regulation of the interferon-like factor Vagos [137,143]. In addition to the above signaling pathways, the MAPK, scavenger receptor, Wnt, and Jun signaling pathways are also involved in shrimp humoral immunity [19,147–149].

Cellular immune resposne is another important part of shrimp innate immunity. *L. vannamei* lymphocytes usually contain three types of hemocytes: transparent cells, semi-granular cells, and granulosa cells [150]. The transparent cells mainly participate in hemolymph coagulation, while the granulosa cells and semi-granular cells play corresponding roles through the cell phagocytosis and phenoloxidase cascade systems [150,151]. The activation of the cellular immune response depends on upstream pattern recognition receptors (PRRs), including β-1, 3-glucan binding protein, and lipopolysaccharide binding protein [152,153]. PRRs interact with and activate hemocytes. Once activated, hemocytes immediately initiate several types of immune responses. In crustaceans, the phenoloxidase prophenoloxidase (proPO) cascade is the most well-studied [154]. In shrimp, prophenoloxidase activating enzyme (PPAE) is activated by pathogenic infections or *in vitro* physical and chemical damage. PPAE then activates prophenoloxidase (PPO) and phenol oxidase (PO); this process is known as the proPO cascade [155,156]. The activation of PO eventually catalyzes the production of cytotoxic intermediates, including melanin, ROS, and quinones, which are deposited around invasive pathogens or other foreign bodies. This processes leads to blackening, hardening, enhanced wound healing, and increased immune protection. The proPO cascade mainly includes PRPs, proPO, PPAE, the regulator of the proPO system, and other related factors. Three PRRs are associated with the proPO cascade in shrimp: β-1, 3-glucan-binding protein-lipoprotein (βGBP-HDL), C-Lectin and lipopolysaccharide glucan binding protein 3 (LGBP3). Three shrimp proPOs have also been identified [125,157,158]. Hemolymph coagulation is also closely related to the proPO cascade reaction. Hemolymph coagulation is mediated by the shrimp clotting mechanisms, which not only prevents the loss of hemolymph from wounds but also inhibits invading microorganisms [159]. Indeed, components of the shrimp clotting system might also be involved in some immune defense processes [160,161]. In addition to the proPO cascade reaction, shrimp cellular immune reactions include the respiratory burst (RBB) and encapsulation [162]. RBB uses large amounts of oxygen to activate bodily enzymes, leading to the production of high concentrations of superoxide anions and a variety of reactive oxygen intermediates. These are used to kill bacteria. Encapsulation is used to deal with large invaders, including parasitic organisms, protists, and nematodes. In this process, a multilayer capsule is formed around the intruder. Subsequently, intravasal invaders are poisoned or suffocated by the ROS and RNS in the shrimp lumen [150]. It is thus clear that ROS play an important role in the shrimp cellular immune response. In addition, both granular and semi-granular cells of shrimp have phagocytic effects; these cells can directly engulf and kill pathogenic microorganisms [162,163].

4. Influences of environmental stress on the shrimp innate immune response

4.1. Influences of environmental stress on shrimp immunity

The influence of environmental stress on the macroscopic indices of physiological state and immune response have been well studied. In general, strong or enduring environmental stressors negatively impact shrimp innate immune function, and different environmental factors have slightly different effects on shrimp innate immunity. The intestinal cell wall is the first line of defense to foreign matter invasion in *L. vannamei*. The efficacy of the intestinal wall depends on the integrity of the cellular wall structure, the composition of the intestinal microbes, and the immune components in the intestinal mucus. However, ammonia-nitrogen exposure destroys the intestinal mucosa and disturbs the composition of intestinal microorganism, reducing intestinal immune function in *L. vannamei* [164]. The pH of cultured water is closely related to total hemocytes count (THC) and total hemocyte pPO in *Fenneropenaeus indicus* [165]. In *L. vannamei* subjected to cold stress (12 °C), plasma RB activity, malondialdehyde (MDA) level, and hemocyte DNA damage level increased significantly, while plasma THC, total protein content, and osmotic pressure decreased [166]. Salinity alterations within a certain range (22‰–14‰) did not affect *L. vannamei* THC, but significantly decreased pO activity in increased WSSV replication [167]. It has been shown that water pH, temperature, and other physical and chemical factors weaken the immune system of *Penaeus penaeus*. However, some studies have shown that environmental stress of the appropriate intensity may induce immune-like effects in shrimp, conferring a certain degree of protection. It also been reported that in *L. vannamei,* heat stress (33 °C) during the early stages of WSSV infection effectively increased WSSV resistance and reduced cumulative shrimp mortality [168]. Indeed, cold shock as well as heat shock reduced the cumulative mortality of the shrimp infected with WSSV [169]. In addition, injection with β-glucan increased ROS and caused oxidative stress, but significantly reduced WSSV copy number in WSSV-infected shrimp; however, the cumulative mortality rate of the infected shrimp remained higher than that of the control group [170].

4.2. Environmental stress-modified shrimp innate immune signaling pathways

Transcriptomic and proteomics studies in *L. vannamei* have shown that some genes in the humoral immune signaling pathway were differentially expressed in response to environmental stress. Thus, environmental stressors may both directly and indirectly affect the humoral immune signaling pathways. The genes differentially expressed in response to environmental stress were associated with various signaling pathways, primarily including the TLR/IMD−NF−κB, JAK-STAT, MAPK, and Wnt signaling pathways [21,129,131,133,143]. Most of the differentially expressed genes (DEGs) were found in the TLR/IMD−NF−κB signaling pathway, including antimicrobial peptide, *Spz*, and peptidoglycan binding protein. Molecular ammonia is highly toxic to shrimp, and constitutes the most harmful type of stress for cultured shrimp. A previous study identified 12 DEGs in the hepatopancreas after acute ammonia-nitrogen stress; these genes included *Pellino*, *Crustin*, *alpha-2-macroglobulin*, *Penaeidin-2a,* and *Penaeidin-4a,* all of which are members of the TLR/IMD−NF−κB signaling pathway [23]. A transcriptomic study of *L. vannamei*, hemocytes found that *TRAF6* and other immune genes were significantly differentially expressed under ammonia-nitrogen stress [171]. These results indicate that ammonia-nitrogen stress significantly affects the TLR/IMD-κB signaling pathway in shrimp.

Under osmotic (hypotonic) stress, both the TLR/IMD−NF−κB and the MAPK signaling pathways were enriched in *L. vannamei* hemocytes. Osmotic stress also affects the phagocytic activity of *L. vannamei* cells and increases the cellular immune response associated with ROS [172]. In addition, a proteomics analysis showed that, although hypoxia stress did not specifically activate an immune signaling pathway, it affected the expression of some immune factors, including *ferritin*, *carboxypeptidase A2*, and the zinc proteinase *Mpc1* [173]. Repeated hypoxic exposure significantly affected the expression of several immune factors, including *chitinase Beta-1, 3-glucan binding protein, hemocyanin,* and *lectin* in the hepatopancreas [174].

To investigate the types of environmental stresses that induce ER-stress and activate the UPR, we analyzed the transcriptomes of *L. vannamei* hemocytes after artificial UPR activation. We found that more than 16 immune factors or genes associated with immune signaling pathways were dramatically differentially expressed [7]. Of these DEGs, six immune factors were encoded by genes downstream of the TLR/IMD−NF−κB signaling pathway, while others belonged to the Wnt signaling pathway. Surprisingly, the expression of *Dcier2*, *Ago2,* and *SID1* in the RNAi signaling pathway were also significantly upregulated. JAK-STAT signaling pathway is involved with the environmental stress response as well as antiviral immunity. Yet recent shrimp studies have only focused on the role of the JAK-STAT pathway in disease resistance and the immune response. Whether the JAK-STAT pathway is involved in the environmental stress response remains unknown [175].

It is thus clear that environmental stress affects both the humoral immune response and the cellular immune response in shrimp. However, two important difficulties remain to be addressed. First, most studies focus on determining the expression level of stress-induced immune factors, without examining the intermediate process. Second, the influences of environmental stress on immune signaling pathways are often complicated and difficult to disentangle. Although specific types of environmental stress may seem to have significant effects on specific immune signaling pathways, environmental stress always effects multiple immune-related signaling pathways simultaneously. It is therefore difficult to predict the overall impact of various environmental stressors on innate immunity in shrimp.

5. The impacts of environmental stress on WSS in cultured shrimp

The effects of environmental factors on viral infection in shrimp were detected since 90's of 20th century. Li et al. finded that ammonia nitrogen, nitrite nitrogen and salinity of aquatic water had effects on shrimp monodon baculovirus (MBV) infection in *P. monodon* [176]. Later, WSSV replaced MBV, as the most harmful virus to Shrimp. Since WSS first outbreak in 1992, it caused serious losses to cultured shrimp every year. At present, shrimp carrying WSSV in shrimp farms is still common. Both in production practice and laboratory research, it has been proved that shrimp WSS is closely related to environmental stress [177–179], and its mechanism was gradually revealed in recent years (Fig. 1).

5.1. Environmental stress effects WSSV infection

To clarify the mechanisms of environmentally-induced WSS **i**n shrimp, the effects of various types of environmental stressors on WSSV infection have been studied. It has been shown that HSP70 transcription increased significantly under heat stress (32 °C), and that stressed shrimp used RNAi to reduce *HSP70* expression; the shrimp were more susceptible to WSSV than the control group at the same temperature [26]. Previously, we showed that appropriately increasing or reducing the water temperature enhanced the resistance of *L. vannamei* to WSSV; WSSV replication in shrimp cultured at 32 °C or 22 °C was slower than in shrimp cultured at 28 °C [25]. Molecular ammonia nitrogen is highly toxic to shrimp. WSSV copies in the hepatopancreas, hemolymph, and swimming feet of shrimp exposed to ammonia nitrogen were significantly more abundant than in control shrimp [180]. Increased osmotic pressure (35 g/L to 50 g/L, 35 g/L, or 20 g/L) increased WSSV susceptibility; WSSV susceptibility also increased when salinity was altered to 10 g/L, 7 g/L, or 5 g/L [181]. Thus, osmotic stress weakened the ability of shrimp to resist WSSV infection. Osmotic stress also increased WSSV susceptibility *Fenneropenaeus chinensis*: WSSV copy numbers increased two fold as compared to the control group [182]. The ROS produced by oxidative stress inhibit WSSV replication in shrimp. However, excess ROS are harmful to shrimp: it was shown that, although WSSV copy numbers were lower in shrimp under oxidative stress, cumulative mortality remained higher than the control shrimp [183–185]. It has also been reported that shrimps are more susceptible to WSSV under hypoxic conditions, possibly because fewer ROS are produced under anoxic conditions [186]. Thus, most environmental stressors reduce WSSV resistance in shrimp.

5.2. Interaction between the UPR and WSSV infection in shrimp

Several recent studies have focused on the molecular mechanisms underlying the induction of WSS by environmental stress. Some progress has been made towards the characterization of the UPR and environmental stress response.

5.2.1. UPR BRLZ transcription factors are involved in the regulation of WSSV gene transcription

It has been shown that WSSV activates the PERK-ATF4 signaling pathway and IRE1-ASK1-JNK signaling pathway, promoting WSSV replication [11,13]. Previously, we analyzed the WSSV genome and found that promoter regions of several WSSV genes carried UPR BRLZ transcription factors binding sites. Indeed, the *L. vannamei* UPR BRLZ transcription factors XBP1 and ATFβ were involved in the transcriptional regulation of WSSV genes *wsv023/wsv069*, *wsv083,* and *wsv059/wsv166*, respectively. When these WSSV genes were knocked down, both WSSV copy numbers in shrimp muscles and cumulative shrimp mortality decreased significantly. Indeed, the WSSV early gene *wsv023* is regulated by ATF4, which encodes a protein similar to that of host γ-tubulin complex associated protein 3 (GCP3). The interaction between ATF4 and the γ-tubulin complex associated protein 2 (GCP2) inhibits the formation of microtubules in host cells and promotes viral infection via unknown mechanisms [187]. Moreover, the ATF6 signaling pathway in shrimp is activated by WSSV infection, and shrimp ATF6α is associated with the transcriptional regulation of five WSSV genes: *wsv083*, *wsv129*, *wsv222*, *wsv249,* and *wsv343* [28].

5.2.2. WSSV infection causes cellular apoptosis via the UPR

Cellular apoptosis induced by acute WSSV infection is mediated by the PERK-ATF4 and IRE1-ASK1-JNK signaling pathways in the hemocytes of *L. vannamei* [125,188]. When the key genes of UPR-mediated apoptosis, activation of apoptosis signal-regulating kinase 1 (ASK1) [125] and ER oxidoreductin 1-α (ERO1-α) [188] were reduced in

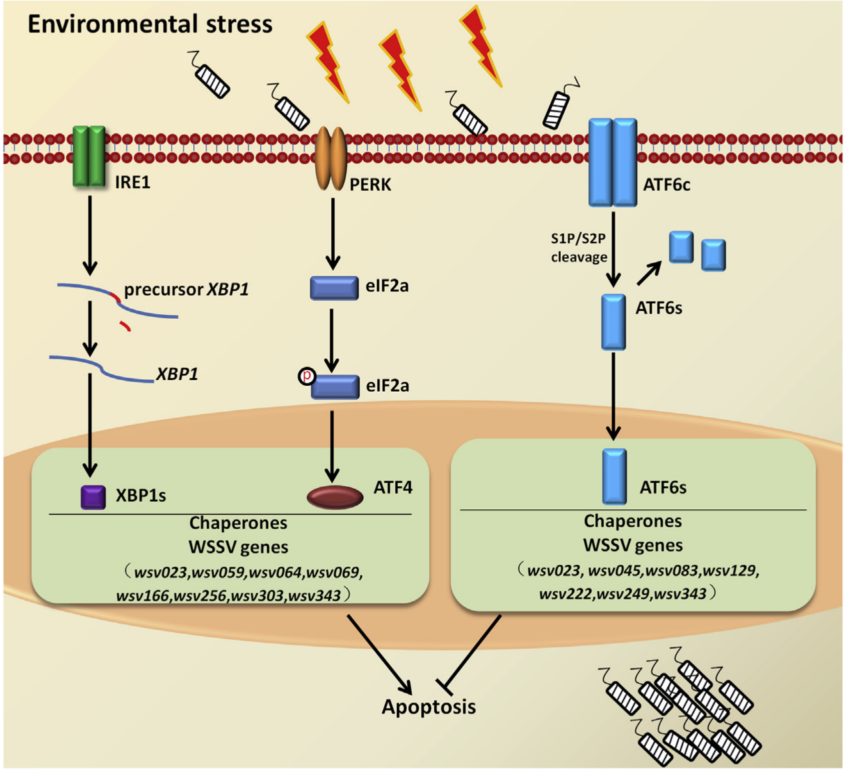

Fig. 1. Illustration of relationship between L. vannamei UPR system and WSSV infection.

WSSV-infected hemocytes using RNAi, apoptosis and cumulative mortality decreased significantly in *L.* vannamei. In addition, the artificial activation of the *L. vannamei* UPR caused the hemocyte apoptosis as well as shrimp death. Thus, persistent ER-stress may induce UPR-mediated apoptosis, while the PERK-ATF4 and IRE1-ASK1-JNK signaling pathways may increase WSSV-related mortalities in *L. vannamei* [188,189].

In contrast, the hemocyte apoptosis rate in shrimp infected with WSSV increased significantly after *ATF6α* knockdown [28]. In *ATF6α* knockdown shrimp, real-time RT-PCR showed that both *ASK1* and *c-Jun* in the ASK1-JNK signaling pathway were upregulated, suggesting that ATF6α might reduce WSSV-induced hemocyte apoptosis by inhibiting the ASK1-JNK signaling pathway. The shrimp *ATF6α* promoter possesses three c-Jun binding sites, and ASK1, JNK, and c-Jun expression significantly increases the *ATF6α* promoter activity. WSSV infection also activates the ASK1-JNK pathway, upregulating *c-Jun*. Thus, the WSSV-activated ASK1-JNK apoptosis signaling pathway may upregulate *ATF6α* via c-Jun. c-Jun may also inhibit the ASK1-JNK signaling pathway and reduce WSSV-induced hemocyte apoptosis via a negative feedback loop. However, these results are incongruent with previous studies of the PERK-ATF4 and IRE1-ASK1-JNK signaling pathways. In addition to these UPR-associated signaling pathways, the ATF6 signaling pathway also enhances WSSV infection in *L. vannamei* and *P. japonicus* [11–13,28]. This enhancement may be related to the timing of the activation of these three signaling pathways, but this speculation requires further study.

WSSV infection also upregulated of *Macrobrachium rosenbergii* calreticulin (MrCRT), an important factor in the UPR, and the MrCRT-gC1qR complex inhibited WSSV-induced apoptosis [190].

5.2.3. Roles of protein chaperones in WSSV infection

CRT expression is significantly upregulated during the early stages of WSSV infection; CRT interacts separately with the viral proteins VP15 and VP28. The interaction between CRT and VP15 increases WSSV replication. CRT acts as a molecular chaperone for VP28, leading to the formation of the VP28-VP26 dimer; this dimer promotes the assembly of viral particles [191]. It has recently been reported that the Bip protein is localized on the cell membrane of *L. vannamei* and acts as a receptor for WSSV [27].

In contrast, other studies have shown that some molecular chaperones increase WSSV resistance in shrimp. For example, at higher water temperatures (32°C-34 °C), the WSS breakout rate was lower than that at 28 °C. In addition, the cumulative mortality of shrimp during the early stages of WSSV infection was lower than that of the control group at 32 °C [192]. Thus, the shrimp response to temperature stress may also act against WSSV. In fact, both heat shock and cold shock increased WSSV resistance [25]. It was subsequently shown that, at 32 °C, the expression of NAD-dependent aldehyde dehydrogenase (ALDH) and HSP70 in *L. vannamei* were upregulated, suggesting that these two proteins inhibited WSSV replication at high temperatures (32°C-34 °C) [26].

Another heat shock protein, LvHSC70-5 from *L. vannamei*, also plays a role in WSSV resistance. However, both the cumulative mortality of WSSV-infected *L. vannamei* and the number of WSSV copies in the muscles of *LvHSC70-5* knockdown *L. vannamei* were significantly higher than the control group, indicating that LvHSC70-5 increased host tolerance of WSSV [25]. Indeed, flow cytometry analysis indicated that LvHSC70–5 may increase WSSV tolerance by reducing the formation of protein aggregates in the cells [25].

Luo et al. found that the WSSV proteins IE1 and VP28 were almost undetectable at 32 °C, but two proteins involved in the UPR were significantly upregulated [26]. Thus, it is possible that temperature stress activates the UPR PERK-eIF2a signaling pathway, inhibiting the translation of most proteins (including WSSV proteins), and inhibiting WSSV proliferation to some extent.

However, additional problems remain in this area of study. First, studies of the environmental stress mechanisms affecting WSSV infection have mainly focused on the transcriptional regulation of WSSV genes. Thus, the mechanisms regulating WSSV protein synthesis, viral particles assembly, and viral envelope formation require additional intensive study. Second, the roles of innate immunity and substance metabolism during WSSV infection under environmental stress remain unclear. Third, the threshold of environmental stress response favoring WSSV or favoring the host must be determined. Answers to these questions will help us to better understand the relationship between environmental stress and WSSV infection.

6. Further research

Several fruitful areas of study remain to be addressed with respect to the environmental adaptation mechanisms of shrimp. In terms of scientific and basic research, more systematic in-depth research of shrimp environmental adaptation mechanisms is required. Recent studies of the environmental adaptation mechanism of shrimp have primarily focused on gene function. Such studies are useful and necessary in order to understand the environmental adaptation mechanisms of shrimp. However, the macroscopic effects and control logic of this interlocking web of pathways and systems remain unclear. Environmental adaptability is one macroscopic effect of this network. Therefore, once enough genes related to environmental adaptation have been identified, future research should focus on the relationships among the relevant signaling pathways and systems.

Genes known to be associated with environmental adaptation or molecular markers associated with stress resistance should be used to breed stress resistant shrimp varieties. Breeding shrimp varieties with strong stress resistance is an effective way to reduce the impact of disease on the shrimp-farming industry. However, first it is necessary to identify these key genes or molecular markers. A previous study showed that a single nucleotide polymorphism in the Hsp70 gene in *L. vannamei* was associated with WSSV susceptibility and post-infection mortality [193]. Although several molecular markers have been described in shrimp, most of these are related to immunity. Only a few markers associated with environmental adaptation have been identified. Such genes require identification and further study.

The ecological control of shrimp diseases should be further improved. The ecological control of shrimp diseases has been shown to be effective in practice and has been widely used. This technique is mainly based on ecological control theory applied to aquaculture water. Once the environmental adaptation mechanisms in shrimp have been characterized, these can be used to augment ecological practices to increase efficacy.

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Appendix A. Supplementary data

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