Review

The White Spot Syndrome Virus: Emerging Savior or Killer of Crustaceans' Future Generations?

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The White Spot Syndrome Virus: Emerging Savior or Killer of Crustaceans' Future Generations?

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Abstract

Emerging viruses pose enormous challenge to humanity. The sole member of the *Nimaviridae* family, in the genus *whispovirus*, the white spot syndrome virus, has spread to all around the world, and its infection cycle devastated shrimp aquaculture, menacing significatively the world market of food production. The comprehension of the mechanisms and factors involved in the emergence of novel viruses allow us to prevent and control the surge of new virus, and consequentially benefit the humanity, wherever avoiding human or animal disease acquisition, and particularly, to preserve food production from shrimp farming.

Keywords: white spot syndrome virus; crustacean; shrimp; environment; endogenous virus

Introduction

Nutrient production is an essential activity of modern civilization that aims to constantly maintain food security, as defined by the World Food Summit in 1996 [1]. Marine aquaculture systems have an important role in the global food supply chain [2], and demands extraordinary care to be protected from a variety of adverse factors, including infection and diseases by harmful microbial agents, mainly expressed in confined and altered environments as it happens in farming of aquatic metazoa organisms [3]. Particularly referring to shrimp farming, a viral disease erupted in 1992-1993, in Asia, devastating marine shrimp production in captivity [4,5], rapidly expanding to other continents, imposing surmount economic losses in various countries dedicated to high density shrimp farming [5,6].

According to Santos et al. (2013), a crustaceans' disease etiologically linked to the White Spot Syndrome Virus (WSSV) has impacted the global economy, mainly on shrimp farming, with a loss of one billion dollar by year [7]. In Brazil, the initial reports of the WSSV infection of farming shrimps, *Litopenaeus vanamei*, was reported in 2005, causing huge impact in the local economy, in the Laguna area of Santa Catarina State, with shrimp mortality reaching 80 %, and loosing approximately 3 million dollars at that time. Also, other Brazilian regions, in the coastal northeast, representing the most productive areas of shrimps in captivity, were also heavily affected [8].

The etiological agent of the White Spot Syndrome was initially misunderstood as a baculovirus, as it is encompassed in the group of "the nuclear arthropod large DNA viruses" [9–11]. The WSSV is presently classified by the International Committee on Taxonomy of Viruses as a member of the *Nimarividae* family, genus *Whispovirus*, considered to be the largest virion infecting the animal phyla [11]. The virus isolation was firstly reported by Inouye et al. (1994) from, kuruma shrimp, *Penaeus japonicus*, in 1993, from farm ponds in western Japan [4], even though, the characteristic disease was previously reported from shrimp farms in Taiwan and Korea [12,13].

WSSV infected shrimps develop 2-6 mm white spots in the inner side of the cuticle, and body's red discoloration. Clinically, in experimental conditions, the disease can be asymptomatic, progressing to the anorexic state and the final death, that usually takes place 36 hours post-infection (4,12,13). The main pathological features of the white spot syndrome in *Penaeus japonicus* refer to epithelial cells' degenerative lesions of the cuticular epidermis and stomach, as also of the connective

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tissues and lymphoid organs [11,13]. Virions display an outer envelope lipoprotein, and a protein tegument linking the envelope to the nucleocapsid, exhibiting a robust and long oval shape morphology, measuring 353±55 nm and 179±22 nm, by cryogenic electron microscopy technique. Viral particles were described with and without tail-like structures. The nucleocapsid, assembled by 14 capsomere units, generates a ring-like structure proposed to conforms a helix or stacked-ring structure linked by filaments, that in any case, packs the double circular DNA strain of 305-307 kbps [14,15].

In the infectious cycle, the *per os* infectivity factor (PIF) complex plays a major role in the initial process of virion internalization in the host cell [11,16]. Either way, the viral envelope protein 28 (VP28) attaches to the host cells' membrane proteins, and complemented by the interaction of the virion tegument protein 24 (VP24) to multiple cell receptors, among them, the transmembrane polymeric immunoglobulin receptor (pIgR) as also the Na^+-K^+-ATPase alpha subunit (*Pv*ATP1A), the virion envelope fuses to the cytoplasmic cell membrane. The pIgR and *Pv*ATP1A are extensively expressed in shrimp cells, allowing WSSV infection of the epidermis, gills, foregut, hindgut, lymphoid organ, muscle, heart, and gonads. The binding of VP24 to the pIgR or *Pv*ATP1A promotes the clathrin-dependent or the caveolin-mediated virion endocytosis and/or micropinocytosis associated to the AP-2 protein [17,18]. The endocytosed virion is coupled to the cell's calmodulin which triggers the mTORC1 signaling pathway, ultimately promoting viral protein translation [19]. Previously, the viral envelope is merged to the endosome membrane, to traffic the capsid to the nucleopore, mediated by cellular microtubules, and transported by *Cq*Importin α1/β1 to the nuclear compartment [20], where the viral DNA is driven-pressure ejected from the viral capsid [21]. The WSSV genome is composed of more than 180 open reading frames (ORFs), most of them coding at least for 59 structural proteins, of them, 35 are assembled in the envelope and tegument, and 9 proteins constitute the nucleocapsid [22,23]. Despite these early findings, the complete genome of a WSSV Korean isolate yielded 515 ORFs, among them 90 ORFs had any homology to known proteins in the current databases. The other 425 ORFs correspond to translated products of enzymes participating in the metabolism of nucleotides, genome replication and transcription besides main structural proteins [23]. Marks et al. (2006) experiments results suggest that the viral DNA immediate early genes' transcription operates via the host cell RNA polymerase II transcription machinery [24]. Non-structural proteins transcribed from the immediate early genes are mostly transcription factors, essential for viral DNA replication, which modulates the expression of both viral and host cell genes. Early and late genes, regulated by the immediate early gene products, express structural proteins, which are transported to the cell's nuclear compartment for virion assembly [25]. The opposite poles of the oval form nucleocapsids exhibit a portal cap and a closed base. The portal cap works as a complex molecular motor that translocate the viral genome into the capsid, whilst the closed base is open during DNA ejection, which suggested by electron microscopy, an image of filaments at this capsid pole, of both ejected DNA and DNA associated proteins. Mature capsids, containing the DNA genome, are surrounded by the tegument and envelope. All processes of virion morphogenesis take place in the host cell nuclear compartment, and the virion progeny are released by cell lysis (14,20).

Naturally, crustaceans display a diversity of antiviral mechanisms. Commonly, host cell pattern recognition receptors recognize the WSSV through their expressed pathogen associated molecular patterns leading to the activation of the crustacean immune system, the cellular and humoral response, eventually activating the transcription of antimicrobial genes. So, innumerous antimicrobial peptides exert antiviral activity by intercalating themselves in the viral envelope, which disturb the integrity and function of the envelope viral proteins involved in the attachment and interaction with host cell membrane proteins and virus cell receptors, as also other mechanisms during the stages of virus cell infection [26–29]. Other host cell mechanisms look for defense against viral infection as the RNA interference [30–33], the circular RNA named the Quaking RNA-binding protein (34,35), or Heat Shock Protein 70 [36], the C3 like complement factor [37], among others. Nevertheless, virus encoded factors counteract host cell immune mechanisms or utilize the antiviral factors for its own benefit to accomplish the infection process [38].

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Discussion

The emergence of new viruses is subjected to many factors considering that the hijacked host cell biochemical machinery is utilized by the virus molecules to guide the synthesis of its own molecules including the genome replication and transcription to yield the viral structural and non-structural proteins, including key enzymes, as also necessary molecular modifications to assemble new progeny virions [14–27]. During this process, host cell via different pathways counter acts the viral infection mechanism [28–37]. Successful virus infection and progeny release from host cell is usually accompanied by virus genome mutations caused by the cell's selective pressure, and also inherent errors of virus and cell's polymerases mechanisms to generate virus genome and transcripts, as also the failure of the enzyme's repair mechanisms (38,39).

Besides the mechanisms of host cell virus interaction, environment factors play a significative role in the evolution of viruses [40]. Crustacean's production in captivity involves different scenarios, as the density of cultivated species, quality of water determined by animal's excreta as the pH, salinity, turbidity and so on. All these external pressure factors demand crustaceans' adaptation to the new environment, which could lead to the selection of adapted ones, and death of unfit animals [41–43].

Some researchers have found possible WSSV ancestrals, such as endogenous nimaviruses integrated in different species of crustaceans. One of these endogenous viral elements were found in the genome of the marine white leg shrimp, *Penaus vannamei*. So, 43 WSSV genes sequences are closely related to the endogenous nimavirus, which encodes the dUTPase and nucleocapsid proteins [44]. Other work detected an endogenous nimavirus in the Jamaican bromeliad crab, *Metopaulias depressus*, sharing 68 putative ORFs with the WSSV genome, that code for non-structural proteins participating in the mechanisms of replication and nucleotide metabolism, and also code for structural proteins of the nucleocapsid, tegument and envelope [45]. Also, from the genome of the isopod crustacean *Armadillidium vulgare*, gene fragments coding for peptides of 42 and 43 aminoacids were detected with 73 % to 74 % homology to peptides of the WSSV envelope (46,47). The search in the crustacean genome database, of 14 species, revealed five novel nimavirus genomes, encompassing 28 core genes, including proteins of unknown function, homologs of 5 baculovirus PIF and a sulfhydryl oxidase which denotes that nimavirus and baculovirus share the same phylogenic origin [48]. Most recently, Hirono's group proposed the existence 2 major WSSV phylotypes that time diverged, estimated by the Bayesian statistical analysis, between 1970 and early 1980, concluding that the phylotype I and the ancestor nimavirus were etiologically involved in the 1990s pandemic, and the phylotype II was restricted to Asia and Australia. In addition, 2 cross-phylotype recombinants have been detected [49].

Conclusion

Based on the hypothesis that host cells, under environmental stress, work as epigenetic factors (3,50,51) that wake-up endogenous genic segments, and promote the genomic organization of these endogenous elements, that are capable to assembly in mature viral particles, enabling the new progeny virions to leave the host cell in a "instinct" to survive and to keep essential genes for future generations [52]. Therefore, the novel exogenous virus continues the exercise of infecting new host cells to maintain the existence of "running genes", now as viral genes. It is interesting to note that since the emergence of WSSV, the mortality in the elapsed time was fast and very high, reaching 100 % (4,5,13,14), besides the initially very virulent isolates of WSSV had bigger genome than the less virulent and recent ones [53–55], possibly explained by the deletion of unnecessary genes which would optimize the virus' mechanisms in its infection cycle. Certainly, the host cell and WSSV interactions will, time by time, attenuate the virus pathogenicity. Let's say in a colloquial form, "the rude virus is educated by the cell biochemical machinery to behave", instead of a "disastrous virus that destroys of all host cells". It becames more "cautious and intelligent", it replicates, producing millions of new progeny virus and dispose of host cell to maintain its genes, until the time it is safe to endogenize itself and keep the genes useful for the host organism. All biochemical tools for all

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processes of genome organization, virion assembly and budding or cell lysis as also, the mechanisms of viral genome endogenization, are available by the host cell molecular paraphernalia [56–58].

Both RNA and DNA viruses have endogenous relatives (58,59). There are evidences suggesting that inhospitable cell's microenvironment triggers virus evasion, and it would explain the emergence of new viruses and catastrophic epidemics (48,49,60).

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