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Mini Review
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Mini review on Vibrio Infection-A Case Study on *Vibrio harveyi* Clade

Denicia Atujona[1,2,3], Shuanghu Cai[1,2,3*] and Eric Amenyogbe[1,2]

[1]*College of Fisheries, Guangdong Ocean University, Zhanjiang, Guangdong Province, China*

[2]*Guangdong Provincial Key Laboratory of Aquaculture in the South China Sea for Aquatic Economic Animals, Zhanjiang, China*

[3]*Guangdong Provincial Key Laboratory of Pathogenic Biology and Epidemiology for Aquatic Economic Animals, Zhanjiang, China*

***Corresponding author:** Shuanghu Cai, College of Fisheries, Guangdong Ocean University, Zhanjiang, Guangdong Province, China, Tel: +8613729039109; E-mail: cshcai@163.com

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Abstract

Pathogens respond to host immunity by secreting virulence factors which facilitate their proliferation and survival in host. Most bacteria including *Vibrio harveyi* coordinates gene expression by cell-cell communication termed quorum sensing. Quorum sensing (QS) involves the production, detection, and response of molecules to extracellular signals to enable bacteria monitor population density and induce specific genes in response to changes in cell number. Quorum sensing systems regulate virulence, bioluminescence, biofilm formation and antibiotic production which are necessary factors to induce infection. *V. harveyi* interacts inter-specially and intra-specially to overcome host defences and cause detrimental infections to a wide range of aquatic host. This review reflects the mechanism aiding infection in Vibrio species, considering *V. harveyi* clade.

Keywords: *V. harveyi*; Quorum sensing; Virulence

Introduction

Aquaculture is one of the fastest growing food production sectors globally, with Asian aquaculture significantly contributing to total global output (http://www.fao.org). Output consistency is challenged by diseases resulting from ubiquitous opportunistic bacterial pathogens in the aquatic environment [1,2]. *V. harveyi* is a bioluminescent marine bacterium free- living in seawater column, adhered to abiotic surfaces, as a constituent of biofilm and in pathogenic associations with marine and estuarine organisms [3,4]. *V. harveyi*, among Vibrio species are short, curved rod-shaped, monotrichous, luminescent, motile marine bacterium associated with normal marine flora and pathogenic to most marine species; largely a cause of global economic losses especially to young population of aquatic vertebrates and invertebrates including shrimp and finfish [5-7].

Bacteria quorum sensing uses extracellular signals known as auto-inducers (AI) to monitor population density and induce gene expression in response to cell number. Auto-inducer (AI) concentration increase and decrease proportionally with bacterial population to activate group and individual responses respectively at any given time. Understanding the mechanism of operation in Vibrio species will help device and adapt means to reduce infection incidences. Environmental conditions including water temperature and oxygen fluctuation as well as related stresses are first-hand susceptors of host to infections. Effective environmental management is therefore, a prerequisite to disease control and healthy aquaculture.

Effects of *V. harveyi* Infection on Mariculture

Portal of entry of *V. harveyi* is species dependent, in some species it enters through the mouth to forms plaques, then spread to innards, appendages and limbs. The severity of havoc is dependent on host exposure to a concentration enough to cause infection [8].

Reports exist on epizootic outbreaks by *V. harveyi* over a wide geographical range in marine organisms [9]. *V. harveyi* has been associated with massive mortalities in aquaculture in France, Japan, Australia, Korea, and China [10,11]. Communication skills of *V. harveyi* have been revealed with major effects of their interaction with the environment in terms of virulence expression or expression of defence mechanisms. Understanding the parameters causing the proliferation of pathogenic *V. harveyi* has been of immerse importance over the years in combating and reducing its infestation and impact on Maricultured organisms.

The bacterium is pathogenic to a wide range of organisms especially fish and invertebrates [5,12] and a major cause of most serious bacteria diseases, growth retardation and huge mortalities in both vertebrates and invertebrates including groupers, elasmobranches, rainbow trout, Atlantic salmon, olive flounder, black rockfish, sea bream, turbot, penaeid shrimp and bivalves. The bacterium identified to be opportunistic is associated with serious production losses in marine fish farms with a potential to eliminate a whole population of affected juvenile species [13,14] resulting in significant economic impact on the industry.

Depending on the fish species, Vibriosis affected organisms exhibit a variety of clinical signs including abnormal swimming behaviour, dark pigmentation, distended abdomen, skin ulceration, gastroenteritis, ascites, inflammation of the circulatory system or eye, skin lesions, presence of white spots on foot and inflammation of the pericardial tissue resulting in impaired mobility and septicemia in various species of vertebrates and invertebrates [15,16].

Diseases of *V. harveyi* include vasculitis [17,18] and luminous vibriosis. Luminous vibriosis has been a leading cause of death among commercially farmed shrimp and other aquaculture [5]. *V. harveyi* has been a common cause of vibriosis outbreaks in Orange spotted grouper

(*Epinephelus coioides*) in the Guangdong province of China since 2008 [19]. In European abalone *Haliotis tuberculata*, *V. harveyi* has been responsible for massive mortalities during summer spawning period both in natural populations and farmed stocks [11].

Pathogenicity of *V. harveyi*

Though the pathogenicity of *V. harveyi* is not well elucidated, some virulence indicators have been identified: Extracellular products (cysteine protease, phospholipase and haemolysin), lipopolysaccharide, bacteriophage, bacteriocin-like substance and quorum sensing factors [5]. The pathogenicity of *V. harveyi* is strain-dependent, reflecting a synergistic interaction between individual or coupled factors of hydrophobicity, biofilm formation, survival ability in fish skin mucus and serum, and the proteolytic, hemolytic, cytotoxic activities of ECPs [20].

The life cycle of pathogenic bacteria consists of two phases; environmental phase regulated by environmental conditions and host phase characterized by virulence factors [21]. The production of virulence factors is strongly influenced by environmental conditions. Conditions that initiate bacterial infection occur in three stages: colonization, adhesion of the pathogen to host where it multiplies and penetrate to establish itself; invasion of host organs by expression of virulence factors to initiate disease; exit of pathogen and disease transmission to neighbouring host [22].

Pathogens multiply and deliver effector proteins into host to invade host defences and establish diseases. Bacterial adhesion to host surfaces is one of the initial steps in microbial pathogenesis; hydrophobicity and biofilm formation are thought to be determining factors of adhesion and survival for pathogens in host cells [20,23,24]. The cell wall of *V. harveyi* consists of an outer membrane of lipopolysaccharides, an important adhesion factor for host attachment [25].

Vibrio species vary in their modes of infection in different host, among these; *V. anguillarum* penetrates preferentially through gastrointestinal tract in turbot *Scophthalmus maximus* [26], through skin and gills in Atlantic salmon (*Salmo salar*) and rainbow trout (*Salmo gairdneri*) [27,28], portal of entry of Vibrio pathogens into mollusks is predicted organic matrix of the shell [29,30].

Virulence regulation in *V. harveyi*

Virulence of *V. harveyi* is predicted to be achieved by attachment mechanisms, biofilms formation, bacterial secretions and extracellular products. Vibrio bacteria pathogens and *V. harveyi* for that matter regulates virulence expression to initiate and maintain disease. Gene expression is regulated by population density in a process known as quorum sensing; cell-to-cell communication, effected by "hormone like" organic compounds, signal molecules known as autoinducers (AIs). *V. harveyi* integrates AI signals of different strength and unique encoding information about neighbouring species content in a phosphor relay signaling system [31].

Bacterial densities are influenced by multiple factors including nutrients, temperature, osmotic strength, pH and oxygen concentration, with maximal growths at optimal conditions of species and strains [32] for example increased bacteria concentration facilitates virulence. The mechanisms of quorum sensing are dependent on signal peptide regulation of LuxO. AI-1 and AI-2 are signal molecules [33,34] involved in LuxO phosphorylation and dephosphorylation. AIs switch intermittently between individual and group existence mechanisms at low and high population densities respectively to produce and preserve bacterial virulence. Phosphorylation of LuxO occurs at low signal molecule concentration due to low bacteria density to activate the expression of genes that repress the production of master transcriptional regulator protein LuxR mRNA. Increased signal molecules as a result of rise in bacteria cell density terminates the expression of master transcriptional regulator protein LuxR repressive or inhibitory genes, dephosphorylate LuxO and translate luxR mRNA [35-38]. Gene expression regulation results in secretion of effector proteins that allow pathogens infect and damage their host.

Quorum sensing facilitates the production, secretion, and detection of virulence mechanisms in a wide range of bacteria strains in which it is conserved [7]. Quorum sensing influences virulence of most pathogens with type III secretion systems [39,40]. To regulate activities of virulence, antibiotic production, biofilm formation, symbiosis, motility, conjugation and bioluminescence, *V. harveyi* utilizes AI signals for intra-species communication (AI-1) and interspecies communication (AI-2) [41,42]. AI-2 functions as a broad-spectrum antibiotic which disrupts quorum-sensing systems, a potential for development of synthetic inhibitors to disrupt virulence factors along communication pathways [43].

Bioluminescence in V. harveyi: Bioluminescence is a biological process of light production and emission. Though the mechanism of bioluminescence is not well elucidated, luminescence is found in symbiotic, saprophytic, parasitic, as well as in free-living bacteria [44]. Bioluminescence is regulated by a signaling pathway in response to cell density. Signaling result in production of luciferase, an enzyme that generates light in the visible range causing bacterial glow in response to activated quorum sensing pathways [3]. Most bioluminescent organisms are resident in oceans, where they emit light for biological activities including attraction of prey or to find food, to attract mates and escape predators, also aids intra-species communication among bacteria population [45-48].

Bioluminescence is important for efficient DNA repair, an evolutionary drive for luminescent bacteria due to its inefficient DNA repair; non-luminescent bacteria on the other hand have efficient DNA repair systems [49]. *V. harveyi* luminescence stimulates DNA repair by activation of photoreactivation process, indicative of DNA repair stimulation being an evolutionary drive for bacterial luminescence [50]. Origin of bioluminescence is considered a problematic question of the Charles Darwin theory of evolution [51] because its function is believed to have direct association with visual behaviour of organisms, raising questions about its attributed benefits to organisms with weak luminescent systems. Bioluminescence in *V. harveyi* protects bacteria against oxidative stress [52].

Unless a selective pressure is provided luminescence is disadvantageous to bacteria due to high cell energy requirement to emit radiation, efficient system development requires positive environmental pressure to select individuals bearing more and more effective systems among whole populations [49]. A conclusion can be reached that *V. harveyi* bioluminescence stimulation of DNA repair improves pathogenic efficiency against their host under selective pressure.

Biofilm formation in V. harveyi: Biofilm is critical for the survival and persistence of *V. harveyi* and its infection. Biofilms are complex, multicellular bacterial communities adhered to surfaces and

threatening host immune systems, causing economic and health problems [53,54]. A biofilm is formed by bacterial cell attachment to surfaces, micro-colonies formation and further maturation into biofilm, their structural basis are composed of proteins, nucleic acids, lipids and exopolysaccharides [55,56]. Exopolysaccharides are virulence factors which protect bacteria from the environment and host immunity [57]. Biofilm association with quorum sensing aids neighbouring cell communication over short distances among bacteria population [58,59].

Biofilm formation protects bacteria against antibacterial agents [60], biofilm formation occurs in the presence of the antibiotics tetracycline and chloramphenicol [61]. This is an advantage for bacteria to express virulence mechanism and infect host in the occasion of antibiotic use. The importance of biofilm and its resistance to antibiotics limit effectiveness of antibiotics treatment against pathogens and make it imperative to search alternatives to antimicrobials.

Antibiotic Resistance-An Advantage to Bacteria

Several strategies have been attempted to control bacteria diseases, however, the rate of destruction remains alarming in most environments due to factors including antibiotic resistance. Disease maintenance with antibiotics proved effective against a reasonable range of bacteria, leading to its widespread in aquatic systems; building up chemical residues in useful microorganisms to deteriorate the environmental [62,63]. Regular and continuous use of high doses of antibiotics increased its concentration in culture environments, limiting its effectiveness and conferring resistance as well as resistance transfer to other bacteria [64]. Bacteria develop resistance to antibiotics overtime expressed by chromosomal genes or acquired through mutation of plasmids and transposons; bacteria survive stress from antibiotics and respond by development and improvement of adaptive measures to new environments, mutation inactivates or modifies antibiotics to reduce drug accumulation and permeability [65]. A resistant bacterium survives and persists in the presence of antimicrobial agents in concentrations subjective to infection.

Conclusion

Aquaculture supplements depleting wild catch and must be protected against disease of which bacteria Vibrios are a leading cause. Quorum sensing regulated mechanisms influence virulence of vibrio pathogens and its components may be targeted to curb the devastating effects of quorum sensing bacterial infection.

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Conflict of Interest

The authors declare no conflicts of interest.

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