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The fight for invincibility: Environmental stress response mechanisms and *Aeromonas hydrophila*

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ABSTRACT

Aeromonas hydrophila is a freshwater-dwelling zoonotic bacterium that has economic importance in aquaculture. In the past decade, *Aeromonas hydrophila* has become increasingly important because of its emergence as a food-borne zoonotic pathogen that is resistant to different treatment regimes. Being an aquatic bacterium, *Aeromonas hydrophila* is frequently subjected to several stressful environmental conditions, including changes in temperature, acidic pH and starvation that challenge its survival. To cope with these stressful conditions, like every cell, *A. hydrophila* possesses stress response mechanisms, such as alternative sigma factors, two-component systems, heat shock proteins, cold shock proteins, and acid tolerance response systems that eventually lead the fittest to survive. Moreover, the establishment of genetic variations among the strains related to environmental stress is also of great concern. This review presents the understandings based on inter-strain variations and stress response behavior of *A. hydrophila* that are important to control the increasing outbreaks of this bacterium in both human populations and aquaculture.

1. Introduction

Bacterial pathogens are frequently exposed to a variety of stresses in their natural environment and in their host systems, which may lead to increased virulence, adaptability and resistance [1]. Environmental factors, especially sublethal factors, may interact with bacterial machinery and induce a temporary or permanent change in bacterial response behavior [2]. This response behavior of unicellular organisms is one of the key reasons for their emergence and re-emergence [3,4] and poses a great threat in the areas of health and economics [5].

Aeromonas hydrophila is an emergent bacterial pathogen [6]. As a well-known pathogen of humans and in aquaculture, *Aeromonas hydrophila* is found in several different aquatic environments, foods, and food processing and storage systems [7]. *A. hydrophila* is able to persist and propagate in continuously changing environments, as exemplified by its viability over a large range of temperatures (from 40 °C to 4 °C) [3]; other environmental factors, such as nutrition, pH, temperature, glucose, salinity, osmotic stress and incubation time, affect *A, hydrophila* in a similar fashion [8–14]. Moreover, environmental conditions can also affect its virulence and production of harmful cytotoxic products [15]. Upon detecting a suitable surface, *A. hydrophila* can form biofilms, thereby showing increased coordinated behavior under adverse conditions [16]. The existence of multiple-antibiotic-resistant strains of *A. hydrophila* with multiple plasmids and mobilomes is also of great concern [17]. *A. hydrophila* can wreak havoc in the future since it carries all the characteristics of a potential pathogen.

With a functional understanding of key aspects of the environmental stress response, *A. hydrophila* can serve as a model for studying the environmental regulation of gene expression. Regulatory pathways, including those involved in the minimal stress proteome and in cross-talk between different circuits, may shed light on the persistence and emergence of *A. hydrophila*. This review aims to highlight some of these important sensory and regulatory networks that have the capacity to facilitate rapid reprogramming of global gene expression profiles. Inter-strain variation has also been discussed with respect to evidence produced from comparisons of different databases and local alignments.

2. General survival mechanisms

Bacteria possess a variety of regulatory systems that regulate different mechanisms related to survival in various environments [18]. These regulatory mechanisms include both general and specific mechanisms to adapt to or cope with varying environmental conditions [19]. Continuous variation in environmental stress factors, such as heat and cold stress, acid shock, nutrient deprivation, sublethal antibiotic stress, and UV radiation, can lead to physiological adaptations at a genetic level in bacteria [20,21] which is the basis for the emergence of novel pathogens. *A. hydrophila* is also included among pathogens that

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were once considered opportunistic pathogens but are now considered emerging pathogens because they can adapt to their environment and alter gene expression by activating a number of different regulatory mechanisms [22]. Like other bacteria, *A. hydrophila* also possess a range of different mechanisms, such as alternative sigma factors, two-component regulatory systems, chaperones, DNA-damage repair pathways and stringent response, to adapt to diverse environments [23–26].

Moreover, there is also variability in these adaptive mechanisms among the large number of spatially distinct strains of *A. hydrophila* [27]. There are 62 sequenced (at the time of this study) and functionally annotated genomes of *A. hydrophila* available in public databases. Similar to *Listeria*, the ability of *A. hydrophila* to survive and grow under stress may vary between strains [28]. This variation could be the result of mutations that often occur as trade-off effects during adaptation to constantly changing environments and are the likely source of a great deal of intra- and interspecies diversity [29]. Trade-off effects impact metabolism, motility, biofilm formation, virulence, DNA repair, and resistance to phage, antibiotics, or environmental stress [30].

2.1. Two-component regulatory systems

Two-component regulatory systems (TCSs) are systems consisting of two conserved proteins and are crucial in maintaining the bacterial response to environmental stress [31]. Many gram-negative bacteria, including *A. hydrophila*, possess TCSs to respond to several environmental stress factors through a number of pathways, including pathways involved in ion-transport regulation, quorum sensing, biofilm formation, membrane integrity response, polar flagellar synthesis and basic metabolism [32,33]. TCSs contain two components consisting of a membrane-bound sensor kinase and a DNA-binding response regulator. In response to specific stimuli, the sensor kinase is phosphorylated at a conserved histidine residue and then the phosphoryl group is transferred to a conserved aspartate residue on the response regulator. Phosphorylation of the response regulator triggers a conformational change, which drives the dimerization and high-affinity DNA binding activity of the response regulator [34]. There is variation in the number of TCSs among bacteria, which can have anywhere from just a few to hundreds of TCSs [35]. Similar variation is found among different bacterial strains. *Escherichia coli* K-12 contains approximately 36 TCSs [36], while approximately 200 TCSs exist in *Myxococcus xanthus* [37]. These inter-species or intra-species variations depict a strong relationship between bacterial ecological niches and the sophistication of organism behavior (see Fig. 1).

In *A. hydrophila*, approximately 20 functioning TCSs have been reported with five major gene families [38,39]. Like other bacteria, different strains of *A. hydrophila* have different TCSs, as shown in Table 1 (Fig. 2). The AdeS-AdeR (antimicrobial resistance) and TorS-TorR (trimethylamine N-oxide respiration) TCSs vary among strains and their presence significantly enhances survival and pathogenesis of the bacteria. For example, trimethylamine N-oxide (TMAO)-respiring bacteria can survive better at high pH and under conditions of high salinity [40]. This inter-strain variation is possibly due to horizontal gene transfer or gene duplication in fluctuating environments. A detailed bioinformatics analysis identifying orthologous TCSs along with a phylogenetic analysis might be a good approach for further analysis of this inter-strain variation. Furthermore, there are numerous auxiliary factors that regulate environmental responses [35]. Being an important component of bacterial defense pathways, TCSs could be targeted for the development of novel antibacterial and vaccine therapies.

2.2. Alternative sigma (σ) factors

Gene expression can be modified at a transcriptional level and/or at a post-transcriptional level when environmental stress factors trigger the bacterial response [49]. During transcription, the production level of sigma factors changes and eventually leads the core RNA polymerase to recognize only those regulons that would be helpful in combating stress [50].

There is a rough correlation between the apparent complexity of the environment and the number of alternative sigma factors. For instance, pathogens living in only one environment, such as *Mycoplasma sp.*, possess only the primary sigma factor and no secondary or alternative sigma factors, while *E. coli*, which is found in several environments, has seven alternative sigma factors [51]. This number could be higher if the bacteria inhabit multiple environments. The same correlation can be seen among various strains of the same species [52]. Therefore, the ability of bacteria to acquire sigma factors based on their environment, regardless of species or strain, represents their adaptability and survivability.

A. hydrophila also possess alternative sigma factors [15,53,54]; there are six sigma factors reported (Table 2). All the sigma factors in *A. hydrophila* are co-expressed and affect each other based on different

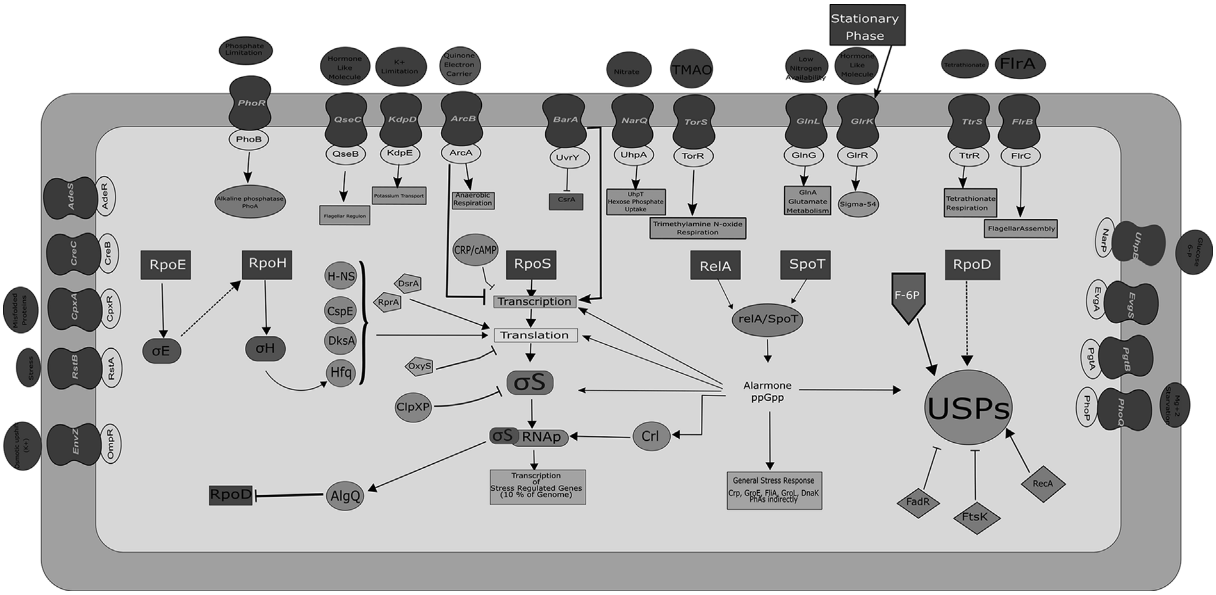

Fig. 1. TCSs are very well understood in other bacteria, such as *E. coli*, but their function is not well elucidated in *A. hydrophila*. → shows the stimulation of pointed process or protein. ⊣ represents the inhibition of certain process or protein.