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Nature to the natural rescue: Silencing microbial chats

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A B S T R A C T

Communication is the sole means by which effective networking and co-existence is accomplished amongst living beings. Microbes have their own chit-chats. Science has overheard these microbial gossips and have concluded that these aren't just informal communications, but carefully coordinated signals that plan their effective strategies. Tracking one such signal molecule, *N*-acyl homoserine lactone (AHL), led to a fundamental understanding to microbial quorum sensing (QS). Furtherance of research sought for ways to cut off communication between these virulent forms, so as to hinder their combinatorial attacks through quorum sensing inhibitors (QSIs). A clear understanding of the inhibitors of these microbial communication systems is vital to destroy their networking and co-working. The current review, consolidates the solutions for QSIs offered from natural sources against these micro components, that are capable of slaughtering even nature's most fit entity-man. The applications of effective out sourcing of this QSI technologies and the need for development are discussed. The importance of silencing this microbial chatter to various aspects of human life and their implications are discussed and elaborated.

1. Introduction

Since the discovery of penicillin in 1928, antibiotics have transformed modern medicine and saved millions of lives. The rapid emergence of resistant bacteria is a real challenge to the efficacy of antibiotics. Coordinated efforts to implement new policies, renew research efforts, and pursue steps to develop as new agents to treat bacterial infections are greatly needed to manage the crisis [1].

Through a cell-to-cell communication mechanism, bacteria coordinate their population dependent interactions and it is known as quorum sensing (QS). It is well studied that the QS controlled behaviors occur when the bacterial population grows until a threshold concentration is reached. In Gram-negative bacteria, QS systems use *N*-acyl homoserine lactones (AHLs) as signal molecules, but a peptide mediated quorum sensing (QS) system is commonly employed in the Gram-positive bacteria, though there are other signal molecules reported. QS-regulated biofilm formation and virulence factor secretion are particular concern as they are involved in surface-attachment, antimicrobial agent resistance, toxicity, and pathogenicity. Many of pathogenic microorganisms of human beings, animals and plants have been reported to be QS controlled in their virulence. It may be possible that treating infections of pathogenic bacteria that produce resistant biofilms may be feasible using QSI (Quorum Sensing Inhibitory) treatments that can control either initial biofilm attachment or the biofilm architecture. Also, there are many reports on the role of environmental strains of biofilm forming bacteria in biofouling of membranes in water and waste water industry [2,3]. Since the 1990s, the number of studies on QS has continuously increased, with a remarkable diversification of the explored areas.

Targeting QS is a promising strategy to inhibit undesirable bacterial traits. This strategy, referred to as quorum quenching and it involves disruption of the bacterial QS systems by naturally occurring QSI molecules. Since the first report of QQ in natural systems, there has been huge interest in agents that selectively interfere with the QS systems of bacteria and several such, has been reported. More recently synthetic QSI molecules have also been developed as potent QS inhibitors [4].

QSI molecules are reported in many of natural ecosystem interactions. Plant-based antimicrobials have reported having great potential to combat bacterial, fungal, and viral diseases without any known side effects. Such plant metabolites include quinines, alkaloids, polypeptides, flavones, flavonoids, coumarin, terpenoids, essential oils and tannins and other. Honey and propolis disrupted bacterial signaling in *C. violaceum* and *E. coli* [5]. Even though, several spices such as turmeric, clove, black pepper, garlic, etc., have been used since ancient times to prevent gastrointestinal, pulmonary and urinary tract infections, their precise mechanism of antimicrobial functionality had not

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been completely understood. They are known to produce a great spectrum of secondary metabolites ranging from phenolics, quinones, flavonoids, alkaloids, terpenoids and polyacetylenes, many are found to have QSI properties. Several soil bacteria, fungi, and marine bacteria have been found to produce QSI molecules of varying capacity. In addition to several marine bacteria and algae, many marine animals are also known to produce QSIs, most being soft corals and sponges, but gorgonians, hard corals, bryozoans and ascidians also are reported to produce QSIs [6]. In recent years, obtaining non-toxic anti-QS active substances from natural plant resources takes much attention of researchers.

This review focuses on QQ is various natural ecosystems and also various QSI molecules. QSIs from natural sources are discussed. Various reports on QSIs from marine bacteria, algae and animals too are dealt with. Special emphasis is given on the applications of quorum quenching and associated technologies in various fields such as agriculture, medicine and antifouling.

2. Quorum sensing

Quorum sensing is a means of communication between bacteria of the same species (intra-species communication) and it was first reported by Nealson et al. [7] in the marine bacterium *Vibrio fischeri*. QS, basically is the capacity of bacteria to monitor their population density *via* chemical signaling and regulate gene expression accordingly (Fig. 1). QS signaling involves the synthesis, exchange and perception of bacterial compounds, called autoinducers (AIs), that are constitutively synthesized intracellularly and are then passively, or actively exchanged with the surrounding environment [8]. AIs are structurally diverse and used by bacteria to regulate a wide variety of genes and functions (Fig. 2). Out of all bacterial signals identified to date, *N*-acyl homoserine lactones (AHLs) are the most common QS signals that are produced by Gram-negative bacteria. Fuqua et al. [9] described the role of acylated homoserine lactone-mediated *luxR/luxI* as QS regulatory system in Gram negative bacteria. Generally, AHLs are synthesized by *LuxI* synthases and *LuxR* codes for receptor proteins, using the substrates *S*-adenosylmethionine (SAM) and an acylated acyl carrier protein (acyl-ACP) [10] The *LuxI/LuxR* homologous has been identified in more than 100 Gram-negative bacterial species [11]. More than 200 different Gram-negative bacteria have been described to produce AHLs of varying carbon chains and *N*-acyl side chains; AHLs containing 4–18 carbons and various additional modifications [12]. Upon synthesis, AHLs diffuse freely across the cell envelope and accumulate in the local environment. When a critical concentration threshold is reached, AHL and a LuxR-type receptor protein interact in the cytoplasm, resulting in modulation of target gene regulation.

Gram-positive bacteria employ modified oligopeptides or autoinducer peptides (AIPs) as their signal molecules and are actively transported out of the cell through specialized transporters. Either at the surface of the cell or intracellularly, these peptide signals are detected by membrane-bound sensor kinase, thereby leading to the activation of QS target genes. Production of the signal, AI-2 was detected in many Gram-positive and Gram-negative bacteria for interspecies communication [13]. Other quorum-sensing signals that include Pseudomonas quinolone signal (PQS), diffusible signal factor (DSF), and autoinducer-3 (AI-3) [14].

Each cell of a population, in QS, synthesize and release a QS signal, and the total concentration of it refers to the cell density of this population. Once a threshold concentration is reached, the signal can be sensed and the expression of the target genes regulated. The QS-controlled genes and functions contribute to functional categories *viz*. cell maintenance; cell behaviors such as biofilm formation; horizontal gene transfer; and microbe-microbe/host-microbe interactions [15,16]. Even though the response of microorganisms to QS is organism-dependent, some traits are commonly regulated through QS, such as production of antibiotics, exopolysaccharides, or exoenzymes, expression of secretion systems, swarming motility, and biofilm formation. However, little is known about the cascade of genes associated with various mechanisms controlled by the QS system.

QS was originally identified from the luminescent marine bacterium, *Vibrio fischeri*. The bioluminescent phenotype of this bacterium is exploited by *Euprymna scolopes* in order to perform a behavioral phenomenon called counter-illumination [17]. Bacterial QS is implicated in various functions including pathogenicity of many pathogens, biofilm formation and food spoilage [18]. In plant pathogenic bacteria, the virulence-contributing factors like extra-polysaccharide (EPS), degradative exoenzymes, horizontal gene transfer (HGT), and effectors' secretion are controlled by quorum sensing [19]. Similar mechanism works also in beneficial bacteria in plant growth promotion interaction with plants [20]. QS has been reported as mechanism behind the biofouling of membranes used in water and waste water industry [2]. Since the first discovery of QS systems in the microbial world, there has been numerous reports of similar systems in various natural ecosystems.

3. Quorum quenching

Quorum quenching (QQ) describes, all processes that are involved in the disturbance of QS, leading to inhibition of bacterial phenotypes, as first described by Dong et al. [21,22]. Nature has evolved different tools to interfere with bacterial QS. Certain fungi have been shown to release QSIs to its micro-environment to inhibit competing bacteria from production of antifungal compounds. Similarly, plants could be producing QSIs to control plant pathogens whose virulence depends on QS systems. Also, there has been several QS based systems identified in marine ecosystems. They may have evolved QSI mechanisms to

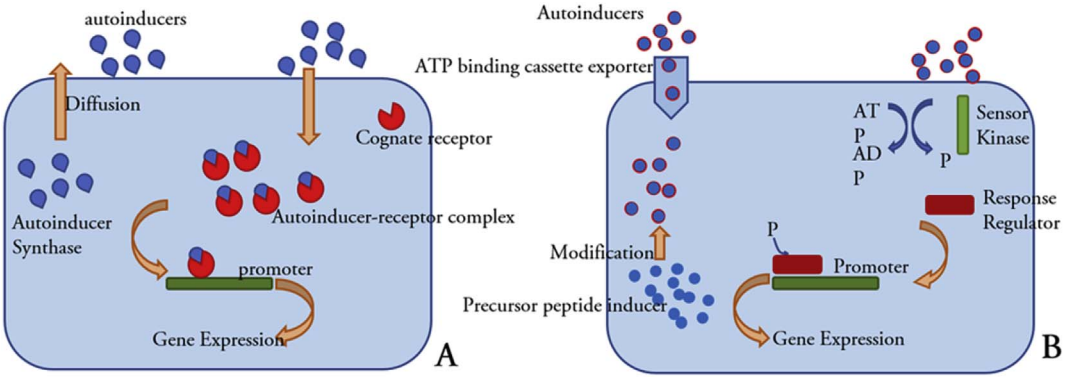

Fig. 1. General scheme of Quorum Sensing in Gram negative (A) and gram positive (B) bacteria. A signal synthase produce the autoinducers which is transported to the extracellular environment. At a high autoinducer molecule concentration, the cognate receptor forms a complex with the signal. The autoinducer-signal complex in turn induce the expression of a gene cascade.