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The Emergence of Anti-Quorum Sensing Therapy as a Novel Strategy to Counter Bacterial Virulence- An Indian Perspective

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ABSTRACT

Bacteria use specific chemical messengers or signaling molecules called autoinducers (AIs) to share information and communicate among themselves. This molecular communication system is known as Quorum Sensing (QS) which synchronizes the expression of many genes involved in their viability and virulence. Quorum sensing also serves to assess the density of a bacterial population. To interfere with the communication themselves, bacteria use quorum sensing inhibitors (QSIs) to block the action of AIs and quorum quenching (QQ) enzymes to degrade the signaling molecules. These natural strategies that interfere with bacterial signaling have been extensively studied in recent years, examining their potential for systemic use in controlling bacterial growth. Recent studies have shown that these strategies are indeed promising routes to decrease bacterial pathogenic response and decrease biofilm production, potentially enhancing bacterial susceptibility to antimicrobial agents including antibiotics and bacteriophages. Numerous phytochemicals have likewise turned out to be amazingly viable in hindering quorum sensing in bacteria. The viability of these QSIs has been tested in different animal models and is presently considered to be used as better alternatives or in combinations to traditional medical strategies against superfluous bacterial infections, thereby largely increasing the therapeutic arsenal against all virulent bacteria.

INTRODUCTION

We find ourselves facing a disastrous moment in modern health care where many antibiotics have lost their effectiveness in treating life-threatening and debilitating diseases. Meanwhile, as the world's population continues to increase rapidly, agricultural markets are tasked with meeting worldwide nutritional needs. The expanding global distribution of crops has placed an added incentive on finding new ways to increase production and enhance disease resistance of plants and to extend the shelf lives of plant-derived products. Unfortunately, bacterial pathogens have outpaced our abilities to manage them. There is a critical need to discover new antimicrobial compounds and to identify new methods for disease prevention and treatment. Drugs recently developed to thwart emerging antibiotic resistance, such as resistance to vancomycin, linezolid, and the latest beta-lactams, have themselves already lost effectiveness against some bacterial strains (1). Even more discouraging, development of new drug leads has slowed dramatically over the past 10 years, and newer drugs that have been successfully developed are strictly reserved to treat only the most serious infections, so as not to repeat over usage mistakes of the past. It is, therefore, more important than ever to develop therapies that will provide sustainable, long-term effectiveness against bacterial pathogens (2). Since current therapies rely on antibiotic treatments that result in the death of invading bacteria and their clearance from the body, they place a strong selective pressure (arguably the strongest possible) on bacteria to develop resistance mechanisms (3). Generating new therapies that minimize pressures selecting for resistance would, in theory, be possible by avoiding growth-inhibitory effects. Newer strategies have sought to target components of bacteria that are responsible for pathogenesis rather than targeting components that are essential for growth and, as such, have garnered the name “antivirulence” or “aetiopathogenesis” therapies (4). Antitoxin therapies and some vaccines fit into this design for new treatments, and these strategies will undoubtedly continue to lead to new effective products (5). This article focuses on understanding the basics of quorum sensing and quorum sensing inhibition along with summarizing the development and current status of strategies that target this efficient bacterial communication system(6).

What is Quorum sensing?

Quorum sensing is the mechanism of regulating bacterial gene expression in response to fluctuations in cell-population density. We owe most of our current understanding about quorum sensing to Dr. Bonnie Bassler whose work revolutionized microbiology (7). Specific

chemical signal molecules called autoinducers are produced and released by quorum sensing bacteria that increase in concentration as a function of cell density (8). The detection of a minimal threshold stimulatory concentration of an autoinducer leads to an alteration in gene expression. Gram-positive and Gram-negative bacteria use quorum sensing communication circuits to regulate a diverse array of physiological activities including virulence, conjugation, antibiotic production, sporulation, biofilm formation etc. (9). In general, Gram-positive bacteria use processed oligo-peptides whereas Gram-negative bacteria use acylated homoserine lactones to communicate (10). Recent advances in the field indicate that cell-cell communication via autoinducers occurs both within and between bacterial species (11). Furthermore, there is mounting data suggesting that bacterial autoinducers elicit specific responses from host organisms (12). Although the nature of the chemical signals, the signal relay mechanisms, and the target genes controlled by bacterial quorum sensing systems differ, in every case the ability to communicate with one another allows bacteria to coordinate the gene expression, and therefore the behavior, of the entire community (13). Presumably, this process bestows upon bacteria some of the qualities of higher organisms. The evolution of quorum sensing systems in bacteria could, therefore, have been one of the early steps in the development of multicellularity (14).

Anti-Quorum sensing therapy

The term "anti-pathogenic compounds" has attracted great interest in the medical field. It refers to those substances that do not kill the bacteria and do not lead to the development of resistant strains over time like the way many bactericidal substances do (15). They act on the attenuation of bacterial virulence, preventing the establishment of successful infection. Inhibition of the QS system is considered as a novel strategy for the development of antipathogenic agents, especially for combating bacterial infections caused by antibiotic-resistant strains (16). *Chromobacterium violaceum* (*C. violaceu*s) is the most used bacterial species as a monitor strain for studying quorum sensing inhibition activity. This bacterium has the ability to produce a violet pigment as a result of quorum sensing. QS Inhibitors (QSIs) will lead to loss of the violet pigmentation without actually killing the bacterial cells (17). Therefore, it acts as a good QS Inhibition screening candidate. The most widely known QSIs are the halogenated furanones which have many limitations for human use due to their toxic side effects and carcinogenic properties making them unsuitable for pharmaceutical usage. Accordingly, a lot of researches are looking into discovering new chemicals that have

QSI activity with reduced or absent side effects. In the past few years, inhibition of QS has become an intense area of research because of its applications in medicine, industry, and biotechnology. In the quest for QS inhibitors, studies have demonstrated that many eukaryotes, particularly plants, and even bacteria themselves produce anti-QS substances (18). Ajoene from garlic, catechin from Combretumalbiflorum, and iberin from horseradish specifically inhibit QS in reporter strains. As an adaptive evolution, many plant species produce metabolites that can control the growth of microbes and have traditionally been used to treat human diseases, particularly microbial infections (19). *Centella asiatica* is used as a medicinal herb in Ayurvedic medicine, traditional African medicine, and traditional Chinese medicine. *C. asiatica* is one of the chief herbs for treating skin problems, healing wounds, as well as being an antibacterial and antiviral agent (20). The therapeutic substances in C. asiatica are saponin-containing triterpene acids and their sugar esters, of which asiatic acid, made classic acid, and asiaticosides are considered to be the most important. Such natural quorum sensing interfering compounds are also reported in exudates of several vegetables and spices and are also found to be secreted by Penicillium spp. and Chlamydomonasreinhardtii (21, 22). Considering the enormous number of plant varieties and the chemical diversity that plants inherently possess, screening plants for medicinally significant compounds seems rational. Various medicinal plants have been screened for their anti-QS potential, and several phytochemicals have been shown to affect the expression of pathogenicity via disruption of QS (23).

Anti-quorum sensing therapy in Indian research

Discovery of (halogenated furanones) from Australian macroalgae, Delisseapulchra has generated community to screen compounds7. Anti-QS compounds have reported from Penicillium species Discovery of anti-QS compounds (halogenated furanones) from Australian macro algae, Delisseapulchra has generated community to natural and synthetic compounds7. Anti-QS compounds have reported from Penicillium species plant extracts the range of 2 to 3 mg/ml. Interestingly, all the five plants reduced the swarming PAO1 at $P \leq 0.05$ compared to the control (Table 3). Maximum reduction of swarming motility was recorded by the extract of P. corylifolia followed by P. granatum, M. indica, H. indices, and H. antidysenteric.

In India, lots of scientists are working on evaluating the potential role of phytochemicals as quorum sensing inhibitors. Iqbal Ahmed and colleagues from Aligarh Muslim University in

their study conducted in 2010 tested the ethanolic extracts of 24 Indian medicinal plants by agar well and disc diffusion assay for anti-QS activity using Chromobacteriumviolaceum reporter strains (24). Effect on swarming-motility of Pseudomonas aeruginosa was also recorded at sub-MIC concentrations of extracts. Of the 24 medicinal plants screened Hemidesmusindicus (L.) Schult (root), Holarrhena antidysenterica (Roth), Mangiferaindica L. (seed) Punicagranatum L. (pericarp) and Psoraleacorylifolia L. (seed) demonstrated a varying level of inhibition of violacein production in the reporter strains. Moreover, a significant reduction in swarms was recorded over control. The inhibition of violacein production and swarming motility may be due to direct or indirect interference on QS by active constituents or the interactive effect of different phyto compounds present in the extracts. In a qualitative study, published from Mumbai in 2014, Dr. Shukla and Dr. Bhathena have reported that several tannin-rich crude extracts show a broad spectrum of anti-QS activity (25). Another qualitative study on anti-AHL activity of pericarp of Punicagranatum and an ethyl acetate fraction of S. cumini leaves by the same team has also been reported. These reports draw attention to the fact that tannin-rich extracts of medicinal plants influence quorum sensing mechanisms. In 2015, Dr. Mala Majumdar and her group from Bangalore has reported that the phytochemical screening of methanolic extract of some Indian spices identified the presence of tannins, flavonoids, terpenoids, cardiac glycosides, carbohydrates, alkaloids and phenolic compounds (26). Among all the spices, the total phenol and flavonoid contents were found to be highest in *Syzygiumaromaticum*. *S. aromaticum* exhibited the highest quorum sensing inhibition and dose-dependent inhibition of virulence factors and swimming motility against clinically isolated strains of *Pseudomonas aeruginosa*. Dr. Shukla and Dr. Bhathena has again in 2016 reported that the plant extracts from, P. emblica, T. bellirica, T. chebula, P. granatum, S. cumini, and M. indica (flower), rich in hydrolyzable tannins exhibit a broad spectrum anti-QS activity, i.e, affecting activity of acyl homoserine lactones as well as autoinducers over a wide range of subinhibitory concentrations (27).

CONCLUSION

In spite of the fact that the revelation of antibiotics has been a boon to human civilization, the current conventional antibiotics need to be reviewed for their efficacy because of the increasing occurrence of multidrug-resistant strains (29). One novel therapeutic approach to overcome the problem of resistance is the use of antipathogenic drugs that target key regulatory bacterial systems responsible for the expression of virulence factors. Since quorum

sensing leads to prompts articulation of virulence genes in several known pathogens, agents that can interrupt bacterial communication can be used as antipathogenic drugs (30). The wide impact of Quorum sensing on the physiology of bacteria shows that inhibiting this process would be an appropriate strategy not only to reduce bacterial virulence but also in terms of restoring antibiotic tolerance by decreasing biofilm formation and in terms of decreasing bacterial phage resistance, paving the way for future combination therapies (31). More investigations are expected to outline the impacts actuated by the anti-quorum sensing strategies at both the single bacterial species level and in the context of communities. Future investigations will decide the broadness of the activity of the anti-quorum sensing molecules and their potential in being utilized as therapy, combination therapy and as coating agents in medical devices.

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