Quorum Sensing and Its Inhibition: Biotechnological Applications

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Abstract

Microorganisms have long been used in various areas of biotechnology. In the recent times what has gained fascination is the communication among microbes, known as Quorum sensing (QS). Fascinating information has been generated on understanding the significance of QS, and its inhibition (QSI), especially in plant, animal and human pathogenesis. Focus has now shifted on exploiting QS and QSIs for biotechnological applications in designing: (i) genetic circuits for producing novel products, (ii) biosensors, (iii) molecules for cancer therapy, etc. Here, we cover a few applications in Health, Agriculture, Aquaculture, Energy and Bioremediation sectors.

Keywords

Aquaculture · Bioenergy · Biofouling · Bioremediation · Cancer · Food · Health · Plants · Pathogens · Quorum sensing

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Abbreviations

3OC12HSL	N-(3-oxododecanoyl)-L-HSL
3OC6HSL	N-(3-oxohexanoyl)-L-HSL
3OC8HSL	N-(3-oxooctanoyl)-L-HSL
3OHC6HSL	N-(3-hydroxyhexanoyl)-L-HSL
AHL	Acylhomoserine lactone
AI	Autoinducer
AIP	Autoinducing peptides
C10-HSL	N-decanoyl-L-HSL
C12HSL	N-dodecanoyl-L-HSL
C12HSL	N-dodecanoyl-L-HSL
C4HSL	N-butanoyl-L-homoserine lactone
C6HSL	N-hexanoyl-L-HSL
HSL	Homoserine lactone

1.1 Introduction

Microbial associations exist with plants (rhizosphere and phyllosphere), animals and human beings (skin surface and gut) (Doebeli and Ispolatov 2010; Ryall et al. 2012). A few of these associations especially the pathogenic, lead to economic losses. Efforts are being made to inhibit microbial growth and pathogenicity and restrict the damage. The discovery of antibiotics was hailed as a boon and perceived as a solution to fight off all bacterial attacks. However, bacteria were quick to respond to this threat to render the novel drug – antibiotic – ineffective (Davies and Davies 2010). The pharmaceutical industries are getting apprehensive and are not keen on investing in R&D for developing novel antibiotics. On the other hand, scientists are looking for novel and innovative ways to deal with pathogenic microbes.

Infectious diseases are generally caused by biofilm forming microbes, through a cell density dependent phenomenon – quorum sensing (QS). Biofilm shield bacteria, which can now resist antibiotic concentrations, up to 1000 times more than those which are enough to kill their free living counterparts (Rasmussen and Givskov 2006). QS allows bacteria to sense their neighbouring cell density through the release of signal molecules, leading to the expression of virulent behaviour. Inhibiting the synthesis or interaction of signal molecules with receptors and their transcription, also known as QS inhibition (QSI) can repress virulence and the bioactive molecules so employed can act as drugs to fight diseases (Kalia 2013). On the other hand, this biofilm formation can also be exploited in scenarios like bioremediation, where it can act as “immobilization” support and ensure high cell density.

1.2 Biotechnological Applications of Quorum Sensing Systems

A few areas, where QS has been found to have the potential to generate bioproducts of high values include bioenergy, waste treatment, food preservatives, biosensors, health, and agricultural activities, etc.

1.2.1 Bio-energy

Bio-hydrogen (H_2) has been recognised as the cleanest fuel of the future. Microbes have an ability to produce H_2 from different substrates including bio-wastes (Patel and Kalia 2013; Yasin et al. 2013). An innovative strategy can be to combine H_2-production with biofilm formation abilities of potential H_2-producers: *Bacillus, Clostridium, Streptococcus, Sinorhizobium, Enterobacter, Klebsiella, Caldicellulosiruptor* and *Escherichia* (Kalia and Purohit 2008; Pawar et al. 2015). QS has also been reported to be of use in bioethanol and biodiesel production. Generation of bioelectricity by Microbial Fuel Cells and H_2 and biomethane by Microbial Electrolysis Cells require strong biofilms (Zhou et al. 2013; Hu et al. 2015).

1.2.2 Bioremediation

Bioremediation process is limited by the insolubility and hence availability of the pollutants to the bacteria. Bio surfactants – Rhamnolipids and Surfactins produced through QS, find use in removal of oil and toxic metals from contaminated sites and soils (Chakraborty and Das 2014; Oslizlo et al. 2014). QS mediated processes like denitrification, ammonium oxidation and exoenzyme production are reported to enhance biodegradation (Shukla et al. 2014; Yong et al. 2015).

1.2.3 Food and Health

QS signalling molecules – AIPs -Nisin, Bacteriocins or lantibiotics, produced by *Lactococcus lactis, Bacillus,* etc. have antimicrobial properties useful for pharma industries and as preservatives in food industry (Nishie et al. 2012; Dobson et al. 2012; Camargo et al. 2016). Various other lantibiotics including cinnamycin, plantaricin C, pep5, epidermin, MU1140, hold a potential as novel antibiotics with some under clinical trials (Dischinger et al. 2014; Field et al. 2015; Li and Tian 2015).

1.2.4 Detecting Metals and Pathogens

QS has also been used to design plasmid biosensors by integrating AHL receptors in RP4 vector, for detecting microbes in the environment (Choudhary and Schmidt-Dannert 2012; Hsu et al. 2016).

1.2.5 Cancer Therapy

Certain oligopeptides of gut microbiota are reported to promote the angiogenesis having a potential to influence metastasis. The toxins, cytokines, tumor antigens can be exploited as a novel and effective treatment of cancer (Hong et al. 2014; Kwon et al. 2014; De Spiegeleer et al. 2015; Wynendaele et al. 2015).

1.2.6 Industrial Products

Microbial QSS produces various extracellular products such as enzymes, rhamnolipids, isobutanol and 1,3-propanediol, 2,3-butanediol with commercial applications (Bernstein and Carlson 2012; Liu and Lu 2015; Chang et al. 2015).

1.2.7 Genetic Devices

Engineering based techniques have long been used in biology to construct synthetic gene networks (Davis et al. 2015). Engineered LuxI/LuxR system fused with antigen proteins have been used to produce vaccines (Choudhary and Schmidt-Dannert 2012; Sturbelle et al. 2013; Chu et al. 2015).

1.3 Biotechnological Applications of QSI

The topic has been reviewed during the last few years (Kalia and Purohit 2011; Kalia 2013). The information described below emphasizes on the developments on the biotechnological applications of QSI, during the last 3 years.

1.3.1 Food Industry

Fruits and vegetables processing industries face economical as well as safety issues due to bacteria which are responsible for problems like. Plant and fruit extracts known as phytochemicals including limonoids, flavanoids, polyphenols, furocoumarins, phenolics, etc. have been tested and reported to act as QSIs to prevent food poisoning and spoilage (Kerekes et al. 2015; Zhu et al. 2015; Oliveira et al. 2016; Venkadesaperumal et al. 2016). Essential oils such as from ginger, eucalyptus, rose and tea tree are reported to have anti-QS effects and may find use as sanitizers and as food preservatives (Kerekes et al. 2015).

1.3.2 Aquaculture

Aquaculture being an important food producing industry world-wide suffers heavy losses due to aquatic pathogens like *Vibrio* spp.and *Aeromonas* spp. killing fishes, prawns, shrimps and molluscs (Niu et al. 2014; Zhao et al. 2014). Halogenated furanones have been holding great promise in protecting fishes (Defoirdt et al. 2007; Benneche et al. 2011). However, thiophenones are proving to be less toxic (Defoirdt et al. 2012; Yang et al. 2015). Supplementation of fish feed with variant of lactonases and peptides have been reported to inhibit QS mediated pathogenicity (Zhang et al. 2015; Sun and Zhang 2016).

1.3.3 Health Care

In infectious diseases, such as cystic fibrosis, bacterial endocarditis, chronic prostatitis, oral cavities, etc., bacteria express their virulent behaviour through QS mediated biofilm formation. Recent efforts have been focussed on developing a strategy to effectively disarm a pathogen through the use of QSIs. Bioactive molecules and nanoparticles are being searched aggressively for they have the potential usage as antimicrobials and QSIs (Gui et al. 2014; Arasu et al. 2015; Balakrishnan et al. 2015; Bandyopadhyay et al. 2015; Bose and Chatterjee 2015; Dobrucka and Długaszewska 2015; Go et al. 2015; Szweda et al. 2015; Begum et al. 2016; Wadhwani et al. 2016; Ahiwale et al. 2017; Azman et al. 2017; Saini and Keum 2017).

1.3.3.1 QSIs from Microbes

Prokaryotes being easy to culture and handle, become a choice of many when it comes to the need of producing novel health care products (Karumuri et al. 2015; Shiva Krishna et al. 2015; Jeyanthi and Velusamy 2016; Varsha et al. 2016; Sanchart et al. 2017; Thakur et al. 2017). Norspermidine, Maniwamycins, Solonamides play role in QSI – inhibit biofilm formation in *S. aureus*, *S. epidermis* and *E. coli* (Nesse et al. 2015; Baldry et al. 2016; Qu et al. 2016). Efforts have also been made to develop synthetic compounds – Thiazolidinedione (TZD) that could inhibit QS in gram negative as well as in gram positive bacteria (Lidor et al. 2015).

1.3.3.2 QSIs of Plant Origin

Epigallocatechin-3-gallate (EGCG), a major catechin in *Camellia sinensis,* green tea leaves is known for its antioxidative, anticancerous and antimicrobial properties (Yin et al. 2015; Fournier-Larente et al. 2016). Secondary metabolites produced by plants – dietary phytochemicals – ajoene, iberin, limonoids, furocoumarins, through their antimicrobial and QSI activities are known to provide health benefits (Kazemian et al. 2015; Sarkar et al. 2015; Brackman et al. 2016). Plant extracts such as *Piper betle* extract, vanillin, flavanoids, etc. also inhibit biofilm formation and thus hold the potential to be used as antifouling agents (Igarashi et al. 2015; Siddiqui et al. 2015). Quercetin, a flavanol is found in various fruits and vegetables such as apples, grapes, onion and tomatoes and finds use as anticancerous, antiapoptotic and anti-oxidative agent (Ouyang et al. 2016).

1.3.3.3 QSIs of Animal Origin

Meat extracts such as those from turkey and beef patties, chicken breast and beef steak have shown AI-2 signalling inhibition (Lu et al. 2004; Soni et al. 2008). Cattle's milk has anti-QSIs compounds (Abolghait et al. 2016; Hernández-Saldaña et al. 2016). Mare colostrum inhibits biofilm forming and virulence factors producing characteristic of *S. aureus* (Srivastava et al. 2015).

1.3.4 Anti-biofouling

Quenching the bacterial communication to target bio-fouling might be a boon to a number of sectors including aqua industries, naval departments and water treatment plants (Ponnusamy et al. 2013; Cheong et al. 2014; Lee et al. 2014; Kim et al. 2015; Wu et al. 2015).

1.3.5 Agriculture

Rhizospheric bacteria, certain epiphytes, essential oils, facilitates easy clearance of pathogen (Corral-Lugo et al. 2016; Des Essarts et al. 2016). Biocontrol agents *Bacillus* spp. A24 as well as *Pseudomonas fluorescens* expressing *aiiA* gene showed reduced rot and gall symptoms by the phytopathogens (Helman and Chernin 2015; Sánchez-Elordi et al. 2015; Kang et al. 2016).

1.4 Synergism Between Antibiotics and QSIs

Another encouraging feature in this battle against pathogens, is the potential synergism between QSI and antibiotics (Zhang et al. 2011; Ma et al. 2012).

1.5 Fais Attention à QSI

A few studies have shown evidence of emergence of microbial resistance to QSI (Kalia et al. 2014; García-Contreras et al. 2016; Koul et al. 2016). Hence, we may need to be more cautious and look for QSI which are QS signal independent (Lee et al. 2015).

1.6 Field Trials

In spite of the fact that mechanisms of QS and QSI have been widely studied, their testing at field and clinical level has been limited (Reuter et al. 2016). Application of QSI under field conditions is necessary before the same can be extended for commercialization (Kim et al. 2014, 2017).

1.6.1 Protecting Plants

Chromobacterium sp. has been successfully employed to control ginseng and pepper from *Alternaria* and *Phytophthora* infections (Kim et al. 2008, 2010, 2014). The pre-treated plants of rice, tomato and wheat were protected from their respective pathogens in a large scale trial (Kim et al. 2017).

1.6.2 Drinking Water

In order to tackle the trouble caused by biofouling encountered during drinking water treatment, QSI enzyme-acylase coated nanofiltration membranes and by using encapsulated bacteria were shown to be stable and enzymatic activity (Kim et al. 2011; Jahangir et al. 2012; Maqbool et al. 2015; Lee et al. 2016).

1.6.3 Health Sector

Short term clinical trial on guinea pig and 24 h trial on human volunteers were tried with QSIs – fimbrolides or furanones. Clinical trial on employing QSI as therapeutics for treating cystic fibrosis in human patients was reported by Prof. Givskov and his team (Smyth et al. 2010). A QSIs formulation patented by Colgate-palmolive for oral care to inhibit biofilm formations is an encouraging sign (Grandclément et al. 2016).

1.7 Opinion

Human trials on the effects of QSIs on infectious diseases have been conducted on a limited scale. We may have to wait for some more time till the confidence level goes up. In this scenario, a stop-gap arrangement has to be made to provide QSIs through: (i) the use of dietary sources rich in phyto-nutrients, (ii) use as inducers to cause pseudo-induction of QS and make bacteria susceptible to immune system, and eradicate pathogens with low antibiotic doses, and (iii) attack those bacteria which promote QSS in pathogens.

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