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Review Article

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Anti-quorum sensing agents: a potential alternative for antibiotics

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ABSTRACT

Quorum sensing (QS) is a bacterial cell to cell communication, which helps bacteria to mount population-density-dependent infection to overcome the defence responses from host. In this mechanism some diffusible chemical signalling compounds are involved, known as autoinducers, which are directly proportional to the population cell density. The main role of QS is to coordinate the expression of several collective traits, including the production of virulence factors, secondary metabolites with antimicrobial activity, pigment production, siderophore production, epiphytic fitness, bioluminescence, plasmid transfer, motility and biofilm formation. Due to the growing bacterial resistance to the antibiotics that have been overused, it has become necessary to search for alternative antimicrobial therapies. One of them is anti-quorum sensing agents/anti-biofilm agents/quorum sensing inhibitors that disrupts the bacterial communication. This study discusses the various QS-disrupting mechanisms used by anti-quorum sensing agents such as, inhibition of AIs synthesis inhibition of AI transport, degradation of AIs using enzymes, sequestration of AIs using monoclonal antibodies, QS signal competition (QS mimicry), as well as the different techniques applied artificially to inhibit the QS pathways in bacteria and thus protecting plant from bacterial diseases.

Keywords: Autoinducers, Biofilm and Quorum sensing

INTRODUCTION

'Quorum' is a Latin word which means the number of members of a group required to be present to carry out an activity legally. Quorum sensing was first reported in 1970 by Nealson *et al*. in *Vibrio fischeri* and *Vibrio harveyi*, a luminous marine gram-negative bacterium (Mukherjee *et al*., 1998). Word 'quorum sensing was coined by Fuqua et al. (1994). Quorum sensing is the regulation of gene expression in response to fluctuation in cell population density (Miller and Bassler, 2001). This allows them to carry out colony wide function and help them to survive, compete, and persist in nature or to colonize a particular host. QS involves the exchange of low molecular weight, diffusible signal molecules between members of a localized population, known as autoinducers, which are directly proportional to the population cell density. Three major autoinducers involved in QS are N-Acylhomoserine lactones (AHLs) in gram negative bacteria, Oligopepetides in gram positive bacteria, Autoinducers 2 (AI-2) in both gram positive and gram-negative bacteria. These signal molecules are secreted by bacteria extracellularly and after reaching some threshold level it diffuses inside the cell and binds to receptor protein. The main role of QS is to coordinate the expression of several collective traits, including the production of antibiotics (Bainton *et al*., 1992), bioluminescence (Nealson and Hastings, 1979), virulence factors (Barber *et al*., 1997), bacterial swarming (Eberl *et al*., 1996), plasmid conjugal transfer (Fuqua and Winans, 1994) and exopolysaccharide biosynthesis (Beck von Bodman and Farrand, 1995).

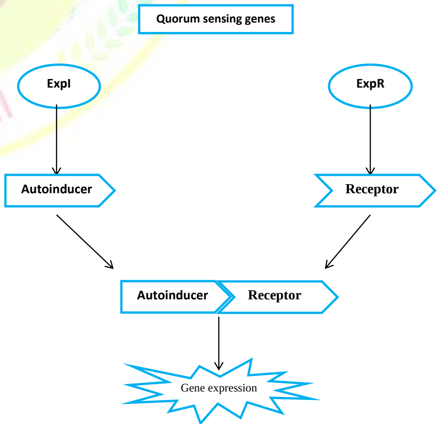


Fig.1 ExpIR mediated signalling in *Erwinia carotovora*

QS mechanism (Gram negative bacteria)

The plant pathogenic bacterium *Erwinia carotovora* causes soft-rot in potato and other vegetables. Cell wall degrading enzymes such as cellulase and pectinase are virulence factors and the production these virulence factors are coordinated by quorum sensing. A cognate pair of ExpI/ExpR (LuxI/LuxR homologues) is involved in extra-cellular enzyme secretion (Hinton *et al*., 1989; Loh *et al*., 2002). ExpI produces primary AHL, 3-oxoC6HL whereas, ExpR encodes for ExpR regulator protein. Mutants defective in *ExpI* do not produce extracellular enzymes and fail to secrete harpin. Therefore, they are completely non-pathogenic (Bainton *et al*., 1992; Chatterjee *et al.*, 1995; Cui *et al*., 1996). At high AHL density, 3-oxoC6HL binds with regulator protein and forms active complex which triggers the expression of target genes encoding for cellulase, pectinase and polygalacturonase.

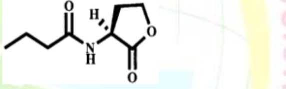
Table 1.1 Various quorum sensing (QS) signals and QS-dependent phenotype of plant-pathogenic bacteria

Phyto-pathogenic Bacteria	QS signal molecule	Phenotype	References
Agrobacterium tumefaciens	3-oxo-C8-HSL	Ti plasmid conjugal transfer	Tannières *et al*., 2017
Burkholderia glumae	C6-HSL, C8-HSL	Toxoflavin biosynthesis and transport	Gao *et al*., 2015
Pantoea stewartii ssp. *stewartii*	3-oxo-C6-HSL	EPS stewartan, biofilm development, host colonization	Koutsoudis *et al*., 2006
Pectobacterium atrosepticum	3-oxo-C6-HSL, C6-HSL, 3-oxoC8-HSL and 3-oxo-C10-HSL	Pectolytic enzymes, antibiotic carbapenem, virulence factor	Crépin *et al*., 2012
Pectobacterium carotovorum	3-oxo-C6-HSL, C6-HSL, 3-oxoC8-HS	Extracellular cell wall-degrading enzymes, antibiotic carbapenem, harpin HrpN	Crépin *et al*., 2012
Pseudomonas syringae pv. Syringae	3-oxo-C6-HSL	Exopolysaccharide (EPS), oxidative stress tolerance, extracellular degrading enzymes, negative regulator of swarming	Cheng *et al*., 2016
Pseudomonas syringae pv. Tabaci	3-oxo-C6-HSL, C6-HSL	Negative regulation of biosurfactant, extracellular polysaccharides, iron acquisition, virulence	Taguchi *et al*., 2006
Ralstonia solanacearum	3-Hydroxy palmitic acid methyl ester	EPS, endoglucanase, pectin methyl esterase	Mori *et al*., 2017
Xanthomonas oryzae pv. oryzae	DSF, BDSF, CDSF	EPS, extracellular xylanase	Zheng *et al*., 2016
Xanthomonas campestris pv. campestris	DF, DSF	Xanthomonadin, EPS, extracellular enzymes, biofilm dispersal, oxidative stress	He *et al.* 2011
Xyllela fastidiosa	DSF (*Xyllela*)	Biofilm formation in insects	Ionescu *et al.* 2014

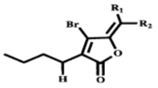
★C8-HSL, N-octanoyl-L-homoserine lactone; C6-HSL, N-hexanoyl-L-homoserine lactone; 3-oxo-C6-HSL, N-(3-oxohexanoyl)-L-homoserine lactone; 3-oxo-C8-HSL, N-(3-oxooctanoyl)-L-homoserine lactone; 3-oxo-C10-HSL, N-(3-oxodecanoyl)-L-homoserine lactone; DF, dodecenoic acid, 3-hydroxybenzoic acid; DSF, 12-methyl-tetradecanoic acid; BDSF and CDSF, cis-11-methyldodeca-2, 5-dienoic acid.

ANTI-QUORUM SENSING AGENTS

Inactivation and disruption of quorum sensing signalling is known as **quorum quenching** and the agents involved are known as **anti-quorum sensing agents/anti-biofilm agents/quorum sensing inhibitors.** The ideal **anti-QS agents** should be chemically stable, low molecular weight and it should not posses any toxic side effects on the bacteria, posses high degree of specificity for the QS receptor protein (Asfour, 2018). Givskov *et al*., 1996 identified first anti-QS compound, **halogenated furanone** produced by the benthic marine Australian macro-alga, *Delisea pulchra* inhibited the QS-regulated behaviours in *Serratia liquefaciens* (opportunistic human pathogen) by competitively bind with the **SwrR** (LuxR type proteins).



N-butanoyl-L-homoserine lactone (BHL)



Halogenated furanone

WORKING MECHANISM OF ANTI-QUORUM SENSING AGENTS

Inhibition of AIs synthesis
Inhibition of AI transport
The degradation of AIs using enzymes
Sequestration of AIs using antibodies
QS signal competition (QS mimicry)

Inhibition of AIs synthesis

Anti-quorum sensing agents working under this mechanism targets the precursors of AHL synthesis such as acyl-ACP and SAM (S-adenosyl-methionine). Analogues of SAM, namely sinefungin (an SAM-like antibiotic), competitively binds with AHL synthase thus, inhibit the synthesis of AHL. Triclosan is another good example of AHL synthesis inhibitor which targets the enoyl-ACP reductase activity (Hoang and Schweizer, 1999). Chung *et al.* (2011) identified another AHL antagonists (named J8-C8), which is an acyl-ACP carrier competitive inhibitor. Precursors involved in autoinducing peptide signal synthesis in gram-positive bacteria are also good targets but till now no inhibitors targeting these proteins have been reported (Brackman & Coenye, 2014).

Inhibition of AI transport

In *Escherichia coli* quorum sensing is mediated by the signal generation, secretion, and uptake of autoinducer-2 via ABC transporter (ATP Binding Cassette protein). Inside the cell AI-2 gets phosphorylated in to phospho-AI-2 in the presence of LsrK (AI-2 kinase), which triggers gene expression. Phospho-AI-2 degrades overnight to 2-phosphoglycolic acid (PG). Roy *et al.*, 2010 added LsrK and ATP outside the cell which phosphorylated AI-2 into phospho-AI-2 which apparently prevented from being transported inside cells, in this way QS mechanism was quenched.

The degradation of AIs using enzymes

QS signals can be enzymatically degraded by using AHL lactonases and AHL acylases which hydrolyze the homo-serine lactone ring and amide bonds of AHL molecule, respectively. Whereas, AHL oxidases and AHL reductases do not degrade the AHL molecule instead they modify it by reducing carbonyl or hydroxyl groups (Brackman & Coenye, 2014). Bacterial species such as *Agrobacterium tumefaciens*, *Arthrobacter*, *Acinetobacter* spp., *Bacillus* spp., *Bosea* spp., *Delftia acidovorans*, *Pseudomonas. Aeruginosa*, *Sphingomonas* spp., have been reported to produce enzymes which are capable of degrading AHLs (Uroz *et al.*, 2009). Apart from these eukaryotes like plants and root associated fungi including *Hordeum vulgare*, *Lotus corniculatus* and *Pachyrhizus erosus* can degrade AHLs (Uroz & Heinonsalo, 2008). To date no AIP or AI-2 QS signal specific degrading enzyme have been described.

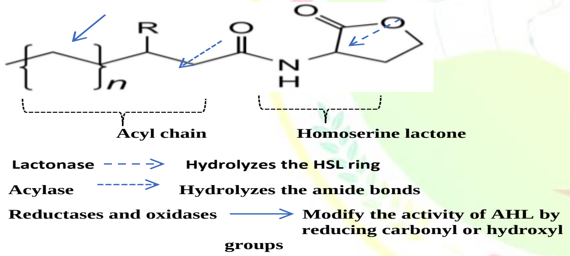


Table 2. Genetically engineered plants producing Ais degrading enzymes

Genetically engineered host plant	aiiA gene donor	Pathogen	References
Nicotiana tabacum and Solanum tuberosum	*Bacillus* sp. 240B1	*E. caratovora*	Dong *et al.*, 2001
Amorphophallus konjac	*Bacillus thuringiensis*	*Erwinia carotovora subsp. Carotovora* (Ecc) SCG1	Ban *et al.*, 2009

Different ways to expose phyto-pathpathogenic bacteria to AIs degrading enzymes

1.) Biotization

2.) Mutagenesis

3.) Transgenic plants producing AHLs-ase

Biotization

Biotization is the process by which non-native microbes (AHLs degrading enzymes producing microbes) are introduced inside plant. These microbes increase plant immunity against phytopathogens by helping them to obtain more transition metals by producing siderophores (Fones and Preston, 2013). Apart from producing AHL-degrading enzymes these quorum quenching microbes will occupy most of the intercellular space thus leaving very few spaces for later-invading phyto-pathogenic bacteria (Alagarasan *et al.*, 2017).

Table 1. Quorum sensing inhibiting endophytes that have been identified

Host plant	Endophytic organisms	Disrupts QS of pathogens	References
Potato & tomato	*Bacillus* sp. A24, ★*P. fluorescens* P3/pME6863 strain	*Pe. carotovorum* and *A. tumefaciens*	Molina *et al.*, 2003
Tobacco	*Bacillus* sp., *Lysinibacillus* sp., *Acinetobacter* sp., *Serratia* sp.	Tobacco pathogens	Ma *et al.*, 2013
Rice	★*Burkholderia* sp. KJ006–engineered with aiiA gene of *Bacillus thurungiensis*	*Burkholderia glumae*	Cho *et al.*, 2007

★ Genetically engineered

Mutagenesis

In *A. tumefaciens*, production of the AHL lactonase is encoded by attM which in normal condition gets suppressed by the negative transcription factor attJ. Zhang *et al.* (2003) knocked attJ out by transposon (Tn5) mutagenesis which resulted in biosynthesis of AHL lactonase, which degraded AHL and thus, QS-dependent conjugal transfer of Ti plasmid in plants was inhibited.

Transgenic plants producing AHL-ase

Plants can be genetically transformed by engineering it with aiiA gene (autoinducer inactivation gene) from *Bacillus spp*. which encodes for lactonase enzymes.

Sequestration of AIs using antibodies

Anti-AHL monoclonal antibodies that sequester the AHL signal molecules was first time used against *P. aeruginosa* (Kaufmann *et al*., 2007). Marin *et al.* (2007) have made further efforts on the synthesis of QQ catalytic antibodies which bear analogy to the transition-state structure of AHL-ring hydrolysis thus effecting quorum sensing process.

QS signal competition (QS mimicry)

In this mechanism signal analogs compete with AHL signal molecules and competitively bind with the receptor protein which leads to the conformational change in the protein. Rasmussen *et al*. (2000) used halogenated furanone compounds (AHL analog) produced by the Australian marine macro-alga *Delisea pulchra*, which inhibited AHL-regulated processes, especially extracellular enzyme production, which is virulence factor in *E. carotovora*. Biofilm formation of *Serratia marcescens* and *P. aeruginosa* was drastically affected when bacetria was treated with AHL analogs in which the HSL ring was replaced by a cyclopentyl or a cyclohexanone ring (Morohoshi *et al*., 2007; Ishida *et al.,* 2007) whereas, when the amide function in AHL was replaced by a triazolyldihydrofuranone, affected biofilm formation in *B. cenocepacia* and *P. aeruginosa* (Brackman *et al.*, 2012)

Anti-QS agents Vs. Antibiotics

Antibiotics	Anti-QS agents
Antibiotics kill or slow down the growth of bacteria and therefore are more likely to yield resistant phenotype in bacteria.	Anti-QS do not threaten bacteria with life-or-death situations instead they attenuate bacterial virulence and therefore are less likely to yield resistant phenotype.

Challenges in developing Anti- Quorum Sensing agents -

The first objection	The selectivity of anti-quorum sensing agents Theory says that the anti-quorum sensing agents are highly specific but if we are using anti-QS agents targeting AI-2 i.e. interspecific type signal molecule may affect non-target bacteria also.
The second objection	The inhibition of virulence by anti-quorum sensing agents There are various reports suggesting that the deletion of *luxS* (Δ*luxS*) increased the pathogenicity features in *Helicobacter pylori* (Cole *et a*l., 2004; Anderson *et al*., 2015), *Vibrio cholerae* (Ali and Benitez, 2009), and *Haemophilus parasuis* (Zhang *et al.*, 2002).
The third objection	Inability to develop resistance against quorum quenching therapies Maeda *et al*. (2012) in reported *P. aeruginosa* could develop resistance to against furanones by mutating genes encoding efflux pumps, which are proteins responsible for the removal of harmful substances from cells.

CONCLUSION

Quorum-quenching mechanisms act by targeting key steps of quorum sensing by: Blocking signal generation, Signal degradation, Signal competition, Signal transportation, Signal sequestration. They have promising potential in basic research as well as biotechnological applications. There is a novel possibility of exploiting the QQ endophytes as a systematic and sustainable tool for plant disease management.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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