

Quorum Sensing Inhibitor: A New Strategy Against Pathogenic Bacteria

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Received December 23, 2020; Revised February 18, 2021; Accepted May 21, 2021

ABSTRACT

Due to the increasing resistance of antibiotics from the last few decades, it is crucial to find new techniques against pathogenic bacteria. Quorum sensing (QS) is the alternative target to introduce a new strategy. The gene expression of QS has occurred in a cell density-dependent manner. Synthetic and natural QS inhibitors (QSIs) play a crucial role to inhibit these QS signals. In this review, we highlight some examples of natural and synthetic QSIs. This short review also focuses on the inhibition of QS mechanisms with some of its applications.

Keywords: Quorum sensing, Pathogenic bacteria, QS inhibitors

INTRODUCTION

The insecure and excessive use of antibiotics causes several problems like the emergence of multi-drug resistance of pathogenic bacteria and thus becomes a serious problem to the health system of human and domestic animals [1,2]. A large number of infectious diseases are linked to the enormous growth of bacterial biofilm formation [3]. Quorum sensing (QS) controls this bacterial behavior by the secretion of signal molecules in a cell density-dependent manner [4,5]. So, QS is gaining now as an important therapeutic target because QS inhibitory drugs have more specific effects than traditional antibiotics [6]. Quorum sensing inhibitor (QSI) has been widely studied in recent times due to its feasibility and applicability in combating pathogens. Generally, two types of QSIs are found. One type contains small molecule QSIs, extracted from either natural resources or obtained from chemical synthesis [7,8]. The other type contains quorum quenching (QQ) enzymes includes acyl-homoserine lactones (AHLs) and autoinducer-2 (AI-2) kinases as signaling molecules [9-11].

QUORUM SENSING SIGNALS

Acyl-homoserinelactones (AHLs), autoinducing peptides (AIPs) and autoinducer-2 (AI-2) (Figure 1) are mainly found in forming bacterial QS signals by the formation of biofilm, conjugation of plasmid and finally affect the antibiotic resistance due to survival capacity of bacteria from difficulty in the environment [12]. The process of QS signaling cell to cell communications is fully different for both Gram-positive and Gram-negative bacteria. Gram-negative bacteria mainly produce AHL signaling molecules whereas, Gram-positive bacteria produce AIP signaling molecules but AI-2 signals

are produced from both of these two bacteria [13-15] (Figure 2).

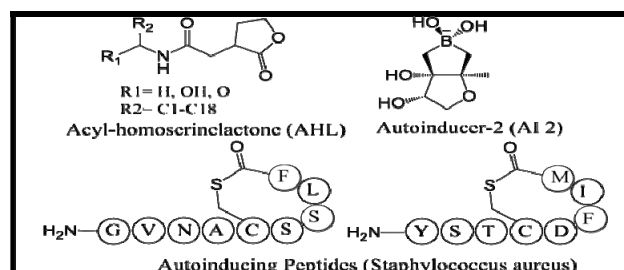


Figure 1. Chemical structures of QS signaling molecules

Characteristic of QSI

Firstly, an ideal QSI has a low molecular weight which significantly reduces the expression of QS controlled genes. Secondly, QSI has shown a higher degree of specificity for the QS regulator (LuxR homologue). Thirdly, this QSI should be chemically stable with metabolic resistance and disposed of by a higher host organism [16].

Quorum sensing inhibition mechanism

The working principles of most of the QSIs are based on the

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Citation: Sarkar K & Das RK. (2021) Quorum Sensing Inhibitor: A New Strategy Against Pathogenic Bacteria. Adv Res Endocrinol Metab, 3(1): 109-113.

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following schemes [17].

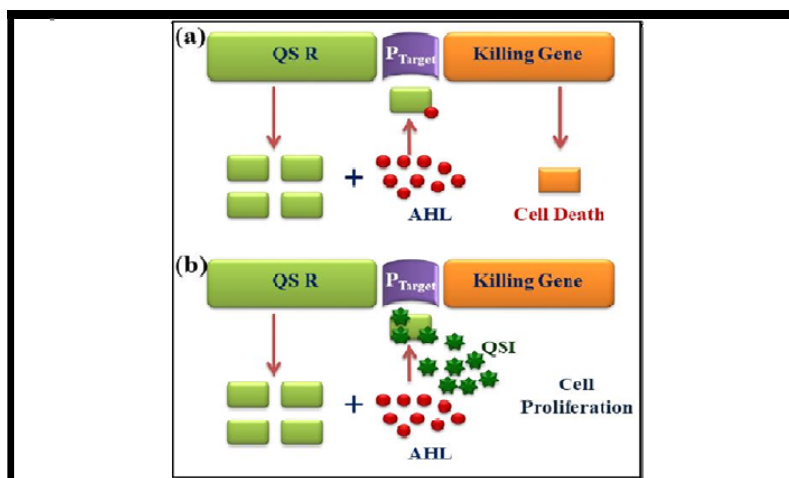


Figure 2. Diagram of QSI selector (QSIS). (a) Exogenous supply of AHL signal activate an AHL receptor with LuxR homologue (QS R), which induces the expression of killing gene from a QS-regulated promoter (P_{Target}) leading to cell death. (b) Presence of QSI block the receipt AHL signal and expression of the killing gene is now prevented, allowing for the growth of the screening bacterium.

Degrading QS signals

Degradation of the QS signal can happen either by enzymatically or nonenzymatically. Generally, three types of enzymes are responsible to target AHL signals. AHL lactonase hydrolyzes ester bond (homoserine lactone ring) of AHL [6,18]. Acylase is another enzyme that degrades the AHL signal and forms homoserine lactone (HSL) and 3-oxodecanoic acid as major products [19]. Oxido-reductase is the third enzyme, responsible for QS signal degradation by degrading AHL [20].

Biosynthesis of inhibited QS signal

The suppression of AHL production can be occurred theoretically by hampering *S*-adenosylmethionine (SAM) biosynthesis or by inactivating synthase enzyme [6]. Some QSIs are generated by targeting LuxS. QSI activity to inhibit LuxS was first found by *S*-anhydroribosyl-L-homocysteine and *S*-homoribosyl-L-cysteine [21]. Recently, some potent small molecules are found that quenched *S. mutans* QS by inhibiting the peptidase activity of the ComA cassette [22].

Detected QS signal inhibition

Detected QS signal can be inhibited by altering downstream signals of non-productive signal-receptor complexes. Computer-aided structural modification of known inhibitors is another possibility to improve QS inhibitory activity [6]. Some researchers also found non-AHL based pharmacophores that inhibit LuxR proteins [23,24].

Antibiotics as QS inhibitors

There are many shreds of evidence for the use of antibiotics that target QS. Antibiotics such as azithromycin, ceftazidime,

and ciprofloxacin also have QSI activity [6]. Zosteric acid (phenolic compound) is another compound that has inhibitory activity against *Candida albicans* [25]. Similarly, ursolic acid suppresses the biofilm formation of *E. coli*, *P. aeruginosa*, *Vibrio harveyi* [26].

EXAMPLE OF QSIS

Natural quorum sensing inhibitors

Due to the co-existence of various plants and fungi with QS bacteria, they have evolved natural QSIs to reduce bacterial infection. Cyclic Sulphur compounds, halogenated furanones and penicillanic acid belong to this category [27-29].

Plant-based QSI

Garlic extracts with 4-nitropyridine-N-oxide have an inhibitory activity of QS activated virulence genes [30]. Chloroform and methanol extract of clove also have inhibitory activity towards QS signaling in *E. coli* [31]. Γ -amino butyric acid (GABA) produced from plants have promoted the AHL signal degradation by lactonase [32,33]. Pyrogallol from *Embllica Officinalis* have antagonism activity against AI-2 [34]. Curcumin from *Curcuma longa* reduces the virulence genes expression of *P. aeruginosa* [35]. Furocoumarins, limonoids, and cinnamaldehyde derivatives also have QSI abilities [36,37]. Flavonoids such as kaempferol, apigenin, naringenin, and quercetin have various QSI activities [38].

Fungus based QSIs

Antibiotics are produced as secondary metabolites from fungi. Since penicillin has quite an activity to control bacterial infections and thus act as QSI (1). *Auricularia*

auricular created natural pigments which have QSI activity to inhibit violacein production in *C. violaceum* [39].

Marine organism-based QSIs

Delisea pulchra produced halogenated furanones which inhibit bacterial AHL signals of QS mediated activity. Cyanobacteria (marine organisms) also inhibit QS gene expression. Lyngbyoic acid and malyngolide (isolate from *Lyngbya majuscula*) also inhibit violacein production in *C. violaceum* and pyocyanin elastase production in *P. aeruginosa* [40,41]. In *P. aeruginosa*, Malyngamide-C, and 8-epi-malyngamide (extracted from *L. majuscula*) are also developed as QSI [42].

Synthetic quorum sensing inhibitors

Substitution of C-3 atom by Sulphur in the acyl side chain of AHL created compounds that effectively block QS expression in both LasR and LuxR. Similarly, aryl substitution at the end of the side chain produced other successful QSIs [43]. The QSI potency of aryl AHL can be further increased by substituting the carbonyl group (C-1) of the side chain with the sulphonyl group [44].

APPLICATION OF QSIS

QSI has a wide range of applications in various fields like the human health system, food industry. Hentzer et al. suggested that QSI can effectively reduce biofouling of surgical implants (caused by *P. aeruginosa*) on the surface device [45]. QS signal of *Vibrio cholera* is targeted by some QSI for developing cholera therapy [46]. The combined form of antibiotics with anti QS strategies can also develop some QSIs for medicinal treatment [6]. Endophytic QS inhibitors owing to biodegradable are more suitable for the food preservation industry [47].

CONCLUSION

In conclusion, QSI gives a new approach with promising activity in the battle against antibiotic-resistant pathogenic bacteria. Hence, combine the effect of QSI with antibiotics may be useful in clinical treatment. Though QSI has a wide range of applications in the enormous field, its production at a large scale is still a matter of great concern. In the future, we hope that more types of QSI will come as safe and suitable antimicrobial drugs.

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