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Quorum Sensing Systems Analysis in Pseudomonas aeruginosa

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PSEUDOMONAS aeruginosa is an important opportunistic human pathogen that causes serious infection diseases. The quorum sensing (QS) system is a cell to cell signaling mechanism that it has important role in the regulating of bacterial genes. *Pseudomonas aeruginosa* has two important QS systems including *lasIR* and *rhlIR*. Therefore, our aim was introduced these systems in the topic bacteria *P. aeruginosa*.

Keywords: Quorum sensing systems, *lasIR*, *rhlIR*, *Pseudomonas aeruginosa.*

Introduction

Pseudomonas aeruginosa causes serious infection diseases that vary from local to systemic infections, especially in people with immune system disorders [1,2]. This bacterium is also intrinsically is resistant to many antimicrobial agents [3]. In addition to intrinsically resistant, however, the misuse of antimicrobial agents causes to increase multi-drug resistance strains [4,5]. Quorum sensing is actually a cell to cell signaling mechanism that each bacteria existing in a population respond to extracellular signals molecules (autoinducer molecules) which is produced by the bacterial cells. Quorum sensing system is regulated to expression of many bacterial genes such as genes related to virulence, antibiotic resistance, biofilm formation, toxin-antitoxin systems and others. Generally, when the concentration of autoinducer molecules came to a certain threshold, they connected to the receptor molecules (protein R). These receptor molecules are connected to autoinducer molecules (from N-terminal section) and DNA molecule (from C-terminal section) that formed receptor-autoinducer complex. The receptor-messenger complex is result in regulation of diverse bacterial genes (Fig.1,2) [6-12]. Therefore, we conducted current study for a good knowledge of these systems in *P. aeruginosa*.

The types of quorum sensing systems in P.aeruginosa:

Previous studies have been shown that there are two QS systems (*las* and *rhl*) in *P. aeruginosa* and the autoinducer molecule is AHL or N-acylatedhemoserine lactone. The performance of the two QS systems is as follows (Fig. 2) [6, 8-10, 12, 14, 15]:

(a) las system

lasI: producer C4-HSL autoinducer molecules

lasR: Induces gene expression in complex with the C4-HSL

(b) rhl system

rhlI: producer 3-OXO-C12-HSL autoinducer molecules

rhlR: Induces gene expression in complex with the 3-OXO-C12-HSL

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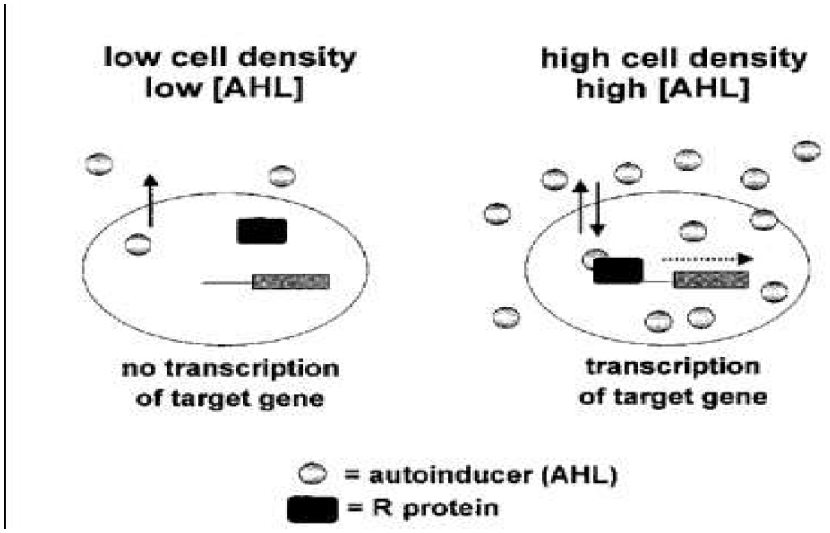

Fig. 1. A schematic bacterial quorum sensing system [13].

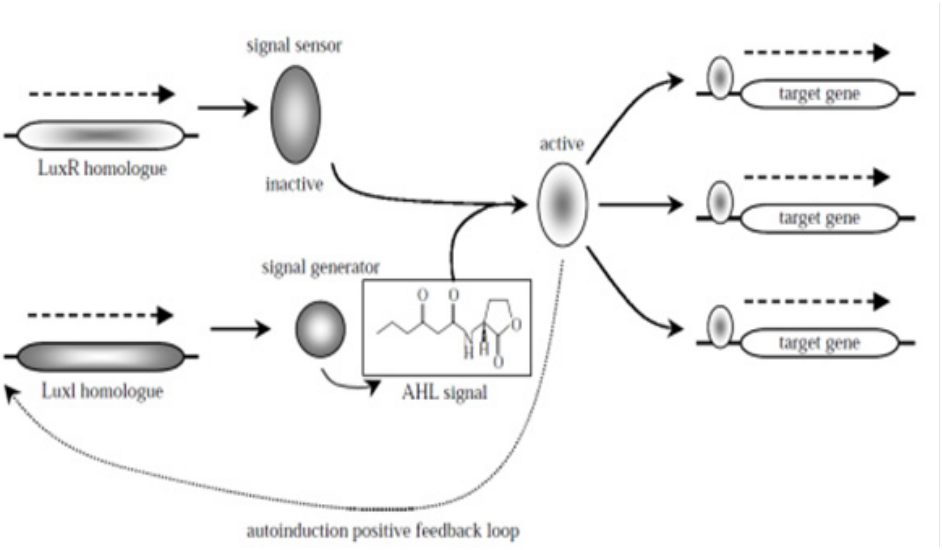

Fig. 2. The receptor-autoinducer complex formation: When the bacteria population reaches to a certain threshold concentration, autoinducer molecules are connected to protein R (LasR and RhlR) and the formation of this complex will result in gene expression.

Regulating quorum sensing systems in P. aeruginosa bacteria

The quorum sensing system is a global regulation system. Some bacterial genes are under the control of this system, and others regulated specifically. These systems are connected to *lux*-box specific sequences that in *P.aeruginosa* called *las*-box. The LasR molecule has multimer structure, but the RhlR molecule has dimer structure. However, the Las and Rhl are not compatible systems. Therefore, the RhlI-produced C4-AHL molecule cannot activate LasR, and also the LasI-produced 3-oxo-C12-AHL cannot activate RhlR. In addition, studies have been shown that many genes controlling the QS systems (Quorum sensing-controlled genes, qsc) should be classified based on temporary response patterns in the presence of Las AHL and Rhl AHL signal. Additional settings on the regulation systems of QS should be applied in different stages of bacterial life. Some *qsc* genes quickly respond to extracellular signals, while others only when bacteria are in late phase development can respond to AHL signals. Studies have been shown that *P. aeruginosa* in vitro can have a strong effect on the activation of *qsc* genes by increasing extracellular AHL molecules. However, some areas containing inhibitors that are affect on the

activating of *qsc* genes. Importantly, *P. aeruginosa* has several global regulatory factors that influence and regulate QS circuitry (Fig.3) [15-18].

The functions of quorum sensing systems in P. aeruginosa

In this way, mutant strains with mutations in QS genes were used. Results showed that the mutant strains had less pathogenicity compared to wild strains. Nevertheless, the mutant strains had effects on severity of disease that suggests these genes are not the only factor necessary for disease but also the other factors are effective in the development of disease [19].

The quorum sensing systems as a potential target for antimicrobial agents

Recently, we see an increase in *P. aeruginosa* strains with multiple drug resistance. Awareness of the diverse QS systems function in bacterial cells, it has provided these systems as unique targets for new antimicrobial drugs. Several components of these systems are considered as

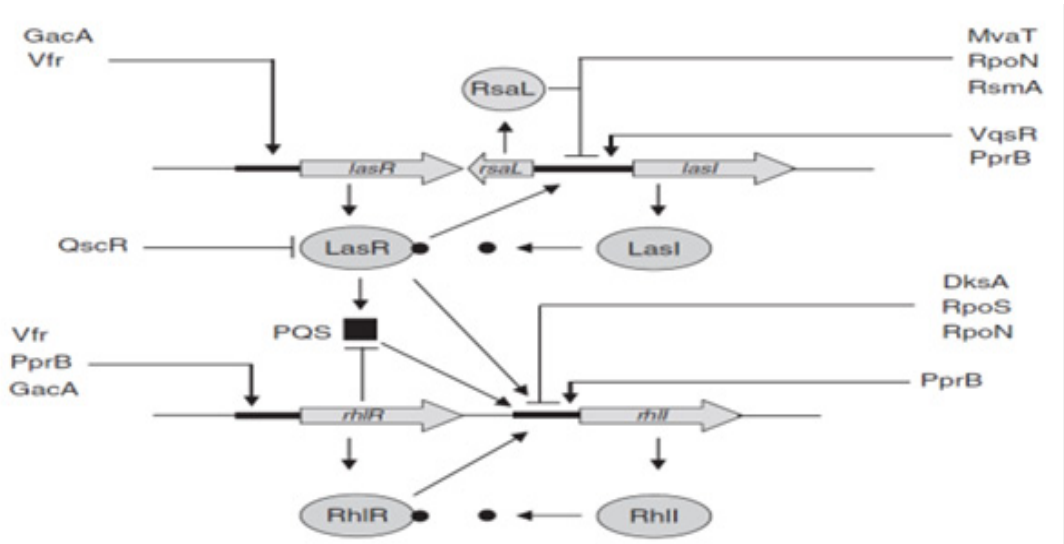

Fig. 3. Regulation of QS systems in *P. aeruginosa*. Arrows in the promotor region indicate a positive regulation and small parallel lines indicate negative regulation. The Quinolone signaling molecule 2-heptyl-3-hydroxy-4-quinolone (PQS) molecules provide the connection between las and *rhl* systems [17].

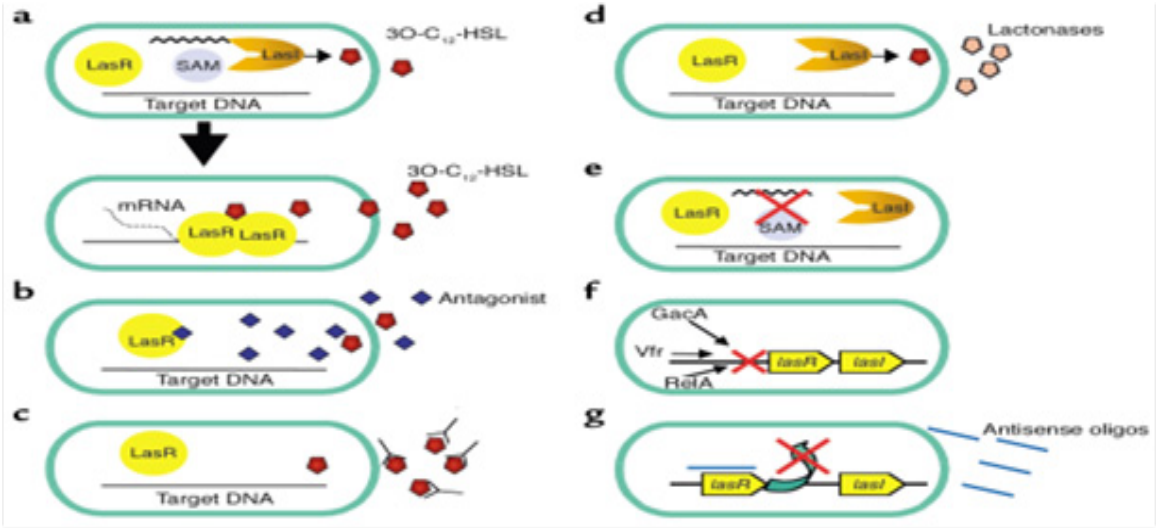

Fig. 4. Different potential targets of QS systems for antimicrobial agents: antagonistic analogues (b), specific antibodies (c), lactonases as degradation molecule (d), target the expression of QS components (e), drugs that inhibit *las*R and *las*I (f), specific antisense oligonucleotides (g) [19].

ideal targets for drug development including: (1) Inhibition of activation of LasR and RhlR through AHL analogs that acts as antagonists of 3O-C12-HSL and C4-HSL molecules, (2) inhibiting of active AHL molecules by specific antibodies and (3) inhibition of *las I*/*R* and *rhl I*/*R* expression (Fig.4) [20].

Conclusions

Pseudomonas aeruginosa has two QS systems *las* and *rhl*. These systems regulate expression of many bacterial genes that affect various its physiologic functions. These systems can provide suitable targets for novel antimicrobial agents. However, there are many ambiguities about these systems that need further studies.

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Conflict of interest

Authors declare no conflict of interest.

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