Quorum sensing as a potential therapeutic target against *Pseudomonas aeruginosa*

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Introduction

P. aeruginosa is an opportunistic pathogen and it is commonly associated with nosocomial infections, infections in immunosupressed hosts and is a leading cause of death in severe respiratory infections, such as chronic lung infections in cystic fibrosis (CF) patients. Infections with *P. aeruginosa* are difficult to eradicate, due to their high levels of antibiotic resistance and growth in biofilms [1].
To facilitate the establishment of infection, *P. aeruginosa* produces an impressive array of virulence factors, many of which are under the control of the quorum sensing (QS) regulatory system (Figure 1)[10]. For this reason, QS has been considered an attractive target for the development of new therapeutic strategies.

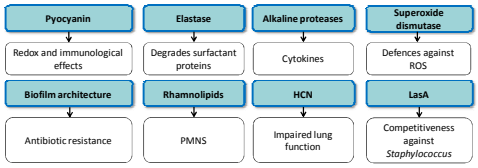


Figure 1. *Pseudomonas aeruginosa* QS-regulated virulence factors [10].

QS in *P. aeruginosa* virulence

QS controls virulence gene expression through the production of diffusible signal molecules termed autoinducers (AIs). In *P. aeruginosa*, and most Gram-negative bacteria, the autoinducers are acyl homoserine lactones (AHLs) (Figure 2)[1].

Up to 10% of the *P. aeruginosa* genome is controlled by QS. At least three intertwined QS systems (LasR-LasI,RhlR-RhlI and PQS) and one orphan autoinducer receptor (QscR) affect the ability of *P. aeruginosa* to cause disease (Figure 3)[7].

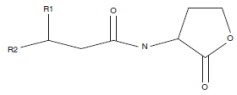
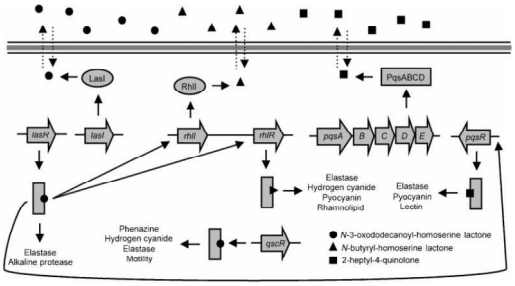


Figure 2. Basic structure of the AHL signal molecule where R1= H, OH, or O and R2=C_1–C_{18} [7].

Figure 3. AHLs (3OC12HSL, C4HSL) and PQS accumulate during growth. Once a critical concentration has been reached, AHLs can bind to and activate cytoplasmatic receptor proteins which can bind to promoter regions of target gens to activate their transcription [1].



Strategies to interfere QS signaling

The discovery of new therapeutic approaches to target bacterial virulence is essential, owing to the increasing emergence of bacterial strains that are acquiring resistance to antibiotics (Figure 4)[6].

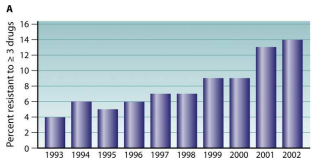


Figure 4. Increasing prevalence of multidrug resistance among *P. aeruginosa* isolates from ICU patients in the United States [6].

The process of interfering with or destroying the QS signals (quorum quenching) can be carried out in a number of ways (Figure 5) [9]:

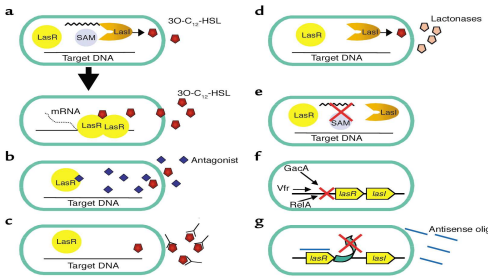


Figure 5. Potential QS targets for the inhibition of *P. aeruginosa* virulence [9].
(a) *P. aeruginosa* LasI synthase utilizes *S*-adenosyl methionine (SAM) and acyl-ACP to form 3O-C12-HSL.
(b) Antagonistic analogues of cognate AHLs compete for binding to LasR.
(c) Specific antibodies bind to AHLs as they exit the bacteria, inhibiting their interaction with host cells.
(d) Lactonases degrade AHLs as they leave the bacteria, thus inhibiting their activation of LasR and host cells.
(e) Targeting the expression of LasI substrates would prevent the production of 3O-C12-HSL, and thus QS activation.
(f) Drugs that inhibit regulated *lasR* and *lasI* factors would result in altered QS activation.
(g) Specific antisense oligonucleotides (oligos) pair with *lasR* or *lasI* RNA and inhibit gene translation and thus protein production.

Quorum sensing inhibitors (QSIs)

Blocking the AHL receptors site with an AHL analogue is a classical pharmacological approach to receptor antagonism. Promising QSIs belonging to different chemical classes have been discovered by screening random libraries of synthetic and natural compounds. The application of these compounds for treatment of human patients is limited due to very low concentration of the active principle, instability and toxicity [5,7].

A promising way is searching for anti-QS side activity among the thousands of drugs approved for clinical use in the treatment of different diseases.

By screening a library of FDA-approved chemicals, the anthelmintic drug niclosamide, was characterized in detail for its anti-QS activity. Niclosamide strongly inhibits the *P. aeruginosa* QS response and have a marked inhibitory effect on the levels of QS-regulated secreted virulence factors (Figure 6)[4].

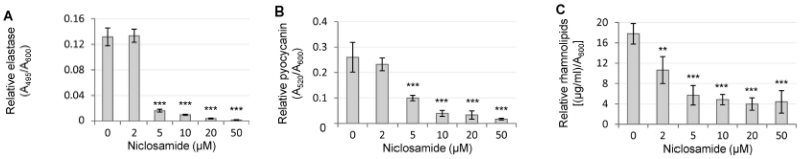


Figure 6. Effects of niclosamide on the production of QS-regulated extracellular virulence factors [4].

Conclusions

- ✓ *P. aeruginosa* regulates much of its virulence via QS.
- ✓ QS becomes attractive for novel antimicrobials, given the resistance of many *P. aeruginosa* isolates to available antibiotics.
- ✓ Presumably, therapies that affect bacterial behavior will not be as prone to resistance as are the targets of traditional antibiotics.
- ✓ Clinical application of QSIs identified so far is still distant, likely due to their unsuitability for use in humans.
- ✓ The major outcome is the identification of a strong anti-QS activity in a compound already approved for use in humans. Niclosamide, an anthelmintic, provides a new promising drug candidate against *P. aeruginosa,* although clinical applications remain far away.

References

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