Modulation of the Quorum Sensing Regulation in *Pseudomonas aeruginosa*

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In opportunistic pathogen *Pseudomonas aeruginosa*, quorum sensing (QS) plays a crucial role in microbial infection and biofilm formation. *P. aeruginosa* possesses three acyl-homoserine lactone (acyl-HSL) QS systems, LasR-I, RhlR-I, and QscR. LasI catalyzes the synthesis of *N*-3-oxododecanoyl HSL (3OC12) and LasR is a transcription factor that requires 3OC12 as a ligand. RhlI catalyzes the synthesis of *N*-butanoyl HSL (C4) and RhlR is a transcription factor that responds to C4. QscR is an LasR-RhlR homolog that requires 3OC12 produced by LasI to regulate its target genes. LasR, RhlR, QscR, and their cognate signal synthase genes control the transcription of hundreds of genes including the virulence genes of *P. aeruginosa*. So, the modulation of QS regulation has been considered as a good target of new anti-bacterial strategy. The QS modulation may be achieved in several different ways; 1) the modulation of the external signal context, 2) the functional modulation of the QS signal receptors or QS transcriptional regulators, and 3) the modulation of the QS-related cellular physiology. In *P. aeruginosa*, the modulation of the external signal context has been mostly addressed through the exploration of QS signal inhibitors and signal-degrading enzymes. In this study, we have developed new QS inhibitors based on the predicted 3-D structure of LasR. A series of 3OC12 analogues were analyzed by a ligand-receptor docking study, and the analogues that have high binding energy were synthesized and tested for the *in vivo* QS inhibition activity. Some of these analogues showed a good inhibitory effect on the QS signaling and biofilm formation. Alternately, we have tried the differential modulation of the *P. aeruginosa* QS regulation. Since QscR exhibits a relaxed acyl-HSL specificity compared to LasR, the same 3OC12-cognate signal receptor, QscR might respond to the non-*P. aeruginosa* acyl-HSLs made by other bacteria in mixed bacterial communities, independently of LasR-I system. This feature might be molecular basis of the QS modulation by the inter-species signaling in a mixed bacterial population. Here we addressed the differential activation of QscR by non-*P. aeruginosa* signals produced by *Burkholderia cepacia* and *Pseudomonas fluorescens 2-79* that usually coexists with *P. aeruginosa* in nature. These signals were able to preferentially activate QscR to LasR. In single culture of *P. aeruginosa*, LasR and QscR share 3OC12 synthesized by LasI and LasR is always activated in advance of QscR. However, our results imply that QscR might be separated from this conventional QS cascade in the mixed population of *P. aeruginosa* and other bacteria that more closely resembles the natural habitat. Finally, we will introduce our new approaches for the QS modulation by the functional modification of the QS receptors and the QS-related cellular physiology.

Key words; *Pseudomonas aeruginosa*, quorum sensing modulation, QscR, LasR, Acyl-homoserine lactone, inter-species communication