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The function of SpnR and the inhibitory effects by halogenated furanone on quorum sensing in *Serratia marcescens* AS-1

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Abstract: By secretion and detection of a series of signaling molecules, bacteria are able to coordinate gene expression as a community, to regulate a variety of important phenotypes, from virulence factor production to biofilm formation to symbiosis related behaviours such as bioluminescence. This widespread signaling mechanism is called quorum sensing. There are several quorum sensing systems described in *Serratia*. *Serratia marcescens* AS-1, isolated from soil, had the LuxI/LuxR homologues called SpnI/SpnR. *S. marcescens* AS-1 produced two kinds of *N*-acyl-L-homoserine lactones, *N*-hexanoyl-L-homoserine lactone and *N*-(3-oxohexanoyl)-L-homoserine lactone as signal molecules, which involved in quorum sensing to control the gene expression in response to increased cell density. By gene replacement method, the *spnR* mutant was constructed, named *S. marcescens* AS-1R. SpnR acted as a negative regulator for the production of prodigiosin, swarming motility and biofilm formation, which were regulated by quorum sensing. Halogenated furanone, known as a natural inhibitor of quorum sensing, could effectively inhibit the quorum sensing of *S. marcescens* AS-1 but without interrupting AHL-SpnR interaction. All results will be helpful to understand the mechanisms of halogenated furanone inhibition on quorum sensing and the potential application of halogenated furanone in effectively preventing infection disease caused by *Serratia* strains.

Keywords: Quorum sensing; SpnR; Repressor; Halogenated furanone
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1 INTRODUCTION

Quorum sensing is a regulatory system for controlling gene expression in response to increasing cell density. *N*-acyl-L-homoserine lactones (AHLs), produced by gram-negative bacteria, are used as quorum sensing signal molecules. LuxI protein family synthesizes AHLs and LuxR protein family binds AHL to regulate expression of many genes responsible for the expression of virulence factors, the secretion of extracellular protease, pectinase or rhamnolipid, and the biofilm formation [1,2]. Thus, interfering with AHL-mediated quorum sensing could be an effective means of preventing infection disease. As a natural inhibitor, halogenated furanone (Fig.1), produced by the red algae *Delisea pulchra*, could inhibit quorum sensing in a wide range of gram-negative bacteria [3~5]. It was reported that halogenated furanone could accelerate the turnover of LuxR [6] or compete with the AHLs to bind LuxR homologues [7].

Serratia marcescens is a gram-negative and opportunistic human pathogen which is responsible for an increasing number of serious nosocomial infections [8]. *S. marcescens* also produces a red pigment called prodigiosin (2-methyl-3-pentyl-6-methoxyprodigiosin), regulated by quorum sensing [8], showed antifungal, antiprotozoan, and immunosuppressant activities [9]. *S. marcescens* AS-1, isolated from a soil sample, had the LuxI homologue (SpnI) and produced two AHLs, which were *N*-hexanoyl-L-homoserine lactone (C_6-HSL) and *N*-(3-oxohexanoyl) -L-homoserine lactone (3-oxo-C_6-HSL) (Fig.1) [10]. AHLs produced via SpnI interacted with LuxR homologue (SpnR) resulting in the de-repression of the production

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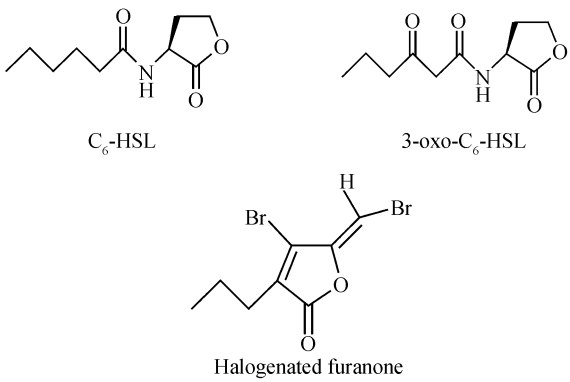

Fig. 1 Structures of AHLs produced by AS-1 and quorum sensing inhibitor.

of prodigiosin, swarming motility and biofilm formation [10]. It was reported that halogenated furanone could affect swarming motility in *S. marcescens* (*liquefaciens*) MG1 [7]. However, inhibitory effects on the other features in *Serratia* strains, such as prodigiosin production and biofilm formation, were not identified. In this study, we constructed the *spnR* mutant named AS-1R, in which the chromosomal AHL-receptor gene (*spnR*) was disrupted, and it was revealed that SpnR acted as a negative regulator of quorum sensing related to the production of prodigiosin, swarming motility and biofilm formation. We also investigated the inhibitory effect of halogenated furanone on quorum sensing of *S. marcescens* AS-1 and found that halogenated furanone didn't interrupt AHL-SpnR interaction. These results would be helpful on the further research about the inhibition mechanisms of halogenated furanone to the bacteria quorum sensing.

2 MATERIALS AND METHODS

2.1 Bacterial strains, plasmids, compounds and growth conditions.

The bacterial strains and plasmids used in this study are listed in Table 1. All the bacterial strains were cultured in Luria-Bertani (LB) medium [11]. *S. marcescens* strains were grown at 25ºC for testing prodigiosin production, swarming motility and biofilm formation. *Escherichia coli* was grown at 37ºC and *Chromobacterium violaceum* CV026 was grown at 30ºC. AHL standards and 4-Bromo-5-(bromomethylene)-3-butyl-2(*5H*)-furanone (halogenated furanone) were synthesized by previously described method [12, 13]. Antibiotics were added as required at final conditions of 100 mg/mL ampicillin and 10 mg/mL chloramphenicol.

2.2 Disruption of chromosomal SpnR gene

Chromosomal DNA was extracted by the standard protocol [11]. Then, the DNA was amplified by PCR using the following primers, 5′-GATCCGAGGCTCAGCAAACA-3′ and 5′-AGTGTGGTTTAACGTCAGCGC-3′, digested by *Sac*I and *Sph*I, and then inserted into the *Eco*RV site of pGP704Sac38 for construction of pGP704IR. The 0.9-kb chloramphenicol cassette (Cm^r) was cut-out by *Sac*I digestion from pKRP10 and inserted into the pGP704IR digested by *Sac*I. Disruption of chromosomal *spnR* gene in AS-1 was performed by the bacterial conjugation [12]. Conjugation was conducted between *E.coli* S17-1 λ*pir* with pGP704IRC and AS-1. The chromosomal disruption of

Table 1 Bacterial strains and plasmids used in this study

Strains or plasnids	Description	Source or reference
Serratia marcescens		
AS-1	natural isolate	Laboratory-maintained strain
AS-1R	AS-1 *spnR*::Cm^r	This study
Escherichia coli		
S17-1 λ*pir*	*thi pro hsdR hsdM*$^+$ *recA* RP4 2Tc::Mu-Km::Tn7	14
Chromobacterium		
violaceum CV026	Mini-Tn5 mutant derived from *C. violaceum* ATCC31532, Hg^r, *cvil*::Tn5 *xyl*E, Kan^r, plus Spontanegous Sm^r, AHL biosensor	15
Plasmids		
pGP704Sac38	pBR322 derivative with R6K *ori*, mob RP4, polylinker from M13 tg131 containing sacB;Ap^r	16
pGP704IR	pGP704Sac38 containing *spnR*	This study
pGP704IRC	pGP704Sac38 containing *spnR*::Cm^r	This study
pKRP10	Cloning vector; Cm^r, Ap^r	This study

spnR was checked by PCR using the primers of 5′-TTCCACTTATTCTGATGAATGGGTTGAGCT-3′ and 5′-AATGGGTTTTACCATATCCATATGATGT-CG-3′ and this mutant was designed AS-1R.

2.3 Extraction and bioassays of AHLs

Bacteria were grown for 15h, inoculated into 100mL fresh LB medium (a 1% inoculum) and incubated for 20h. Cells were removed by centrifugation and the supernatant was mixed with 100 mL acidified ethyl acetate. The ethyl acetate layer was transferred to the new flask, evaporated to dryness and added 10 mL distilled water to dissolve the residue, and then mixed with 80 mL chloroform. The chloroform layer was transferred to another flask and evaporated to dryness again. Dissolved the residue with 1mL of dimethyl sulfoxid, transfer into the microtube and conserved under 4ºC. For AHLs detection, 0.25mL of an overnight culture of *C. violaceum* CV026 biosensor was mixed with 25mL of 1.5% LB agar and poured in a petri dish. The 8-mm-diameter paper disks were placed on an agar plate and 10 uL of culture extract was added and the plates were incubated overnight at 28ºC. The area of purple pigment was measured as an amount of AHLs. To confirm the species of the AHLs, thin-layer chromatography (TLC) was used [15].

2.4 Prodigiosin production assay

Prodigiosin production was determined using the same method as described on [10]. Effects of inhibitors were evaluated as the relative prodigiosin production (A_{534}/OD_{600}), of which the control value equals to 100%.

2.5 Swarming motility assays

LB medium was used for swarming motility assay and the swarming assay plates contained 25mL of 0.35% (w/v) agar LB medium. The bacteria were planted on the center of the plates by the sterile toothpick and the plates were incubated for 20h.

2.6 Biofilm formation assay

The biofilm formation assay used in this work was a method of described on [10]. The polypropylene microtiter plates were put on 25ºC for 20h and biofilm formation was analyzed at 570 nm by using a Spectra Max 250 spectrophotometer (Molecular Devices).

3 RESULTS AND ANALYSIS

3.1 The validation of the spnR mutation

By using the primers of 5′-TTCCACTTATT-CTGATGAATGGGTTGAGCT-3′ and 5′- AATGGG-TTTTACCATATCCATATGATGT CG-3′ a part of the *spnR* gene, which about 370bp could be amplified by PCR. As the chloramphenicol cassette inserted, the length of this area would increase to about 1.3kb. After electrophoresis, the image of electrophoresis showed that the *spnR* gene from *spnR* mutation was disrupted successfully (Fig.2) and the mutation was just the bacterium what we needed.

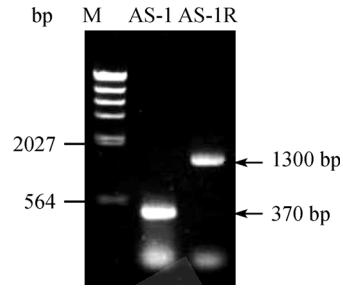

Fig. 2 The images of electrophoresis of the *spnR* gene segment from AS-1 and AS-1R. M: Marker.

3.2 Effect of the *spnR* mutation on the quorum sensing system.

S. marcescens AS-1 was isolated from a soil sample, the AHL-synthesis gene (*spnI*) and AHL-receptor gene (*spnR*) had been cloned from the AS-1 chromosome [9]. Using a gene replacement method, we constructed the *spnR* mutant named AS-1R. At first, whether the disruption of the *spnR* gene affected the biosynthesis of AHLs was checked. AHLs were extracted from culture supernatant and visualized by *C. violaceum* CV026 biosensor. As the result, AS-1 and AS-1R showed obvious AHL production (Fig.3-A). TLC analysis revealed that AS-1 and AS-1R produced the same AHLs, which corresponded to 3-oxo-C_6-HSL and C_6-HSL (Fig.3-B). These results demonstrated that the disruption of the *spnR* did not affect the biosynthesis of AHLs.

It was reported that the mutation of *spnI*, in which the chromosomal AHL-synthesis gene (*spnI*) was disrupted, caused deficient in the prodigiosin production, swarming motility and biofilm formation, but could restore by adding exogenous AHLs [10]. To investigate the role of SpnR in AS-1, those phenotypes between AS-1 and AS-1R were compared. Contrary to the *spnI* mutant, the disruption of *spnR* activated prodigiosin production, swarming motility and biofilm formation (Fig.4) and even more active than AS-1, especially swarming motility and biofilm formation, which were almost increased up to 200%. The effects

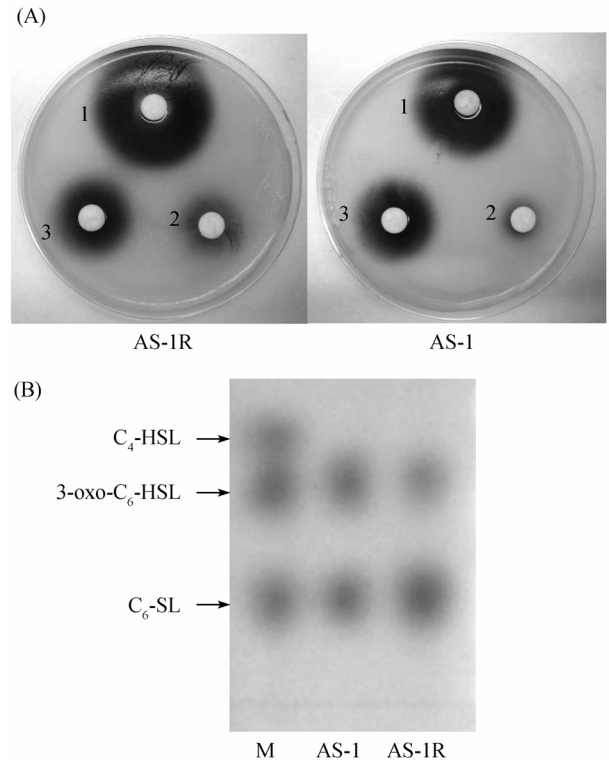

Fig. 3 Identification of AHLs produced by *S. marcescens* AS-1 and AS-1R. A: Three pieces of 8-mm-diameter paper disks were placed on the plates with culture extract (1), 1/10 concentration of culture extract (2) and standard AHL solution (C_6-HSL, 10mmol/L) (3), respectively. AHLs were visualized by *C. violaceum* CV026 biosensor. B: TLC analysis of AHLs produced by strain AS-1 and AS-1R, and identified after comparison with the standards C_4-HSL, C_6-HSL and 3-oxo-C_6-HSL.

of exogenous AHL (C_6-HSL) on AS-1 and AS-1R were also determined. The results showed that the levels of those phenotypes in strain AS-1 were elevated by adding C_6-HSL, but no or just a slightly effects in AS-1R. In *S. marcescens* SS-1, the LuxR homologue acted as a repressor of quorum sensing [17]. On the other hand, the LuxR homologue in *S. marcescens* MG1 acted as a positive regulator [18]. As a positive regulator, the LuxR homologue-AHL complex could activate the expression of QS-controlled genes, but as the repressor, the existence of the LuxR homologue would repress the QS-controlled gene expression and the default of LuxR homologue could restore those phenotypes. As inactivation of *spnR* in AS-1 caused the constitutive expression of quorum sensing regulated phenotypes, SpnR from AS-1 acted as a repressor of quorum sensing in AS-1, same as the LuxR homologue in SS-1.

3.3 Effect of halogenated furanone on prodigiosin production

It was reported that halogenated furanone affected swarming motility in *S. marcescens* (*liquefaciens*) MG1 [10], which was regulated by quorum sensing. Therefore, the inhibitory effect of halogenated furanone on the quorum sensing system in AS-1 was investigated. At first, the inhibitory effect of halogenated furanone on prodigiosin production was determined. Various concentration of halogenated furanone was added to the culture of AS-1 and AS-1R

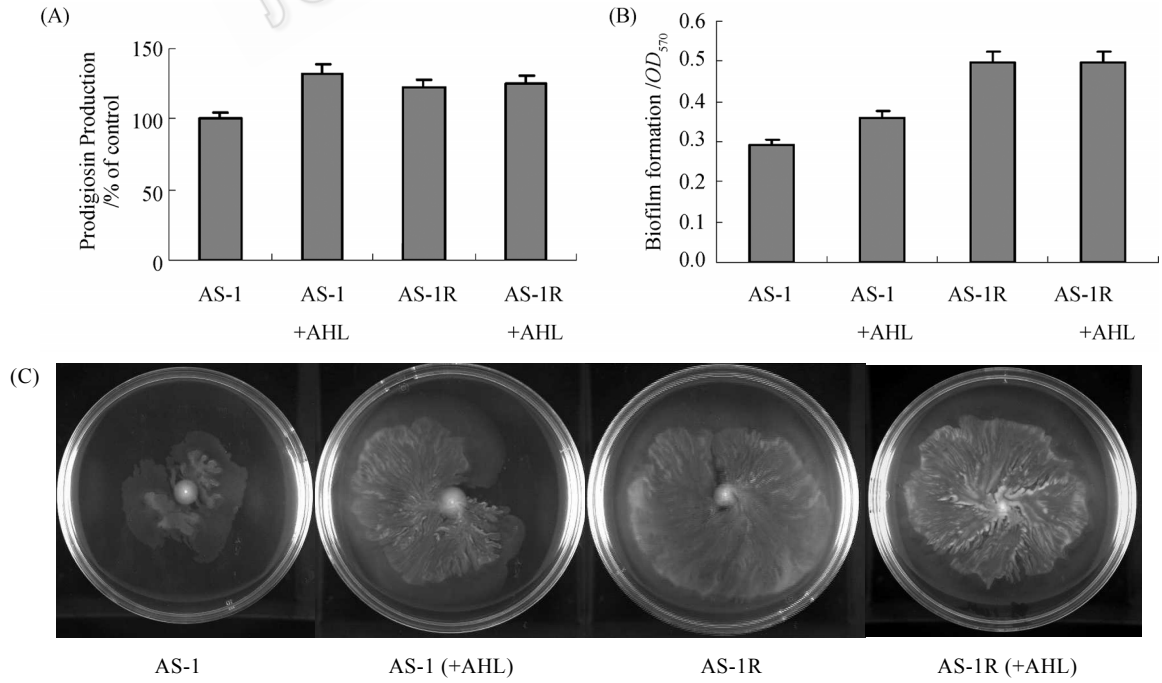

Fig. 4 Comparison of the phenotypes of prodigiosin production (A), biofilm formation (B), and swarming motility (C) with or without exogenous AHLs (C_6-HSL) between AS-1 and AS-1R. C_6-HSL was added at 5μmol/L.

and the prodigiosin production was estimated. The prodigiosin production of AS-1 was decreased by adding halogenated furanone and the addition of 100 μmol/L halogenated furanone decreased the prodigiosin production rate almost down to 40% (Fig.5-A). Interestingly, halogenated furanone inhibited the prodigiosin production in AS-1R as well as in AS-1. The disrupted of *spnR* gene made the prodigiosin production of AS-1R increase to 120%, but the addition of 100μmol/L halogenated furanone to AS-1R decreased the prodigiosin production down to almost the same levels as addition to AS-1 (Fig.5-B) and addition of C_6-HSL didn't affect to the ability of halogenated furanone (data not shown). Further more, halogenated furanone showed no effect on the growth of AS-1 and AS-1R (data not shown).

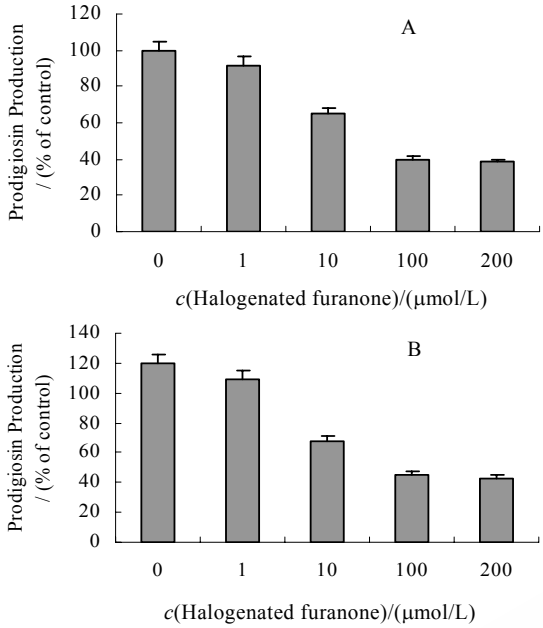

Fig. 5 Effects of halogenated furanone on prodigiosin production in AS-1(A) and AS-1R (B).

3.4 Effects of halogenated furanone on swarming motility and biofilm formation

In order to investigate whether the halogenated furanone inhibit other phenotypes regulated by quorum sensing, biofilm formation and swarming motility in AS-1 were also determined. For swarming motility assay, halogenated furanone were added into the plates at the various concentrations. As the result, the swarming area of *S. marcescens* AS-1 was decreased on the swarming plate containing halogenated furanone (Fig.6-A). The swarming motility of AS-1R was also inhibited by halogenated furanone (Fig.6-B). And at the concentration of 100μmol/L, the swarming area of AS-1 and AS-1R was obviously decreased to less than half.

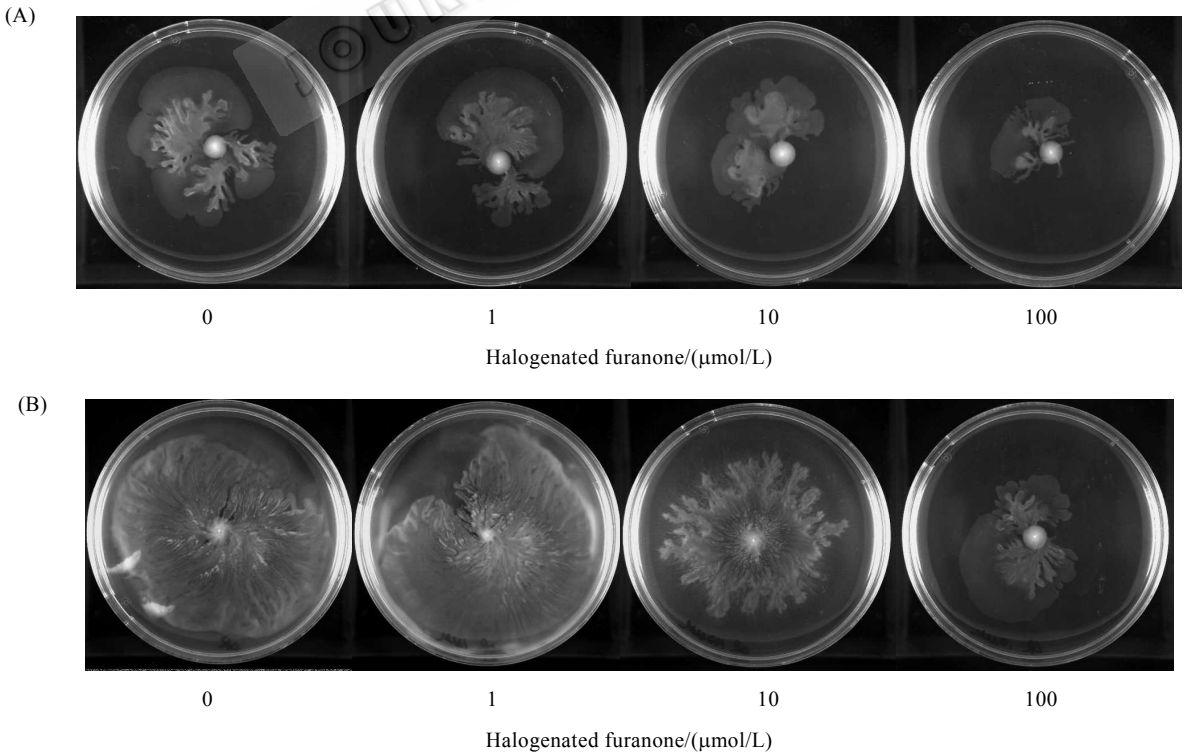

Fig. 6 Effects of halogenated furanone on swarming motility in AS-1(A) and AS-1R (B).

Biofilm formation was tested on the polypropylene plastic surface. By adding halogenated furanone, the adhere biomass of AS-1 (Fig.7-A) and AS-1R (Fig.7-B) was decreased in a dose-dependent manner and the half inhibition was happened when 100 μmol/L of halogenated furanone was added.

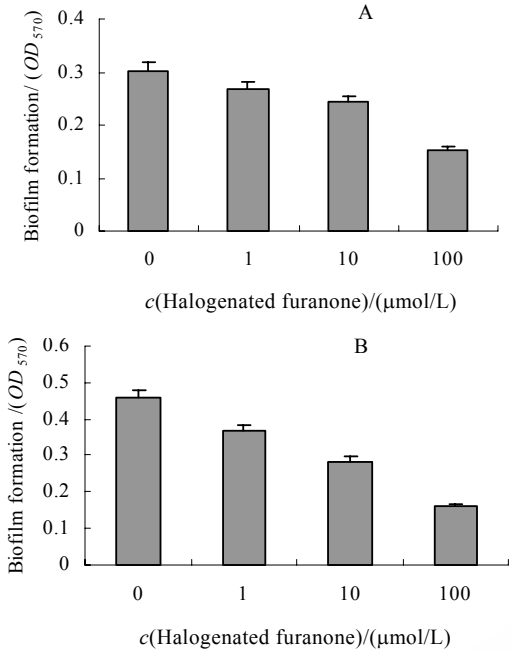

Fig. 7 Effects of halogenated furanone on biofilm formation in AS-1 (A) and AS-1R (B)

4 DISCUSSION

In this article, we demonstrated that the SpnR acted as a repressor in *S. marcescens* AS-1, and halogenated furanone inhibited the prodigiosin production, swarming motility and biofilm formation, which were regulated by quorum sensing, in AS-1 and AS-1R. Our work is firstly to report about the inhibition of halogenated furanone on prodigiosin production and biofilm formation of *Serratia* strain.

In *Serratia* sp., it has been widely reported that the LuxR homologue acted as a repressor of quorum sensing, such as SpnR of *S. marcescens* SS-1[17] and *S. marcescens* AS-1, SmaR of *Serratia* sp. ATCC 30096[8], SprR of *S. proteamaculans* B5a[19] and SplR of *S. plymuthica* RVH1[20]. These data indicated that negative control of AHL-regulated phenotypes might be a more general trait in the genus *Serratia*.

S. marcescens causes nosocomial infections including respiratory tract, urinary tract and wound infections, as well as meningitis, septicaemia, and pneumonia. For the *Serratia* infections treatment, the drug-resistance problems may become increasingly important. Here, we approved that the halogenated furanone could effectively inhibit the production of prodigiosin, swarming motility and biofilm formation of *S. marcescens* AS-1, which were considered the part of major virulent factors. And for the half inhibition, the concentration of halogenated furanone was about 100 μmol/L. In the future, halogenated furanone might be able to be applied to antipathogenic drugs for *Serratia* infection, as a substitute for current antibiotic drugs.

In general, it was thought that halogenated furanone inhibited the quorum sensing by mimicking the native AHL signal and occupying the binding site on the putative regulatory protein LuxR homologues [6]. We found that the *spnR* mutant, in which SpnR was deleted, was still influenced by halogenated furanone. These interesting findings showed that the halogenated furanone might affect the quorum sensing without interrupting AHL-SpnR interaction in *S. marcescens* AS-1. It was reported about a novel protein component of the quorum sensing regulon named SpnT in *S. marcescens* SS-1, that *spnT* and *spnI* formed an operon and SpnT was involved in the negative regulation of prodigiosin production and sliding motility [17]. In *S. marcescens* AS-1, except the SpnIR, there might be another protein or even another system to regulate the prodigiosin production, swarming motility and biofilm formation. So the quorum sensing of AS-1 can still be inhibited when SpnR absence. In a word, quorum sensing in AS-1 is complicated and the inhibition mechanism of halogenated furanone to quorum sensing in AS-1 is still worth to research deeply.

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粘质沙雷氏菌 AS-1 中 SpnR 功能及卤化呋喃对其群体感应的抑制

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摘要: 通过分泌和感知一系列信号分子, 细菌能够根据自身菌体密度的变化调控基因的表达, 从而控制一系列重要的表现型, 包括毒力因子的产生, 生物膜的形成以及菌体发光等。这种广泛存在的信号机制被称为群体感应。在沙雷氏菌种中已经发现了多套群体感应机制。粘质沙雷氏菌 AS-1 从土壤中分离, 其中含有 LuxI/LuxR 的同类蛋白, 被称为 SpnI/SpnR。粘质沙雷氏菌 AS-1 合成 AHLs 分子 *N*-hexanoyl-L-homoserine lactone (C_6-HSL) 和 *N*-(3-oxohexanoyl)-L- homoserine lactone (3-oxo-C_6-HSL)作为其信号分子, 通过群体感应感知菌体密度来控制基因的表达。通过基因替代的方法制得了 *spnR* 基因破坏的变异株, 命名为粘质沙雷氏菌 AS-1R。对粘质沙雷氏菌 AS-1R 的研究表明 SpnR 蛋白消极的调控沙雷氏菌红色色素的产生, 运动性以及生物膜的形成等一系列由群体感应控制的性状; 另一方面, 作为一种天然的群体感应抑制剂, 卤化呋喃能够有效的抑制粘质沙雷氏菌 AS-1 的群体感应, 但并不干扰 AHL-SpnR 的相互作用。为运用粘质沙雷氏菌群体感应调节抑制其致病性提供了方法和依据, 同时也为卤化呋喃对群体感应抑制机理的研究提供了新的思路。

关键词: 群体感应; SpnR; 抑制型; 卤化呋喃

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