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Review

Acyl-homoserine lactone-based quorum sensing and quorum quenching hold promise to determine the performance of biological wastewater treatments: An overview

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HIGHLIGHTS

- Endogenous AHL-based QS and QQ are coexisting in biological wastewater treatments.
- Exogenous regulation by selective enhancement of AHL-based QS or QQ is proposed.
- Exogenous addition of AHLs or AHL-producing bacteria enhances sludge performance.
- Exogenous AHL-based QQ effectively improves membrane flux in MBRs.

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ABSTRACT

Quorum sensing (QS) is a communication process between cells, in which bacteria secrete and sense the specific chemicals, and regulate gene expression in response to population density. Quorum quenching (QQ) blocks QS system, and inhibits gene expression mediating bacterial behaviors. Given the extensive research of acyl-homoserine lactone (AHL) signals, existences and effects of AHL-based QS and QQ in biological wastewater treatments are being subject to high concern. This review summarizes AHL structure, synthesis mode, degradation mechanisms, analytical methods, environmental factors, AHL-based QS and QQ mechanisms. The existences and roles of AHL-based QS and QQ in biomembrane processes, activated sludge processes and membrane bioreactors are summarized and discussed, and corresponding exogenous regulation strategy by selective enhancement of AHL-based QS or QQ coexisting in biological wastewater treatments is suggested. Such strategies including the addition of AHL signals, AHL-producing bacteria as well as quorum quenching enzyme or bacteria can effectively improve wastewater treatment performance without killing or limiting bacterial survival and growth. This review will present the theoretical and practical cognition for bacterial AHL-based QS and QQ, suggest the feasibility of exogenous regulation strategies in biological wastewater treatments, and provide useful information to scientists and engineers who work in this field.

Abbreviations: QS, quorum sensing; QQ, quorum quenching; AHL, acyl-homoserine lactone; AIP, autoinducing peptides; AI-2, autoinducer-2; SBR, sequencing batch reactor; MBR, membrane bioreactor; SAM, S-adenosyl-L-methionine; acyl-ACP, acyl-acyl carrier protein; acyl-CoA, acyl-coenzyme A; OHHL, N-(3-oxo)-hexanoyl homoserine lactone; 5′MTA, 5′-methyl-thioadenosine; holo-ACP, holo-acyl carrier protein; AHS, N-acyl homoserine; HSL, homoserine lactone; TLC, thin layer chromatography; HPLC, high performance liquid chromatography; LC-MS/MS, Liquid Chromatograph Mass Spectrometer/Mass Spectrometer; GC-MS, Gas Chromatography-Mass Spectrometer; PQS, Pseudomonas quinolone signal; DGGE, gradient gel electrophoresis; OLAND, oxygen-limited autotrophic nitrification/denitrification; AnAOB, anoxic ammonium-oxidizing bacteria; EPS, extracellular polymeric substances; TMP, trans-membrane pressure; MEC, magnetic enzyme carrier; NF, nanofiltration; CMV, ceramic microbial vessel; COD, chemical oxygen demand; C_4-HSL, N-butanoyl-homoserine lactone; C_6-HSL, N-hexanoyl homoserine lactone; C_8-HSL, N-octanoyl-homoserine lactone; C_{10}-HSL, N-decanoyl homoserine lactone; C_{12}-HSL, N-dodecanoyl homoserine lactone; C_{14}-HSL, N-tetradecanoyl homoserine lactone; C_{16}-HSL, N-hexadecanoyl homoserine lactone; 3-oxo-C_6-HSL, N-(3-oxo)-hexanoyl homoserine lactone; 3-oxo-C_8-HSL, N-(3-oxo)-octanoyl-homoserine lactone; 3-oxo-C_{10}-HSL, N-(3-oxo)-decanoyl homoserine lactone; 3-oxo-C_{12}-HSL, N-(3-oxo)-dodecanoyl homoserine lactone; 3-oxo-C_{14}-HSL, N-(3-oxo)-tetradecanoyl homoserine lactone; *A.*, *Aeromonas*; *Ac.*, *Acinetobacter*; *C.*, *Comamonas*; *P.*, *Pseudomonas*.

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Contents

1. Introduction

Quorum sensing (QS) is a term used to describe an environmental sensing system that allows bateria to synchronize their gene expression and physiological behavior in a cell-density dependent manner (Fuqua et al., 1994, 2001; Bassler and Losick, 2006). It is mediated by the small-molecule signal chemicals termed autoinducers that are constitutively synthesized intracellularly and are then passively, or actively exchanged with the surrounding environment (Kaplan and Greenberg, 1985; Pearson et al., 1999; Galloway et al., 2011); the accumulation of signals remains a proportional increase with bacterial population (Bassler and Losick, 2006). When the signals reach a threshold concentration, cognate receptors bind the signals and trigger signal transduction cascades that bring about the population-wide alteration in their gene expression (Atkinson and Williams, 2009; Ng and Bassler, 2009; Galloway et al., 2011). Quorum quenching (QQ), an adversarial one of quorum sensing, refers to the process in which autoinducer-based quorum sensing can be interfered and disrupted, thereby inhibiting gene expression mediating bacterial behaviors. Bacteria are capable of monitoring their own population density in the vicinity through fluctuations of the signal concentration and then determining whether to activate the expression of certain genes. It is apparent that the signals play key roles in the processes of quorum sensing and quorum quenching. There are numerous signal molecules identified so far in the bacterial community, and they have been broadly classified into three major types: acyl-homoserine lactones (AHLs) produced by Gram-negative bacteria; modified oligopeptides or autoinducing peptides (AIP) generally employed by Gram-positive bacteria; autoinducer-2 (AI-2) used by both Gram-negative and Gram-positive bacteria for interspecies communication (Taga and Bassler, 2003; Waters and Bassler, 2005; Shrout and Nerenberg, 2012; Lade et al., 2014c). Among them, AHLs are the most extensively studied; the characterization of AHLs has been the subject of investigations in the last decades and has become a paradigm for bacteria intraspecies signaling (Wang et al., 2011). Certainly, quorum sensing mechanisms are extremely complex; some bacteria species use more than one signal and/or more than one type of signals to communicate (Miller and Bassler, 2001; Bassler and Losick, 2006). To date, researchers in the field of biology and other related fields have developed various analytical methods for the characteristic identification of signal molecules (Steindler and Venturi, 2007; Wang et al., 2011); an increasing number of quorum sensing bacteria and quorum quenching bacteria species are isolated and identified (Ochiai et al., 2013; Lade et al., 2014a); informations on quorum sensing circuits and their controlled phenotypes in specific bacteria species are also more comprehensive (Miller and Bassler, 2001; Taga and Bassler, 2003); meanwhile, discovery and application of quorum sensing inhibitors as well as exploration of quorum quenching mechanisms are also in progress (Geske et al., 2008; Kalia and Purohit, 2011; Kalia, 2013). Furthermore, the researches and applications in terms of quorum sensing and quorum quenching have made great progress in the fields of aquaculture, plant cultivation, animals and human health (Dong et al., 2000, 2001; Defoirdt et al., 2004; Li et al., 2004; Smadja et al., 2004; Njoroge and Sperandio, 2009; Kalia, 2013; Li et al., 2013). In recent years, their existences and applications in biological wastewater treatment systems are also increasingly concerned.

Biological wastewater treatments contain the large quantities of dense microbial consortia in the form of biofilm, flocs or granules (Shrout and Nerenberg, 2012; Song et al., 2014), in which Gram-negative bacteria hold the dominant position and utilize AHLs as their major language to communicate with each other (Dobretsov et al., 2009). With advances in molecular biology techniques and analytical detection methods, the production of AHLs or AHL-like molecules was detected in various biological wastewater treatments (Morgan-Sagastume et al., 2005; Liu et al., 2010b; De Clippeleir et al., 2011; Lade et al., 2014a; Li et al., 2014). Furthermore, AHLs-producing QS bacteria and AHLs-degrading QQ bacteria were isolated from many activated sludges (Valle et al., 2004; Morgan-Sagastume et al., 2005; Cheong et al., 2013; Oh et al., 2013; Yong and Zhong, 2013). Impressively, AHL signals can be of great importance in biological wastewater treatments, in particular, biofilm formation and maturation (Eberl et al., 1996; Davies et al., 1998; Lynch et al., 2002; Labbate et al., 2004; Parsek and Greenberg, 2005), microbial aggregation and stabilization (Valle et al., 2004), exoenzyme activity (Chong et al., 2012), and granule formation and sludge structure stability (Ren et al., 2010; Tan et al., 2014). Furthermore, the positive roles of AHL-based QS regulatory in biodegradation of organic pollutants have been found, such as

phenol biodegradation (Valle et al., 2004; Yong and Zhong, 2010), ammonium oxidation (De Clippeleir et al., 2011), anthranilate degradation (Chugani and Greenberg, 2010), and denitrification (Toyofuku et al., 2007); on the contrary, AHL-based QS regulating biofilm formation on the membrane surface in MBRs results in the decline of membrane filtration fluxes. The modulation of AHL-based QS could exert an important role for the improved performance of biological wastewater treatments. To date, the exogenous regulation by selective enhancement of AHL-based QS or QQ coexisting in biological wastewater treatments, such as the artificial supplementation of AHLs and AHL-producing bacteria as well as AHL-degrading enzymes or bacteria, has been considered as an innovative and attractive strategy for enhanced wastewater treatments, which possesses incomparable benefits and superior research values compared with other strategies. Certainly, the present studies also indicate that this strategy still suffers from some technical and economic obstacles that impede its widespread application (Yeon et al., 2009b; Wang et al., 2011; Oh et al., 2012; Kim et al., 2013b, 2015a), which are expected to be solved with the improvement of molecular biology techniques as well as the in-depth studies of quorum sensing and quorum quenching.

The specific aim of this review is to center on AHL signals, present a systematic knowledge background about AHL-based QS and QQ, and analyze their potential role in biomembrane processes, activated sludge processes and membrane bioreactors, and then discuss the intuitive effect by exogenous regulation strategy on the improved wastewater treatment performance and point out its feasibility and prospect.

2. Acyl-homoserine lactone (AHL) signal molecules

2.1. AHL structure

Acyl-homoserine lactone (AHL) molecules are the primary signals that the Gram-negative bacterial QS utilizes to sense and signal their cell density, which are composed of a common lactonized homoserine moiety with an acyl chain (Fig. 1) (Fuqua and Greenberg, 1998; Churchill and Chen, 2011; Shrout and Nerenberg, 2012). The length of acyl chain varies between 4 and 18 carbons (Marketon et al., 2002), usually by increments of two carbon units (C_4, C_6, C_8 etc.) (Fuqua and Greenberg, 2002). It can be modified by a 3-oxo substituent or, a 3-hydroxy substituent, a terminal methyl branch, and can contain varied degrees of unsaturation (Thiel et al., 2009; Churchill and Chen, 2011).

The overall hydrophobicity of AHLs reaches a balance between the hydrophobic side chain and the somewhat hydrophilic lactonized homoserine moiety (Fuqua et al., 2001). AHLs as amphipathic molecules are expected to freely diffuse through cell membranes and keep stable for long time in aqueous environments; specifically, the diffusion is determined by the nature of acyl chain, and AHLs with longer chains might not be as diffusible as short ones (Kaplan and Greenberg, 1985; Pearson et al., 1999; Fuqua et al., 2001; Shrout and Nerenberg, 2012).

2.2. AHL synthesis

More than 100 species of Proteobacteria have been identified to produce AHLs, and three different types of enzymes, including those in the LuxI, LuxM and HdtS families, have been demonstrated to synthesize AHLs *in vivo* (Fuqua and Greenberg, 2002; Waters and Bassler, 2005; Churchill and Chen, 2011; Li and Nair, 2012). Most known AHL synthases are members of the LuxI protein family (Gilson et al., 1995; Christensen et al., 2014). Biochemical studies, both *in vitro* and *in vivo* (Val and Cronan, 1998; Parsek et al., 1999), revealed the LuxI-type synthase utilized two substrates, S-adenosyl-L-methionine (SAM) as the amino donor for formation of the homoserine lactone ring moiety and an appropriate acyl-acyl carrier protein (acyl-ACP) as the precursor to the acyl side chain, to synthesize AHL signals (Fig. 2) (Hanzelka and Greenberg, 1996; Parsek et al., 1999; Watson et al., 2002; Rasmussen and Givskov, 2006a; Galloway et al., 2011). The LuxM families of enzymes exist only in a few species of γ proteobacteria (Churchill and Chen, 2011). The AinS and VanM enzymes showing homology with LuxM were also found to produce AHLs (Gilson et al., 1995; Milton et al., 2001). Their substrate requirements for AHL synthesis are similar to the LuxI family of synthases except for the utilization of acyl-coenzyme A (acyl-CoA) (Hanzelka et al., 1999; Churchill and Chen, 2011). The HdtS belongs to a member of the lysophosphatidic acid-acyl transferase family (Laue et al., 2000), and can utilize both acyl-ACP and acyl-CoA as substrates for acylation of lysophosphatidic acid (Shih et al., 1999; Cullinane et al., 2005) whereas the enzymatic mechanism of AHL synthesis catalyzed by HdtS still remains uncharacterized (Fuqua and Greenberg, 2002; Churchill and Chen, 2011).

2.3. AHL degradation

The attenuation of AHL signals is a significant target not only for basic researches such as exploring AHL functions or cellular AHL regulation, but also for applied researches such as alleviating the detrimental effect of biofilm on the surface or developing the effective strategies against aggregated microbes (Xu et al., 2003).

There are three different mechanisms reported for AHLs degradation including chemical, metabolic and enzymatic degradation (Kalia and Purohit, 2011). The chemical degradation primarily refers to the process in which alkaline pH results in the opening of the lactone ring (Yates et al., 2002) and leads to loss of the activity of AHL signal (Byers et al., 2002). However, the lactone ring re-cyclizes and the activity of AHL signal can be reversed at acidic pH (Yates et al., 2002; Kalia and Purohit, 2011). Some bacteria such as *Pseudomonas* strain PAI-A and *Variovorax paradoxus* are examined for the ability to metabolize AHL signals for growth (Leadbetter and Greenberg, 2000; Huang et al., 2003). It is recognized that AHL signals can be completely degraded or inactivated by quorum quenching enzymes including AHL-lactonases, AHL-acylases and oxidoreductases (Fig. 3) (Dong et al., 2000; Lin et al., 2003; Chowdhary et al., 2007; Lade et al., 2014b, c). AHL-lactonases cleave the ester bond of the homoserine lactone ring of AHLs in a hydrolytic and reversible manner into their cognate N-acyl homoserine (AHS) derivative (Dong et al., 2000; Uroz and Heinonsalo, 2008). Most AHL-lactonases identified so far are of bacterial origin, such as *Bacillus* sp. strain 240B1, *Acidobacteria* sp. and *Agrobacterium tumefaciens* C58 (Dong et al., 2000; Riaz et al., 2008; Haudecoeur et al., 2009; Wei-Hua et al., 2013; Fetzner, 2015). In addition, the root-associated fungi of the *Ascomycota* and *Basidiomycota* capable of degrading AHL signals were also found to possess lactonases (Uroz and Heinonsalo, 2008). AHL-acylases can break the amide linkage between homoserine lactone moiety and the acyl chain in an irreversible manner, and released free homoserine lactone (HSL) and corresponding fatty acid (Leadbetter and Greenberg, 2000; Lin et al., 2003; Fetzner, 2015). The degradation products do not hold further residual signalling activity; the fatty acid generated by acylases is usually readily metabolized (Lin et al., 2003; Fetzner, 2015). A broad spectrum of AHL-acylases has been identified in various bacteria, such as *Pseudomonas aeruginosa*, *Anabaena* sp. PCC7120 and *Ralstonia* strains (Lin et al., 2003; Huang et al., 2006; Romero et al., 2008). Oxidoreductases are found to catalyze acyl side chain in an oxidative or reductive manner, which make the structure of AHL signal modified without degradation (Chan et al., 2011). The structural change of AHL signal affects its

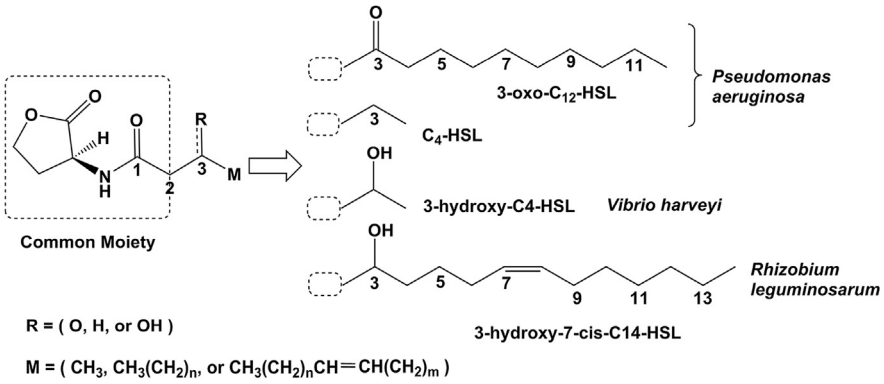

Fig. 1. Chemical structure of acyl-homoserine lactone (AHL).

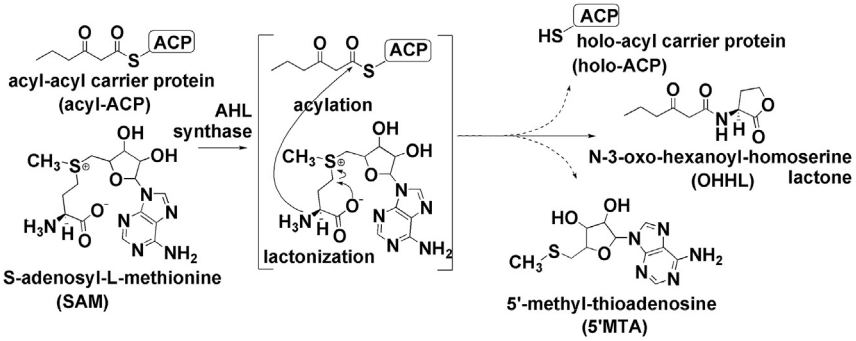

Fig. 2. Schematic diagram of AHL synthesis reaction.

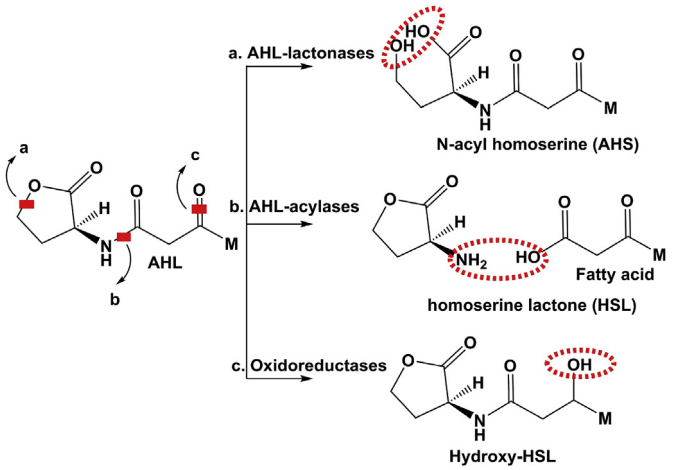

Fig. 3. Degradation or modification mechanism of AHL signals by quorum quenching enzymes: AHL-lactonases, AHL-acylases and Oxidoreductases.

specificity and recognition, and then results in the disturbance of the activation of QS phenotypes by modified AHL (Uroz et al., 2003; Lade et al., 2014b). Until now, only a limited number of bacterial species, such as *Rhodococcus erythropolis* strain W2 and *Bacillus megaterium*, are reported to possess the oxidoreductase activity (Uroz et al., 2005; Chowdhary et al., 2007).

2.4. AHL detection and quantification

Many different kinds of AHL signals have been widely recognized in the last decades, and the structure and concentration of AHLs are of vital importance for studies of AHL-based QS and QQ. Until now, various methods for detection and quantification of AHL signals have been developed (Brelles-Marino and Bedmar, 2001; Englmann et al., 2007), in which bacterial biosensors, thin layer chromatography (TLC) coupled with biosensor and high performance liquid chromatography (HPLC) are frequently used.

Bacterial biosensors for AHL detection have been widely utilized in QS systems (Steindler and Venturi, 2007; Wang et al., 2011; Garcia-Aljaro et al., 2012). These biosensors having a deletion in their AHL biosynthesis are capable of making the phenotypic responds when exposed to exogenous active AHL signals in the surroundings (Andersen et al., 2001; Brelles-Marino and Bedmar, 2001; Steindler and Venturi, 2007). The representative AHL biosensors include *Chromoterbacium violaceum* CV026 (McClean et al., 1997; Milton et al., 2001), *Escherichia coli* plasmid pSB401 (Winson et al., 1998), *Agrobacterium tumefaciens* NT1 plasmid pZLR4 (Cha et al., 1998; Farrand et al., 2002) and *Agrobacterium tumefaciens* A 136 (pCF218) (pCF372) (Fuqua and Winans, 1996; McLean et al., 2004). *Chromobacterium violaceum* CV026 produces the characteristic purple pigment violacein in response to AHLs with acyl chains from C_4 to C_8 in length, with varying degrees of sensitivity (McClean et al., 1997). The plasmid sensor pSB401 (Winson et al., 1998) based on *Escherichia coli*, producing bioluminescence, is most sensitive to cognate 3-oxo-C_6-HSL and exerts relatively good sensitivity towards C_6-HSL, C_8-HSL and 3-oxo-C_8-HSL. *Agrobacterium tumefaciens* NT1 (pZLR4) produces β-galactosidase in response to a broader range of AHLs including 3-unsubstituted-HSLs with side-chains from C_6 to C_{14}, 3-hydroxy-HSLs with side-chains from C_6 to C_{10}, and 3-oxo-HSLs with side-chains from C_4 to C_{12} (Milton et al., 1997; Farrand et al., 2002). Similarity, through β-galactosidase production, *Agrobacterium tumefaciens* A 136 harboring pCF 218 and pCF 372 plasmids can respond to a variety of AHLs with side-

chains ranging from C_6 to C_{14} with more sensitivity (Fuqua and Winans, 1996; Zhu et al., 1998; McLean et al., 2004). Biosensor technique for AHL detection is fast and effective whereas it can not determine the precise structure and concentration of AHL signals. Alternatively, separation by TLC coupled with detection by AHL-biosensors produces a direct, visual catalog of AHL signals that can be used for detection and quantification of AHL signals (Shaw et al., 1997; Steindler and Venturi, 2007; Wang et al., 2011). The specific structure of AHL signals cannot be determined by TLC; nevertheless, their chromatographic properties are well suited to assigning tentative structures, as R_f value calculated for AHL samples can be compared with that of AHL standards (Shaw et al., 1997; Steindler and Venturi, 2007; Yeon et al., 2009a). The area of spots on TLC is converted into AHL concentration via a calibration curve obtained from AHL standards with known amounts (Dong et al., 2000; Park et al., 2003; Yeon et al., 2009a; Wang et al., 2011). High-performance liquid chromatography (HPLC) has also been used for qualitative and quantitative analysis of AHL signals. AHL extracts are separated on the HPLC chromatographic column with water-methanol or water-acetonitrile mobile phases and isocratic and/or gradient elution (Lewenza and Sokol, 2001; Morin et al., 2003; Delalande et al., 2005; Fekete et al., 2007). AHLs identification is based on their specific retention time in the HPLC chromatographic column, and logP value (P is the retention time) maintains a proportional relation to acyl side-chain length of AHL signals (Kumari et al., 2008; Wang et al., 2011). It is worth noting that HPLC technique for analyzing AHLs from the biological sample (extracted from a real-word sample) may require more time to establish the assay method and process AHL samples (e.g. the addition of a preconcentration step) (Frommberger et al., 2004; Gould et al., 2006).

Several novel analytical techniques have been developed for detection and characterization of AHL signals, such as MALDI-MS, LC-MS/MS, GC-MS and magnetic molecularly imprinted polymer nanoparticles based electrochemical sensor (Wagner-Dobler et al., 2005; Ortori et al., 2011; Kim et al., 2015b; Jiang et al., 2016). The efforts for analytical techniques of AHL signals will greatly contribute to unveiling the exact mechanisms of AHL-based QS and QQ.

3. AHL-based quorum sensing and quorum quenching

3.1. AHL-based quorum sensing

AHL-based QS system has been studied widely and understood profoundly for cell-to-cell communication in Gram-negative bacteria. The system operates through three major components: (i) AHL signals; (ii) an AHL synthase protein to produce signals; (iii) a regulatory protein that perceives and responds to the surrounding concentration of AHL signals (Shrout and Nerenberg, 2012; Lade et al., 2014c). In AHL dependent bacterial QS regulatory system, a single synthase-regulator complex is responsible for the expression of certain genes (Kalia, 2013). AHL signals are produced constitutively by AHL synthase gene (such as *luxI*) and are distributed out the cells first at a low cell density, and then get accumulated in the surroundings (Rasmussen and Givskov, 2006b; Kalia, 2013). At higher cell density, AHL signals bind to and activate their receptor protein (LuxR); the activated AHL-LuxR protein complex most often homodimerizes and binds adjacent to QS promoters, which activates the transcription of target genes controlled by QS system (Fig. 4) (Fuqua et al., 2001; Zhang et al., 2002; Geske et al., 2008). It is worth noting that examples of transcriptional repression upon AHL-receptor binding have also been reported, but this outcome seems to be far less common (Geske et al., 2008).

Some Gram-negative bacteria have been found to use two or more AHL signals, along with other signals and receptors, to operate the QS systems (Geske et al., 2008; Churchill and Chen, 2011; Kalia, 2013). For example, *Pseudomonas aeruginosa* produces two AHL signals, C_4-HSL and 3-oxo-C_{12}-HSL, which bind to their respective transcriptional regulators, RhlR and LasR, for QS (Brint and Ohman, 1995; Davies et al., 1998; Parsek and Greenberg, 2000; Wagner et al., 2003). The AHL-LasR complex not only activates a variety of target genes including *lasI* but also activates the expression of *rhlI* and *rhlR* (Seed et al., 1995; Whiteley et al., 1999; Waters and Bassler, 2005). Another signal designated as Pseudomonas quinolone signal (PQS) connects the two QS systems (Pesci et al., 1999; de Kievit and Iglewski, 2000; McKnight et al., 2000); the expression of PQS is under control of the *las* system, and RhlR is required for PQS activity (de Kievit and Iglewski, 2000; Chugani et al., 2001; Lequette et al., 2006).

The presence of single or multiple autoinducer signal synthase gene/transcriptional regulator gene systems leads to the regulation of various QS phenotypes in one organism, which include biofilm formation (Labbate et al., 2004), swarming motility (Labbate et al., 2004), pigmentation (McClean et al., 1997), bioluminescence (Bassler et al., 1994), plasmid conjugal transfer (Danino et al., 2003), antibiotic biosynthesis (Pierson et al., 1994), root nodulation (Schripsema et al., 1996), virulence factor (Dunphy et al., 1997), etc.

3.2. AHL-based quorum quenching

Given the importance of AHL-based QS system to Gram-negative bacteria, it should not be surprising that host organisms or competing bacteria might benefit from interfering with and disrupting AHL-based QS system, and many studies have reported these quorum quenching (QQ) activities (Pappas et al., 2004). In principle, there are three obvious targets including synthase (I), AHL signals, and receptor (R) within the LuxI/LuxR-type QS system, and external intervention of any one of three components within QS circuit could break the bacterial communication (Fig. 5) (Geske et al., 2008; Galloway et al., 2011). It should be noted that this categorization is a generalization; in some bacteria species such as *P. aeruginosa*, the situation can be more complex (Galloway et al., 2011). Each QQ approach correspondingly based on the modulation of the three major components is discussed in turn below.

Inhibition of AHL synthesis appears to be a conceptually simple approach to block the QS system (Geske et al., 2008). However, there are relatively few reported studies to target the LuxI-type synthase protein (Parsek et al., 1999; Watson et al., 2002; Geske et al., 2008). The LuxI-type synthases catalyze AHL synthesis from an acyl-ACP and SAM (see in section 2.2). SAM is a necessary and unique intermediate for AHL synthesis, and thus a largest body of studies on the inhibition of AHL synthesis has centered on the utilization of various analogues of SAM (Hentzer and Givskov, 2003; Rasmussen and Givskov, 2006a; Galloway et al., 2011). In addition, homologues and analogues of purine nucleotides, homoserine lactone derivatives and certain macrolide antibiotics have also been found to suppress AHL synthesis (Hentzer and Givskov, 2003; Galloway et al., 2011). The second target is AHL signals. Degradation of AHL signals would disrupt the bacterial normal communication pathway. There are three options reported including chemical, metabolic and enzymatic degradation, and their respective degradation mechanisms have been described in detail in section 2.3. The final target is the LuxR-type protein. The majority of studies on QS inhibition have focused on the blockage of AHL-LuxR interaction (Koch et al., 2005; Chen et al., 2011). The antagonist agents capable of competing or interfering with the native AHL signals for binding to the LuxR-type receptor have been found to block QS (Hentzer and Givskov, 2003; Chen et al., 2011). AHL analogs as antagonists have been reported to achieve

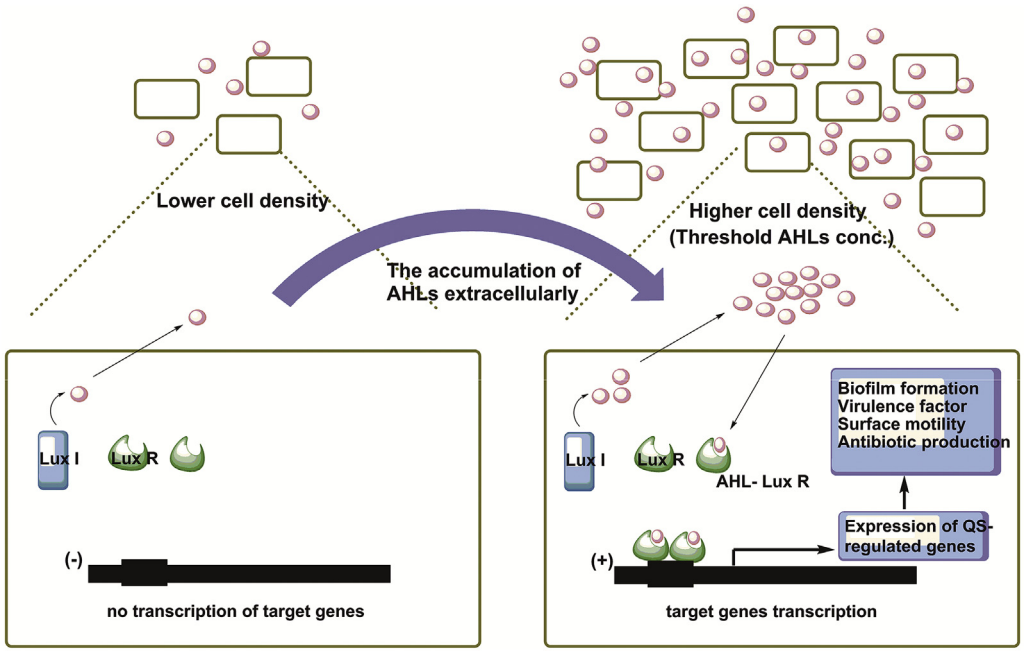

Fig. 4. Schematic representation of AHL-dependent LuxI/LuxR regulatory system.

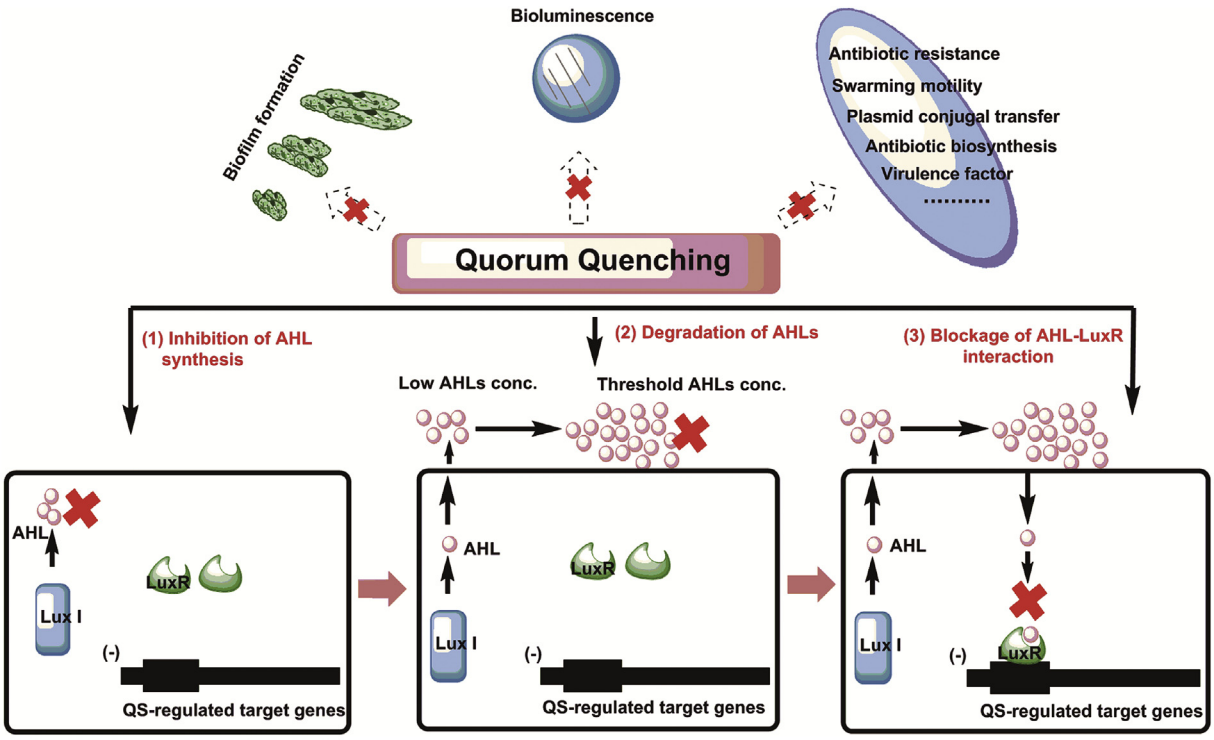

Fig. 5. External intervention of three major components within bacterial LuxI/LuxR-type QS system.

inhibition of QS circuits (Schaefer et al., 1996; Zhu et al., 1998; Hentzer and Givskov, 2003; Rasmussen and Givskov, 2006a). Indeed, modification of the acyl side chain of AHL signals can generate inhibitors but most compounds turn out to be agonists; only a few substitutions in the homoserine lactone moiety can produce compounds capable of binding to the LuxR (Rasmussen and Givskov, 2006a).

Those QQ approaches interfere with and disrupt AHL-based QS system, and then inhibit gene expression mediating bacterial desired phenotypes.

3.3. Environmental factors on AHL-based quorum sensing and quorum quenching

Many bacteria reside in spatially structured and multi-species communities, such as biofilm on submerged surfaces or flocs in

the aquatic environment (Davey and O'Toole, 2000; Hall-Stoodley et al., 2004; Horswill et al., 2007). It is apparent that environment can be profoundly important for bacterial AHL-based quorum sensing and quorum quenching. The different levels of AHL-based quorum sensing and quorum quenching are closely linked to AHL concentration; AHL concentration available is affected by environmental factors outside bacterial cells, whether abiotic factors or biotic factors (Platt and Fuqua, 2010).

Among abiotic factors, the alkaline pH favours the hydrolysis of AHL signals with shorter acyl-chains, and AHL signals require an acyl chain with at least four carbons to keep stable under pH conditions encountered by most bacteria (Yates et al., 2002; Decho et al., 2009). AHLs with longer acyl chains (>C12) are more resistant to alkaline lysis (Decho et al., 2010). It is also demonstrated that the AHL production in the cellular environment highly depends on the growth temperature, concurrent with phenotypic changes (Atkinson et al., 1999; Kirwan et al., 2006; Kimes et al., 2012). AHL accumulation and concentration are also susceptible to mass transfer processes by diffusion or advection. The quorum sensing is actually diffusion sensing, where AHL signals can determine whether secreted molecules will rapidly move away from the cell, thereby allowing cells to regulate exoenzyme secretion and other effectors to minimize losses (Redfield, 2002; Hense et al., 2007). Advection refers to a process in which AHL signals are transported by circulating fluids, which exhibits a significant role at the local scale, notably when bacteria form biofilms (Horswill et al., 2007; Boyer and Wisniewski-Dye, 2009). In addition, survival medium conditions, such as nutrient composition and oxygen composition (Wagner et al., 2003; Duan and Surette, 2007), appear to significantly affect AHL concentration.

The concentration of AHL signals is also altered by many biotic factors, including cell density, spatial distribution of cells, degradation and the production of the same signal by third parties, etc (Hense et al., 2007). AHL concentration increases accordingly with cell density, and coordinates action of a group of cells once exceeding a threshold. However, AHL concentration at the cell location can be more strongly dependent on the spatial distribution of cells than on cell density (Hense et al., 2007). AHL degradation by bacterial enzymes, lactonases and acylases, has been discussed in section 2.3. In addition, many quorum quenching compounds mainly produced by eukaryotes, such as algal compounds, plant-made compounds, fungal compounds and animal compounds, can lead to AHL inactivation (Boyer and Wisniewski-Dye, 2009; Kalia, 2013). Evidence is also presented that AHL structural mimics produced by other species may act as QS activators (Holden et al., 1999) or QS antagonists by competing with AHL for receptor binding (Teasdale et al., 2009).

Environmental factors can profoundly influence AHLs availability, thereby affecting the levels of AHL-based quorum sensing and quorum quenching in the surrounding environment. Therefore, the regulation of bacterial AHL-based quorum sensing and quorum quenching in real and complex environments are far more than simple matters.

4. AHL-based quorum sensing and quorum quenching in biological wastewater treatments

4.1. Coexistences of AHL-based quorum sensing and quorum quenching phenomena

AHL-based QS and QQ are two antagonistic processes. In previous studies, the presence of AHL within biofilms, activated sludge flocs or granules, was confirmed; some bacteria with AHL-based QS activity were found in wastewater treatment bioreactors (Kämpfer et al., 1996; Morgan-Sagastume et al., 2005; Liu et al., 2010b; De Clippeleir et al., 2011). It was certain for endogenous existence of AHL-based QS phenomenon in biological wastewater treatments. On the other hand, several bacteria with AHL-based QQ activity have been isolated from wastewater treatment bioreactors; addition of isolated QQ bacteria to bioreactors was found to affect the QS (Cheong et al., 2013; Kim et al., 2013b; Oh et al., 2013). Meanwhile, the existence of AHL-based QQ phenomenon in biological wastewater treatments also aroused the concern. Soon after, in a lab-scale MBR study by Song et al. (2014), for the first time, AHL-degrading enzymatic activity, a typical QQ effect, was detected *in situ* in activated sludge and found to greatly affect QS detection results. The coexistence of AHL-based QS and QQ bacteria in activated sludge was further confirmed by bacterial screening and denaturing gradient gel electrophoresis (DGGE) analysis. Similarly, Li et al. (2016) also revealed the coexistence of the AHL-producing and -quenching bacteria as well as other irrelevant species in aerobic granules cultivated in a lab-scale SBR; specifically, the number of AHL-quenching isolates was far greater than that of AHL-producing isolates. Given that all results above, it is indicated that endogenous AHL-based QS and QQ are existing and coexisting in biological wastewater treatments; the leading role for AHL-based QS or QQ phenomenon in biological wastewater treatments can be determined by bacterial AHL concentration.

A table of bacteria that are identified in biological wastewater treatments and are known to possess AHL-based QS or QQ activity is shown in Table 1. Certainly this list includes only selected bacteria important to biological wastewater treatments but the number of bacteria with AHL-based QS or QQ activity continues to increase with the in-depth investigations.

4.2. Potential role of AHL-based quorum sensing in biomembrane processes

Biomembrane processes, also known as fixed-film processes, are all dependent on the adhesion of microbial cells to form a biofilm on the inert support medium with a large specific surface area for maximum biofilm development for removal of dissolved and colloidal organic pollutants (Costerton et al., 1995; Hall-Stoodley et al., 2004; Shrout and Nerenberg, 2012; Feng et al., 2013). Specifically, biofilm represents the core component in various biofilm reactors, and its property is crucial to overall performance and efficiency of the treatment as well as effluent quality.

Quorum sensing and biofilms are inextricably linked, and they are the central features of bacterial social behaviors (Davey and O'Toole, 2000; Hall-Stoodley et al., 2004; Bassler and Losick, 2006; Kaufmann et al., 2008; Lade et al., 2014c). It has been found that quorum sensing can be of great importance in initial biofilm formation, defining the biofilm composition, and determining the behavior of biofilm communities (Davies et al., 1998; Hancock and Perego, 2004; Parsek and Greenberg, 2005; An et al., 2006; Shrout and Nerenberg, 2012). Therefore, quorum sensing and biofilms are considered be important for the improved performance of biofilm reactors. In a study by De Clippeleir et al. (2011), the presence of C_{12}-HSL in the oxygen-limited autotrophic nitrification/denitrification (OLAND) biofilms from the OLAND rotating biological contactor was confirmed, and AHL-based QS, by means of C_{12}-HSL addition, dealt with the need for a minimum biomass concentration dependency of anoxic ammonium-oxidizing bacteria (AnAOB) activity, and significantly increased ammonium oxidation rate in OLAND biofilms. Currently, available reports for the effects of AHL-based QS on biofilms in fixed-film processes are very limited; however, various studies have examined the role of AHL-based QS in pure-culture bacterial system. AHL-based QS in monospecies biofilms has been found to regulate different aspects of biofilm formation and maturation, such as the formation of bacterial

Table 1
Quorum sensing bacteria and quorum quenching bacteria based on AHLs present in biological wastewater treatments.

Type	Bacterial strains	Bacterial genus	Major AHLs produced/ degraded	QS/QQ regulated activities	Treatment processes	Wastewater types	Sources	Reference
Quorum sensing bacteria	*Ac. baumannii* strain M2	*Acinetobacter*	3-hydroxy-C_{12}-HSL	Biofilm formation Biofilm development Surface motility	EBPR aerobic-anaerobic process Conventional aerobic activated sludge process	Municipal/ Industry wastewater	Activated sludge Wastewater	(Jorgensen and Pauli, 1995; Niu et al., 2008; Gaddy and Actis, 2009; Clemmer et al., 2011)
	A.hydrophila	*Aeromonas*	C_4-HSL, C_6-HSL	Biofilm development	Activated sludge process	Municipal wastewater	Activated sludge	(Lynch et al., 2002; Morgan-Sagastume et al., 2005)
	C. testosteroni	*Comamonas*	Unknown	Hormone degradation	Activated sludge process	Municipal wastewater	Activated sludge	(Dias and Bhat, 1964; Pruneda-Paz et al., 2004; Andersson et al., 2008)
	Nitrosomonas europaea	*Nitrosomonas*	C_6-HSL, C_8-HSL C_{10}-HSL	Unknown	Activated sludge process	Industrial wastewater	Nitrifying-denitrifying activated sludge	(Juretschko et al., 2002; Burton et al., 2005)
	Nitrobacter winogradskyi	*Nitrobacter*	Unknown	Unknown	Activated sludge process	Industrial wastewater	Nitrifying-denitrifying activated sludge	(Juretschko et al., 2002; Starkenburg et al., 2006)
	P. putida *P. aeruginosa*	*Pseudomonas*	C_4-HSL, C_6-HSL 3-oxo-C_{12}-HSL	Biofilm formation and development Virulence factors production EPS production	Activated sludge process	Municipal wastewater	Activated sludge	(Jorgensen and Pauli, 1995; Davies et al., 1998; Wagner et al., 2003; Morgan-Sagastume et al., 2005)
	Sphingomonas paucimobilis	*Sphingomonas*	Unknown	Unknown	EBPR aerobic-anaerobic process/Conventional aerobic activated sludge process	Municipal/ Industry wastewater	Activated sludge Wastewater	(Jorgensen and Pauli, 1995; Enya et al., 2007)
Quorum quenching bacteria	*Rhodococcus* sp. BH4	*Rhodococcus*	C_6-HSL, C_8-HSL C_{10}-HSL, C_{12}-HSL 3-oxo-C_6-HSL 3-oxo-C_8-HSL 3-oxo-C_{10}-HSL 3-oxo-C_{12}-HSL	Inhibit biofilm formation in MBR	Real MBR plant	Municipal wastewater	Activated sludge Biocake	(Oh et al., 2012; Kim et al., 2013b; Oh et al., 2013; Kim et al., 2015a)
	Pseudomonas sp. 1A1	*Pseudomonas*	C_6-HSL,C_8-HSL C_{10}-HSL, C_{12}-HSL 3-oxo-C_8-HSL 3-oxo-C_{10}-HSL 3-oxo-C_{12}-HSL	Inhibit biofilm formation in MBR	Lab-scale MBR/Activated sludge process	Municipal wastewater	Activated sludge	(Cheong et al., 2013; Ochiai et al., 2013; Cheong et al., 2014)
	Variovorax paradoxus strain VAI-C	*Variovorax*	C_4-HSL, C_6-HSL C_8-HSL, C_{10}-HSL C_{12}-HSL 3-oxo-C_6-HSL	Degrade other species AHLs	Activated sludge process	Industrial wastewater	Nitrifying-denitrifying activated sludge	(Leadbetter and Greenberg, 2000; Juretschko et al., 2002; Huang et al., 2003)
	Acinetobacter sp. strain Ooi24	*Acinetobacter*	C_{10}-HSL	Unknown	Activated sludge process	Unknown	Activated sludge	(Ochiai et al., 2013; Ochiai et al., 2014)

EBPR: enhanced biological phosphorus removal.

clusters (Davies et al., 1998; Lynch et al., 2002) or structurally homogeneous biofilms (Steidle et al., 2002), surface colonization via cell motility (Lindum et al., 1998), biofilm thickness (Labbate et al., 2004), and overall biofilm depth and architecture (Kjelleberg and Molin, 2002). It was found that *Nitrosomonas europaea* AHL QS, by means of AHL addition, accelerated the recovery of nitrifying biofilms from starvation (Batchelor et al., 1997; Burton et al., 2005; Geets et al., 2006; De Clippeleir et al., 2011).

Given that all results above, it is conceivable that bacterial AHL-based QS is important for biofilms, which might provide a possible strategy to improve the performance of biofilm reactors by artificially enhancing AHL-based QS activity, i.e., AHLs exogenous supplementation.

4.3. Potential role of AHL-based quorum sensing in activated sludge processes

Activated sludge processes are the principal approaches for

biological wastewater treatments, which are based on biological coagulation, adsorption and oxidation of microorganisms in activated sludge to successfully remove the bulk of organic compounds. Till now, activated sludge processes and their improved derivatives are most widely used for wastewater treatments. Specifically, sludge property is crucial to overall performance and efficiency of the treatment as well as effluent quality in various activated sludge processes.

In conventional activated sludge process, activated sludge flocs are complicated aggregates containing inorganic and organic particles as well as a high-density microbial consortium embedded in a matrix of extracellular polymeric substances (Frølund et al., 1996; Biggs and Lant, 2000; Jin et al., 2003). The high cell density of flocculates is likely to result in a great amount of interactions between cells (Chong et al., 2012), and there have been a few studies so far to elucidate the possible presence of bacterial AHL-based QS in activated sludge and its impacts on activated sludge property. In a study by Morgan-Sagastume et al. (2005), based on the thin layer chromatography and biosensor overlays, the production of AHLs or AHL-like autoinducers is confirmed from municipal, hospital and pharmaceutical activated sludges, and different strains of *Aeromonas* spp. and *Pseudomonas* spp. having AHL activity were isolated from municipal activated sludge. Valle et al. (2004) reported that seven proteobacterial strains isolated from the phenol-degrading activated sludge were found to produce compounds with AHL-like activity. AHL additions with 2 and 20 μM to activated sludge sustained phenol degrading activity over the 14 days whereas that in control system without such additions faltered after 10 days and was lost after 14 days; such AHL treatments induced a large shift in activated sludge community composition with a dominant functional member of the *Thauera* genus transiently replaced by a member of the *Comomonas* genus. The results demonstrated that AHL-mediated gene expression played a role in mediating composition and function of an activated sludge community in an industrial activated sludge process (Valle et al., 2004). Further, the relationship of AHL-based quorum sensing and exoenzyme activity in activated sludge was observed; elevated 3-oxo-C_6-HSL concentrations hourly with 10 μM in activated sludge generated a rapid 10-fold increase in extracellular chitinase activity between 60 and 90 min (Chong et al., 2012). It was speculated that AHL-dependent production of extracellular chitinase could underpin the success of some *Aeromonas* lineages in activated sludge, which might create opportunities for the improved sludge performance.

In sequencing batch reactor activated sludge process (SBR), aerobic granular sludge, a new form of microbial aggregates, has been cultivated for biological wastewater treatments (Beun et al., 1999). Compared to the flocculent activated sludge, it possesses strong attachment potential, high density, compact structure, excellent settleability as well as resistance against toxic substances and organic loading shock (Su and Yu, 2005; Adav et al., 2008; Gao et al., 2011; Show et al., 2012; Lv et al., 2014b). The formation of aerobic granules is a gradual process developed from activated sludge to compact aggregates, further to granular sludge, and finally to matured granules (Wang et al., 2004; Su and Yu, 2005). AHL signals have also been detected in aerobic granular sludge (Ren et al., 2010; Xiong et al., 2014). Based on bacterial biosensors, it was found that granular sludge contained more AHLs than flocculent sludge for the SBRs by comparing with the size of color zone induced (Liu et al., 2010b; Li et al., 2014; Lv et al., 2014a; Xiong et al., 2014). Moreover, a positive correlation has been well-characterized between bacterial AHL-based QS and aerobic sludge granulation in SBRs. It has been demonstrated that extracellular polymeric substances (EPS) and microbial attachment played the important roles in formation and development of aerobic granules (Wang et al., 2006; Chen et al., 2007; Lv et al., 2014b). AHL-based QS not only facilitates EPS component productivity of microorganisms in activated sludge and contributes to aerobic granulation (Jiang and Liu, 2012; Tan et al., 2014; Xiong et al., 2014) but also promotes the microbial attachment of aerobic granule through the regulation of extracellular proteins as EPS hydrophobic components (Lv et al., 2014a). In AHLs add-back studies by Tan et al. (2014), the exogenous additions of 40 μL AHLs significantly increased the production of both extracellular polysaccharides (14–36%) and proteins (7–16%) and the microbial aggregation by the floccular sludge community. However, there may be some drawbacks for the AHL exogenous regulating strategy; the AHL high cost limits their wide use for both laboratory and practical engineering researches; moreover, adding the identical synthetic signals also may not maintain a continuous positive effect on sludge granulation because of their considerable degradation. To date, Ding et al. (2015) have cultured a designated microbial strain which secrets a specific type of signals to increase the concentration of "beneficial" signals to combine native signals to accelerate anaerobic granulation simultaneously, which might provide an exogenous supplementation strategy of AHL-producing bacteria for aerobic granulation in SBRs. Therefore, the sustainable and economic QS regulation strategy in aerobic granulation should be continuously explored.

AHLs are ubiquitous in activated sludge and aerobic granule sludge, and AHL-based QS exerts a significant role on sludge property in various activated sludge processes. Meanwhile, attempts to improve sludge performance and accelerate SBR aerobic granulation by artificially enhancing AHL-based QS activity, i.e., the exogenous supplementation of AHLs and AHL-producing bacteria, are worthy of special attention.

4.4. Potential role of AHL-based quorum quenching in membrane bioreactors

Membrane bioreactors (MBRs) have been considered as a high quality wastewater treatment technology of choice for various wastewater treatments, which are composed of common bioreactors with membrane filtration units for biomass retention (Drews, 2010). Membrane biofouling remains to be one of the most serious operational problems for MBR applications, which results in permeate flux and water quality decline, trans-membrane pressure (TMP) and operating costs increase, frequent membrane cleaning and replacement necessary (Miura et al., 2007; Mahendran et al., 2011; Guo et al., 2012; Malaeb et al., 2013). Membrane biofouling is considered as undesirable accumulation of microorganisms, which occurs by the adhesion, growth and multiplication of living microorganisms and eventually forms a biofilm layer on the membrane surface (Liu et al., 2010a; Guo et al., 2012).

Quorum sensing and biofilm formation are strongly linked (Davies et al., 1998; Stuckey, 2012; Ren et al., 2013), and several studies have linked the presence of AHL signals with biofilm formation and revealed the problem of membrane biofouling in MBRs (Yeon et al., 2009a; Kim et al., 2012, 2013a; Lim et al., 2012; Lade et al., 2014c). In a study by Yeon et al. (2009a), TLC chromatographic analysis of the mixed cultured biocake from MBR has suggested the presence of C_6-HSL and C_8-HSL. Over a long period of MBR operation, biocake exhibited strong AHL activity simultaneously with sharp increase in the trans-membrane pressure (TMP). Similarity, HPLC characterization by Kim et al. (2013b) detected C_8-HSL and 3-oxo-C_8-HSL from biofilm formed on the membrane surface in MBR. In addition, Lade et al. (2014a), using TLC with a bioassay and HPLC technology, detected eight different AHL signals including C_4-HSL, C_6-HSL, C_8-HSL, 3-oxo-C_8-HSL, C_{10}-HSL, C_{12}-HSL, 3-oxo-C_{12}-HSL and C_{14}-HSL in activated sludge extract from MBR. It was also reported that several groups of

bacteria identified in MBRs such as *Enterobacter*, *Aeromonas*, *Citrobacter*, *Raoultella*, *Klebsiella*, *Pseudomonas* and *Serratia* were able to produce AHL signals and regulate biofilm formation on the membrane surface (Lade et al., 2014a). Those studies indicate that AHL-based QS is universally regulating biofilm formation and then results in membrane biofouling in MBRs.

Based on quorum quenching principles, interference with bacterial quorum sensing leads to the inhibition of desired phenotypes like biofilm formation (Lade et al., 2014c). It is envisioned that such strategy not only solves the limitations (e.g. low resource utilization, high cost of operation, management inconvenience) of the traditional antifouling methods (e.g. membrane modification, membrane cleaning, tuning mixed liquors properties) (Xu and Liu, 2011; Huang et al., 2012, 2014a, 2014b; Malaeb et al., 2013; Jeong et al., 2014; Shuai et al., 2014) but also prevents the use of antimicrobial compounds or antibiotics from the risk of multi-drug resistance and water pollution (Davies, 2003; Hook et al., 2012; Lade et al., 2014c). Until now, studies in terms of quorum sensing and quorum quenching in biological wastewater treatments have mainly concentrated on quorum quenching mediated strategies for control of membrane biofouling in MBRs. Since 2009, studies for AHL-based quorum quenching in term of membrane biofouling control in MBRs have presented a trend developed from free enzyme to immobilized enzyme, from quorum quenching enzyme to quorum quenching bacteria, and from pure bacteria to wastewater indigenous bacteria.

Enzymatic quenching of AHL signals using acylases or lactonases has proved its high potential for the efficient biofouling control in membrane processes including MBRs. The first study in a laboratory-scale MBR was conducted by Yeon et al. (2009a), who demonstrated that direct addition of the free acylase I (quenching AHLs with amide bond cleavage) to MBRs could effectively retard trans-membrane pressure (TMP) rise. Considering the technical limitations (e.g. short catalytic lifetime and easy loss) of the free enzyme under a long-term continuous MBR operation, researchers tried to immobilize enzyme on various carriers which may be more stable for MBR wastewater treatment. A magnetic enzyme carrier (MEC) by immobilizing acylase I on magnetic particles was developed to control membrane biofouling in MBRs treating synthetic wastewater (Yeon et al., 2009b). The results showed that TMP in MBR with MEC maintained almost its initial value of around 10 kPa after a 48-h operation, whereas that of the MBR without MEC increased to 30 kPa. Similarity, Lee et al. (2014) immobilized and stabilized acylase in magnetically separable mesoporous silica to maintain its highly effective and sustainable antifouling activity even under harsh conditions of low enzyme dosage and high organic loading. In addition, Kim et al. (2011) immobilized the acylase onto the nanofiltration membrane surface by forming a chitosan-acylase matrix. The results of the lab-scale nanofiltration (NF) system demonstrated that the flux with the acylase-immobilized NF membrane still maintained more than 90% of its initial flux after a 38-h operation while that with the raw NF membrane started to decline after 12 h and continuously decreased to 60% accompanying with severe biofouling, which suggests the newly developed approach has great potential towards effective antifouling solution in MBRs. Furthermore, attention is being focused on the exact mechanisms of enzymatic quorum quenching for membrane biofouling control in MBRs. Kim et al. (2013a) made an analysis of microbial communities in MBRs with and without acylase using pyrosequencing. The results demonstrated that the proportion of AHL-producing bacteria in the mature biofilm in MBR with acylase is relatively smaller than that in MBR without acylase. Proteomic analysis using the *Enterobacter cancerogenus* revealed that enzymatic quorum quenching could depress protein expression related to the microbial attachments to solid surfaces and the agglomeration of microorganisms.

In fact, a large number of bacteria are known to produce quorum quenching enzymes, and enzymatic quenching mechanism of AHL signals is also present in enzyme-producing bacteria, such as *Anabaena* sp. PCC7120, *Ralstonia* sp. XJ12B, *P. aeruginosa* PAO1, *Agrobacterium tumefaciens* C58, *Bacillus* sp. strain 240B1, *Rhodococcus erythropolis strain W2* (see in section 2.3). Given the practical issues on high extraction and purification cost as well as low stability of enzymes, interspecies quorum quenching by bacteria cell could be further elaborated as efficient and economically feasible antibiofouling strategy in MBRs (Oh et al., 2012; Kim et al., 2013b; Lade et al., 2014b). The recombinant bacteria (e.g. *the recombinant Escherichia coli* producing AHL-lactonase) has been proved to be effective for biofouling inhibition in a laboratory scale MBRs but it may not survive well in the real MBRs (Oh et al., 2012), and thus more attention is focused on the indigenous quorum quenching bacteria for the real MBRs wastewater treatment. Oh et al. (2012) encapsulated quorum quenching *Rhodococcus* sp. BH4 isolated from a real MBR plant into a microporous membrane (i.e., "microbial-vessel"), and put it into the submerged MBR to inhibit membrane biofouling; the results showed that it took about 40 h to reach the TMP of 50 kPa in the control MBR without BH4 but 115 h to reach the same TMP in the MBR with BH4 (Oh et al., 2013). In addition, quorum quenching effect of microbial-vessel was maintained over 80 days of MBR operation, during which chemical oxygen demand (COD) removal efficiency (96–98%) was not affected compared with the control MBR (Oh et al., 2012). Similarity, Cheong et al. (2014) developed a ceramic microbial vessel (CMV), which was prepared with the indigenous quorum quenching *Pseudomonas* sp. 1A1 and a monolithic ceramic microporous membrane, and operated the laboratory-scale MBR treating synthetic wastewater with the inner flow feeding mode; it was found that production of extracellular polymeric substances was substantially decreased and biocake formation on membrane surface was efficiently reduced in MBR with CMV. Furthermore, it was confirmed that specific allocation of microbial-vessel as well as recirculation rate of mixed liquor largely influenced the quorum quenching effect on membrane biofouling in the external submerged MBR (Jahangir et al., 2012). Such a vessel is submerged in a fixed place in the MBR so that only soluble AHLs that are capable of diffusing into the vessel can be degraded (Kim et al., 2013b), and thus more attention is focused on free-moving beads entrapped quorum quenching bacteria. Kim et al. (2013b) developed the free-moving alginate beads entrapped with *Rhodococcus* sp. BH4 to mitigate membrane biofouling by dual roles of physical friction and biological quorum quenching, which was proved to be more efficient than using microbial vessel. Similarity, *Rhodococcus* sp. BH4 entrapping microcapsules coated by a polymeric membrane layer also showed an excellent anti-biofouling capacity in continuous MBR (Kim et al., 2015a). However, informations on bacterial quorum quenching including source and isolation of quorum quenching bacteria, bacterial adaptability and its quenching effects as well as its impact on biofilm formation and evolution in MBRs are not fully comprehensive, and thus a lot of in-depth studies should continue.

Membrane biofouling is a persistent obstacle for MBR treating wastewaters; AHL-based quorum quenching can mitigate membrane biofouling effectively and enhance the membrane treatability without impacting microbial activity and pollutant degradation, which is a brand-new, bio-friendly and environment-friendly membrane biofouling control strategy. Therefore, it now is viewed as an innovative and promising alternative to control membrane biofouling in MBRs by artificially enhancing AHL-based quorum quenching activity, i.e., dosing AHL-degrading quorum quenching enzymes or bacteria exogenously.

5. Conclusions and future research needs

Basic researches on the characterization of AHL signals as well as AHL-based QS and QQ mechanisms have made progress. Consideration of existences and effects of AHL-based QS and QQ in biological wastewater treatments holds promise to determine the bioreactor performance. AHL-based QS involves in the processes of biofilm formation and development as well as SBR aerobic granulation; applications by AHL-based QQ exert the important roles in the treatment of membrane biofouling in MBRs. The exogenous modulation of AHL-based QS and QQ, such as AHL signals and AHL-producing bacteria supplementation, AHL-degrading enzymes or bacteria addition, has shown a great potential as an innovative and promising strategy with eco-friendliness, low risk of bacterial resistance development, high anti-biofouling efficiency over other strategies for the improved wastewater treatment performance. More researches on AHL-based QS and QQ in biological wastewater treatments will focus primarily on the applications of quorum quenching bacteria developed from recombinant bacteria to wastewater indigenous bacteria and then immobilized indigenous bacteria for the control of membrane biofouling in MBRs.

Clearly there are many research needs in this area that can be best answered by continuously investigating existences and roles of AHL-based QS and QQ important to biological wastewater treatments. These research needs are summarized as follows:

1) Informations on the structure and concentration of AHLs are of great importance not only for basic cellular researches but also for wastewater treatment applications. Hence, continuous exploration of more convenient and effective methods is required for qualitative and quantitative analysis of AHLs.
2) Given that high enzyme extraction and purification costs as well as enzyme instability, more researches with enzymatic quorum quenching should focus on its universal effectiveness and exact mechanisms than its practical application in the control of membrane biofouling. The main elements, such as the settleability and particle size of sludge, apparent viscosity and zeta potential of mixed liquor, microbial community, as well as characteristics and function of EPS and SMP, are responsible for membrane biofouling in MBRs. Therefore, understanding and characterizing the relationship among three aspects from enzymic quorum quenching, biofouling elements and the effectiveness of biofouling control is expected to serve as a stepping stone for the development and application of biological-based antifouling strategies.
3) Continued researches with bacterial quorum quenching are likely to include exploitation of more appropriate QQ bacteria and immobilized microorganism techniques. There exist many QQ bacteria available in fact, and their characteristics, such as degradation rates of AHL signals, QQ enzyme location, growth rate and survival competition with other bacteria, are closely linked to their QQ activity against AHLs (Christiaen et al., 2011; Cheong et al., 2013). Meanwhile, immobilization not only provides nutrients for the target bacteria without competing with other bacteria but also protects them from environmental stress (Kim et al., 2015a). Hence, continuous searching for more effective QQ bacteria as well as more stable immobilization materials and relatively simple immobilization methods is necessary to realize its widespread application for biofouling control in MBRs.
4) AHL-based QS systems and controlled phenotypes of some model bacterial species are well identified by pure-culture research under laboratory conditions, and the additional species related to biological wastewater treatments should continue to be study. Meanwhile, experiments should also be conducted to study the valid effects of AHL-based QS in mixed-culture systems with 3–4 known QS species important to biological wastewater treatments. On the other hand, in spite of the success of exogenous regulation strategies for the improved reactor performance (e.g. QQ strategies in MBRs), such experiments are needed to perform the scale-up of these results to real wastewater treatments and verify their effectiveness using real wastewater.
5) Bacterial AHL-based QS and QQ, as response of microbial community to environmental conditions, are thus very sensitive to the fluctuation of these conditions (Song et al., 2014). It is worth noting that operational parameters, wastewater compositions, etc., are expected to largely impact the effectiveness of exogenous regulation strategies in wastewater treatment bioreactors. Systematic correlations that link exogenous regulation strategies to important operational and environmental parameters are lacking; specifically, future studies should be also committed to combining exogenous regulation with optimum parameters to realize its maximum effectiveness for improving bioreactor performance.

Certainly, improved understanding and potential applications of AHL-based QS and QQ will help to engineer biological wastewater treatment systems successfully.

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