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Review

Production, detection and application perspectives of quorum sensing autoinducer-2 in bacteria

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ABSTRACT

Autoinducer-2 (AI-2) is a major signal molecule in bacterial quorum sensing (QS) besides N-acyl homoserine lactones (AHLs or AI-1). AI-2 mediated QS pathways have been proved to regulate gene expression and physiological behaviors of bacteria in either intraspecies or interspecies communication. Recent reviews have mainly summarized AI-2 structures, AI-2 mediated QS pathways and the role of AI-2 in gene regulation, etc. In this article, we present a comprehensive review of AI-2 production, detection and applications. Firstly, intracellular AI-2 synthetic routes were outlined and environmental influences on AI-2 production were focused. Furthermore, recent advances in AI-2 detection and quantification were elucidated from an overall perspective. An in-depth understanding of mechanisms and features of various detection methods may facilitate development of new technologies aimed at signal molecule detection. Finally, utilization of AI-2 mediated QS in health improvement, water treatment and drug production indicate promising and extensive application perspectives of QS strategies.

1. Introduction

Quorumsensing (QS) is a phenomenon discovered mainly in bacteria. When the cell population density increases, specific signal molecules would reach a concentration threshold, further inducing signal transduction in QS pathways and regulating gene expression of microbes (Miller and Bassler, 2001). This interesting phenomenon attracted wide attention. Recent studies focusing on QS have provided insights into bacterial intraspecies communication, regulation mechanisms of physiological functions and novel approaches to combating diseases caused by pathogens (Dong and Zhang, 2005; Jayaraman and Wood, 2008; Ng and Bassler, 2009; Rasmussen and Givskov, 2006; Roy et al., 2011; Waters and Bassler, 2005). In-depth explorations of QS may be significant for disease control in agriculture, aquaculture, animal husbandry and even human health (Boyen et al., 2009; De Kievit and Iglewski, 2000; Zhao et al., 2015). QS based strategies are expected to be used extensively due to environmental compatibility and safety concerns (Chinabut and Puttinaowarat, 2005; Subasinghe, 2009).

AI-2, as a major type of signal molecule in bacterial QS systems, has been widely studied in recent years. To date, structures of two AI-2 type signal molecules have been revealed: (2S, 4S)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuranborate (S-THMF-borate, BAI-2) in *Vibrio harveyi* and (2R, 4S)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran (R-THMF, AI-2) in *Salmonella typhimurium* (Chen et al., 2002; Miller et al., 2004). In the QS system of certain bacteria, AI-2 mediated signaling pathway is parallel to and integrated with the pathways mediated by another two types of signal molecules: N-acyl-homoserine lactones (AHLs) and (S)-3-hydroxytridecan-4-one (CAI-1). Collectively, pathways mediated by different signal molecules constitute QS network architectures in bacteria, among which *V. harveyi* is a prominent representative (Jayaraman and Wood, 2008). The multi-channel QS pathways cooperatively function and regulate gene expression, however, the contribution of each QS pathway to overall gene expression might be different (Mok et al., 2003; Waters and Bassler, 2006). Although the role of AI-2 in QS systems remained to be explored, research has implicated that AI-2 mediated QS pathway participates in multiple physiological functions, including cell signaling and processes, metabolism, release of virulence factors, stress response, etc (Di Cagno et al., 2011).

Due to the important status of AI-2 in microbial signaling and increasing interest in this signal molecule, AI-2 mediated QS pathway and the role of AI-2 in gene regulation were reviewed recently. However, AI-2 production, detection and applications were rarely the topic of focus. In this article, we outline intracellular AI-2 synthesis and perception, together with the exceptional cases of microbes without AI-2

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synthesis or receptor proteins, evaluate influences of different environmental factors on AI-2 production and review the developments in AI-2 detection and quantification methods. Current applications of AI-2 based QS strategies will also be summarized, highlighting the application perspectives of AI-2 and AI-2 inhibitors based on QS signaling and quenching.

2. AI-2 synthesis and perception in bacteria

To date, two types of AI-2 synthetic pathways have been proposed. The canonical synthetic route has been depicted as follows: S-adenosylhomocysteine (SAH), as an intermediate of S-adenosylmethionine (SAM), is catalyzed by S-adenosylhomocysteine nucleosidase (Pfs) to produce S-ribosylhomocysteine (SRH). LuxS converts SRH into 4,5-dihydroxy 2,3-pentanedione (DPD) and homocysteine. DPD is unstable and finally forms AI-2 (Schauder et al., 2001). In this route, Pfs might contribute more than LuxS in AI-2 production (Wang et al., 2013). Besides the generally accepted synthetic route, another semi-biosynthetic pathway has been deduced in hyperthermophiles: with no LuxS but only Pfs, hyperthermophiles use SAH hydrolase to cleave SAH to adenosine and homocysteine. Adenosine is converted by nucleoside phosphorylase to ribose-1-phosphate (ribose-1-P), which is then isomerized by phosphosugar mutase to ribose-5-phosphate (ribose-5-P). Finally, ribose-5-P is converted to DPD and AI-2 by heat induction (Nichols et al., 2009). However, a previous report proposed different opinions, suggesting ribulose-5-phosphate (ribulose-5-P) instead of ribose-5-P could convert into AI-2 in *luxS*-lacking microorganisms. It further indicated that ribulose-5-P would exist as an intermediate of the pentose phosphate metabolism pathway and form AI-2 (Tavender et al., 2008) (Fig. 1(a)).

Above LuxS-independent AI-2 synthetic pathways indicated that AI-2 synthesis proteins were not indispensible. This situation also occurs for AHL synthesis. For instance, AHL synthesis proteins don't exist in *Escherichia coli* and *Salmonella enterica* while AHL receptor proteins do exist (Smith et al., 2011). AHL receptors in microorganisms with no AHL synthase, named as LuxR orphans or solos, have attracted much attention. Surprisingly, LuxR orphans may constitute a high proportion of LuxR-type receptors in prokaryotes. Certain bacteria may harbor more than one LuxR orphan. LuxR orphans can either be accompanied by LuxI-associated LuxRs or exist alone. Therefore, LuxR orphans could either use self-produced AHLs or respond to exogenous AHLs for interspecies communication. However, lack of AHL binding motifs of many LuxR orphans indicate that they might sense signal molecules other than AHLs (Patankar and González, 2009; Hudaiberdiev et al., 2015; Subramoni et al., 2015). Recently discovered signal molecules in two *Photorhabdus* species have confirmed this speculation. The orphan LuxR-type receptors PluR and PauR could sense pyrones and dialkylresorcinols as signal molecules in *P. luminescens* and *P. asymbiotica* respectively. Novel signal molecules and the diversity of LuxR orphans indicated the existence of alternative types of QS signalling circuits besides AHL QS circuits (Brachmann et al., 2013; Brameyer et al., 2015).

Similar to the microorganisms with no AHL synthase but with LuxR orphans, *Riemerella anatipestifer*, *Sinorhizobium meliloti* and *Rhodobacter sphaeroides* seemed not to have a *luxS* homolog encoding AI-2 synthesis protein, however, they have AI-2 receptors to perceive exogenous AI-2 (Han et al., 2015; Pereira et al., 2008) (Fig. 1(b)). Therefore, perception of exogenous AI-2 is another channel for AI-2 acquisition besides endogenous synthesis of AI-2. Overall, LuxS was not essential for AI-2 synthesis. Even if LuxS exists in a given genome, it may not function as AI-2 synthesis protein, since certain LuxS homologs may be acquired by horizontal gene transfer and only possess metabolic functions (Rezzonico and Duffy, 2008).

For AI-2 perception, three types of AI-2 receptors have been discovered, including the LuxP protein in *Vibrios*, LsrB protein in *Escherichia coli* and *Salmonella Typhimurium*, as well as RbsB protein in *Aggregatibacter actinomycetemcomitans*. Certain microorganisms such as *A. actinomycetemcomitans* even possess two AI-2 receptors LsrB and RbsB with different AI-2 binding affinities (Bansal et al., 2008; Henke and Bassler, 2004; Miller et al., 2002; Pereira et al., 2009; Shao et al., 2007; Taga et al., 2003). To date, researches have revealed different functions of LuxP and LsrB receptors. Upon binding to AI-2, the LuxP receptor will trigger a cascade of signal transduction and regulate downstream gene expression. In contrast, LsrB is responsible for AI-2 internalization. Internalized AI-2 is phosphorylated and bind to LsrR to initiate expression of the Lsr system, in turn accelerating AI-2 up-take

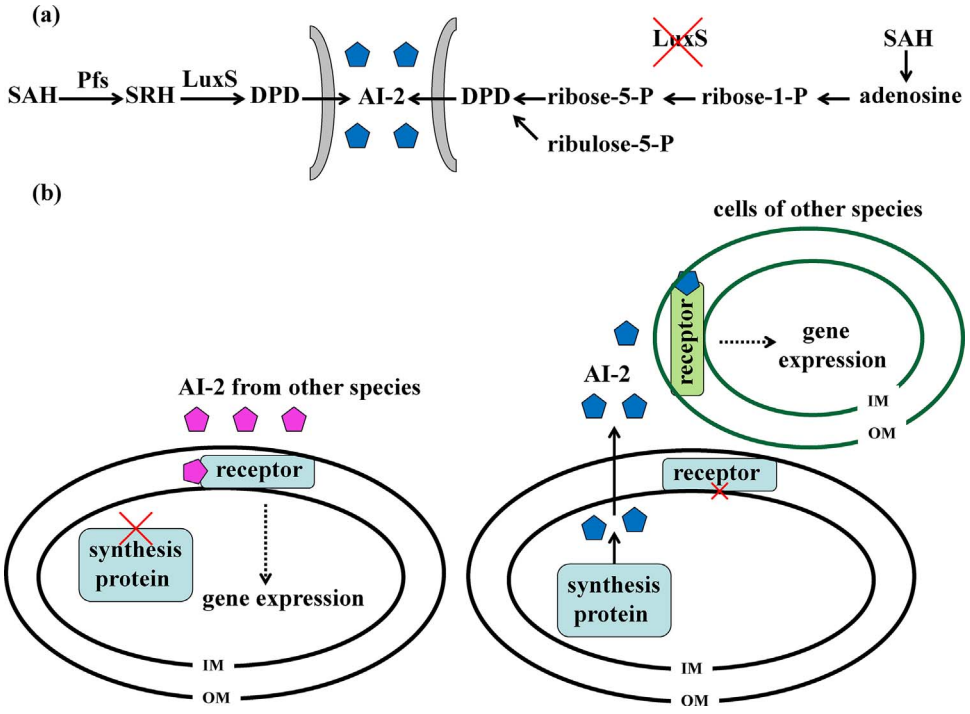

Fig. 1. AI-2 synthesis and perception in bacteria. (a) AI-2 synthetic routes with or without LuxS. (b) Intra-/interspecies communication with AI-2. For bacteria without AI-2 synthesis proteins or receptor proteins, AI-2 could be used for intra-/interspecies communication, including participating in signal transduction and regulating downstream gene expressions of other microbes. IM, inner membrane; OM, outer membrane.