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Molecular Basis Underlying LuxR Family Transcription Factors and Function Diversity and Implications for Novel Antibiotic Drug Targets

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ABSTRACT

LuxR is a widespread and functional diverse transcription factors and belongs to TetR protein superfamily. It could both activate and inhibit the expression of many genes contingent on the contexts, thereby involving in many crucial physiological events, such as virulence factors production, biofilm formation, quorum sensing (QS), acetate metabolism, motility, bioluminescence, and ecological competition. We summarized the function diversity of LuxR and underlying mechanisms. The interchangeability of some transcriptional factors for secondary metabolites biosynthesis opens new avenue to obtain new chemical entities or higher yield of antibiotics via the manipulation of regulators instead of structural genes. Inhibitors of pathogen QS are under intensive screening for better new antibiotics against the drug resistance. A compendium of compounds capable of inhibiting LuxR family transcriptional factors is also presented. J. Cell. Biochem. 112: 3079–3084, 2011. © 2011 Wiley Periodicals, Inc.

KEY WORDS: LuxR; TRANSCRIPTION FACTOR; INHIBITOR

Transcription factors are proteins specifically binding to DNA sequences to ensure that the optimum spatiotemporal expression of target genes via enhancement or attenuation. LuxR is a member of TetR protein superfamily transcriptional factor widespread among gram-negative bacteria containing a helix-turn-helix in C-terminal of the DNA binding domain [Pompeani et al., 2008; Liu et al., 2011].

Bacteria are social microbes that can interact with the adjacent bacteria in the same niche [Rasmussen and Givskov, 2006]. *Pseudomonas aeruginosa* QS (Quorum sensing) is an intricate regulatory system depend on cell density controlling the virulence [Schaefer et al., 1996], biosynthesis of exoenzymes, motility, nutritional intake, and biofilm formation [Liu et al., 2011]. QS represents a major mode that gram-negative bacteria regulate genes expression.

Unlike other TetR factors, LuxR transcription factor regulates a wide range of genes in addition to adjacent genes and self-regulation, and it can activate or repress considerable genes [de Bruijn and Raaijmakers, 2009]. Based on their activation mechanisms, LuxR-type regulons can be divided into two classes, (i) the regulons belong to two component system and activated by phosphorylation, such as FixJ of *rhizobium* [Lee et al., 2008], (ii) the regulons that are activated by binding to autoinducer (AI), such as N-AHL and LuxR of *Vibrio fischeri* [Lee et al., 2008]. There are many other LuxR-type regulons with a helix-turn-helix in C-terminal in addition to the abovementioned regulons subfamilies.

FUNCTION DIVERSITY OF LuxR

CYCLIC LIPOPEPTIDES (CLPS) BIOSYNTHESIS

CLPs produced by many *Pseudomonas* are crucial to *Pseudomonas* due to their diverse biological functions, such as surface motility, biofilm formation, virulence factor production, and antibiotic activity [Lee et al., 2008]. Few are known about the genes involved in CLP biosynthesis, although about eight *pseudomonas* CLPs

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biosynthesis genes have been identified and sequenced during the last decade [Lee et al., 2008]. The LuxR regulon includes a DNA-binding helix-turn-helix region but lacks *N*-acylhomoserine lactone-binding or reaction domain [Lee et al., 2008]. Those LuxR-type transcription regulon are exchangeable among different *Pseudomonas* strains to regulate the biosynthesis of CLPs with distinct structures [Lee et al., 2008]. This interchangeability endows enormous potentials to produce new derivatives with various specificity or enhanced activity, and opens new avenues to the genetic engineering of nonribosomal peptide synthetases (NRPS) or PKS biosynthesis genes. For example, exchanging the genes involved in daptomycin and carotenoid biosynthesis has generated a new derivatives library for possible better antibiotics [Lee et al., 2008]. Two plant pathogen *Pseudomonas syringae* genes, designated salA and syrF, were identified as LuxR-type transcriptional regulators for syringomycin and syringopeptin biosynthesis. The ability of syringomycin/syringopeptin production in *salA* mutant is completely destroyed. CLPs production in syrF mutant strain reduces about 88% according to *Ceotruchum candidum* activity assay [Lee et al., 2008].

QUORUM SENSING

Quorum sensing is used to describe the ability of bacteria to detect the AI molecule concentration produced by bacteria to communicate with other microorganisms in the same niche [Ferluga, 2009]. When the cell density and the AI concentration reach threshold, the transcription would be triggered and the pathway alternates accordingly [de Kievit and Iglewski, 2000]. It can regulate many physiological processes, such as antibiotic production, exocellular enzyme release, virulence factor production, splicing plasmid movement, biofilm formation, and bioluminescent [Ferluga, 2009; Liu et al., 2011]. On the contrary, at low cell density, phosphorylated LuxO activates the transcription of five small RNAs (*qrr*1, *qrr*2, *qrr*3, *qrr*4, and *qrr*5) that play a role in attenuating the LuxR transcription through inhibiting the production of LuxR [Halfmann et al., 2007a; Tu and Bassler, 2007]. Increased AI concentration reverses the phosphorylation. Meanwhile, quorum sensing is known to regulate numerous phenomena, including the production of exopolysaccharides in soil organisms such as *Rhodobacter sphaeroides, Ralstonia solanacearum, Pantoea stewartii* subsp. *stewartii*, and *Pseudomonas aureofaciens* [Marketon et al., 2003]. But the underlying mechanisms remain unknown. In general, LuxR can control the expression of genes of quorum sensing regulon directly or indirectly.

A typical AHL QS system is mediated largely by two proteins, namely LuxR and LuxI protein family member. AHLs synthesized by LuxI-type protein interaction with their cognate LuxR-type proteins, then this complex usually binds to specific promoter sequences called lux-box and affects expression of QS target genes [Ferluga, 2009]. In gram-negative bioluminescence marine bacteria, it is very complicated that a single transcriptional system can control the expression of bioluminescence. LuxI and LuxR can activate the transcription of lux operon. Autoinducer synthetase LuxI produces soluble autoinducer 3-oxygen-acetyl-L-homoserinelactone (3-O-C6-HSL). 3-O-C6-HSL and autoinducer-dependent LuxR activating agent can form a compound when 3-O-C6-HSL concentration is high, the binding of this compound to the LuxR box within promoter region can enhance the bioluminescence.

ACETATE METABOLISM

Corynebacterium glutamicum is a nonpathogenic, aerobic gram-positive soil bacteria that can grow on various saccharides and organic acid as the sole or major carbon source and energy source. Utilization of acetate necessitates glyoxylate shunt, including the uptake of and subsequent activation of acetate by coenzyme-A. For *Corynebacterium glutamicum* growth on acetate as sole carbon source and energy source, four enzymes were indispensable, namely acetokinase (AK), phosphotransacetylase (PTA), isocitrate lyase (ICL), and malate synthase (MS) of glyoxylate cycle [Cramer et al., 2006]. The activity of *Corynebacterium glutamicum* AK, PTA, ICL, and MS is significantly upregulated with acetate in the media.

A new LuxR-type transcriptional regulate factor, namely RamA (Fig. 1), is essential for *Corynebacterium glutamicum* to grow on acetate medium through activating the expression of AK, PTA, ICL, and MS using acetate as the sole carbon source [Cramer et al., 2006]. Purified RamA protein can bind to corresponding promoter/operon region, consisting with the data from the RamA deletion mutants [Cramer et al., 2006].

TUMOUR-INDUCING (TI) PLASMID TRANSFORMATION

Plant pathogen *Agrobacterium tumefaciens* can elicit crown gall nodule in higher plant through transferring independent DNA fragment (T-DNAs) of tumour-inducing (Ti) plasmid to the nucleus of infected cells [Fuqua and Winans, 1994]. Induction gene (tra) of nopaline-type Ti plasmid pTiC58 is regulated by a diffusible compound named conjugative factor and a TraR protein [Fuqua and Winans, 1994]. TraR is a transcription factor of LuxR family number [Zhu and Winans, 1999; Cramer et al., 2006], a QS regulon of *Agrobacterium tumefaciens*, it regulates the genes that necessary to

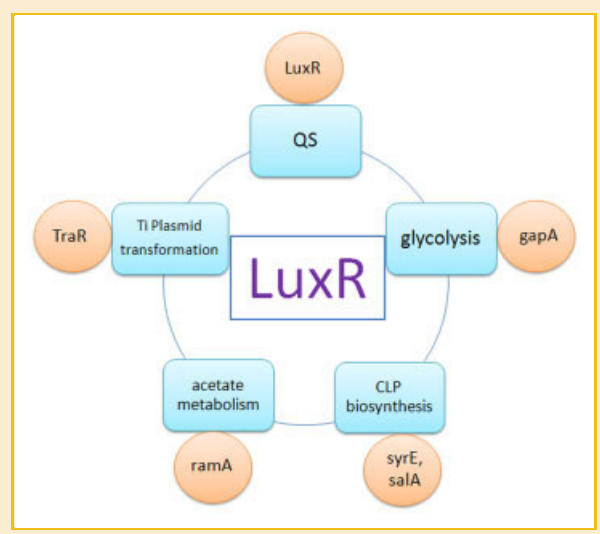

Fig. 1. Function diversity of LuxR family transcription factor. The physiological processes (blue) and the main LuxR family transcription factors (orange) involved. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/jcb]

vegetative propagation tumour-inducing (Ti) plasmid transformation [Fuqua and Winans, 1994; Li and Farrand, 2000]. Conjugative factor (N-3-HSL) is an analogue of *Vibrio fischeri* autoinducer VAI, a diffusible compound capable of activating microorganism luminescence operon (lux) [Fuqua and Winans, 1994]. Both the structure and function similar of VAI enable the conjugative factor as *Agrobacterium tumefaciens* autoinducer (AAI) [Fuqua and Winans, 1994]. Nopaline-type Ti plasmid conjugative transform regulator TraR is homologous to *Vibrio fischeri* LuxR protein [Fuqua and Winans, 1994]. LuxR is the receptor of VAI, and it can activate the expression of VAI genes. LuxR regulatory system functions depend on cell density [Fuqua and Winans, 1994]. The similarity between TraR (Fig. 1) and LuxR suggests that the conjugation of ligand of Ti plasmid might be regulated by similar diffusion mechanisms.

GLYCOLYSIS

D-Glyceraldehydes-3-dehydrogenase (GAPDH), use NAD^+ as cofactor to oxidize D-glyceraldehydes-3-phosphoric acid into 1,3-diphosphoglyceric acid, is critical in glycolysis [Toyoda et al., 2009]. There are two GAPDH, GapA and GapB. GapA is necessary for glycolysis, while GapB is dispensable, but GapB is pivotal in gluconeogenesis [Toyoda et al., 2009]. GapA is essential for *Corynebacterium glutamicum* glycolysis. RamA (Fig. 1), a LuxR-type transcriptional regulator, regulates the expression of gapA gene via binding to its promoter region. RamA was firstly demonstrated to be a gene involved in acetate metabolism, including *pta-ack* operon, transcription regulator of aceA and aceB expression, coding phosphotransacetylase, acetokinase, isocitrate lyase, and malate dehydrogenase, respectively. RamA mutant strain cannot grow on the medium with acetate as sole carbon sources [Toyoda et al., 2009]. RamA also involves in regulating the gene expression of PS2 protein (cspB), which is a *Corynebacterium glutamicum* cell coat component [Toyoda et al., 2009], a RamA suppressor involved in acetate metabolism (ramB) [Gerstmeir et al., 2004; Cramer et al., 2007], alcohol dehydrogenase (adhA) [Halfmann et al., 2007b], recovery promoting factor (rpf2) [Jungwirth et al., 2008]. Thus, RamA is a global regulator rather than acetate specific regulator. The research expands the role of ramA regulon to glycometabolism. The negative effect on *Corynebacterium glutamicum* growth on glucose-contained exerted by RamA inactivation might be partly due to the low expression of gapA operon.

MECHANISMS UNDERLYING LuxR TRANSCRIPTION FACTOR FUNCTION DIVERSITY

DIVERSE LuxR FAMILY TRANSCRIPTION FACTOR MEMBERS

The diverse LuxR transcriptional factors are the foundation for function diversity, such as ExpR of *Alfalfa rhizobia*, SdiA of *E. coli* [Yao et al., 2006] and *Salmonella typhimurium* [Ahmer et al., 1998], regulatory protein pcaO of protocatechuic acid branch key enzyme in β-ketone of adipic acid of *Corynebacterium glutamicum* aromatic compounds degradation [Zhao et al., 2010].

LuxR STRUCTURE FEATURE

The main structure of LuxR family transcription factor consists of two thirds N-terminal and one-third C-end. N-terminal is signal-binding region, and C-terminal contains DNA-binding H-T-H motif [Pompeani et al., 2008; Liu et al., 2011]. Both two regions are important for transcription factor binding to signal molecules, then triggering the transcription of genes by its binding to promoter DNA regulated by cognate transcription factor. The two-conserved region exist in many LuxR family transcriptional factors as evidenced by the existence of the conserved 7–211 amino acid and 164–205 amino acid in Rv0195.

MULTIPLE EFFECTOR OF LuxR FAMILY TRANSCRIPTION FACTORS

At least one LuxI protein can bind to LuxR family transcription factor, then the complex formed can bind to their target genes [Subramoni and Venturi, 2009]. But for LuxRs lack cognate LuxI AHL synthase, the difference with other LuxR family proteins is the length of the conserved amino acid sequence in AHL-binding region [Subramoni and Venturi, 2009]. These LuxR proteins either have relaxed or different specificity to AHL binding regions, or there are other ligands produced by adjacent bacteria. The latter scenario might reflect a competitive relationship with surrounding bacteria [Subramoni and Venturi, 2009].

MISCELLANEOUS SIGNAL MOLECULES

In addition to previous discovered PI and M factor, there are many new signal molecules in *Streptomyces avermitilis* [Bibb, 2005], such as cholesterol oxidase, glycerol (signal molecule in *Streptomyces avermitilis*). The *Pseudomonas aeruginosa* signal molecules differ in the length and structure of the C chain.

Mycobacterium tuberculosis LuxR FAMILY TRANSCRIPTION FACTORS

There are seven transcription factor (TF)-encoding genes in *M. tuberculosis* genome. In consideration of the extremely crucial role of transcription factors in gene transcription and translation, and few studies on the *M. tuberculosis* luxR (Table I), we speculate that endeavors on these molecules and regulatory network are highly desirable both from the perspective of fundamental biology and novel drug target discovery.

LuxR transcription factor in various bacteria and the genes regulated thereof (Table II), from these LuxR and their luxR-regulated genes we may find the LuxR transcription factor that is critical to *M. tuberculosis*.

Table I The *Mycobacterium tuberculosis* LuxR family transcription factors

Rv0195: 211 aa, Contains probable helix-turn-helix motif at aa 166–187. Contains probable helix-turn-helix motif at aa 166–187 (Score 1,164, +3.15 SD).

Rv0386: 1085 aa, Contains PS00017 ATP/GTP-binding site motif A (P-loop), PS00622 Bacterial regulatory proteins, luxR family signature and probable helix-turn-helix motif at aa 1042–1063 (Score 1,025, +2.68 SD).

Rv0491 (regX3): 227aa, response regulator protein (sensory transduction protein),

TABLE I. The *Mycobacterium tuberculosis* LuxR Family Transcription Factors

Genes	Functional description	Length	Location of DNA-binding site
Rv0195	Possible two component transcriptional regulatory protein (probably LuxR-family)	211aa	H-T-H (166–187aa)
Rv0386	Possible transcriptional regulatory protein (probably LuxR/UHPA-family)	1085aa	H-T-H (1042–1063aa)
Rv0491	Two component sensory transduction protein REGX3(transcriptional regulatory protein) (probably LuxR-family)	227aa	P-loop
Rv0890c	Possible two component transcriptional regulatory protein (probably LuxR-family)	882aa	H-T-H (836–857aa)
Rv0894	Possible transcriptional regulatory protein (probably LuxR-family)	393aa	P-loop
Rv2488c	Possible transcriptional regulatory protein (LuxR-family)	1137aa	H-T-H (1086–1107aa)
Rv3133c	Two component transcriptional regulatory protein DEVR (probably LuxR/UHPA-family)	217aa	H-T-H (166–187aa)

Rv0890c: 882 aa. Contains PS00017 ATP/GTP-binding site motif A (P-loop), PS00622 Bacterial regulatory proteins, luxR family signature, and probable helix-turn helix motif from aa 836 to 857 (Score 1,559, +4.50 SD).

Rv0894: 393 aa. Contains PS00017 ATP/GTP-binding site motif A (P-loop).

Rv2488c: 1137 aa. Contains PS00017 ATP/GTP-binding site motif A (P-loop), PS00622 Bacterial regulatory proteins, luxR family signature, probable coiled-coil from aa 585 to 616 and probable helix-turn-helix motif at aa 1086 to 1107 (score 1,206, +3.29 SD).

Rv3133c (devR): 217 aa. Contains bacterial regulatory proteins, LuxR family signature (PS00622) near C terminus as seen in bvgA, comA, dctR, degU, evgA, fimZ, fixJ, gacA, glpR, narL, narP, nodW, rcsB, and uhpA. Helix-turn-helix motif at 166–187 (+3.15 SD)

LuxR INHIBITORS

Quorum-sensing regulon regulates virulence of many opportunistic pathogens. In *Pseudomonas aeruginosa*, QS regulates biofilm formation, resistance to common germifuga and congenital immunity system of host [Musk and Hergenrother, 2006]. QS is a distinct target of new germifuga. In order to direct the discovery of QS inhibitor (QSI), some basic rules have been extracted: low molecular weight, profound effect on QS regulated gene expression, species-specific to minimize the adverse effect on normal micro-flaura, chemically stable [Musk and Hergenrother, 2006].

FURANONES

Furanones can inhibit TraR in *Agrobacterium tumefaciens*, 5 among 100 furanones were active against *Agrobacterium tumefaciens* QscR [Rasmussen and Givskov, 2006]. QscR triggers gene transcription by

TABLE II. LuxR Transcription Factor in Various Bacteria and the Genes Regulated Thereof

Microorganism	LuxR family	Function	Targets
A. tumefaciens	TrlR	Inhibit conjugation of Ti plasmid [Patankar and González, 2009]	The tra,trb operons
P. aeruginosa	QscR	Inhibit premature activation of the las/rhl regulon, virulence factor production [Patankar and González, 2009]	PA1897(PAO1operon)
Erwinia sp.	VirR/ExpR2	Production of plantcell wall-degrading enzymes [Patankar and González, 2009]	The global repressor rsmA
	CarR	Antibiotic production [Patankar and González, 2009]	carA-H operon
Serratia sp. ATCC39006	CarR	Antibiotic production [Patankar and González, 2009]	carA-H operon
R. leguminosarum bv.viciae	BisR	Symbiotic plasmid conjugation [Patankar and González, 2009]	cinI,traR
S. meliloti	ExpR	Exopolysaccharide production,repression of motility [Patankar and González, 2009]	visN
	NesR	Stress adaptation,competition for plant nodulation [Patankar and González, 2009]	nesR
	SMc00878	Putative role in the denitrification pathway [Patankar and González, 2009]	
A. vitis	AviR	Necrosis in grape hypersensitive response in tobacco [Patankar and González, 2009]	
	AvhR		
S. enterica	SdiA	Resistance to host defenses [Patankar and González, 2009]	rck (resistance to complement killing) operon and srgE (sdiA-regulated gene) a gene of unknown function
X. campestris	XccR	Plant pathogenesis [Patankar and González, 2009]	xccR
X. oryzae	OryR	Plant pathogenesis [Patankar and González, 2009]	oryR
B. melitensis	VjbR	Virulence [Patankar and González, 2009]	ftcR
	BlxR	Virulence [Patankar and González, 2009]	
B. mallei	BmaR4	Virulence [Patankar and González, 2009]	
	BmaR5	Virulence [Patankar and González, 2009]	
B. pseudomallei	BpmR4	Virulence [Patankar and González, 2009]	
	BpmR4	Virulence [Patankar and González, 2009]	
B. thailandensis	BtaR4	Virulence, metabolism [Patankar and González, 2009]	
	BtaR5	Virulence, metabolism [Patankar and González, 2009]	
P. aeruginosa	LasR		xcp, lasB
A. tumefaciens	TraR		tra promoter
P. aeruginosa	LasR	Virulence [Patankar and González, 2009]	lasB, lasA, aprA, toxA, lasI,rsaL
Vibrio fischeri	TraR		traM and the tra, trb and rep operons of the Ti plasmid.

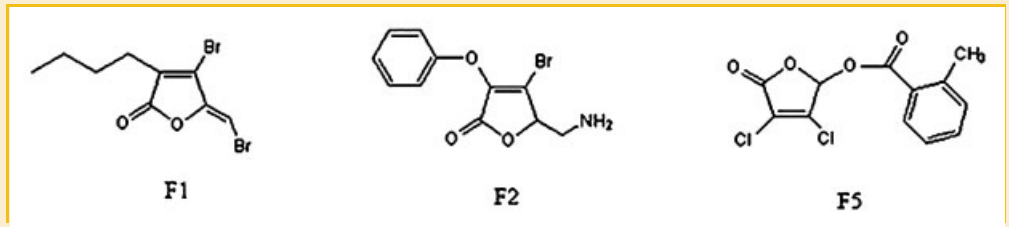

Fig. 2. The structures of F1, F2, and F5 [Rasmussen and Givskov, 2006].

binding to the signal molecule 3OC12-HSL secreted by *Agrobacterium tumefaciens*, followed by binding to promoter P1897 [Rasmussen and Givskov, 2006]. Among the five furanones, F1, F2, and F5 are active both in vivo and in vitro. The structure commonality among these leads might be valuable to guide the inhibitor design of LuxR-type transcriptional activation protein QS [Rasmussen and Givskov, 2006].

MECHANISM OF ACTION OF QS INHIBITORS

QS inhibitors can function via following mechanisms: block AHL production, signal molecule inactivation, and interfering signal receptor. Natural QSI can be separated from plants or fungi that co-evolve with QS-containing bacteria during the long evolution [Rasmussen and Givskov, 2006]. Two compounds with QS activity obtained by screening 50 *Penicillium* that grow on different media, are penicillic acid (*Pe. radicicola* produced) and patulin (*Pe. coprobium* produced), respectively. The two compounds do target LasR and RhiR QS regulon. These compounds will accelerate the LuxR turnover. This demonstrated that QSI can inhibit most QSs [Rasmussen and Givskov, 2006].

Figure 2 Principle of QSI system functions. luxR or luxR homologue can usually bind to bacteria secreted AHLs, trigger the expression of kill gene by binding to QS target promoter, then other bacteria are killed by the QS bacteria secreted virulence factors. QSI can suppress these processes.

The crucial role of LuxR transcription factor is best witnessed by their widespread distribution. Natural inhibitors of LuxR are good start points for better novel antibiotics to improve our arsenals to handle the ever-increasing drug resistant pathogens, especially the causative agent of the notorious tuberculosis—*Mycobacterium tuberculosis*.

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