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Illuminating bacterial behaviors with optogenetics

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ABSTRACT

Optogenetic approaches enable light-mediated control of cellular activities using genetically encoded photoreceptors. While optogenetic technology is already well established in neuroscience and fundamental research, the implementation of optogenetic tools in bacteriology is still emerging. Engineered bacteria with the specific optogenetic system that function at the transcriptional or post-translational level can sense and respond to light, allowing optogenetic control of bacterial behaviors. In this review, we give a brief overview of available optogenetic systems, including their mode of action, classification, and engineering strategies, and focus on optogenetic control of bacterial behaviors with the highlight of strategies for use of optogenetic systems.

1. Introduction

Synthetic biology aims to construct new biological systems or reprogram existing ones for user-defined functions [1,2]. Similar to natural biological systems, synthetic biological systems can sense and respond to various environmental signals through engineered biosensing circuits [3], which facilitates the direct manipulation of biological processes with an external stimulus. Compared with chemical inducers and other environmental triggers like pH or temperature, optical input has the advantage of fast, easy tunability and high spatiotemporal resolution [4–6]. Therefore, optogenetic approaches are extensively adopted in eukaryotes [7–9] for real-time, precise, and non-invasive control of cellular behaviors. Notably, the development of optogenetics has revolutionized the field of neuroscience by enabling the nervous system to be dissected at a single cell level with a resolution of the order of milliseconds [10].

Since Levskaya and colleagues constructed the first synthetic light sensor in *Escherichia coli* by fusing the *Synechocystis* phytochrome Cph1 to an *E. coli* EnvZ histidine kinase domain [11], more and more researchers developed optogenetic systems in bacteria or exploited optogenetic systems as a powerful tool to modulate bacterial behaviors [5,12]. In this review, we revisit different optogenetic systems that have been used in bacteria and summarize the application of these optogenetic systems for the control of bacterial behaviors. Here, we give a glimpse of the advances in optogenetic application in bacteria, hoping to inspire interested readers to think beyond the horizon and facilitate their research (see Tables 1 and 2).

2. Optogenetic systems

A variety of optogenetic systems have been developed for light-mediated modulation of cellular activities [12] based on photoreceptors originating from different organisms, including plants, algae, bacteria, fungi, and higher eukaryotes [13]. These natural photoreceptors typically consist of a photosensory module and an effector domain. Upon illumination with a specific wavelength, the chromophore bound in the photosensory module absorbs photons and undergoes a photochemical transformation [14,15]. This causes conformational changes in the light-sensing domains and these changes are transmitted to the effector domain [15,16]. As a result, the effector domain initiates biological responses, such as enzymatic activity or protein interaction [16].

Photoreceptors employed in the design of bacterial optogenetic systems can be divided into several classes according to their light-sensing protein domains and the corresponding chromophores. Light-oxygen-voltage sensing (LOV) domain, a member of the Per–Arnt–Sim (PAS) protein family, is the most frequently used photosensory module [17]. LOV domains bind flavin, including flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), and riboflavin (RF), as a chromophore and absorb blue light [17]. The blue-light-utilizing flavin (BLUF) domain-based photoreceptors and cryptochromes also belong to flavoproteins and can sense blue light [18–20]. Yet cryptochromes react to blue light through the FAD chromophore only. Phytochromes and

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Table 1
Summary of photoreceptors and some representative optogenetic systems characteristics.

Optogenetic System	Chromophore	Source Organism	Light Source On/Off	Reference
LOV domain				
YtvA	FMN/FAD/RF	*Bacillus subtilis*	Blue/Dark	[23]
VVD	FMN/FAD	*Neurospora crassa*		[24]
EL222	FMN	*Erythrobacter litoralis*		[25]
AsLOV2	FMN	*Avena sativa*		[26]
RsLOV	FMN	*Rhodobacter sphaeroides*		[27]
BLUF domain				
bPAC (BlaC)	FAD/FMN	*Beggiatoa* sp.	Blue/Dark	[28]
EB1	FAD	*Magnetococcus marinus*		[29]
BlrP1	FAD/FMN	*Klebsiella pneumoniae*		[30]
Cryptochrome				
CRY2-CIB1	FAD	*Arabidopsis thaliana*	Blue/Dark	[31]
Cyanobacteriochrome				
UirS/UirR	PCB	*Synechocystis* sp. PCC 6803	Violet/Green	[32]
CcaS/CcaR	PCB	*Synechocystis* sp. PCC 6803	Green/Red	[33]
Phytochrome				
PhyB-PIF6	PCB	*Arabidopsis thaliana*	Red/Far-red	[34]
BphS	Biliverdin	*Rhodobacter sphaeroides*,		
Synechocystis sp. Slr1143	Red/Far-red	[35]		

cyanobacteriochromes incorporate bilin chromophores autocatalytically [21]. Phytochromes, which harbor a photosensory module consisting of PAS, GAF (cGMP phosphodiesterase/adenylate cyclase/FhlA), and PHY (phytochrome-specific) domains, are sensitive to far-red and near-infrared (NIR) light [21,22]. Cyanobacteriochromes, the photosensory module of which consists of several GAF domains, bind phycocyanobilin (PCB) only, but sense light in the entire visible spectrum owing to variations in the protein–bilin interactions [15].

These natural photoreceptors serve as the templates for the engineering of optogenetic systems. Optogenetic systems can be constructed by rational and random mutagenesis, domain swapping, or combination with other proteins in a modular manner. Optogenetic systems are divided into intramolecular and intermolecular systems. In intramolecular systems (Fig. 1a), light-mediated regulation of protein activity is achieved using the allosteric or steric regulation approach [6,15]. In intermolecular systems (Fig. 1b), light-mediated protein interaction, localization, or activity is achieved through photoreceptor homodimerization, oligomerization, heterodimerization, or dissociation [15,36].

3. Optogenetic regulation

Optogenetic regulation is commonly implemented at the transcriptional level. In general, these transcriptional regulators operate in either two-component or one-component systems, in which the optical input would determine the expression level of downstream target genes. For instance, YF1/FixJ [23], a blue light-inducible two-component system (TCS) originating from *Bradyrhizobium japonicum*, has been frequently opted in a set of studies [37–40]. The chimeric YtvA-based histidine kinase YF1 will be activated under dark and then phosphorylate the cognate response regulator FixJ, the phosphorylated form of which binds the $FixK_2$ promoter and initiates transcription [23]. One component system (OCS) that enables intramolecular signal transduction is also used for light-mediated transcriptional regulation. EL222, which was firstly found in the marine bacterium *Erythrobacter litoralis* [25], is one of the most frequently applied OCS. This protein can function as a transcriptional activator or repressor by forming homodimers and binding DNA when illuminated with blue light [41]. Compared with TCS, one-component system is intrinsically less burdensome and requires less signaling and reversal time, enabling faster and more precise control of gene expression [12].

By circumventing transcription, optogenetic systems that operate at the post-translational level usually enable faster and more direct optogenetic regulation [5]. In such systems, protein function can be modulated directly by light. One category of post-translational regulators is photosensitive enzymes. For example, BphS, a bacteriophytochrome diguanylate cyclase (DGC) originating from the *Rhodobacter sphaeroides* BphG1 protein, exhibits near-infrared (NIR) light-dependent activity, and is used for optogenetic control of cyclic di-GMP (c-di-GMP) level [35]. However, dimerization-based photo-switches, such as Magnets, and PhyB/PIF6 are more widely applied because their dynamic dimerization property enables the control of protein interaction, activity, and localization [42–45].

4. Optogenetic applications for the control of bacterial behaviors

The engineering of optogenetic systems allows bacterial behaviors to be controlled by light. Engineered bacteria with a specific optogenetic system can sense and respond to the tunable optical input. In this manner, the output cellular activities of the bacteria, such as metabolism, cell division, cell death, motility, and biofilm formation, can be dissected precisely and analyzed quantitively.

Light-regulated bacterial metabolism can be achieved by using optogenetic transcriptional switches to control the expression of the metabolic gene. Based on EL222, an optogenetic CRISPRi platform was introduced into *E. coli* to enable light-mediated switch between the growth phase and muconic acid production phase [46]. Tandar *et al.* used a modified cyanobacterial green light activated TCS CcaS/CcaR for transcriptional regulation of a metabolic gene *pgi* to regulate flux distribution between two different glycolytic pathways in *E. coli* [47]. New light-inducible transcriptional regulators derived from chemically inducible gene expression systems have also been developed for the dynamic regulation of metabolic pathways. In a recent study by Romano *et al.*, a set of blue light-inducible AraC dimers in *E. coli* (BLADE) were constructed by swapping the dimerization domain of the L-arabinose-responsive AraC with LOV domain-based photoreceptor VVD and used for the control of the L-arabinose metabolic pathway [48].

Light-mediated expression systems have been used to control cell division. Li *et al.* developed a RsLOV-based one-component system LexRO to control the expression of the *ftsZA* gene in *E. Coli*, achieving blue-light-activated cell division [49]. In another similar study, the gene *nrdAB* encoding ribonucleotide reductase is co-expressed with *ftsZA* under the control of EL222-based activation system BLAT or repression system BLRT to shorten cell division for acetoin production [50].

Light-controlled bacterial cell death is also an area of interest. A common strategy is to induce cell lysis using a TCS or OCS to express the lysis gene or the lysis gene cassette from bacteriophage, which can be combined with optogenetic control of bioproduction for light-mediated recovery of intracellular bioproducts. This is exemplified in the work undertaken by Miyake, in which a TCS CcaS/CcaR was introduced in cyanobacteria to control the expression of the T4 bacteriophage-derived lysis genes encoding holin and endolysin for green light-triggered bacterial lysis and phycocyanin release into the medium for bioproduction [51]. Another strategy is to use an optogenetic system to control the activity or function of the protein related to cell death at the post-translational level. For example, He *et al.* developed a LiPOP2b system by fusing the pore-forming domain GSDMD-NT with blue-light-sensitive

cpLOV2 and used it as a genetically encoded bactericide *in E. coli* to eliminate bacteria in a light-dependent manner [52].

Researchers are interested in light-mediated manipulation of bacterial motility. One approach is to use optogenetic transcriptional regulators like EL222, LexRO, and LEVI for the controlled expression of protein phosphatase CheZ in *E. Coli* [49,53,54]. An alternative approach is to modulate the intracellular second messenger level associated with bacterial motility through the photosensitive enzyme for the conversion of the corresponding second messenger. Ryu *et al.* used the red/near-infrared light-regulated diguanylate cyclase BphS in combination with the blue-light-activated cyclic di-GMP (c-di-GMP) phosphodiesterase EB1 for the bidirectional control of intracellular c-di-GMP level in *E. Coli* and verified the efficacy of this dichromatic optogenetic module by *E. coli* swimming assay [55].

Optogenetic systems also act as a powerful tool in controlling bacterial cell–cell or cell-material interactions. Most applications in this area are based on dimerization events, where the photoreceptor undergoes light-regulated homodimerization or heterodimerization by binding to its interacting partner. This is exemplified in the work undertaken by Chen and Wegner in which the LOV-domain-based Magnet

Table 2
Summary of optogenetic systems used for light-mediated control of bacterial behaviors.

Application	Bacterial Host	Optogenetic System Function Level	Mechanism	Optogenetic System	Photoreceptor Type	Reference
Metabolism	*E. coli*	Transcriptional	Light-mediated activation of *triA* gene expression	CcaS/CcaR	Cyanobacteriochrome	[64]
	E. coli	Transcriptional	Light-mediated activation of *pgi* gene expression	CcaS/CcaR	Cyanobacteriochrome	[47]
	E. coli	Transcriptional	Light-mediated activation of dCpf1 gene expression	EL222	LOV domain	[46]
	E. coli	Transcriptional	Light-mediated activation of araBAD operon	VVD-AraC(BLADE)	LOV domain	[48]
Cell Division	*E. coli*	Transcriptional	Light-mediated activation of *nrdAB* gene and *ftsZA* gene expression	EL222 (BLAT-activation)	LOV domain	[50]
	E. coli	Transcriptional	Light-mediated repression of *nrdAB* gene and *ftsZA* gene expression	EL222 (BLRT-repression)	LOV domain	[50]
	E. coli	Transcriptional	Light-mediated activation of *ftsZA* gene expression	LexRO (eLightOn)	LOV domain	[49]
Cell Death	*cynabacteria*	Transcriptional	Light-mediated activation of lysis cassette expression	CcaS/CcaR	Cyanobacteriochrome	[51]
	E. coli	Transcriptional	Light-mediated repression of *lys* gene expression	YF1/FixJ (pDusk)	LOV domain	[37]
	E. coli	Transcriptional	Light-mediated activation of SRRz lysis cassette expression	YF1/FixJ (pDawn)	LOV domain	[38]
	E. coli	Transcriptional	Light-mediated repression of *ccdB* gene expression	LEVI (LightOff)	LOV domain	[54]
	E. coli	Post-translational	Light-mediated activation of toxic protein	LiPOP2b	LOV domain	[52]
	E. coli	Post-translational	Light-mediated activation of protein amyloidogenesis	LOV543m3–WH1	LOV domain	[65]
Motility	*E. coli*	Transcriptional	Light-mediated activation of *cheZ* gene	LEVI (LightOff)	LOV domain	[54]
	E. coli	Transcriptional	expression	LexRO (eLightOn)	LOV domain	[49]
	E. coli	Transcriptional		EL222	LOV domain	[53]
	P. aeruginosa	Post-translational	Light-mediated activation of enzyme for cAMP synthesis	Bpac(BlaC)	BLUF domain	[61]
	E. coli	Post-translational	Light-mediated activation of enzyme for c-di-GMP synthesis	BphS	Phytochrome	[55]
	E. coli	Post-translational	Light-mediated activation of enzyme for c-di-GMP hydrolysis	EB1	BLUF domain	[55]
Control of Cell-cell or Cell-material Interactions	*E. coli*	Transcriptional	Light-mediated activation of *ag43* gene expression	CcaS/CcaR	Cyanobacteriochrome	[56]
	E. coli	Post-translational	Light-mediated heterodimerization	Magnets	LOV domain	[42]
	E. coli	Post-translational	Light-mediated heterodimerization	Magnets	LOV domain	[43]
	E. coli	Post-translational	Light-mediated heterodimerization	Magnets	LOV domain	[44]
	E. coli	Post-translational	Light-mediated heterodimerization	PhyB/PIF6	Phytochrome	[45]
Biofilm Formation	*E. coli*	Transcriptional	Light-mediated activation of *ag43* gene expression	YF1/FixJ (pDawn)	LOV domain	[40]
	P. aeruginosa	Transcriptional	Light-mediated activation of *PA2133* gene expression	YF1/FixJ (pDawn)	LOV domain	[39]
	S. meliloti	Transcriptional	Light-mediated activation of *wgaAB* gene expression	EL222	LOV domain	[60]
	E. coli	Post-translational	Light-mediated activation of enzyme for c-di-GMP synthesis	BphS	Phytochrome	[66]
	P. aeruginosa	Post-translational	Light-mediated activation of enzyme for c-di-GMP hydrolysis	BlrP1	BLUF domain	[30]
	P. aeruginosa	Post-translational	Light-mediated activation of enzyme for c-di-GMP synthesis	BphS	Phytochrome	[30]
	E. coli	Post-translational	Light-mediated activation of enzyme for c-di-GMP hydrolysis	EB1	BLUF domain	[55]
	E. coli	Post-translational	Light-mediated activation of enzyme for c-di-GMP synthesis	BphS	Phytochrome	[55]
Pathogenicity	*P. aeruginosa*	Transcriptional	Light-mediated activation of sRNAs, rsmY gene andrsmZ gene expression	YGS24/GacA	LOV domain	[62]
	P. aeruginosa	Post-translational	Light-mediated activation of enzyme for cAMP synthesis	Bpac(BlaC)	BLUF domain	[61]

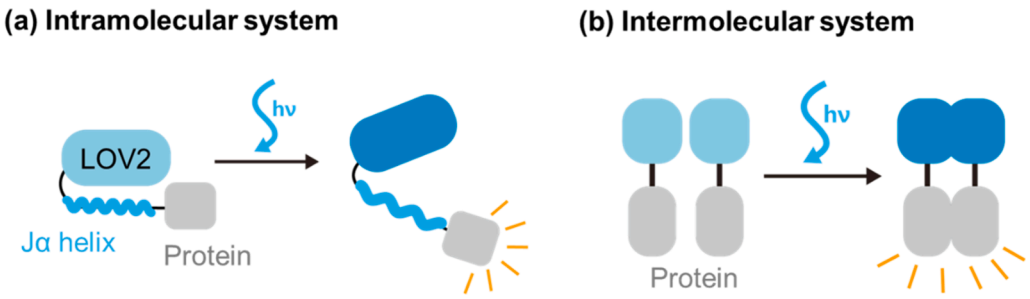

Fig. 1. Schematics of optogenetic systems. (a) Intramolecular system based on steric occlusion mechanism. Photo-induced LOV2-Jα dissociation uncages the fused protein in response to blue light, releasing its activity. (b) Intermolecular system based on photoreceptor dimerization. Blue light induces the dimerization of the photoreceptor module, resulting in the interaction of the attached proteins.

system was used to control bacterial adhesion on the substrate or bacteria-bacteria adhesion [42,43]. Another way is to use an optogenetic system to control the expression of the protein related to bacterial interactions. A good example of this is the study carried out by Nakajima in which the green light-regulated TCS CcaS/CcaR was introduced into *E. Coli* for transcriptional regulation of the gene encoding antigen 43 (Ag43) to achieve light-activated aggregation-mediated cell recovery [56].

Optogenetics has also been widely used to control biofilm formation. Given that biofilm formation and dispersal are tightly controlled by c-di-GMP-dependent signaling pathways in a large number of species [57], it is feasible to use an optogenetic system to control c-di-GMP conversion. Huang *et al.* constructed a dichromatic system, which consists of the blue light-activated c-di-GMP phosphodiesterase BlrP1 and the red light-activated BphS, for the dynamic control of intracellular c-di-GMP level in *P. aeruginosa* and used the engineered bacteria to form patterned biofilms with a high spatial resolution (~10 μm) [30]. As indicated above, this optogenetic toolkit was not specific to one bacterial species as it also functioned well in other species including *E.coli* [58] and *Shewanella oneidensis* [59]. In another study, introducing a c-di-GMP phosphodiesterase gene (PA2133) into the transcriptional regulator YF1/FixJ-based pDawn system enabled blue light illumination to promote biofilm dispersal of *P. aeruginosa* [39]. Adding to the complexity of optogenetics in biofilm regulation, one recent work employed the *bphS-bphO/eb1* circuitry to successfully modulate biomass of the engineered *E. coli* strains, which in turn produced a quorum quenching enzyme to disassociate quorum sensing-dependent biofilm by other bacteria [58]. Apart from the c-di-GMP mediated approach, researchers also used OCS or TCS to control the expression of specific genes related to biofilm formation, such as EL222 controlled expression of *wgaAB* for exopolysaccharide (EPS) II synthesis in *Sinorhizobium meliloti* [60], and pDawn controlled expression of Ag43 in *E. coli* [40].

Another emerging area is light-controlled bacterial pathogenicity. For example, the regulation of the virulence of *P. aeruginosa* could be achieved by modulating the cAMP level with photoactivated adenylate cyclase bPAC [61]. In a more recent study, a blue light-activated YGS24/GacA system was engineered by swapping the LOV domain of YtvA with the input sensor domain of the histidine kinase GacS in the original GacS/GacA system of *P. aeruginosa* and used to control the expression of virulence factors in *P. aeruginosa* via the Gac/Rsm pathway, enabling light-mediated pathogenicity regulation [62].

Apart from those abovementioned examples, it holds great promise to use optogenetics in other fundamental research. Specifically, the light-responsible genetic tools could be employed to conditionally express or inactivate proteins and analyze their impact on bacterial behavior or physiology. For example, CoaA, a prophage capsid protein in *P. aeruginosa* PAO1, was toxic to this bacterium, and its expression strongly inhibited bacterial growth [63]. In this case, devising light-inducible expression of CoaA in this bacterium can facilitate the elucidation of the bactericidal mechanism of this protein (see Fig. 2).

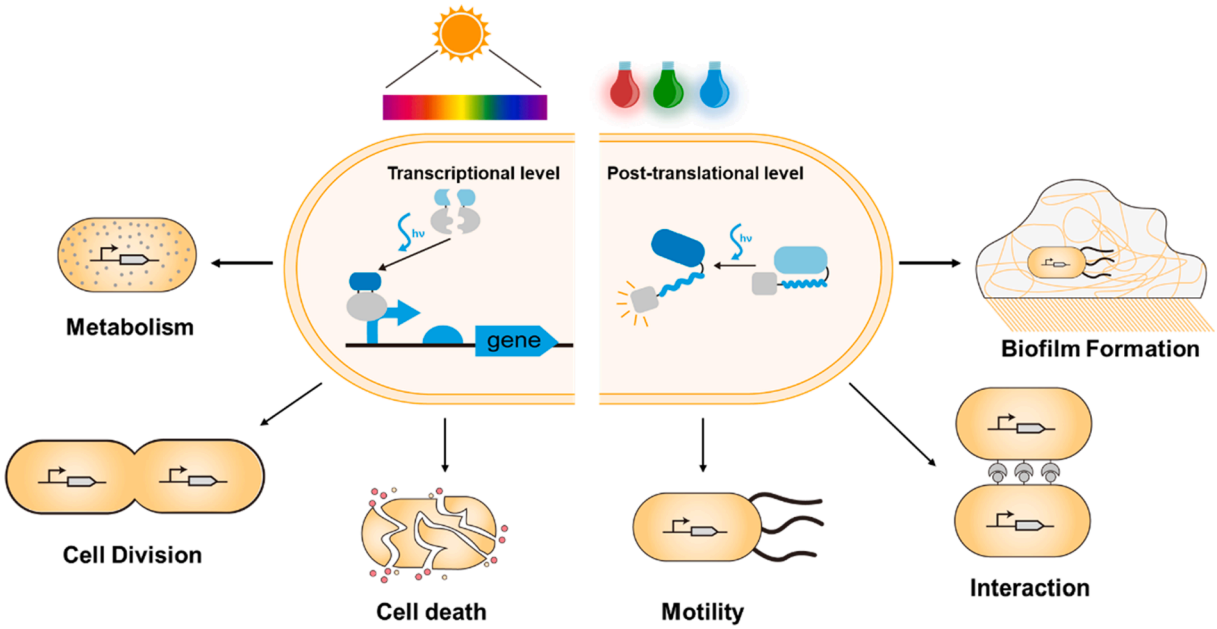

Fig. 2. Optogenetic regulation of bacterial behaviors that operates at the transcriptional level or the post-translational level.

5. Conclusions and future perspectives

With the development of optogenetics, the optogenetic toolkit based on natural photoreceptors has vastly expanded, ranging from blue-light-activated systems to NIR-light-activated systems. These ingenious optogenetic systems open up new possibilities for controlling targeted bacterial behaviors with spatiotemporal specificity, tunable dynamics, and minimal intervention, showing great potential for modulating bacterial phenotypes. Nevertheless, the applications of optogenetic systems for the control of bacterial behaviors still have to be fully explored. Despite the successful implementation of optogenetic systems in eukaryotic cells at the subcellular level, previous research into optogenetics in bacteria mainly focused on bacterial behaviors at the bacterial population level. Efforts should be made to develop the platforms and techniques for the optogenetic control of bacteria at the single-cell level. Well-established optogenetic tools for real-time tracking of the behavior of a single bacterium will facilitate and expand the application of optogenetics in bacteria for future research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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