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Review article

Light-mediated control of Gene expression in mammalian cells

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ABSTRACT

Taking advantage of the recent development of genetically-defined photo-activatable actuator molecules, cellular functions, including gene expression, can be controlled by exposure to light. Such optogenetic strategies enable precise temporal and spatial manipulation of targeted single cells or groups of cells at a level hitherto impossible. In this review, we introduce light-controllable gene expression systems exploiting blue or red/far-red wavelengths and discuss their inherent properties potentially affecting induced downstream gene expression patterns. We also discuss recent advances in optical devices that will extend the application of optical gene expression control technologies into many different areas of biology and medicine.

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1. Introduction

Analysis of cellular gene expression profiles and their regulatory mechanisms has been greatly advanced by the application of live-imaging or next-generation sequencing technologies. For example, development of bright and fast-maturing fluorescent proteins has enabled live-imaging of gene expression dynamics of cells in tissues in three dimensions. Expression of multiple genes can be simultaneously imaged using different colored fluorescent proteins (Miyawaki, 2011; Han et al., 2019). Information on cellular gene expression patterns of different cellular and tissue states can be acquired thanks to recent advances in the development of molecular imaging probes (Sakaue-Sawano et al., 2008; Kohl et al., 2014; Lin and Schnitzer, 2016; Sakaguchi et al., 2018). In addition to fluorescent protein imaging, bioluminescence imaging has also contributed to quantitative analysis of gene expression dynamics (Shimojo et al., 2008; Imayoshi et al., 2013; Imayoshi and Kageyama, 2014; Isomura et al., 2017; Suzuki and Nagai, 2017; Sueda et al., 2019). Although multi-color imaging by bioluminescence probes was originally technically limited, recent development of short and long wavelength luciferases

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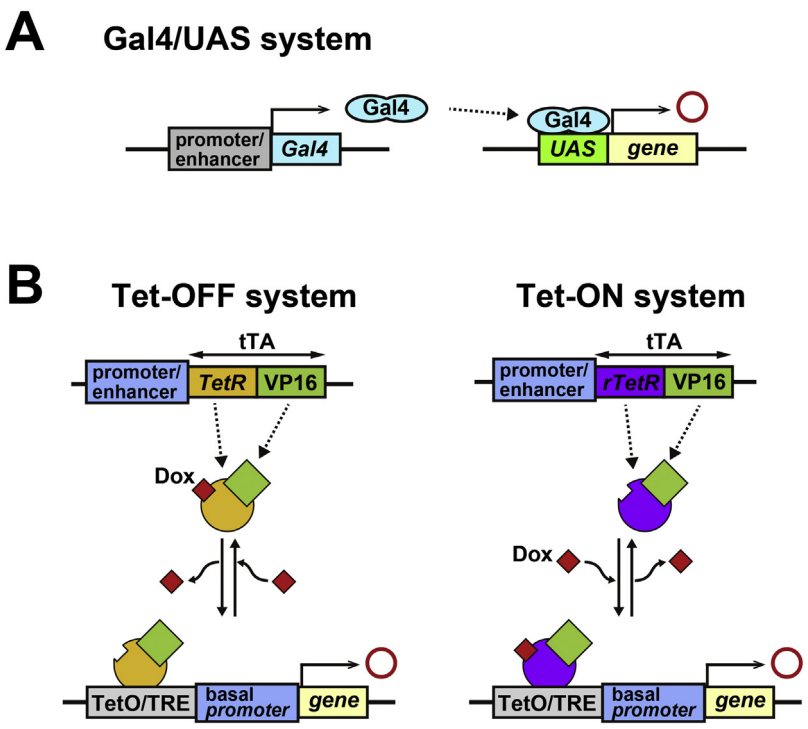

Fig. 1. Two commonly used gene expression control systems. (**A**) The Gal4/UAS system. (**B**) The Tet-OFF/ON system.

and their unique substrates have made it possible to conduct dual or triple color imaging of gene expression. Fluorescent protein has great advantages in three-dimensional tissue or organ imaging when combined with confocal, multi-photon, light-sheet or super-resolution microscopy (Sakaguchi et al., 2018; Seiriki et al., 2017; Winnubst et al., 2019; Schermelleh et al., 2019). These improvements in fluorescent/bioluminescent probes and optical technologies have revealed dynamic changes in cellular gene expression during developmental, functional, and pathological changes in multicellular systems.

Gene expression profiling is also being transformed by the adaptation of next-generation sequencing technology, including RNA sequencing at the single-cell level (Shin et al., 2015; Kumar et al., 2017; Shah et al., 2018; Tepe et al., 2018). By taking advantage of high-throughput and the scalability of this technology, gene expression patterns for each gene in three-dimensional tissues have now been determined at single-cell resolution (Tasic et al., 2018; Rodriques et al., 2019). Development of innovative sample preparation techniques, data analysis and data sharing platforms expanded the use of this technology into many different fields of biology and medicine. By combining imaging approaches and cellular gene expression profiles, their dynamic changes have now been precisely captured with greater spatial and temporal resolution at a level never before possible.

However, to understand causal relationships between gene expression patterns/changes and cellular/tissue functions, we need to systematically survey cellular gene expression and observe functional correlates. For this purpose, it is necessary to develop tools to manipulate gene expression at fine spatial and temporal resolution. Many gene expression control systems have been developed to achieve this aim. For example, the Gal4/UAS system is widely used in different model organisms, including *Drosophila melanogaster* and *Zebrafish* (Fig. 1A). This is a binary gene expression system consisting of Gal4 and UAS (upstream activation sequence). Gal4, a transcription factor originally cloned from yeast, contains a DNA-binding domain and a transcription activation domain, and binds to a specific sequence, UAS. It activates transcription from a basal promoter placed downstream of UAS (Brand and Perrimon, 1993; Habets et al., 2003). In mammalian cells and model animals, Tet-OFF/ON systems are more commonly used (Gossen and Bujard, 1992; Gossen et al., 1995; Orth et al., 2000; Das et al., 2016) (Fig. 1B). Similar to the Gal4/UAS system, the Tet system consists of a transcription factor TetR and its derivatives, and a specific binding sequence, called TetO/TRE. The original TetR of *Escherichia coli* is a transcription repressor, but in the Tet-OFF/ON system, the transcription repression domain was changed to transcription activation domains, such as VP16 (Gossen and Bujard, 1992). These synthetic transcription factors, such as tTA-Ad and rtTA-Ad/Tet-ON 3 G, are used in the latest versions of the Tet-OFF and Tet-ON systems, respectively. The functions of TetR-derived transcription factors can be uniquely regulated by treatment with a small molecule (i.e., tetracycline [Tet] or doxycycline [Dox], a more stable Tet analog) through reversible control of their DNA-binding activities. The Tet-Off system activates downstream gene expression in the absence of Dox, whereas the Tet-On system activates it in the presence of Dox. The original Tet system has been improved significantly for use in mammalian cells aiming at high levels of expression and tight control of expression of exogenous genes.

However, a disadvantage of these gene expression control systems is their limited reversibility and poor spatial control (Das et al., 2016). In the case of the Gal4/UAS system, spatial and temporal specificities of the expressed UAS-downstream genes rely on the activities of the applied tissue-specific promoters that drive the expression of Gal4. The range of manipulatable cells and on/off-timing of the induced gene expression is totally dependent on the characteristics of the applied promoters. Therefore, control of target gene expression in selected cells based on the topological information at the time aimed for is technically impossible. This inherent limitation excludes experiments requiring rapid activation or de-activation of the gene of interest in the spatially restricted cell or cell population.

Intensive efforts to increase spatial and temporal specificity have been made recently, such as spatially intersectional approaches using two specific promoters, and drug-inducible pro-

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moters or Gal4 activators for improving temporal resolution (Potter and Luo, 2011; Riabinina et al., 2015). However, cell-type or tissue-specific promoter-based approaches cannot always target the cells aimed at by experimenters because the variety of available promoters is generally limited and not appropriate for every research plan. In the case of drug-inducible systems, temporal specificity is not always sufficient due to diffusion and the presence of residual regulator molecules in the culture medium or the body of the model organism. This is also the case in the Tet system, because the spatial and temporal expression patterns of the TetR-derived transcription factors are basically determined by the promoter/enhancer activities and characteristics of the gene delivery methods. In addition, there are similar concerns regarding diffusion or the presence of the residual regulator molecule Dox (Cambridge et al., 2009).

In addition to exogenous gene expression control systems, recent advances in genome editing technologies have opened up the possibility of artificially controlling the expression of endogenous genes. The target DNA binding domain of the transcription activator-like effector (TALE) or the endonuclease-mutant of Cas9 (dCas9) with the fused transcription activation domain have been adopted to develop site-specific transcriptional activators of endogenous genes embedded in chromosomes (Polstein and Gersbach, 2015; Konermann et al., 2013; Nihongaki et al., 2015b, 2017). Again, there is an increasing demand for innovative developments enabling tighter and more readily reversible control of gene expression in cells at a greater spatial and temporal resolution.

2. Light-control of cellular functions

Light has two outstanding merits as a way of artificially manipulating cellular functions. First, it can be turned on or off for precise durations at user-selected times. Second, light can be applied to a restricted cell or a group of cells, and even to small subcellular domains. To adapt light exposure to the regulation of biochemical reactions, photo-activatable (PA) compounds were developed. These photo-uncaging compounds have enabled methods of light-induced activation of specific biochemical reactions to be developed, such as activation of ion-channels or signaling pathways. For example, combined with two-photon microscopy, uncaging of caged-glutamate can be induced in statically restricted regions in neural circuits, and this enables single spine manipulation of neurons at narrow time windows (Kantevari et al., 2010). This uncaging strategy was previously applied to the Tet gene expression system. Caged Dox provided spatial and temporal UV light-controlled activation of the Tet-ON system which was confirmed to work in mouse organotypic brain cultures, developing mouse embryos and *Xenopus laevis tadpoles*. However, spatial control of the Tet-system is challenging and manipulation of targeted cells or cell populations is difficult, because activated caged-Dox may diffuse away from the irradiated regions (Cambridge et al., 2009).

Recently, intensive work has resulted in the development of genetically-encoded light-sensitive actuator molecules, which has expanded their use into different fields of biology. The most striking example of the expanded use of these tools involves the light-sensitive ion channel, Channelrhodopsin-2 (ChR2) in neuroscience research. ChR2 was originally cloned in 2003 from a green alga called *Chlamydomonas reinhardtii* (Nagel et al., 2003) and its photo-activatable function demonstrated. ChR2 expressed in the plasma membrane of neurons allows positively charged ions to pass into the cell through the cell membrane under blue-light illumination. This depolarises the membrane, inducing action potentials (Boyden et al., 2005). Importantly, the gene encoding ChR2 can be delivered or expressed in defined sets of neurons by virus vectors or transgenic strategies using cell-type specific promoter/enhancers (Atasoy et al., 2008; Cardin et al., 2009; Ahmari et al., 2013; Kohara et al., 2014; Kitamura et al., 2014; Gompf et al., 2015). In this way, researchers can activate defined sets of neurons at any time by applying light to ChR2-expressing neurons. Point mutations close to the retinal binding pocket of ChR2 have been shown to affect its biophysical properties, resulting in a variety of different tools (e.g. fast/slow cycling, step-function type, etc.) (Ritter et al., 2008; Berndt et al., 2009; Stehfest et al., 2010). Currently, many light-sensitive ion channels or transporters are being identified and proven to depolarize/polarize neuronal membranes in a light-dependent manner, subsequently inducing temporally-precise activation/inhibition of targeted neurons (Zhang et al., 2009). This technology allowing targeted, fast control of precisely defined events in biological systems of genetically defined cells, has been termed “Optogenetics”.

By using other types of PA molecules, such as light-switchable enzymes or protein interaction modules, the application of optogenetic tools has expanded to studies of the regulation of different cellular functions, including cell signaling, subcellular localization, and gene expression (Kennedy et al., 2010; Giordano et al., 2013; Aoki et al., 2017; Konermann et al., 2013; Maiuri et al., 2015; Repina et al., 2017; Okumura et al., 2018). Numerous optogenetic tools that can manipulate gene expression and overcome the technical limitations of conventional chemically-regulated gene expression systems have now been developed (Shimizu-Sato et al., 2002; Yazawa et al., 2009; Liu et al., 2012; Polstein and Gersbach, 2012; Wang et al., 2012; Crefcoeur et al., 2013; Imayoshi et al., 2013; Konermann et al., 2013; Muller et al., 2013b; Hallett et al., 2016; Horner et al., 2017; Motta-Mena et al., 2014; Pathak et al., 2017; Yamada et al., 2018). In this review, we will introduce recent advances in light-mediated control of gene expression in mammalian cells. In particular, we will focus on blue or near-infrared activatable protein-protein interaction systems that were previously integrated into gene expression control systems (Fig. 2). We will also discuss possible parameters to change the magnitude and temporal pattern of light-induced gene expression, and optical devices to precisely target cells using optogenetic tools (Figs. 3 & 4).

3. Gene expression control by blue light

Optogenetic switches have been integrated into strategies for the accurate manipulation of gene expression by light stimulation. In several organisms, many biological processes are controlled by light through endogenous photoreceptor molecules with specialized light-sensitive domains that undergo a conformational change, transforming to an active state in a light exposure-dependent manner (Repina et al., 2017). Such photoreceptor molecules have been proven to work in several model organisms, and engineered to function as optogenetic switches which can be integrated into synthetic light-controlled transcription factors. In the past twenty years, an extensive repertoire of optogenetic switches responding to light of different wavelengths has been developed (Fig. 2).

Currently, there is a wide choice of optogenetic switches sensitive to blue light, such as the cryptochrome 2 (Cry2) photoreceptor and its specific binding protein cryptochrome-interacting basic helix-loop-helix 1 (CIB1) (Kennedy et al., 2010; Wu and Yang, 2010; Jeong et al., 2010; Yu et al., 2010; Keller et al., 2011; Duan et al., 2017), tunable light-controlled interacting protein tags (TULIPs) (Strickland et al., 2012), original light-inducible dimer/improved light-inducing dimer (oLID/iLID) (Hallett et al., 2016; Guntas et al., 2015), and *Neurospora crassa* blue-light photoreceptor Vivid (VVD) and Magnet (Wang et al., 2012; Kawano et al., 2015). These optogenetic switches are light-dependent dimerization systems, based on blue light-induced conformational changes to photoreceptor proteins and subsequent homo-dimerization or hetero-dimerization with their specific binding partner proteins (Fig. 2, Table 1).

The most commonly used optical dimer system is Cry2 and CIB1. *Arabidopsis*-derived Cry2 is a photolyase-like photoreceptor that

Table 1
Ontogenetic switches applied for the light-control of gene expression.

Trigger Light	Name of Optogenetic Switch	Chromophore	Component		Molecular Size (kDa)		Activation / Inactivation		Wavelength (nm)	Origin	References (*selected*)
			Photosensor	Cofactor	Photosensor	Cofactor					
Blue	**CRY2 / CIB1**	**FAD**	**CRY2**	**CIB1**	**70 kDa**	**38 kDa**	**450 nm / Dark**			***Arabidopsis thaliana***	Kennedy et al., 2010; Pathak et al., 2014; Hallett et al., 2016; Yamada et al., 2018
CRY2 (535)	**CIB1N**	**61 kDa**	**19 kDa**								
CRY2 PHR	**CIB81**	**57 kDa**	**9 kDa**								
Blue	**TULIPs**	**FMN**	**LOVpep**	**ePDZ**	**17 kDa**	**21 kDa**	**450 nm / Dark**			***Avena sativa***	Strickland et al., 2012; Pathak et al., 2014; Hallett et al., 2016
LOVprep+	**17 kDa**										
Blue	**oLID**	**FMN**	**oLID**	**Nano (SspB) Nicro (SspB)**	**17 kDa**	**13 kDa**	**450 nm / Dark**			***Avena sativa***	Guntas et al., 2015
Blue	**iLID**	**FMN**	**iLID**		**17 kDa**		**450 nm / Dark**			***Avena sativa***	Guntas et al., 2015; Hallett et al., 2016
Blue	**VVD**	**FAD**	**full-length VVD (1–186 aa)**	***NA***	**21 kDa**	–	**450 nm / Dark**			***Neurospora crassa***	Wang et al., 2012; Kawano et al., 2015
N-terminal truncated version VVD (37–186 aa)	**17 kDa**										
Blue	**Magnet**	**FAD**	**pMag / nMag**	***NA***	**17 kDa/17 kDa**	–	**450 nm / Dark**			***Neurospora crassa***	Kawano et al., 2015
Blue	**FKF1 / GI**	**FMN**	**FKF1**	**dGI (1–960 aa)**	**69 kDa**	**104 kDa**	**450 nm / Dark**			***Arabidopsis thaliana***	Yazawa et al., 2009; Quejada et al., 2017
ful-length GI (1-1,173 aa)		**128 kDa**									
Blue	**EL222**	**FMN**	**EL222 (14–222 aa)**	***NA***	**23 kDa**	–	**450 nm / Dark**			***Neurospora crassa***	Motta-Mena et al., 2014
Red	**PhyB / PIF3 or PIF6**	**PΦB or PCB**	**PhyB (1–450 aa)**	**PIF3 (1–100 aa)**	**49 kDa**	**11 kDa**	**660 nm/740 nm**			***Arabidopsis thaliana***	Shimizu-Sato et al., 2002; Muller et al., 2013a; Pathak et al., 2014; Ruess et al., 2015; Kyriakakis et al., 2018, Noda and Ozawa, 2018
PhyB (1–621 aa)	**PIF3 (1–524 aa)**	**68 kDa**	**57 kDa**								
PhyB (1–650 aa)	**PIF6 (1–100 aa)**	**71 kDa**	**11 kDa**								
PhyB (1-908 aa)		**99 kDa**									
NIR	**BphP1 / PpsR2**	**BV**	**BphP1**	**PpsR2**	**80 kDa**	**51 kDa**	**740–780 nm**	**/•**	**660–700 nm (faster)**	***Rhodopseudomonas palustris***	Kaberniuk et al., 2016; Redchuk et al., 2017
/•	**Dark (slower)**										
NIR	**BphP1 / Q-PAS1**	**BV**	**BphP1**	**Q-PAS1**	**80 kDa**	**19 kDa**	**740–780 nm**	**/•**	**660–700 nm (faster)**	***Rhodopseudomonas palustris***	Redchuk et al., 2017, 2018a; Redchuk et al., 2018b
/•	**Dark (slower)**										

Abbreviation: NIR; Near-Infrared, FAD; flavin adenine dinucleotide, FMN; flavin mononucleotide, PΦB; phytochromobilin, PCB; phycocyanobilin, BV; biliverdin Ixα.

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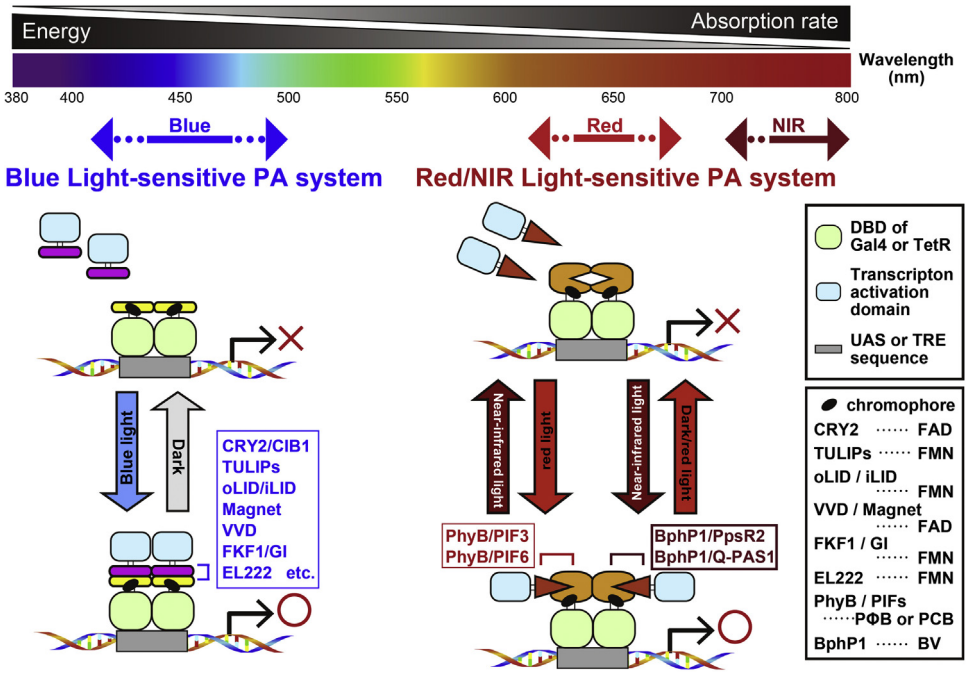

Fig. 2. Light control of gene expression. Examples of blue light-sensitive and red/near infra-red (NIR) light-sensitive gene expression systems. In both examples, dimer formation between the DNA binding domain (DBD) of the transcription factor (e.g., Gal4 or TetR) and the transcription activation domain (e.g., VP16, VP64 or p65) is induced by exposure to specific wavelengths of light. This leads to reversible formation of active transcription complexes near the binding sites of DBDs, inducing transient downstream gene expression.

controls development and growth of plants via circadian clock regulation. Cry2 has 2 domains: photolyase homology region (PHR) at the N-terminal and a cryptochrome C-terminal extension (CCE or CCT). PHR is the chromophore-binding domain that noncovalently binds to the chromophore flavin adenine dinucleotide (FAD). Cry2 can bind to the basic helix-loop-helix (bHLH) transcription factor *Arabidopsis* CIB1 in a blue-light-dependent fashion (Fig. 2, Table 1). It has been shown that truncated versions of Cry2 and CIB1 essential domains act as blue-light dependent heterodimer formation modules, and several point mutations of Cry2 induce faster or slower photocycles (Kennedy et al., 2010; Taslimi et al., 2016). This Cry2/CIB1 system has been successfully adopted for the development of blue light-controllable Gal4/UAS systems in yeast, fish and mammalian cells (Kennedy et al., 2010; Liu et al., 2012; Taslimi et al., 2016; Quejada et al., 2017).

TULIPs are synthetic optical dimer systems consisting of the blue light-sensing light-oxygen-voltage (LOV) domain of *Avena sativa* phototropin 1 (AsLOV2) and an engineered PDZ domain (ePDZ) (Table 1). AsLOV2 contains a flavin mononucleotide (FMN) as the chromophore. A PDZ binding motif in the Jα helix of AsLOV2 cannot access its binding partner ePDZ in the dark, but blue light induces a conformational change within AsLOV2, preventing this binding inhibition and reversibly increasing affinity to ePDZ. The original and mutated TULIPs were shown to be adaptable to light control of cell signaling pathways with varying sensitivities and response times (Strickland et al., 2012). TULIPs and their variants have been tested for use in the optical control of gene expression in yeast and mammalian cells (Hallett et al., 2016; Yamada et al., 2018).

The oLID/iLID system functions in a similar manner to TULIPs, uncaging the *Escherichia coli* SsrA peptide on blue light illumination and promoting binding to its specific partner, SspB (Table 1). In the original light-inducible dimer (oLID) system, an SsrA peptide was embedded in the C-terminal helix of the AsLOV2 domain, creating a blue light-dependent conditional SspB-binding property (Lungu et al., 2012). Guntas et al. developed an improved light-inducible dimer (iLID) that changes its affinity for SspB by over 50-fold on exposure to light (Guntas et al., 2015). oLID/iLID systems have also been tested for optical control of gene expression in yeast and mammalian cells (Hallett et al., 2016; Yamada et al., 2018).

The *Neurospora crassa* blue-light photoreceptor VVD self-dimerizes through its LOV domain on exposure to light (Table 1). Because VVD is the smallest light-oxygen-voltage domain-containing protein, it is expected that it could be integrated into optogenetic switches with a minimum of undesired changes in fused proteins. VVD uses FAD as a chromophore and can rapidly form a homodimer from two monomers in response to blue light. This property of VVD makes it suitable for regulating protein–protein interactions (Schwerdtfeger and Linden, 2003). VVD is used in a light-controllable Gal4/UAS system called "LightOn", in which the PA transcription factor is GAVPO (Wang et al., 2012). GAVPO is extremely sensitive to light, and brief pulses of weak blue light are sufficient to induce high expression levels of downstream genes in mammalian cells and in intact mice. Because GAVPO is very small (56 kDa), it can be expressed in multiple cell types via several different gene delivery methods, including lipofection and electroporation of expression plasmids, and viral vectors, such as lentivirus vectors (Wang et al., 2012; Imayoshi et al., 2013; Shimojo et al., 2016; Isomura et al., 2017). Although VVD has shown appropriate functionality for light-controlled gene expression, its homo-dimerizing feature limits its applications, such as light-activated control of subcellular protein localization through two different proteins. This problem was elegantly solved by the "Magnets" system, where the VVD LOV domain has been engineered to recognize a VVD partner with the opposite electrostatic charge, allowing successful light-control of subcellular protein localization (Table 1). The Magnets system consist of two variants; the I52R/M55R variant has a positively charged arginine at residue 52, called 'positive Magnet (pMag)', and I52D/M55 G has a negatively charged aspartic acid at residue 52, called 'negative Magnet (nMag)' (Kawano et al., 2015). This method has been integrated into PA CRISPR-Cas9 systems for optogenetic genome

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editing, CRISPR-Cas9-based light-controllable transcription systems, and PA Cre/loxP recombination systems (Nihongaki et al., 2015a, b; Kawano et al., 2016; Nihongaki et al., 2017, 2019). This issue was independently addressed by a novel optogenetic switch, FUN-LOV, based on the LOV-domain interaction of two blue-light photoreceptors (WC-1 and VVD) from *Neurospora crassa*, and successfully integrated into the Gal4/UAS system in yeast cells (Salinas et al., 2018).

Light control of the Gal4/UAS system in mammalian cells was independently achieved by using the *Arabidopsis* photoreceptor Flavin Kelch-repeat F-box 1 (FKF1) and its binding partner GIGANTEA (GI) (Yazawa et al., 2009; Quejada et al., 2017). A bacterial LOV protein EL222-based light-inducible gene expression system was shown to have a large dynamic range of reporter gene expression, rapid activation/deactivation kinetics and a highly linear response to light (Motta-Mena et al., 2014). EL222 contains an FMN as the chromophore (Table 1). This system allows light-gated transcription in several mammalian cell lines and intact *zebrafish* embryos with minimal basal gene activation and toxicity.

The Gal4/UAS system is not commonly used for the study of mammalian cells or organisms, likely due to the toxicity of the Gal4 transcriptional activator and the ease of chromatin silencing in the UAS sequence, especially in transgenic animals (Habets et al., 2003). Therefore, development of an efficient and reliable light-controllable gene expression system that can be widely used in mammalian cells and model animals (e.g., the Tet-OFF/ON system), was desired. However, as there were no reports of an efficient blue-light-inducible PA-Tet-OFF/ON system, our research group aimed to optimize the PA-Tet gene expression system in mammalian cells. To this end, we leveraged the Cry2-CIB1 optogenetic switch to develop a robust light-controllable Tet system (Yamada et al., 2018). This PA-Tet-OFF/ON system has a low background, high fold-activation by light, and can be used in different mammalian cells. Compared with other light-controlled gene expression systems, one unique feature of the PA-Tet-OFF/ON system is that it can be controlled via drug application. By systematically changing the intensity of the applied light and varying the Dox concentration, finer, tunable gene expression can be achieved in this system. In addition, by restricting Dox availability, light-controlled gene expression can be conditionally induced during a narrow time window over the course of long-term experiments (Yamada et al., 2018). This dual-control feature of the PA-Tet-OFF/ON technique is advantageous for systems biology experiments where the timing, amount, and pattern of gene expression must be tightly controlled. The conventional Tet-OFF/ON system is widely used in different research models, such as transgenic animals or expression vectors with TRE (or TetO) regulatory sequences. Thus, our PA-controlled TetR regulators will allow the optogenetic manipulation of genes of interest in broad fields of biology. In this review, we focus on the gene expression control by the one-photon activation of optogenetic switches. For the targeted manipulation of cells in the three-dimensional tissues or organs, the two-photon activation of optogenetic switches could be promising. However, some blue-light sensitive optogenetic switches, such as Cry2/CIB1, are not efficiently activated by the two-photon laser. Kinjo et al., 2019 elegantly overcame this limitation by applying the Förster resonance energy transfer (FRET)-assisted strategy to activate Cry2 or LOV2 with the two-photon laser (Kinjo et al., 2019).

Site-specific DNA recombinases, such as Cre, Flp and Dre, have also been integrated into a conditional gene expression strategy (Nagy, 2000; Karimova et al., 2018). These recombinases remove transcription stop sequences (e.g. LoxP-franked cassette) or invert reverse-oriented cDNA sequences (e.g. for the FEEX or DIO strategy). Optogenetic switches, such as Cry2-CIB1, VVD, and Magnets, were applied to PA-site-specific DNA recombinases. In these tools, optogenetic switches were used for light-dependent reconstitution of split recombinases in PA-Cre (Kennedy et al., 2010; Schindler et al., 2015; Kawano et al., 2016; Taslimi et al., 2016), PA-Flp (Jung et al., 2019), and PA-Dre (Yao et al., 2019). The PA-recombinases enabled spatiotemporally-precise, targeted genomic modifications triggered by light, including conditional gene expression, in mammalian cells and model organisms.

4. Gene expression control by Red/Near-Infrared (NIR) light

Most optogenetic switches are sensitive to blue light, but some PA-molecules have been identified that are activated by longer wavelengths, including red/near-infrared (NIR). Among photoreceptors responding to red/NIR-light, those used with the PA-gene expression system in mammalian cells are the plant phytochrome (Phy) B/phytochrome-interacting factors (PIFs) (Shimizu-Sato et al., 2002; Muller et al., 2013a; Pathak et al., 2014; Ruess et al., 2015; Noda and Ozawa, 2018) and the bacterial phytochrome (BphP1)/PpsR2 or Q-PAS1 systems (Kaberniuk et al., 2016; Redchuk et al., 2017, 2018a; Redchuk et al., 2018b) (Fig. 2, Table 1).

In the case of PA-gene expression control using the *Arabidopsis thaliana*-derived PhyB-PIFs (PIF3 or PIF6) system, exposure to red light (660 nm) induces conformational changes in PhyB and promotes specific binding to PIFs. This red light-dependent interaction of PhyB-PIFs allows the formation of an active transcription complex consisting of the specific DNA-binding domains (i.e. Gal4 DBD, TetR DBD) and the transcription activation domains (e.g. VP16, VP64, p65) (Fig. 2, Table 1). In general, the deactivation kinetics of red light induced heterodimer formation between PhyB and PIFs are relatively slow, and red light-induced gene expression therefore lasts >24 h (Kyriakakis et al., 2018). However, PhyB/PIFs complexes can be markedly degraded by NIR-light (740 nm) illumination. Therefore, the turning on and off of downstream gene expression can be manipulated by two different wavelengths of light (Fig. 2).

Rhodopseudomonas palustris BphP1 and its binding partner PpsR2 were shown to act as NIR (740 nm)-sensitive optogenetic switches in mammalian cells. This BphP1–PpsR2 interaction can be reversed by red light (650 nm) or darkness (Fig. 2, Table 1). However, the large size of PpsR2 (464 amino acids) and its intrinsic tendency to oligomerize has limited widespread use of the BphP1–PpsR2 system. Kaberniuk et al. reported optimization of the BphP1–PpsR2-based system using only the Q-PAS1 domain of PpsR2, which reduced the large size of PpsR2 to the minimum (151 amino acids) and altered the oligomerisation properties of PpsR2 to favor homodimerisation. These BphP1-PpsR2 and BphP1-Q-PAS1 systems have been applied to the development of NIR light-controllable tools for gene expression in mammalian cells. In contrast to the PhyB-PIFs system, the duration of active BphP1/PpsR2 (Q-PAS1) complex formation is relatively short, so it is necessary to continuously expose cells to NIR light to achieve long-term gene expression. Because blue light exposure may not be suitable for many *in vivo* studies, the development of these optogenetic tools using red or NIR light extends the potential use of light control systems for cellular gene expression (Figs. 2,3).

Although the PhyB-PIFs system has been applied to red light control of gene expression and protein translocation (Levskaya et al., 2009; Adrian et al., 2017; Yuz et al., 2018), this approach has the major disadvantage that phytochromobilin (PΦB) or phycocyanobilin (PCB), which serve as the chromophores for the phytochrome, must be added to support their function as optogenetic tools (Fig. 2). Because mammalian cells cannot synthesize PΦB and PCB, preparatory work was needed allow the PhyB/PIF system to function in mammalian cells. Although supplying exogenous PCB *in vitro* is easy by simply adding it to the culture medium, it is

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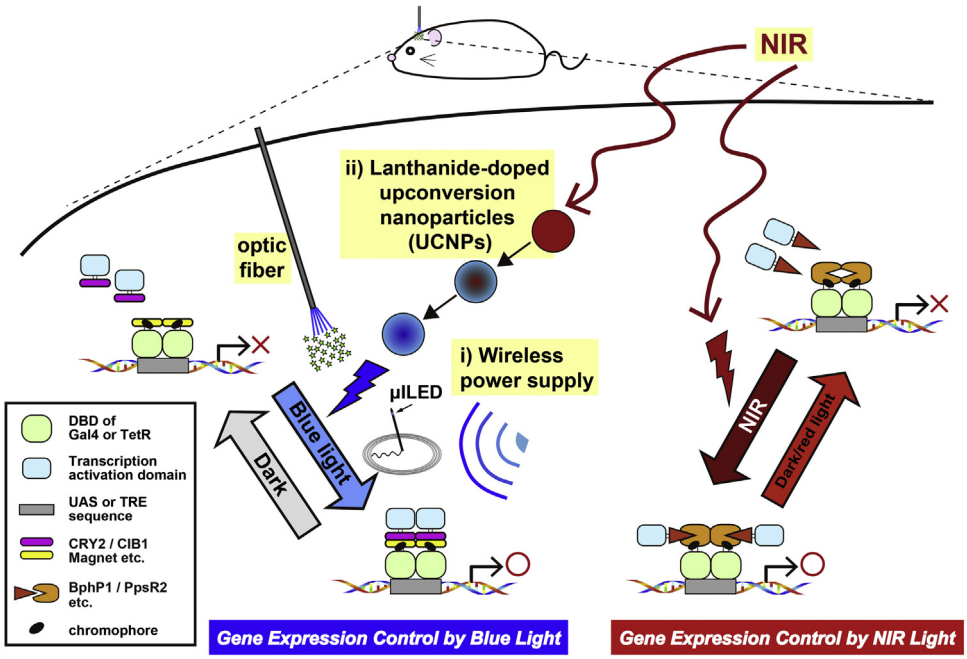

Fig. 3. Strategies for light control of gene expression deep inside the tissue. Because blue light cannot penetrate into the deep regions of tissues or organs, implantation of optical fibers is normally required to illuminate cells deep inside the tissues. Implantable micro-LED devices (u-ILEDs) equipped with wireless power transfer systems enables remote control of light-sensitive transcription factors. Because red and near-infrared (NIR) light has a lower absorption rate and can reach deep tissues, upconversion technologies have been advanced to stimulate blue light-sensitive optical molecules remotely. Lanthanide-doped upconversion nanoparticles (UCNPs) convert near-infrared excitation into visible blue or ultraviolet emission. In addition, optogenetic switches that are directly activated by NIR light, such as BphP1/PpsR2, have recently been identified and integrated into light-control systems for gene expression.

technically more difficult to ensure a constant level of PCB *in vivo*. Therefore, similar to the approach with blue light-controllable optogenetic switches like LOV- and Cry2-based systems, it would be ideal to use endogenous chromophores, such as FMN and FAD (Fig. 2, Table 1). Recently, some studies reported artificial PCB biosynthesis in mammalian cells by combining mis-expression and knock-out/down of several genes Muller et al., 2013b; Uda et al., 2017; Kyriakakis et al., 2018). These methods elegantly eliminated the need for an exogenous supply of PCB, thus making the PhyB/PIF system more applicable for mammalian cells. However, because this strategy has only been shown to work *in vitro*, *in vivo* validation and application is necessary.

The bacterial phytochrome photoreceptor BphP1 offers another alternative. In contrast to plant phytochrome-based systems, BphP uses biliverdin IXα (BV) as its chromophore to absorb NIR light (Fig. 2, Table 1). Because BV is available endogenously in mammalian cells, an external supply of chromophore molecules is not required. However, the amount of BV, or BphP1-BV affinity, might be insufficient for BphP1-PpsR2 (Q-PAS1) systems to function properly in mammalian cells. Indeed, when BphP1 was expressed at high levels in mammalian cells by transient transfection, further treatment with endogenous BV significantly improved the performance of the BphP1-PpsR2 (Q-PAS1) system (Kaberniuk et al., 2016; Redchuk et al., 2017, 2018a; Redchuk et al., 2018b). It should be noted that the properties of PhyB/PIFs and BphP1/PpsR2(Q-PAS1) systems are different when the amounts of their chromophores are insufficient in cells. For example, the PhyB/PIFs system was unable to induce transcription even under red light illumination when PCB or PΦB was lacking (Muller et al., 2013a; Noda and Ozawa, 2018). Thus, leakage of gene expression due to unintended exposure to light, for instance, during ordinary cell-culture maintenance, can be prevented by not adding PCB or PΦB. On the other hand, the BphP1/PpsR2 (Q-PAS1) system showed increased background gene expression in the dark under BV-insufficient conditions. This is probably because light-independent interactions between BphP1 and PpsR2 (Q-PAS1) are promoted when the amount of BV is relatively low in mammalian cells (Redchuk et al., 2018b).

In addition, it has already been shown that two-color controls of transcription can be achieved by applying these PA-gene expression systems that respond to red/NIR light together with other wavelength PA-systems (Muller et al., 2014; Redchuk et al., 2018b). Moreover, NIR light is not absorbed to the same extent by hemoglobin and can easily penetrate deep into tissues (Weissleder and Ntziachristos, 2003) (Figs. 2,3). Therefore, these characteristics of BphP1/PpsR2 (Q-PAS1) systems offer a promising platform for NIR-light optogenetic tool development, including gene expression control in mammalian cells.

Thus far, we have mainly discussed light-mediated control of exogenous gene expression (Fig. 2, Table 1). Recently, however, several research groups have developed optical control systems for controlling endogenous gene expression (Konermann et al., 2013; Polstein and Gersbach, 2015; Nihongaki et al., 2015b, 2017). Konermann et al. reported light-inducible transcriptional effectors (LITEs), which are optogenetic two-hybrid systems combining customizable TALE DNA-binding domains with Cry2/CIB1. Because LITEs do not require additional exogenous chemical cofactors, we can easily customize the target endogenous gene. Light-inducible CRISPR-dCas9 systems were developed as described above. In addition to the systems which respond to blue light (Polstein and Gersbach, 2015; Nihongaki et al., 2015b, 2017), a novel CRISPR-dCas9 system specifically responsive to far-red light was recently developed (Shao et al., 2018).

5. Fine tuning of light-induced gene expression

Similar to other gene expression control systems, such as via chemicals or temperature changes, several parameters affecting the magnitude and patterns of the gene expression induced must be considered also in the case of optogenetic systems. In addition to the properties of the light-sensitive modules integrated into PA-

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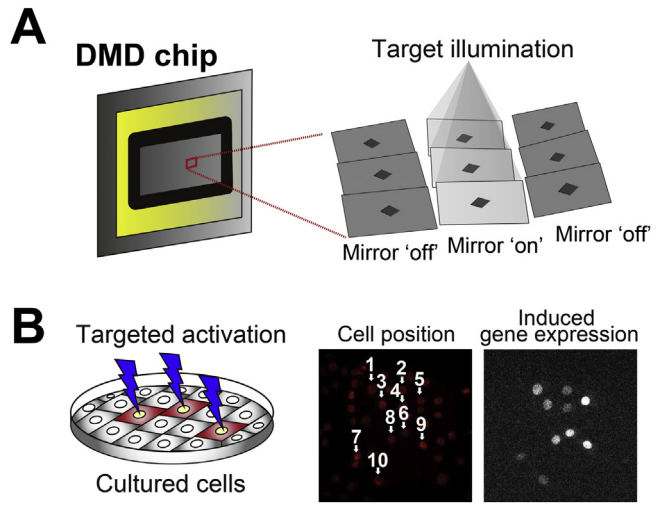

Fig. 4. Targeted illumination with a digital mirror device (DMD). (**A**) Schematic illustration of patterned light generation by DMD. A DMD is a digital imaging chip that reflects light to project and display a certain pattern of the light. It consists of a mirror array of up to 2 million units, each one individually controlled. (**B**) An example of the targeted cell populations illuminated by patterned light generated by a DMD. The patterned light, indicated by blue lightning symbols, was applied to 10 targeted cells (Cells 1–10) simultaneously, and their light-induced reporter expression was monitored. These images are reprinted from Fig. 4D of Yamada et al. (2018).

gene expression systems, the choices of target sequences bound by the DBDs of transcription factors and stability of mRNAs markedly affects the dynamics of the induced gene expression. For example, the copy number of the target sequences in promoters (e.g. UAS, TetO/TRE) changes the amplitude, and also the background level, of the downstream genes.

The degradation rate of mRNA is mainly regulated by sequences embedded in 3′-untranslated regions (UTRs). Therefore, it is necessary to choose suitable types of 3′-UTR sequences depending on the aim of each experiment. For example, the 3′-UTR sequences of several genes such as Hes1, Ascl1, IL-2 (Brown et al., 1996; Masamizu et al., 2006; Imayoshi et al., 2013) or addition of AU-rich elements (AREs) (Damgaard and Lykke-Andersen, 2013) promote rapid mRNA degradation. On the other hand, addition of Woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) to the 3′-UTR of the transgene is reported to increase mRNA stability in the cytosol (Choi and Hope, 2002). These changes of mRNA stability strongly affect the dynamic patterns and amplitude of light-induced gene expression, and experimenters should carefully select appropriate combinations of the transgene structures.

In initial characterization of newly-developed PA-gene expression systems, their properties are normally evaluated by employing common reporters, such as different luciferases, fluorescent proteins, and reporter enzymes. However, the half-life of the protein encoded by a particular transgene could be significantly different from the canonical reporter proteins, and also could be dynamically regulated, in each experimental context. Attachment of a protein degradation-promoting module, such as PEST or mutated ubiquitin (G76 V), to the expressed gene products is occasionally needed to achieve complex expression patterns in combination with appropriate light illumination protocols (Rechsteiner and Rogers, 1996, Masamizu et al., PNAS).

6. Advances in optical Devices/Tools

In this section, we describe recent advances in optical devices and tools used for optogenetic applications (Figs. 3,4).

6.1. Wireless optical devices

Most *in vivo* experiments with optogenetic tools depend on optical fibers to deliver light to the deep regions of tissue or organs (Fig. 3). However, implantation of optical fibers can be a highly invasive procedure, and the regions that can be illuminated by optical fibers are limited. In addition, optical fibers tether animals to limited places and restrict their behaviors. To minimize these tissue damage and stress issues, wirelessly controlled interfaces and small implantable light-emitting diodes (LED) were applied to develop cable-free optogenetic experimental setups (Fig. 3) (Shin et al., 2017). Recent advances in wireless techniques have enabled the development of chronic optoelectronic systems that can improve long-term *in vivo* optogenetics in freely moving animals. Park et al. developed a distinct type of wireless optical device which has multi-channel stretchable antennas and fully implantable multicolor micro-inorganic light emitting diode (u-ILEDs) (Fig. 3) (Park et al., 2016).

6.2. Upconversion nanoparticles

Although most optogenetic tools use conventional blue light, visible light does not reach deep tissues. Relative to blue light, red and near-infrared light have a lower absorption rate and can reach deeper tissues. Recently, upconversion technology has been advanced to stimulate optical molecules remotely. Lanthanide-doped upconversion nanoparticles (UCNPs) have the capacity to convert near-infrared excitation into visible blue or ultraviolet emissions (Fig. 3). UCNPs are a type of fluorophore that can convert low energy photons into high energy photons at an efficient rate. Their unique properties have been adapted to a wide range of applications, such as deep-tissue bioimaging and optogenetics (Wang et al., 2017). Implanting UCNPs close to cells expressing blue-light sensitive optogenetic molecules allows efficient conversion of near-infrared illumination into visible light, and consequently to excite optogenetic molecules (Fig. 3). Recently, some groups reported that UCNP-mediated optogenetics could noninvasively modulate neuronal activity, suggesting that these methods may be helpful for treating neurological disorders (Hososhima et al., 2015; Chen et al., 2018; Miyazaki et al., 2019). Application of this strategy to optogenetic tools for gene expression control is now anticipated (Pan et al., 2019).

6.3. Digital mirror device (DMD)

One of the great advantages of using light to control gene expression is its superior spatial resolution. For this, digital mirror devices (DMD) are commonly used to restrict illumination to a single cell or a group of cells (Fig. 4) (Yamada et al., 2018). The DMD is an array of hundreds of thousands of small mirrors that can be mounted on a microscope. The position of each individual mirror can be programmed to reflect light directly onto the target cells (Fig. 4A). Thus, we can define a target pattern that can be projected onto a sample. Using this DMD device, we demonstrated that gene expression in a single cell can be manipulated in two-dimensional cell cultures (Fig. 4B) (Yamada et al., 2018). In addition to DMD devices, spatial light modulators (SLM) can also be used for patterned light illumination (Ronzitti et al., 2017).

7. Conclusions

Over the past decade, the use of optogenetic approaches has increased in many fields of biology. This technology has overcome the limitations of classical genetic tools to precisely address dynamic changes in different cellular states, including cell signaling

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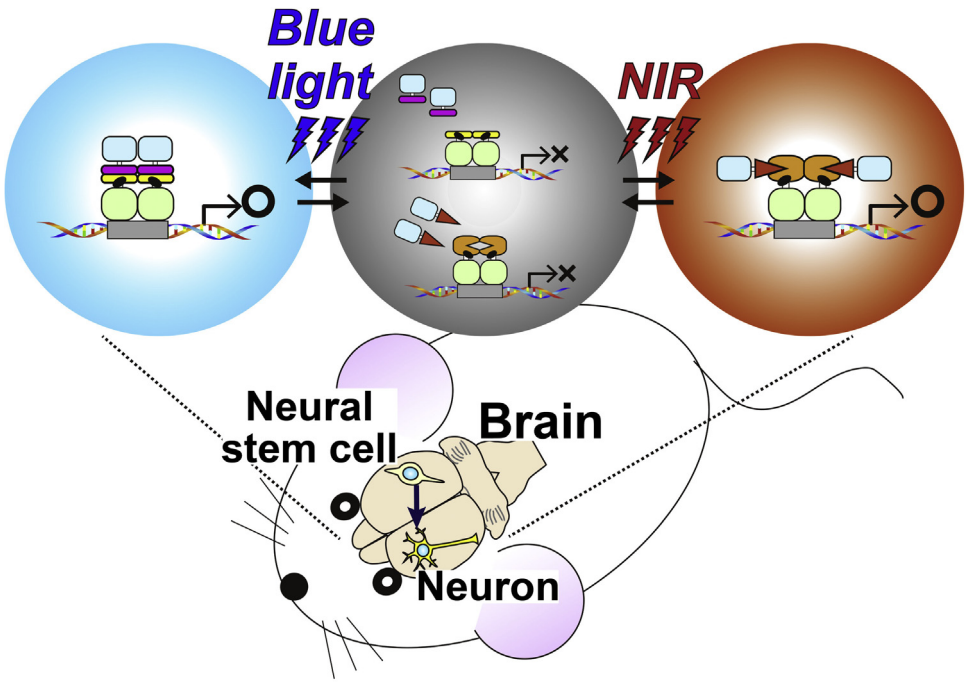

Fig. 5. Future applications of light control gene expression systems in model animals. Recently, systems allowing the expression of multiple genes that can be independently controlled via different colors of light have been developed by combining several PA-gene expression control systems. It is expected that this technology will contribute to the analysis of dynamic changes in gene expression during morphological, functional, and pathological changes of multicellular systems.

and gene expression. Classical genetic approaches, such as overexpression and knock-out/down, typically involve binary gain or loss of function, but do not allow tight control over spatial or temporal variation of a defined cellular event.

Recently, many research groups have exerted much effort to develop PA-gene expression systems by adapting different kinds of optogenetic switches, including light-mediated control of exogenous (e.g., Gal4/UAS, Tet, Cre/Flp-mediated switch) and endogenous (e.g., dCas9, TALE, Zinc finger transcription factor) gene expression. These optical control systems of the gene expression have just started to be applied to biology and neuroscience researches. For example, we previously highlighted the functional importance of dynamic gene expression changes in the bHLH transcription factor Ascl1 during the self-renewal and neuronal differentiation of neural stem cells (Imayoshi et al., 2013; Imayoshi and Kageyama, 2014). In these studies, we adopted the PA-Gal4/UAS system to overcome technical limitations of conventional chemically regulated gene expression systems, such as limited reversibility and poor temporal control. We believe that the PA-gene expression system can be used for precise regulation of gene expression in biotechnology and molecular medicine, as well as for studying dynamic changes in cellular gene expression during morphological, functional, and pathological changes in various multicellular systems (Fig. 5).

The examples of the successful application of PA-gene expression systems in neuroscience fields are still limited. However, many neural circuit studies need more superior temporal resolution. For example, at the functional mapping experiments of activated neurons in combination with immediate early genes (e.g. *c-fos*, *Arc*, *Zif-267*) and chemically-regulated gene expression systems (e.g. Tet system) or drug-inducible recombinases (e.g. $CreER^{T2}$), time windows of the genetic targeting are from several hours to a day (Guenthner et al., 2013; Denny et al., 2014; DeNardo et al., 2019). If the PA-gene expression systems are successfully integrated, activated neurons are expectedly targeted at the narrower time scale. Indeed, such strategies were recently developed to induce gene expression in activated neurons in a light-dependent manner (Lee et al., 2017a, b; Ebner et al., 2019). The PA-gene expression systems can potentially induce selective expression of genes in defined set of neurons, including activated neurons in a specific event, and therefore can be used to interrogate whether the targeted neurons are necessary and/or sufficient for a given brain functions when driving the expression of constructs such as neuronal actuator molecules. In the future, we expect that the PA-gene expression systems will be applied to broad fields of neuroscience to understand various brain functions and their underlying circuit mechanisms, including learning and memory.

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