Cell Calcium xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

Optogenetic toolkit for precise control of calcium signaling

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ARTICLE INFO

Article history:
Received 5 December 2016
Received in revised form 10 January 2017
Accepted 10 January 2017
Available online xxx

Keywords:
Optogenetics
Calcium signaling
Genetically-encoded calcium actuator (GECA)
LOV2
Cryptochrome
Calcium release-activated calcium (CRAC) channel

ABSTRACT

Calcium acts as a second messenger to regulate a myriad of cell functions, ranging from short-term muscle contraction and cell motility to long-term changes in gene expression and metabolism. To study the impact of Ca^{2+}-modulated 'ON' and 'OFF' reactions in mammalian cells, pharmacological tools and 'caged' compounds are commonly used under various experimental conditions. The use of these reagents for precise control of Ca^{2+} signals, nonetheless, is impeded by lack of reversibility and specificity. The recently developed optogenetic tools, particularly those built upon engineered Ca^{2+} release-activated Ca^{2+} (CRAC) channels, provide exciting opportunities to remotely and non-invasively modulate Ca^{2+} signaling due to their superior spatiotemporal resolution and rapid reversibility. In this review, we briefly summarize the latest advances in the development of optogenetic tools (collectively termed as 'genetically encoded Ca^{2+} actuators', or GECAs) that are tailored for the interrogation of Ca^{2+} signaling, as well as their applications in remote neuromodulation and optogenetic immunomodulation. Our goal is to provide a general guide to choosing appropriate GECAs for optical control of Ca^{2+} signaling *in cellulo*, and in parallel, to stimulate further thoughts on evolving non-opsin-based optogenetics into a fully fledged technology for the study of Ca^{2+}-dependent activities *in vivo*.

Contents

1. Shedding light on Ca^{2+} signaling

Ca^{2+} acts as a versatile second messenger to regulate a myriad of cellular activities, ranging from short-term reactions occurring within seconds (*e.g.*, muscle contraction and neurotransmitter release) to long-term processes that last for hours or even days (*e.g.*, gene transcription) [1,2]. The location, amplitude and frequency of

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http://dx.doi.org/10.1016/j.ceca.2017.01.004
0143-4160/

Ca^{2+} signals in mammalian cells undergo constant changes to maintain Ca^{2+} homeostasis while meeting the diverse requirements of different Ca^{2+}-modulated events. This challenging task is made possible through the coordinated actions of a repertoire of Ca^{2+} signaling components situated on the plasma membrane, across membranous organelles, or in the cytoplasm [2–4]. Over the past decade, the technical leap in Ca^{2+} imaging, propelled by the invention of a growing palette of genetically encoded Ca^{2+} indicators (GECIs), makes it a routine practice in numerous laboratories to monitor Ca^{2+} dynamics and report Ca^{2+}-triggered activity in both model cellular systems and living organisms [5–11]. In contrast to the rapid progress in developing optical reporters for Ca^{2+}, the quest for genetically encoded optical actuators to deliver Ca^{2+} signals with user-defined spatial and temporal properties remains relatively stagnant.

Earlier attempts to optically control Ca^{2+} signals in mammalian cells can be traced back to the invention of "caged" compounds in the 1980s. The caged substrates could be Ca^{2+} itself [12–17], or other signaling molecules, such as ATP [18], GTP [19], and IP_3 [20–23], that are intimately involved in the mobilization of intracellular Ca^{2+} in mammalian cells (Fig. 1A). When shielded from light, the encapsulated biomolecule is trapped in an inert or less active state via chelation or formation of covalent bonds with photolabile "cages" [24–27]. For instance, Ca^{2+} cages can be synthesized by introducing photolabile groups, such as *o*-nitrophenyl (Fig. 1A), into commonly used Ca^{2+} chelators (*e.g.*, BAPTA, EDTA or EGTA) [12–16,26]. In the dark, Ca^{2+} tightly binds to these modified metal chelators with a high affinity in the range of 5–150 nM [26]. Upon UV illumination, the photolytic products exhibit a dramatic decrease in affinity for Ca^{2+} by >10,000 fold, thereby unleashing the bound Ca^{2+} to produce Ca^{2+} spikes inside cells [12–16,26]. These photolabile Ca^{2+}-releasing compounds, commercially branded as DM-Nitrophen, NP-EGTA or nitr-5, are often used to trigger or drive Ca^{2+}-dependent 'ON' reactions in living cells [28,29]. Conversely, photoactivatable Ca^{2+} scavengers (*e.g.*, diazo-2) have been devised to chelate free intracellular Ca^{2+} to suppress or terminate Ca^{2+}-dependent activities [30,31].

Photo-inducible control of Ca^{2+} signaling offers two major advantages over conventional pharmacological approaches. First, the high temporal resolution enables the dissection of kinetic requirements of Ca^{2+} signals during mechanistic studies of Ca^{2+}-dependent 'ON' and 'OFF' reactions *in cellulo* [20,30,31]. For example, the fast release of Ca^{2+} makes it possible to photo-activate the contraction of skeletal muscle fibers within tens of milliseconds, a speed that is five times faster than the most rapid solution change method [32]. Another desirable feature of photo-induced Ca^{2+} and IP_3 uncaging is that the amplitude of chemical signals can be conveniently tuned by varying the intensities of incident light. Second, photorelease technology makes it feasible to conveniently program the spatial profiles of Ca^{2+} signals. Both global and local Ca^{2+} signals can be generated to modulate Ca^{2+}-dependent activities at subcellular precision by applying a focused beam of light on the whole cell or at user-defined areas [25,33–35]. However, the spatial resolution might be compromised owing to the rapid diffusion of caged compounds in the cytoplasm. Hurdles hampering the application of caged compounds *in vivo* include irreversibility, low delivery efficiency, limited depth of tissue penetration and strong phototoxicity associated with UV irradiation [24–26,36].

Optogenetics, which combines the use of light and genetics to control cellular activities at high spatiotemporal precision [37], offers an ideal solution to overcome the aforementioned hurdles whilst still preserving the advantages of photorelease technology. Originally designed and most widely adopted to manipulate neuronal activities, optogenetic tools are now gaining wide popularity in biomedical research beyond neuroscience [36,38–43]. At the heart of this revolutionary technology is the integration of genetically encoded photosensitive modules into cells of living tissues to achieve gain or loss of function of defined cellular events. Several photoactivatable domains and photosensory receptors derived from microbes or plants, including the most well-known channelrhodopsin 2 (ChR2) and its variants, light-oxygen-voltage-sensing domains (LOV), cryptochrome 2 (CRY2), phytochrome B (PhyB), UV-resistance locus 8 (UVR8) and Dronpa, have been successfully optimized and exploited to control a growing number of biological processes in mammals [36,38–42]. Very recently, photosensitivity has been engineered into the Ca^{2+} release-activated Ca^{2+} (CRAC) channel (*e.g.*, OptoSTIM1 and Opto-CRAC) [36,44–46], G-protein coupled receptors (*e.g.*, melanopsin and Opto-XRs) [47,48] and receptor tyrosine kinases (*e.g.*, Opto-RTKs) [49–51]. These exciting technical breakthroughs introduce a repertoire of highly Ca^{2+}-selective optogenetic tools to the Ca^{2+} signaling field (Fig. 1B). We name these tools collectively as 'genetically encoded Ca^{2+} actuators' or GECAs, which complement the existing toolbox of GECIs to allow simultaneous perturbation and recording of Ca^{2+} signals. In this review, we will present the current state of the art of the optogenetic toolkit tailored for Ca^{2+} signaling, outline engineering strategies and basic design principles for GECAs, and briefly discuss the strengths and weaknesses of the existing tools. Our goal is to provide a general guide to choosing appropriate GECAs based on the experimental requirements and the biological questions to be tackled.

2. Genetically-encoded photoactivatable Ca^{2+} releaser (PACR)

Inspired by photo-induced uncaging of Ca^{2+} with synthetic 'caged' compounds [13,15–17], Fukuda et al. devised a genetically encoded Ca^{2+}-releasing (PACR) molecular tool [52] by inserting a photosensitive domain LOV2 into a calmodulin (CaM)-M13 fusion protein (Fig. 1B), the latter of which contains four Ca^{2+}-binding sites with each adopting a pentagonal bipyramidal geometry to coordinate Ca^{2+} [3,4,53]. In the dark, owing to the formation of a complex composed of CaM and its target peptide M13, PACR binds Ca^{2+} with a dissociation constant (K_d) of ~16 nM [54], which falls into the physiological range of resting Ca^{2+} and renders PACR to act as a Ca^{2+} chelator in mammalian cells. When exposed to blue light, photoexcited LOV2 disrupted the CaM-M13 interaction, and therefore, restored CaM to its target-free state with subsequent reduction in the affinity for Ca^{2+} (K_d = 3.75 μM) by >200 fold. Consequently, the rate constant (k_{off}) of Ca^{2+} release increased from 0.77 s^{-1} in the dark to 181 s^{-1} following photostimulation [52]. Unfolded PACR recovered to its dark state in a reversible manner with a half time of 41.7 s to allow repeated Ca^{2+} release. The expression of PACR in HeLa cells was shown to moderately elevate cytosolic [Ca^{2+}] by 10–90 nM. The potential application of PACR *in vivo* was demonstrated in *C. elegans* by photo-triggering the firing of touch neurons to elicit a turning behavior [52].

The application of PACR in cellular context, however, will likely be impeded because of its limited Ca^{2+}-releasing capacity and perturbation to the host physiology. The majority of cellular responses require the fluctuation of cytosolic [Ca^{2+}] in the range of a few hundred nanomolar or micromolar, but PACR brings about no more than 90 nM increase in the cytosolic [Ca^{2+}]. Given that the amounts of sequestered Ca^{2+} is proportional to the intracellular concentrations of PACR, this concern might be partially alleviated through overexpression of PACR or PACR concatemers to push the Ca^{2+}-releasing capacity toward the upper limit. However, the presence of excessive amounts of PACR as a Ca^{2+} binding protein might run the risk of imposing buffering effects on intracellular Ca^{2+} and perturbing the host cell functions, particularly a multitude of bio-

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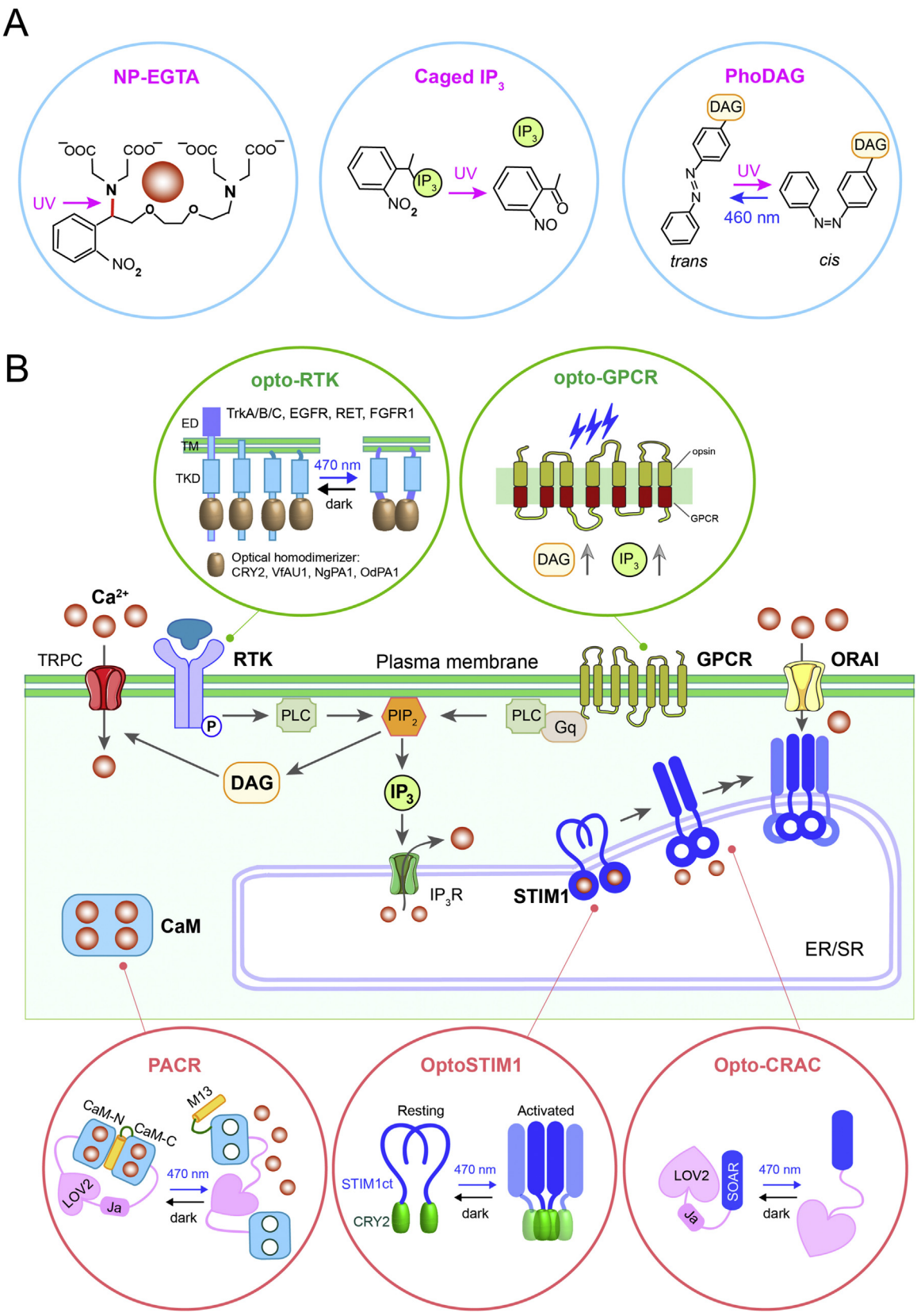

Fig. 1. Tools for photoactivatable control of Ca^{2+} signaling.
(A). Examples of caged Ca^{2+} chelator, caged IP_3 and a photoswitchable DAG (PhoDAG).
(B). Genetically encoded optical actuators engineered from membrane receptors (opto-RTKs and opto-GPCRs), Ca^{2+} sensory proteins STIM1 (OptoSTIM1 and Opto-CRAC) and CaM (PACR).

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logical processes that are dependent on CaM [3,55]. Further tuning of kinetics of Ca^{2+} binding, release and recapture might be beneficial to improve this genetically encoded Ca^{2+} 'cage' and make it widely applicable.

3. Photoactivatable intracellular Ca^{2+} mobilization through the phospholipase C (PLC) pathway

Activation of cell-surface receptors, such as G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs), results in mobilization of Ca^{2+} release from internal Ca^{2+} stores [56–59]. Upon ligand binding to these receptors, PLC is activated to hydrolyze the PM-bound lipid, phosphatidylinositol 4,5-bisphosphate (PIP_2), generating two second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) [56]. DAG is an activator of protein kinase C (PKC) and may directly activate certain types of transient release potential (TRP) channels [60], resulting in Ca^{2+} influx from the extracellular space. Very recently, photoswitchable DAG and its analogs based on the azobenzene photoswitch (Fig. 1**A**) have been developed to modulate PKC dependent pathways [61]. The second messenger IP_3 can diffuse to the ER where it binds and activates ER-resident IP_3 receptors to trigger Ca^{2+} release from ER Ca^{2+} stores [57], which is often followed by store-depletion induced Ca^{2+} entry from the extracellular space (discussed in Section 4). Receptor-induced Ca^{2+} signaling via the PLC pathway works in concert with other receptor activated pathways to modulate important cellular processes, such as synaptic transmission, fertilization, cell migration, and secretion [56,57]. Here we highlight two notable examples of introducing light sensitivities into GPCRs or RTKs to enable photo-inducible intracellular Ca^{2+} mobilization (Fig. 1B).

3.1. Photoactivatable GPCRs

As the largest family of transmembrane proteins in the human genome [62,63], GPCRs, particularly those coupled to G_q protein ($G_{\alpha p}$ or $G_{q/11}$), mediate Ca^{2+} signaling via activation of PLC with subsequent hydrolysis of PIP_2 into DAG and IP_3 [2,57]. IP_3-dependent Ca^{2+} release from ER Ca^{2+} stores directly controls many physiological processes in both non-excitable and excitable cells [64]. Naturally-existing photosensitive melanopsin, a member of the opsin subgroup of GPCRs first characterized in retinal ganglion cells [65], can be expressed in other types of mammalian cells to drive Ca^{2+} dependent reactions when illuminated by blue or green light. Vertebrate melanopsin (or opsin 4, OPN4) and its variants have been used as intrinsic bistable optogenetic switches to generate both sustained and transient Ca^{2+} responses to control Ca^{2+}-dependent transgene expression and GPCR pathways [48,66,67]. By taking advantage of a light-gated human melanopsin (hOPN4) to generate Ca^{2+} oscillations with programmable frequency, peak amplitude, and duty cycle, Hannanta-anan et al. resolved the decoding principle for NFAT by quantitatively assessing the impact of these parameters on NFAT-dependent transcriptional outputs [66]. Results from both optogenetic studies and mathematical modeling converge to support the conclusion that NFAT acts as a signal integrator of Ca^{2+} load rather than a frequency-selective decoder. In another application with the expression of melanopsin in beating embryoid bodies (EBs) derived from mouse ESCs, photoactivation of melanopsin and Gq signaling can generate local pacemaker activity in cardiomyocytes within EBs upon blue light illumination [68].

Given the common structure-function relationships between melanospin and metabotropic glutamate receptor (mGluR), a chimeric receptor, Opto-mGluR6, has been recently generated by combining the light-sensing domain of melanopsin and the intracellular domain of mGluR6 [69]. Once expressed in retina, Opto-mGluR6 recovered vision in blind mice with retinal degeneration. With a similar engineering strategy, photosensitive GPCR chimeras were developed by capitalizing on the structural similarity between class A GPCRs and light-gated ChR2, as most prominently known as 'optoXRs' [47]. optoXRs were devised by replacing the intracellular region of G_t-coupled bovine rhodopsin to that of a human adrenergic receptors [47]. Using a chimeric photoactivatable GPCR named opto-α_1AR, Airan et al. showed that 1 min of light stimulation at ~504 nm at a power density of 7 mW mm^{-2} could generate prominent increase in cytosolic Ca^{2+} in HEK cells. These tools can be further used to photo-tune the firing rate of neurons in mouse nucleus accumbens to control reward-related behaviors in living animals [47].

Since activation of GPCRs mobilizes Ca^{2+} through a series of signaling cascades, the resulting Ca^{2+} signal is greatly amplified [57]. This feature makes the Opto-GPCR tools very sensitive to light stimulus. However, the functional crosstalk between GPCRs in a heterodimeric assembly [70–72] within the host cell may activate multiple signaling pathways and/or ion channels, and thus, make it difficult to discriminate between Ca^{2+}-dependent and Ca^{2+}-independent effects. Furthermore, photo-activation of GPCRs leads to the generation of DAG, a second messenger that is implicated in a plethora of non-Ca^{2+}-dependent cellular signaling events through the activation of protein kinase C (PKC) and phorbol ester receptors [73–75]. This will likely confound the interpretation of the observed phenotypes following light stimulation. Some precautions, therefore, are needed when applying photoactivatable GPCRs to dissect the causal impact of Ca^{2+}-dependent signaling. In particular, control experiments to rule out the contribution of endogenous GPCRs and DAG-dependent signaling are required to reach an unequivocal conclusion.

3.2. Photoactivatable RTKs

RTKs belong to an important family of cell-surface receptors that share a similar molecular architecture, typically consisting of an extracellular ligand-binding domain (ED), a single-pass transmembrane domain (TM), and an intracellular tyrosine kinase domain (TKD; Fig. 1B) [76]. RTKs play instrumental roles in the regulation of cell proliferation, differentiation, cell-cycle progression, survival, migration, and metabolism [77]. Mutations or aberrant expression of RTKs have been tightly linked to cancer and developmental syndromes [77,78]. The signal transduction is often triggered upon the binding of ligands (*e.g.*, growth factors or hormones) to RTKs to induce the dimerization of the extracellular regions and ultimately activate the intracellular TKDs to mediate phosphorylation of downstream targets such as PLCγ [59,76,79]. Activated PLCγ, as described above, cleaves its substrate PIP_2 into DAG and the Ca^{2+}-maobilizing secondary messenger IP_3 [58,59]. Photoactivatable RTKs were generally designed by tagging the C-terminus of TKD with optical dimerizers derived from CRY2 (*e.g.*, the PHR domain) [51,80], LOV domains from aureochrome photoreceptors (*e.g.*, VfAU1, OdPA1, or NgPA1) [49], or the cyanobacterial phytochrome 1 (Cph1) [81]. The extracellular domain was either retained or replaced by PM-targeting motifs (Fig. 1B).

This optogenetic engineering strategy has been applied to a number of RTKs, including fibroblast growth factor receptor 1 (FGFR1) [49,51,81], epidermal growth factor receptor (EGFR) [49], rearranged during transfection (RET) [49] and the tropomyosin-related kinase (Trk) family [49,80–82]. For example, Kim et al. constructed a light-controlled optoFGFR1 by fusing the cytoplasmic TKD of human FGFR1 (aa 398–822) with CRY2-PHR, with the N-terminal extracellular region and the transmembrane segment of FGFR replaced by a myristoylation signal peptide in order to anchor the chimeric protein to plasma membrane [51]. In the absence of the extracellular ligand binding domain, the activation of optoFGFR1 is solely dependent on light-induced homodimerization

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of intracellular TKDs. When optoFGFR1 was transiently expressed in HeLa cells, reversible Ca^{2+} signals at high spatiotemporal resolution could be generated in individual cells by toggling a blue light switch. This effect was dependent on TKD and the PLC pathway since either the addition of an FGFR-specific kinase inhibitor or the expression of a PLC-binding mutant (Y766F) of optoFGFR1 abolished photoswitchable changes in cytosolic Ca^{2+} [51].

Owing to the lack of tools with enough spatiotemporal resolution, the role of FGFR-mediated local Ca^{2+} signaling in the migration of HUVECs remains ill-defined [83]. To address this challenge, Kim et al. used optoFGFR1 to generate Ca^{2+} signals with superior spatial and temporal precision in HUVECs [50]. Local photostimulation of optoFGFR1-expressing HUVECs produced Ca^{2+} puffs around the illuminated area (defined as the "front" of the cell), but surprisingly induced Ca^{2+} sparklets in un-illuminated (or the "rear") area of the cell, thereby creating a front-to-rear increasing Ca^{2+} gradient to maintain morphological polarity during directional migration [50]. The origin of Ca^{2+} sparklets was further traced to Ca^{2+} influx from the extracellular space through L-type Ca_V channels, as the frequency of Ca^{2+} sparklets was greatly diminished by treating HUVECs with by a Ca^{2+} chelator EGTA or a Ca_V channel blocker nimodipine [50]. Nimodipine treatment disrupted the Ca^{2+} gradient and greatly inhibited light-directed migration of HUVECs, thus establishing a functional link between optoFGFR1-generated Ca^{2+} gradient and directed cell migration. This application represents an excellent example of combining the use of optogenetic tools with pharmacological agents to address biological questions that would otherwise be inaccessible with conventional approaches. Nonetheless, one potential caveat users should bear in mind is that photostimulation of OptoRTKs, similar to ligand-induced activation of canonical RTKs, simultaneously activates signaling pathways mediated by PLC, mitogen activated protein kinase (MAPK) and phosphoinositide 3 kinase (PI3K) [77]. Therefore, light will not only induce fluctuations in the cytosolic Ca^{2+}, but also trigger the MAPK/PI3K-associated signaling axis to program cell functions. The latter undesired effects call for caution during the use of optoRTKs to interrogate Ca^{2+}-dependence cellular processes.

4. GECAs engineered from CRAC channels

The CRAC channel is a prototypical example of store operated Ca^{2+} entry (SOCE) [84–90] and constitutes a major route for Ca^{2+} entry in many cell types. Store-operated CRAC channel comprises two major protein families (Fig. 1B): ORAI as the pore-forming subunit on the plasma membrane (PM) [91,92] and the ER-resident stromal interaction molecule (STIM) as the Ca^{2+} sensor for $[Ca^{2+}]_{ER}$ [93–95]. CRAC channels are among the most selective Ca^{2+} channels known thus far with a Ca^{2+}/Na^{+} permeability ratio of >1000 under physiological conditions [96]. Over the past decade, the essential steps required to activate SOCE, particularly the dynamic coupling between STIM1 and ORAI1, have been worked out in great detail through the collective efforts from multiple groups (reviewed in [88–90,97–99]). In brief, the depletion of ER Ca^{2+} store, triggered by ligand binding to cell-surface receptors or through pharmacological manipulation (*e.g.*, ionomycin or thapsigargin), causes the dissociation of Ca^{2+} from the canonical EF-hand Ca^{2+} binding motif, and subsequently induces the oligomerization of the STIM1 EF-SAM domain in the ER lumen [100]. These structural changes further prompt the reorganization of the single-pass transmembrane (TM) domain of STIM1 to transduce luminal signals toward its own cytoplasmic domain (STIM1ct) [101,102]. Next, STIM1ct undergoes a conformational switch to adopt an extended configuration by overcoming the intramolecular autoinhibition mediated by its juxtamembrane coiled coil region 1 (CC1) and the minimal ORAI-activating domain (SOAR, aa 344–442; or CAD, aa 342–448; Fig. 2 A) [101–104], thereby allowing further oligomerization and translocation toward the plasma membrane to directly engage and gate ORAI1 Ca^{2+} channels [105–109]. The efficient targeting of STIM1 from the ER network toward PM, as well as the stabilization of the CRAC channel complex, is facilitated by other protein regulators (*e.g.*, CRAC2A, septin and STIMATE) [110–114] and PM-resident lipids [102,115–118].

Taking advantage of photosensitive domains derived from plants, light sensitivities can be installed into STIM1 to mimic two critical steps during STIM1 activation: oligomerization and conformational switch. Specifically, two engineering approaches have been employed: (i) replacing the STIM1 luminal domain and the transmembrane domain with a light-inducible oligomerization domain (OptoSTIM1; Figs. 1B and 2A) [44]; and (ii) fusion of a photosensory module with SOAR/CAD to recapitulate reversible CC1-SOAR/CAD intramolecular trapping (LOVS1 K, BACCS or Opto-CRAC; Figs. 1B and 2B) [36,45,46,119]. These tools enable light-dependent ORAI-STIM coupling to elicit Ca^{2+} influx through highly Ca^{2+}-selective CRAC channels in both excitable and non-excitable cells.

4.1. OptoSTIM1

The Ca^{2+} dissociation and subsequent oligomerization of the STIM1 luminal domain initiate STIM1 activation [100]. This scenario can be recapitulated by replacing the luminal domain, or the luminal domain plus TM domain of STIM1 [120], with a FKBP/FRB-based chemical inducible dimerization system. When the FKBP-STIM1 and FRB-STIM1 fusion chimeras were co-expressed in mammalian cells, rapamycin-induced heterodimerization of FKBP and FRB, much like Ca^{2+}-depletion induced oligomerization of the luminal EF-SAM domain, triggered STIM-ORAI coupling to evoke Ca^{2+} influx [120,121]. Moreover, covalently crosslinking the N-terminus of STIM1ct at residue 233 has been shown to induce a conformational switch in STIM1ct [102]. Clearly, bringing the N-terminus of STIM1ct into close proximity, either through forced multimerization or via crosslinking, is sufficient to overcome the intramolecular autoinhibition to elicit the ensuing STIM1-ORAI1 functional coupling. Based on these pioneering studies, Kyung et al. hypothesized that an optical dimerizer could likewise oligomerize STIM1 to prompt STIM1-ORAI1 interaction and ultimately trigger Ca^{2+} influx via photostimulation [44]. To test this, the EF-SAM and TM domains of STIM1 were replaced by the N-terminal photolyase homology (PHR; aa 1–498) domain of CRY2 from *Arabidopsis thaliana*, the latter of which binds to the flavin adenine dinucleotide (FAD) cofactor (Fig. 2A) and undergoes light-inducible monomer-to-oligomer transition in a reversible manner [122,123]. After screening a handful of $CRY2_{PHR}$-STIM1ct chimeric constructs, Kyung et al. identified at least three variants (238–685, 238–463, and 342–685) that translocated to the plasma membrane and induced Ca^{2+} influx upon blue light illumination. The most effective construct comprising $CRY2_{PHR}$ and the STIM1ct fragment 238–685 was termed as 'OptoSTIM1′ (Fig. 2A). OptoSTIM1 has an activation kinetics (the time to reach half-maximal Ca^{2+}-responsive R-GECO1 intensity, $t_{1/2}$) of ~1 min and a deactivation kinetics of ~4–5 min upon the withdrawal of blue light (Table 1). A similar construct generated in our laboratory by fusing $CRY2_{PHR}$ with the STIM1ct fragment 233–685 displayed a faster activation kinetics ($t_{1/2,on}$ = 38 s) when assayed with R-GECO1.2 in HeLa cells (Fig. 2C). In the near future, the activation and deactivation kinetics of OptoSTIM1 can be further tuned by introducing key mutations (*e.g.*, L348F, W349R and E490G) into $CRY2_{PHR}$ to expedite or slow down its photocycle [122–127].

The use of OptoSTIM1 to photostimulate Ca^{2+} influx has been demonstrated in various cell types including HeLa, NIH3T3, Cos-7, HEK293, human umbilical vein endothelial cells (HUVECs), human

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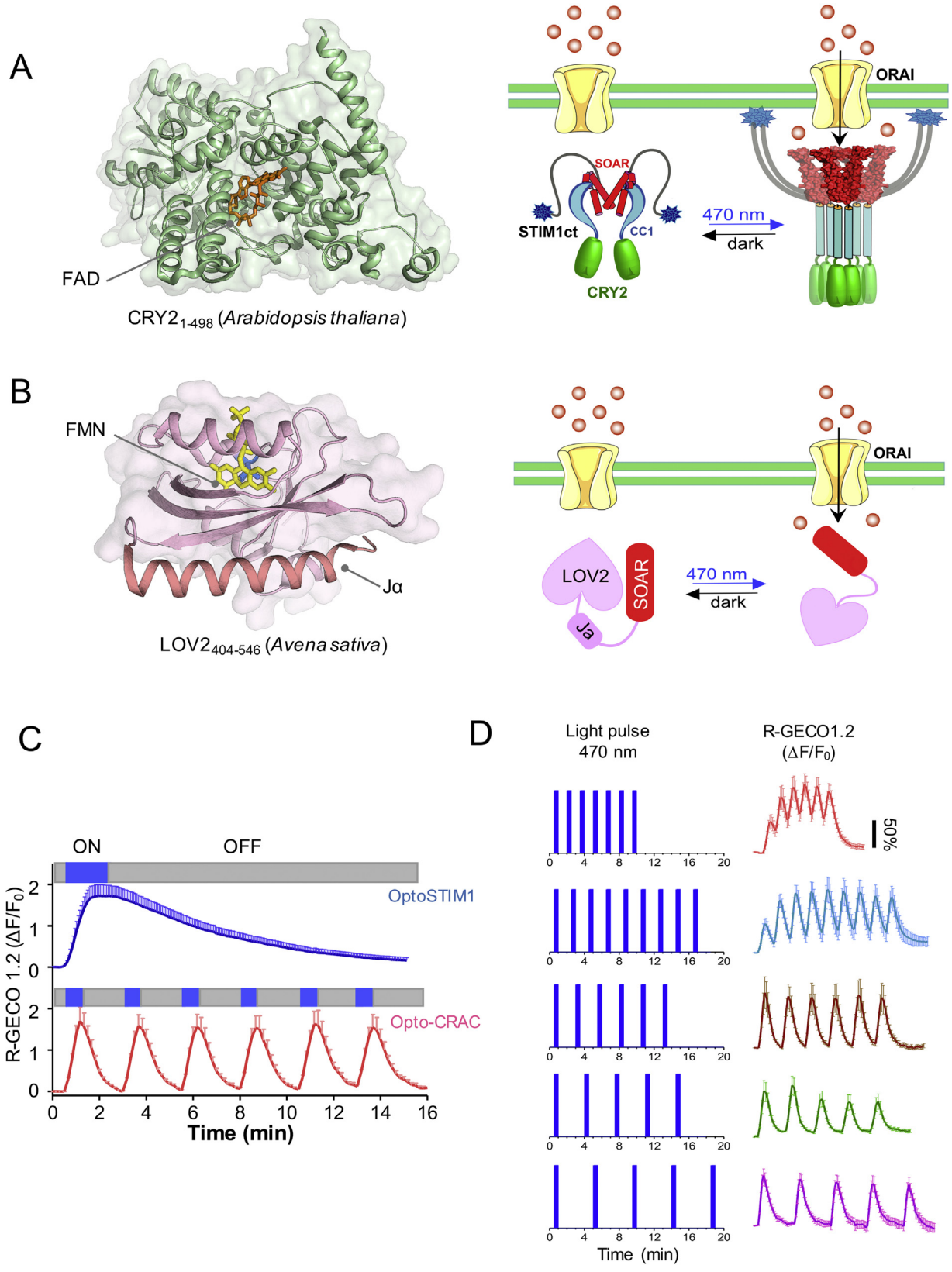

Fig. 2. Optogenetic tools engineered from the CRAC channel activator STIM1.
(A). Schematic of the design of OptoSTIM1. *Left*, the 3D structural model of the PHR domain of atCRY2 generated from the crystal structure of its counterpart in atCRY1 (PDB entry: 1U3D). The cofactor FAD is highlighted in orange. *Right*, the light-inducible multimerization domain CRY2-PHR is fused with STIM1ct. In the dark, the intramolecular interaction between CC1 (cyan) and SOAR (red) keeps CRY2-STIM1ct inactive. Upon blue light illumination, CRY2 undergoes oligomerization to trigger the conformation switch of STIM1ct, thus exposing SOAR toward the PM to activate Ca^{2+} influx through ORAI channels.
(B). Schematic of the design of Opto-CRAC. *Left*, 3D structure of AsLOV2 (PDB entry: 2V0W), with its cofactor FMN highlighted in yellow and the cysteine residue at position 450 in blue. *Right*, LOV2 masks the active site in SOAR to prevent its interaction with ORAI in the dark. Following blue light stimulation, the Jα helix unfolds to release

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Table 1
Summary of STIM1-based GECAs tailored for optical control Ca^{2+} signaling in a reversible manner.

Name	Photosensitive module	Linker	STIM fragment	ON ($t_{1/2}$, sec)	OFF ($t_{1/2}$, sec)	Ca^{2+} reporter	Fold change (F_{max}/F_0 or $\Delta F/F_0$)	Cell types	Ref
CRY2-based GECAs*									
OptoSTIM1	$CRY2_{1-498}$	24 aa	238–685	64.5 ± 4.8	274 ± 23.7	R-GECO1	~10	HeLa	[44]
	$CRY2_{1-498}$	24 aa	238–463	43.2 ± 3.8	383 ± 52.3	R-GECO 1	~8	HeLa	[44]
	$CRY2_{1-498}$	24 aa	342–485	48. 2 ± 5.4	344 ± 34.6	R-GECO 1	~8	Hela	[44]
	$CRY2_{1-498}$	24 aa	233–685	38.4 ± 2.1	320 ± 37.2	R-GECO1.2	8.2	HeLa	*Unpubl***
LOV2-based GECAs**									
Opto-CRAC	$LOV2_{404-546}$	KL	336–486	23.4 ± 4.2	24.9 ± 4.8	R-GECO 1.2	3.0	HeLa	[45]
				36.4 ± 2.4	30.0 ± 1.1	Fura-2 AM	1.2	HeLa	[45]
				31.1 ± 4.9	34.7 ± 4.9	R-CaMP2	0.16	HeLa	[45]
				10.2 ± 3.0		GCaMP6s	4.05	HeLa	[45]
	Lyn-$LOV2_{404-546}$	KL	336–486	2.9 ± 1.1		GCaMP6s	2.52	HeLa	[45]
	2* $LOV2_{404-546}$	KL	336–486	46.2 ± 8.5		GCaMP6s	2.75	HeLa	[45]
	$LOV2_{404-546}$		336–486			GCaMP6s	1.35	HeLa	[45]
	$LOV2_{404-546}$	KLAAA	336–486			GCaMP6s	0.95	HeLa	[45]
	$LOV2_{404-546}$	KL	336–450			GCaMP6s	1.85	HeLa	[45]
	$LOV2_{404-546}$	KL	336–460			GCaMP6s	2.01	HeLa	[45]
	$LOV2_{404-546}$	KL	336–473			GCaMP6s	0.97	HeLa	[45]
	$LOV2_{404-546}$	KL	342–486			GCaMP6s	1.78	HeLa	[45]
	$LOV2_{404-546}$	KL	344–486			GCaMP6s	3.51	HeLa	[45]
	$LOV2_{404-546}$	KL	344–442			GCaMP6s	0	HeLa	[45]
	$LOV2_{404-546}$, C450A	KL	336–486			GCaMP6s	0.11	HeLa	[45]
	$LOV2_{404-546}$, G528A	KL	336–486			GCaMP6s	2.35	HeLa	[45]
	$LOV2_{404-546}$, I532E	KL	336–486			GCaMP6s	0.46	HeLa	[45]
	$LOV2_{404-546}$, N538E	KL	336–486			GCaMP6s	0.32	HeLa	[45]
	$LOV2_{404-546}$, I539E	KL	336–486			GCaMP6s	0	HeLa	[45]
LOVS1K	$LOV2_{404-546}$	KL	233–450			GCaMP6s	1.79	HeLa	[45,119]
hBACCS1	$LOV2_{404-538}$		347–448			Fluo-8 AM	~1.8	HEK293T	[46]
hBACCS2	2* $LOV2_{404-538}$		347–448			Fluo-8 AM	~3.0	HEK293T	[46]
dmBACCS2	2* $LOV2_{404-538}$		413–514			Fluo-8 AM	0	HEK293T	[46]
dmBACCS2	2* $LOV2_{404-538}$		413–514	<30		Fluo-4 AM	~1.6	S2	[46]
dmBACCS2 +dmOrai	2* $LOV2_{404-538}$		413–514	<30		Fluo-8 AM	~5.4	HEK293T	[46]
dmBACCS2 +dmOrai	2* $LOV_{404-538}$		413–514	<30	~50–60	Rhod-3 AM		HEK293T	[46]
dmBACCS2NS +dmOrai	2* $LOV2_{404-538}$ (N425S)		413–514	<30	<30	Rhod-3 AM		HEK293T	[46]
dmBACCS2VL +dmOrai	2* $LOV2_{404-538}$ (V416L)		413–514	<30	>480	Rhod-3 AM		HEK293T	[46]

GECA, genetically encoded Ca^{2+} actuator; h, *Homo sapiens*; dm, *Drosophila melanogaster*.
*Tested in HeLa, NIH3T3, COS-7, HEK293, HUVEC, hESCs, astrocyte, zebrafish embryo and mouse hippocampus.
** Tested in HEK293, COS-7, MEF, HIT-T15, S2 cells, hippocampal neurons, macrophage, dendritic cells, primary and leukemic T cells, and cancer cell lines derived from ovary, prostate, breast, skin, and brain, as well as in olfactory epithelium and lymphoid organs.
***unpublished data by *Ma G* and *Zhou Y*.

embryonic stem cells (hESCs) and astrocyte, as well as in zebrafish embryos and the CA1 hippocampus of mice [44]. When transiently expressed in cultured hippocampal neurons, OptoSTIM1 could trigger spatially-defined Ca^{2+} signals at selected regions of dendrites or soma that were exposed to blue light. OptoSTIM1-induced hippocampal Ca^{2+} influx was further shown to affect contextual fear memory formation and subsequent freezing behavior in mice [44]. This elegant proof-of-concept experiment points to the possibility of applying GECAs *in vivo* to modulate the emotion circuits and enhance the learning capacity of mammals [44,128].

4.2. Opto-CRAC and BACCS

In another optogenetic engineering strategy, STIM1ct fragments bearing the minimal ORAI activating domain were fused to the LOV2 domain (aa 404–546) from *A. sativa* phototropin 1 (designated as 'Opto-CRAC'; Fig. 2B and Table 1) [36,45]. The AsLOV2 module contains a PAS (Period-ARNT-Singleminded) core that binds flavin mononucleotide (FMN) [129–132]. The chromophore FMN is an endogenous cofactor abundantly available in mammalian cells and renders LOV2 sensitive to blue light. In the dark, the Jα helix tightly docks to the PAS core, and LOV2 has a high chance to mask the active site of fused effector domains due to steric hindrance (Fig. 2B). Upon blue light illumination, LOV2 rapidly forms a covalent linkage between the C4a position of the flavin cofactor and the thiol moiety on a conserved cysteine residue (C450). This photo-induced reaction triggers the unfolding of the C-terminal Jα helix to relieve the steric restrictions on the effector domain SOAR/CAD, and subsequently elicits Ca^{2+} flux through ORAI channels [45]. The LOV2-mediated photocycle is reversible owing to the hydrolysis

the effector domain, leading to the functional restoration of SOAR, a potent activator of ORAI Ca^{2+} channels on the plasma membrane.
(C). Representative examples of light-induced Ca^{2+} transients generated by OptoSTIM1 (upper panel; light stimulation at 470 nm programmed at 2 min ON + 14 min OFF) or Opto-CRAC (lower panel; light stimulation at 470 nm: 0.5 min ON and 2 min OFF) in HeLa cells when exposed to repeated light-dark cycles. The red GECI, R-GECO1.2, enabled the recording of the whole course of intracellular Ca^{2+} fluctuations. Blue bar indicates light stimulation at 470 nm with a power density of 40 μW mm^{-2}. Error bars denote s.e.m.
(D). Examples of photo-induced Ca^{2+} oscillations in HeLa cells expressing Opto-CRAC. HeLa cells were exposed to repeated blue light pulses, with the ON time fixed at 30 s while varying the interpulse intervals (top to bottom: 0.5, 1, 2, 3–4 min).

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of the cysteine-flavin bond in the dark at a timescale of dozens of seconds [38,40,45,133]. After screening over 150 constructs through optimization of LOV2, STIM1ct fragments and the linkers, He et al. identified one construct comprising $LOV2_{404-546}$ and $STIM1_{336-486}$ that underwent rapid translocation between the cytosol and plasma membrane in response to blue light illumination ($t_{1/2,on} = 6.8 \pm 2.3$ s; $t_{1/2,off} = 28.7 \pm 6.5$ s). Opto-CRAC and its variants generally have faster 'ON' and 'OFF' kinetics ($t_{1/2,on} = 10–36$ s; $t_{1/2,off} = 25–35$ s) compared with OptoSTIM1. The amplitude and speed of Ca^{2+} responses can be further fine tuned by varying the expression ratio of ORAI1 over Opto-CRAC, designing concatemers and ORAI1 + Opto-CRAC fusions, or tethering Opto-CRAC to PM (Table 1). Opto-CRAC has been successfully used to generate different temporal patterns of Ca^{2+} signals by varying the light pulse frequencies (Fig. 2D), to deliver both global and localized Ca^{2+} signals at user-defined spatial resolutions, and most importantly, to phenocopy the hallmark Ca^{2+}/NFAT-dependent physiological responses in a number of cell types [45].

With a similar strategy, Ishii et al. reported the development of a genetically engineered blue light-activated Ca^{2+} channel switch (BACCS), which is composed of a slightly truncated AsLOV2 (aa 404–538) and a STIM1ct fragment (aa 347–448) [46]. Three variants of BACCS were further designed: a dimeric form of BACCS (hBACCS2), a fusion protein of human ORAI1 and hBACCS2, and a *Drosophila* version of BACCS2 (dmBACCS2) that could only activate *Drosophila* Orai (dmOrai) but not human ORAI1. Among all the variants, dmBACCS2, when co-expressed with dmOrai, exhibited the highest Ca^{2+} amplitude and fastest kinetics. The ORAI1-hBACCS2 fusion protein, surprisingly, induced much less Ca^{2+} influx and took >1 min to reach the half-maximal Ca^{2+} response after blue light stimulation. BACCS is superior over an earlier version of LOV2-baesd GECA called LOVS1 K ($LOV2_{404-546}$–$STIM1_{233-450}$) [119]. LOVS1 K exhibited a lower dynamic range of Ca^{2+} response and failed to respond to blue light in primary cultured hippocampal neurons, HUVEC and NIH3T3 cells [44]. LOVSK1 also showed a high basal activity when expressed in HEK293T cells, as reflected by the constitutive NFAT nuclear translocation in the dark [46]. The inclusion of CC1 in LOVS1 K likely accounts for its low Ca^{2+} response and insufficient caging capability, because CC1 might compete with LOV2 for binding to SOAR/CAD and thus rendering the fusion protein less potent in activating ORAI1 channels.

LOV2-based GECAs have been applied to photo-induce Ca^{2+} influx and control Ca^{2+}-dependent biological processes both *in cellulo* and *in vivo*. They respond to blue light when expressed in cells of the immune system, neurons and cancer cell lines derived from various tissues [45,46]. The relatively small sizes of LOV2-based GECAs (1–3 kb) make them compatible with almost all existing viral packaging systems. Adenoviruses encoding BACCS have been successfully used to infect mouse olfactory epithelium to photo-manipulate the activities of olfactory sensory neurons [46]. Lentiviruses expressing Opto-CRAC or OptoSTIM1 could be used to transduce cells of the immune system [45] and the hippocampus of mice [44]. Furthermore, Opto-CRAC can be retrovirally expressed in murine bone marrow-derived dendritic cells (DCs) to induce Ca^{2+} influx, and act as a genetically encoded 'photoactivatable adjuvant' to promote DC maturation and boost antigen-specific immune response both *in vitro* and *in vivo* [45]. This exciting progress attests to the feasibility of combining optogenetics with immunoengineering to develop light-controllable, smarter immunomodulatory therapeutics [36].

4.3. Practical considerations in the choice of GECAs

The choice of genetically encoded Ca^{2+} actuators (GECAs) may vary depending on the cell type, fluorescence imaging system and Ca^{2+}-dependent processes to be studied. A brief summary of biophysical characteristics of GECAs engineered from CRAC channels is listed in Table 1. In general, the following factors need to be taken into account during experimental design.

1. *Compatibility with existing Ca^{2+}-sensitive dyes and GECIs*. Since both LOV2- and CRY2-based GECAs have activation spectra centered around 400–500 nm, Ca^{2+}sensitive dyes excited in this range, such as Fluo-4, can only be used to monitor the 'ON' phase of photo-induced Ca^{2+} responses. Similarly, GECIs derived from BFP, CFP, GFP and YFP are incompatible with the recording of the 'OFF' phase of Ca^{2+} signals. The ratiometric Ca^{2+} indicator, Fura-2 AM, is suitable for recording both the onset and decay of Ca^{2+} signals by switching on and off the light source. However, the use of Fura-2 tends to cause a drift in the baseline because the excitation at 380 nm overlaps with the photoactivation window of optoSTIM1 or Opto-CRAC [45], albeit to a much lesser extent when compared with blue or green light. Red-color GECIs, particularly R-GECO1, RCaMP, R-CEPIA and their variants [6,10,134,135], are most compatible with optogenetic applications. R-GECO1 has a higher affinity for Ca^{2+} (K_d: 449 nM *vs* 1–4 μM) and exhibits a larger dynamic range than RCaMP (F_{max}/F_{base}: 2.5 *vs* 1.3–2.0 in HEK cells), but it shows significant photoactivation and may cause false-positive artefacts when excited by blue or green light [6,134]. R-GECO1.2 is an improved version of R-GECO1 with higher fluorescence signal but reduced artefacts [134]. Using relatively low-intensity blue light (1–10 $\mu J/\mu m^2$) that was powerful enough to activate Opto-CRAC, we did not observe obvious artefacts associated with R-GECO1.2 during Ca^{2+} imaging [45]. Taken together, to avoid potential conflicts with the activation wavelengths of GECAs, we strongly recommend the use of red Ca^{2+}-responsive dyes, R-GECO1.2, RCaMP or further red-shifted GECIs for measurements of Ca^{2+} dynamics.
2. *Kinetic and spatial profiles of the delivered Ca^{2+}signals*. CRY2-based OptoSTIM1 has a slower activation and substantially prolonged deactivation speed than LOV2-based Opto-CRAC or BACCS2 (Table 1). The onset of hBACCS2-elicited Ca^{2+} influx often delays by 5–10 s upon light stimulation. The deactivation kinetics largely follows the order of OptoSTIM1 « hBACCS2 < dmBACCS2 < Opto-CRAC. For experiments requiring sustained and strong Ca^{2+} signals, OptoSTIM1 is a good choice since it can produce robust Ca^{2+} signals that may last for ~10 min with a single pulse of blue light (Fig. 2**C**). Under similar experimental conditions, we observed that Opto-CRAC could generate six times more Ca^{2+} transients than OptoSTIM1 did in HeLa cells (Fig. 2C), thus placing Opto-CRAC as an ideal GECA to generate repetitive Ca^{2+} signals to mimic physiologically-relevant Ca^{2+} oscillations in mammalian cells (Fig. 2D). All the existing GECAs take advantage of cytosolic fragments of STIM1 that are able to constitutively activate ORAI1 channels without forming puncta at ER-PM junctions. GECAs that are capable of generating Ca^{2+} microdomains at membrane contact sites [136,137] are yet to be developed. The recent development of a light-inducible ER-PM tethering tool (termed 'LIMETER') [110] might provide a potential solution to fulfill this unmet need.
3. *Endogenous levels of ORAI channels and heterogeneity of Ca^{2+}dynamics*. Since both OptoSTIM1 and Opto-CRAC rely on the endogenous ORAI channels to conduct photo-inducible Ca^{2+} influx, the expression levels of ORAI in the assayed cells will affect the amplitude and frequency of Ca^{2+} signals. In addition, following transient transfection, the variable expression of GECAs among cells may further contribute to the heterogeneity of photo-induced Ca^{2+} responses. This complication can be circumvented by generating stable cell lines or transgenic mouse strains. In cell types with very low or no detectable expres-

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sion of ORAI, two strategies can be used: (i) expressing the ORAI1:hBACCS2, or ORAI1:Opto-CRAC fusion constructs; (ii) co-expressing ORAI1 with Opto-CRAC, or dmBACCS2 with dmOrai, by using bicistronic expression systems.

4. *Dark activation and potential perturbations to host physiology*. Given that expressing STIM1ct fragments alone may cause varying degrees of constitutive Ca^{2+} influx [105–109], high expression of GECAs might cause a basal $[Ca^{2+}]_{cytosol}$ increase even in the dark, and thus, perturb Ca^{2+}-dependent reactions in the host cells. This 'dark activation' problem is most evident when co-expressing ORAI1 with OptoSTIM1 or expressing LOVS1K alone [44–46]. In addition, because OptoSTIM1 contains an SxIP EB1-binding motif, it shows light-dependent dynamic movement with the microtubule plus ends [44]. It remains unknown how this might affect the dynamics of cytoskeleton and cell migration of the host cells. This would be less of an issue with Opto-CRAC or hBACCS2 since the EB1-binding motif is not included in the constructs. Finally, because STIM1 has been reported to inhibit L-type voltage-gated Ca^{2+} channels through direct interactions [138,139], we sound a note of caution to use STIM1-derived GECAs in excitable tissues.

5. Conclusions and future directions

The optogenetic applications discussed above have impressively demonstrated the general applicability of GECAs in mammalian cells. GECAs, particularly those engineered from *bona fide* Ca^{2+} channels, offer untapped potentials for remote and non-invasive control of Ca^{2+} signaling with subcellular precision at timescales of seconds to minutes. The combined use of GECAs and GECIs makes it possible to simultaneously perturb and observe intracellular Ca^{2+} signals, and offers novel approaches to aid the screening of chemical modulators for Ca^{2+} channels in the near future. These tremendous advances will greatly facilitate the study of Ca^{2+} signaling in a more quantitative and predictable manner, thereby enabling the dissection of causal relationships between Ca^{2+} signals and cellular or animal behaviors.

GECAs can be applied to achieve remote neuromodulation or optogenetic immunomodulation when integrated into neurons or immune cells. However, the *in vivo* organismal application of existing GECAs is hampered by the inability of blue light to penetrate deep into the biological tissues. For neuromodulation, the use of invasive indwelling optical fibers or implantable miniature light-emitting diode may partially solve the issue. In addition, transcranial photoactivation of opsin-derived photoreceptors now becomes feasible by red-shifting their spectral sensitivity toward the red or far red range [140]. However, these approaches remain largely impractical for tissues deeply buried within the body or cells that are constantly migrating in the circulation system (*e.g.*, DCs or T lymphocytes). To remove this roadblock, we propose herein two potential strategies to shift the photosensitive window of GECAs toward the near infrared (NIR) range. NIR light is able to penetrate much deeper into biological tissues (up to 1–2 cm) compared to visible lights [36,141–143]. The first approach involves the use of cell-targeting upconversion nanoparticles (UCNPs), which act as nanotransducers to convert (NIR) light to visible lights emitting in the range of 400–500 nm [143]. We have successfully demonstrated the use of Opto-CRAC, in conjugation with UCNPs, to achieve *in vivo* NIR photoactivatable Ca^{2+} influx without causing significant heat generation [45]. The second approach requires the substitution of CRY2 or LOV2 in GECAs by NIR light-controllable optogenetic modules, such as the light-inducible heteromerization system made of BphP1 and PpsR2 [144]. Finally, to supplement the existing GECAs, optogenetic actuators tailored for the manipulation of organellar Ca^{2+} signaling in compartments, such as ER, lysosome, Golgi and mitochondria, are yet to be developed.

Conflict of interest

The authors state no conflict of interest.

Acknowledgements

This work was supported by grants from the Leukemia & Lymphoma Society (LLS3013-12 to Y.Z.), the National Natural Science foundation of China (NSFC-31471279 to Y.W.), the Recruitment Program for Young Professionals of China (to Y.W.), the Program for New Century Excellent Talents in University (NCET-13-0061 to Y.W.), the Welch Foundation (BE-1913 to Y.Z.), the American Cancer Society (RSG-16-215-01-TBE to Y.Z.) and the National Institutes of Health (R01GM112003 to Y.Z.).

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Please cite this article in press as: G. Ma, et al., Optogenetic toolkit for precise control of calcium signaling, Cell Calcium (2017), http://dx.doi.org/10.1016/j.ceca.2017.01.004

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