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COMMUNICATION

Luminescent Molecules towards Precise Cellular Event Regulation

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A unique lanthanide complex which responds to near-infrared (NIR) stimulation was developed for remote regulation of cellular events. This molecule can be localized specifically on cell surface. Upon NIR stimulation, strong emission of the complex can successfully modulate activities of light-gated membrane channels and regulate the ion flux *in vivo*.

Cell is known to have complex and heterogeneous structure. The membrane on its surface has a fluid and dynamic nature, which maintains the essential differences between cytosol and extracellular environment. It has been well recognized that a variety of crucial cellular activities such as signal transduction, substance transportation, enzymatic activity etc., are critically dependent on cell membrane.[1] The misregulation of membrane-associated activities is involved in the progression of various degenerative diseases including cancer, atherosclerosis, and neurological disorder.[2] Hence, the precise regulation of dynamic membrane-associated processes would promote better understanding of fundamental physiological processes in living cells. More importantly, it could also facilitate the development of therapeutic strategies for the treatment of various diseases. By right, chemical and genetic perturbation have been the major approaches to the studies of membrane-associated processes in biological systems.[3] Although working successfully in principle, these strategies exhibited limited spatial and temporal resolution, which remains an inherent shortcoming for systematic analysis of dynamic biological phenomena due to the highly complex and heterogeneous nature of cells and living organisms[4].

Recently, optical manipulation of cell activities has gained considerable attention. As a unique strategy based on light stimulus, such high resolution optical control exhibits promising advantages to enable spatial and temporal manipulations of dynamic processes of protein activities and signaling pathways both *in vitro* and *in vivo*.[5] However, most studies on optical regulation of membrane activities were achieved merely by using UV or visible light, which may likely raise the concerns of potential photo-damage, light toxicity, limited deep tissue penetration as well as inherent absorption or scattering caused by endogenous biological molecules.[6] Therefore, simple and specific light-mediated strategy that allows remote manipulation of membrane activities *in vitro* and *in vivo* through non-invasive and tissue-penetrable light irradiation remains a technical challenge. Recently, NIR light-responsive nanoparticles have been reported to regulate membrane-associated processes within deep penetration and minimum light toxicity.[5a, 5c-e, 5g, 5h, 7] Despite their initial success, the strategy may raise concerns associated with the use of nanomaterials such as their size, non-homogeneous composition, potential toxicity, limited batch-to-batch reproducibility etc.[8] Simple and robust small-molecule alternatives with properties such as tunable emissions, deep penetration and good biocompatibility would be highly desirable and may be useful for accurate optical control of cellular activities in living system.

As a promising alternative, small molecule complexes would exhibit promising advantages for their flexibilities in both chemical structures and functions.[9] Basically, versatile desired properties such as strong luminescence, less photobleaching, long lifetime, as well as good biocompatibility can be precisely fine-tuned through simple modifications of their ligands.[10] In addition, small molecule complexes would allow easy and accurate characterization of their composition from single molecule level. More importantly, through rational molecule design, small molecule complexes can respond to deeper tissue penetrating NIR light and exhibit tunable emissions which suggest the potential prospects of these simple and unique complexes towards optical regulation of cellular events[11].

Herein, we introduce a simple and effective approach based on small molecule complex for remote regulation of membrane channel protein. Generally, we first established simple and stable metal complex which have promising optical

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properties such as bright emission, two-photon imaging properties. To allow accurate modulation of the light-gated membrane ion channel, the complex was designed to localize on cell membrane through well-established bioorthogonal reaction (e.g. click reaction). Typically, we introduced N_3-tagged glycans to cell surface through intrinsic metabolic pathways by simply adding a monosaccharide precursor, peracetylated N-azidoacetylmannosamine ($Ac_4ManNAz$) to cell culture medium. In addition, we will further engineer the complex with alkyne moiety on the ligand. To minimize the potential damage to cells, a copper-free click reaction based on the dibenzocyclooctyne-conjugated complex as a bioorthogonal linkage will be used to covalently attach the complex on cell surface. As such, upon NIR light treatment, the complex on cell membrane would produce converted emission, activating light-responsive regulatory proteins on cell membrane and facilitate the regulation of subsequent cell events both in vitro and in vivo.

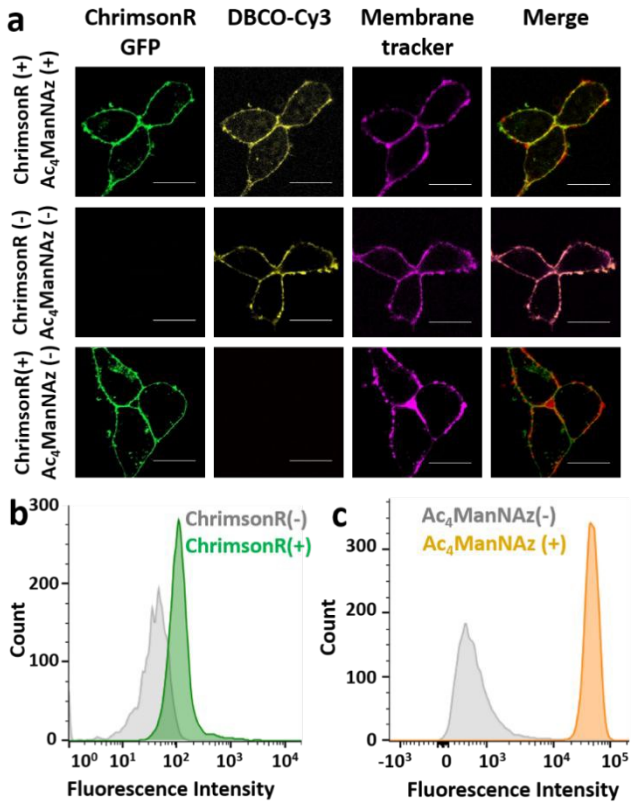

Fig.1 a) Confocal image of HEK293 cells stained with DBCO-Cy3(10μM) and membrane tracker(10μM) scale bar = 20 μm. b) FCM analysis of ChrimsonR expression in HEK293 cells through marker protein GFP. GFP(λ_{ex}=488 nm, λ_{em}= 530/50 nm),DBCO-Cy3(λ_{ex}=543 nm, λ_{em}=580/50 nm), membrane tracker (λ_{ex}=633 nm, λ_{em}=670/50 nm). c) FCM analysis of DBCO-Cy3(10μM) labelled HEK293 cells after treatment with or without Ac4ManNAz (50 μM).

To accurately manipulate membrane channel events, a light-sensitive ion channel ChrimsonR was incorporated onto cell surface in order to induce the influx of ions such as signaling cation Ca^{2+}. The successful incorporation of ChrimsonR on cell surface was monitored *via* the appearance of fluorescence signal from marker protein (GFP) through confocal imaging and flow cytometry (FCM) (Fig.1). In addition, similar cell staining was observed through a well-established membrane tracker CellMask DeepRed, suggesting the successful expression of light-sensitive channel on cell surface. Furthermore, in order to induce NIR light controlled manipulation of membrane channel activities, lanthanide complex (e.g. Eu(III) complex) was utilized as light transducer mainly due to its two-photon optical properties.

In order to promote the localization Eu(III) complex on cell membrane, ring strained alkyne DBCO moiety was conjugated with the ligand molecule 1,10-Phenanthroline-5-amine (Fig.S1, Fig.S2 and Fig.S3, ESI†). Owing to the promising properties of the beta-diketone antenna ligand, the resulting Eu(III) complex (Eu-DBCO) (Fig.S4, ESI†) exhibited stable, strong fluorescence emission at ~615 nm (τ 0.27ms) with (Fig.S5,S6, ESI†) upon two-photon excitation condition (720 nm), which matched very well with the absorption maxima of ChrimsonR[6c]. In addition, it is stabile (Fig.S5, ESI†) under physiological condition suggesting the potential to modulate channel activity of ChrimsonR in biological systems.

To accurately modulate the light-gated ion channel, we localized Eu complex on cell surface. Firstly, cell surface glycans were covalently labeled with azido group via native metabolic biosynthesis pathways[12]. To introduce azide onto cell membrane, $Ac_4ManNAz$ precursor was incubated with cells. Then, a copper-free click reaction between DBCO-conjugated dye (for instance DBCO-conjugated Cy3 or Eu complex) and cell

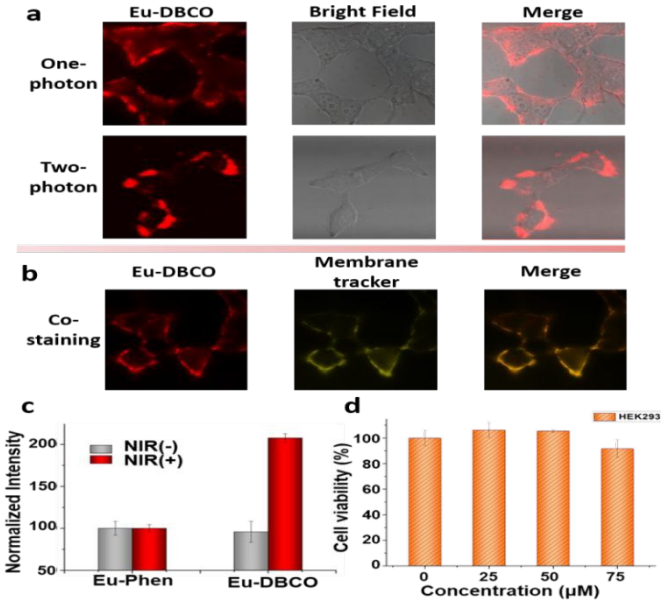

Fig.2 a) Fluorescence images of HEK293 cells labelled with Eu-DBCO (60μM) (λ_{ex}=350nm, one-photon condition; λ_{ex}=720nm, two-photon condition). b) Fluorescence images of azide expressed HEK293 cells labelled with Eu-DBCO(60μM) (Eu-DBCO: λ_{ex}=350nm, λ_{em}=610/50nm, membrane tracker(10μM): λ_{ex}=633 nm, λ_{em}=670/50nm). c) Membrane channel activity manipulated through NIR illumination: fluorescence intensity of Ca^{2+} indicator (10μM) in cells treated with Eu(III) complexes before and after NIR light stimulation. Ca^{2+} indicator: λ_{ex}=561nm, λ_{em}=610/75nm. d) Cell viability of HEK293 cells treated with Eu-DBCO of various concentration.

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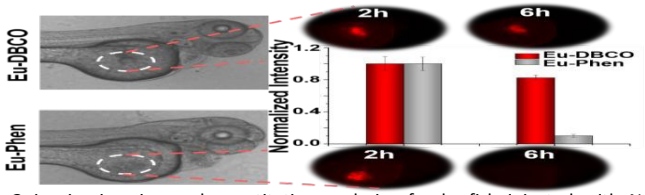

Fig.3 *in vivo* imaging and quantitative analysis of zebrafish injected with N_3 labelled cells and Eu(III) complex (60μM, top: Eu-DBCO, bottom: Eu-Phen, Eu-DBCO and Eu-Phen: λ_{ex}=350nm, λ_{em}=610/50nm).

surface azide was performed. The cell surface labeling was observed through confocal microscopy and flow cytometry. As observed in Fig.1, bright yellow signal of DBCO-Cy3 can be incubated with Ac_4ManNAz. In the meantime, similar staining pattern of cell surface was obtained by well-established cell membrane probe. In contrast, no obvious fluorescence signal was detected from cell which was cultured in the absence of Ac_4ManNAz, suggesting the successful conjugation of azide and DBCO-Cy3 on cell surface. In addition, flow cytometry studies also confirmed the increased signal of DBCO-Cy3 (Fig.1) from Ac_4ManNAz treated cells compared to cells without Ac_4ManNAz treatment. Besides, cell viability assay (Fig.S7, ESI†) revealed that, no obvious toxicity was observed towards HEK293 cells under the current conditions suggesting the feasibility of successful conjugation of functional molecules on cell surface through metabolic biosynthetic pathways. Secondly, the copper-free reaction between cell-surface labelled azide and ring-strained alkyne (DBCO moiety) of Eu-DBCO allowed successful anchoring of Eu complex on cell membrane. It can be seen that red fluorescence signal of Eu-DBCO (Fig.2 and Fig.S8, ESI†) appeared on the surface of HEK293 cells which had been incubated with Ac_4ManNAz. In addition, the obvious overlap (Fig.2) between Eu-DBCO and membrane tracker confirms the localization of Eu complex on cell membrane. In contrast, no obvious fluorescence signal was observed on the membrane of cells cultured without Ac_4ManNAz or azide tagged cells incubated with control molecule (Eu-Phen) without DBCO moiety (Fig.S8, ESI†). These results suggested the successful linkage of luminescent molecules (Eu-DBCO) on the cell surface by means of cell's intrinsic metabolic biosynthetic mechanism.

To evaluate the potential application of Eu(III) complex for precise regulation of membrane-associated events, NIR light was applied to irradiate the Eu(III) complex labelled on the surface of transfected cells. In the presence of NIR illumination, emission of the complex was utilized to stimulate the red light-sensitive membrane channel and induce cation influx (e.g. Ca^{2+}) into the intracellular compartment. In order to monitor the fluctuation of intracellular Ca^{2+}, a commercial Ca^{2+} fluorescent probe (Rhod-3 AM) was used to visualize the change of Ca^{2+} concentration inside cells. Upon treatment of NIR light stimulation, ChrimsonR expressing cells (with Eu-DBCO labelled on their surface) exhibited obvious increase in the intracellular fluorescence signal, while no obvious enhancement in Ca^{2+} probe signal was observed in cell treated with control molecule (Eu-Phen) and NIR illumination (Fig.S9, ESI†). In addition, quantitative analysis (Fig.2) and membrane potential study (Fig.S10, ESI†) confirmed similar enhancement in intracellular Ca^{2+}. The elevated intracellular Ca^{2+} revealed that membrane-localized Eu(III) complex could be utilized as a mediator to accurately manipulate the cation flow across cellular membrane and induce downstream biological event(Fig.S11, ESI†). Moreover, cell viability assay revealed that no obvious toxicity to cells under similar condition of membrane channel manipulation (Fig.2), suggesting its good biocompatibility.

Furthermore, we also evaluate whether precise manipulation of membrane-associated activity can be induced through red lanthanide emission upon NIR light treatment. To this end, confocal microscopy was used to monitor the change of Ca^{2+} inside zebrafish. Generally, ChrimsonR transfected cells (labelled with N_3) with calcium probe (Rhod-AM3) were implanted into the yolk sac of zebrafish larvae at 48 hours post-fertilization. Then, Eu-DBCO was injected into the yolk sac of larvae to facilitate the localization of the complex on cell surface. The obvious fluorescence signal in the abdominal area suggested the successful injection of Eu(III) complex into the larvae (Fig.3). Upon 6h clearance, obvious fluorescence signal in larvae injected with Eu-DBCO could still be observed. However, negligible signal could be visualized in larvae injected with control molecule Eu-Phen without DBCO moiety. Similarly, the effective localization of Eu-DBCO was also revealed by quantitative analysis (Fig.3). Higher mean fluorescence intensity in zebrafish larva injected with Eu-DBCO was observed after 6 h clearance. The obvious difference in labelling effect suggested that metabolic glycan labelling could effectively promote the accumulation of Eu-DBCO under *in vivo* conditions.

Moreover, to remotely manipulate the membrane channel activity NIR light (e.g. 720nm) was applied to irradiate the larvae. The Ca^{2+} flux in zebrafish was monitored by using observing the fluorescence signal of Rhod-AM3. As illustrated in Fig.4, after NIR light treatment, fluorescence enhancement of Ca^{2+} probe can be observed in the larvae which were injected with Eu-DBCO. In contrast, little fluorescence change was observed in the larvae in the control group (Fig.4 Eu-Phen). Additionally, the survival rate (Fig.4b) of zebrafish larva treated with Eu-DBCO

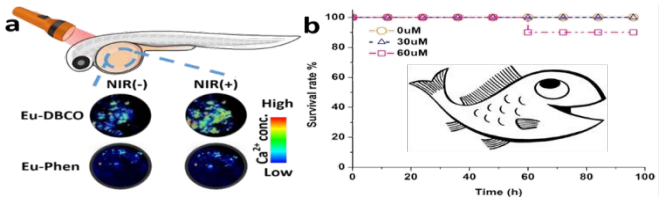

Fig.4 a) Ca^{2+} imaging in zebrafish labelled with Eu(III) complex with or without NIR (720 nm) light treatment, Ca^{2+} indicator(10μM): λ_{ex}=561nm, λ_{em}=610/75nm. b) Survival rate of zebrafish larva after treatment with **Eu-DBCO** of various concentrations (each concentration n=10).

was monitored for 96 hours, revealing that no obvious toxicity to the larva under similar condition of membrane channel activity manipulation. These results demonstrated that the Eu-DBCO labelled in the larvae could successfully modulate the ion channel activity induced by the NIR light treatment under *in vivo* settings.

To summarize, we reported a simple yet effective approach based on small molecule complex for remote regulation of cellular event. Firstly, a simple metal complex which respond to NIR stimulation was established. In addition, the complex can be specific localized on cell surface to facilitate accurate modulation of the light-gated membrane ion channel. With NIR stimulation, the activity of membrane channel can be remotely manipulated and regulate the ion flux in both live cells and animals. Such strategy exhibited promising potential to remotely manipulate biological events under in vivo settings, which is beneficial to better understanding of fundamental physiological processes and promote the development of therapeutic strategies for the treatment of various pathological disorders in the long run.

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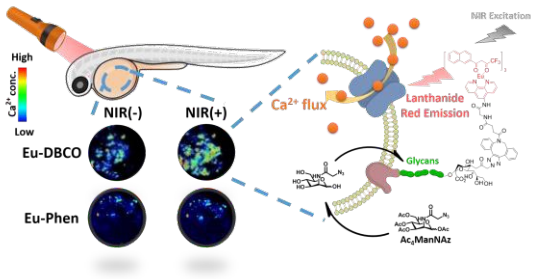

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