細胞膜非透過性薬剤の光照射を用いるエンドサイトーシス非依存的細胞内送達

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Light-controlled Endocytosis Independent Delivery of Cell-Impermeable Therapeutic Compounds

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The delivery of negatively charged drugs like small interfering RNAs (siRNAs) across cytoplasmic membrane are extremely difficult due to the size, hydrophilicity, and electrostatic repulsion. Nevertheless, in the treatment of cancer, neurodegenerative diseases, and some rare diseases, such cell impermeable drugs have great potential. It can be expected that the increased cell uptake of negatively charged drugs will dramatically promote the development of medicine and pharmacy.

Lipid-based and polymer-based nanoparticles for oligonucleotide drugs delivery are well studied and applied to clinical trials. Besides, cell penetrating peptides are powerful tools for the functionalization of various nano carriers. Direct membrane disruption by using light-driven molecular motor has been successfully applied to artificial membrane penetration of small molecules. From our point of view, the study of direct membrane penetration method for cell impermeable drug delivery still has a large space.

We developed a light-driven structure changeable compound **H** which promoted the penetration of negatively charged cell impermeable fluorescent dye **SCy-5** towards living cells (Figure 1). The presence of compound **H** and light irradiation significantly enhanced the fluorescence (FL) intensity of cell impermeable **SCy-5** inside of A549 cells. As expected, without light irradiation, the treatment of compound **H** cannot promote the penetration of **SCy-5**. It indicates that compound **H** shows a potential for the non-endocytosis delivery of oligonucleotide. Compound **H** also successfully enhanced the penetration of fluorescein-labeled peptides and peptide drugs whose molecular weight is over 3000. The delivery efficiency of antisense oligonucleotide (ASO) was enhanced upon treatment of compound **H** and light irradiation.

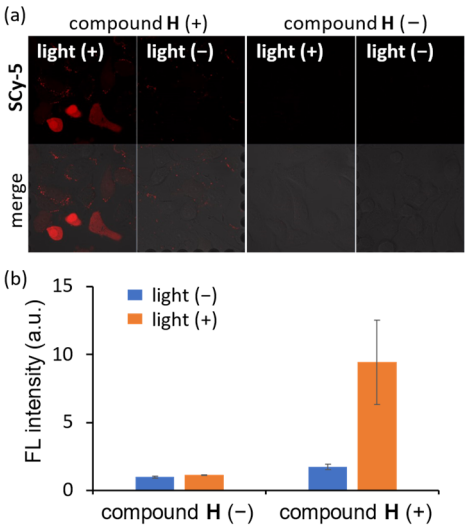

Figure 1. (a) Confocal microscopy imaging of A549 cells incubated with **SCy-5** in the presence or absence of compound **H** and light irradiation. (b) The FL intensity comparison of different cell samples in Figure 1a.