EXPLOR: Exosome Engineering for Drug Delivery

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In 2030, personalized medicines will be commonly prescribed to patients. Doctors will be able to simply isolate extracellular vesicles (EVs) from patients' blood, and engineer them to deliver protein drugs using exosomes for protein loading via optically reversible protein–protein interaction (EXPLOR) technology. Because a patient's body does not recognize such EVs as foreign bodies, the drug within the EVs can avoid the immune response and be delivered efficiently to diseased parts of the body. Patients will thus be able to easily take personalized biopharmaceuticals that have been tailor–made specifically for them.

● We have recently developed EXPLOR, a novel extracellular vesicle–based protein carrier that is capable of delivering therapeutic proteins efficiently in vitro and in vivo using active targeting induced by light stimulation. The technique allows for an endogenous active protein–loading process instead of on exogenous passive loading one. Therefore, not only does this technology eliminate the need for the separation and purification of recombinant proteins, but also most of the intracellular proteins could be targets for high–efficiency, EXPLOR–based therapeutics. We expect that EXPLOR will overcome the limitations of previous protein drug delivery methods, ushering in a new paradigm for biopharmaceuticals in the future.

● Recently, as the importance of biopharmaceuticals has increased, researchers have been actively developing drug delivery systems capable of efficiently delivering protein drugs, which account for the majority of biopharmaceuticals, to specific target cells in the body. In particular, great efforts are being made in the pharmaceutical industry to deliver biologics such as proteins using nanoparticles as next–generation drugs. With current technologies, however, it has been difficult to maintain the biological activity of protein drugs until the time they reach the target cells, and there have been immune reaction problems, making it difficult to put protein drugs into practical use.

● To address the present limitations of biopharmaceuticals, we combined extracellular vesicles, which are naturally produced by the body's cells, with the principle of light–induced protein–protein interaction to develop a new drug–producing platform. Specifically, Cryptochrome 2 (CRY2), a photoreceptor of Arabidopsis thaliana that is capable of binding with CRY–interacting basic–helix–loop–helix 1 (CIB1) by blue light illumination, was conjugated to an intracellular protein drug, and CD9, one of the extracellular vesicle–enriching proteins, was conjugated to CIBN (a truncated form of CIB1) . By expressing these engineered proteins in live cells, the intracellular therapeutic protein can be docked into the extracellular vesicles through blue light illumination and the natural process of exosome biogenesis. The protein can also be detached from the CD9–conjugated CIBN by eliminating the light source, making it possible to release the therapeutic protein into the intraluminal space of the exosomes and efficiently reaching the cytoplasmic compartment of the target cell.

EXPLOR technology showed a protein–loading efficiency in extracellular vesicles of up to 40–times higher than previous protein–loading methods, such as the passive loading of recombinant proteins into extracellular vesicles ex vitro or the conjugation of cytosolic protein to the exosomal membrane. Moreover, it showed not only a high efficiency of cytosolic protein delivery but also the successful delivery of functional proteins, such as mCherry, Cre recombinase, and super–repressor IkB, into neurons in mice as well as cancer cells.

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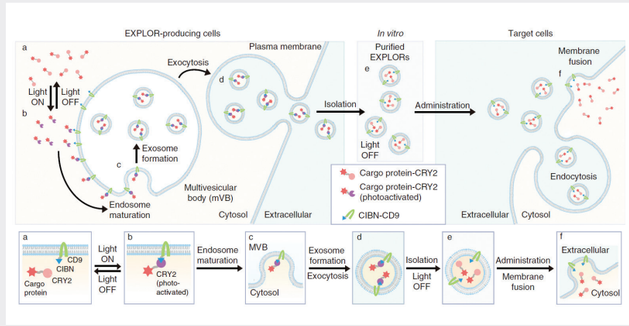

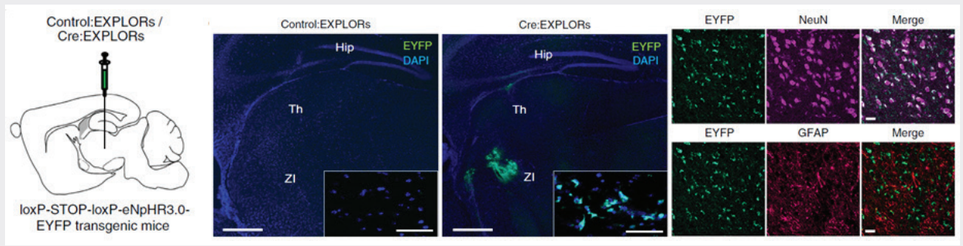

Figure 1. Explor: Exosome Engineering for Drug Delivery

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Research Outcomes
Yim, N. et al., "Exosome engineering for efficient intracellular delivery of soluble proteins using optically reversible protein–protein interaction module," Nature Communications , 7:12277 doi: 10.1038/ncomms12277 (2016).