Development of a novel carrier for selective mitochondrial delivery

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Mitochondrial dysfunction is implicated in a variety of diseases, however, lack of delivery system to mitochondria is a rate limiting step for rational medical therapies for these diseases. The ultimate nanotechnology is expected to control intracellular trafficking of proteins and/or nucleic acids to mitochondria. We previously reported that MITO-Porter, a novel liposome-based nanosystem that can deliver macromolecules to mitochondria via a membrane fusion mechanism. We succeeded in screening fusogenic lipid compositions for MITO-Porter to fuse with mitochondrial membrane with a help of octaarginine. The MITO-Porter could deliver green fluorescent protein (GFP), model macromolecule, to intra-mitochondrial compartment via a fusion mechanism in living HeLa cells. Although the MITO-Porter could deliver macromolecules to mitochondria, most carriers remained in cytosol, which suggested that our carrier have no selective mitochondrial targeting activity. As well known, mitochondrial targeting signal peptide (MTS) makes it possible to deliver even exogenous proteins to mitochondria selectively, however this strategy is severely limited by the size of the cargo. We considered that combination of our membrane fusion system and MTS could achieve selective delivery independent of size and physical property of the cargo. In the present study, we constructed MTS-modified MITO-Porter and evaluated mitochondrial targeting activity of the carrier. When MTS-modified MITO-Porters were added to the homogenate of HeLa cells, the MTS-modified MITO-Porters were delivered to mitochondria more efficiently than non-modified ones. Furthermore, intracellular observation of the carriers performed by confocal laser scanning microscopy. Our novel system can be a promising device for a mitochondrial disease therapy.