Faculty of Pharmaceutical Sciences

Validation of therapeutic strategies using mitochondrial drug delivery systems

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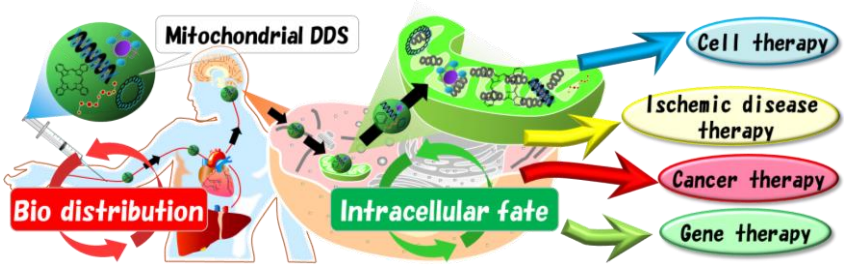

It is now well accepted that mitochondrial dysfunctions are implicated in a variety of diseases, including neurodegenerative diseases, cancer and a variety of inherited mitochondrial diseases. Because of this, mitochondria represent a promising therapeutic drug target, and mitochondrial therapy would be expected to be useful for the treatment of such diseases. To achieve such an innovative therapy, it will be necessary to deliver therapeutic agents to the interior of mitochondria. A number of mitochondrial drug delivery systems (DDS) have been reported during the past decade, but only a limited number of these are actually available in mitochondrial therapy. This is because these strategies face many problems including cell internalization, limitations in the size and the physicochemical properties of the cargos, modification of a functional device, and the denaturation of the cargoes. We recently reported on the development of a MITO-Porter, a liposome-based carrier that can be used to introduce macromolecular cargos into mitochondria *via* membrane fusion (Y. Yamada et al, *Biochim Biophys Acta* 1778: 423-432 (2008), Y. Yamada et al, *Adv. Drug. Deliv. Rev.* 154-155:187-209 (2020)). We are hopeful that this MITO-Porter can be used to deliver a wide variety of carrier-encapsulated molecules to mitochondria. Based on our progress to date regarding the use of the MITO-Porter for mitochondrial DDS, we are currently in the process of expanding collaborative research targeting mitochondria with researchers and clinicians from various fields. In this presentation, we summarize the current state of mitochondrial DDS focusing on our research and show some examples of the use of mitochondrial DDS for regulating mitochondrial function. These studies include the fields of mitochondrial gene therapy, with a focus on mitochondrial RNA therapy in mitochondrial diseased cells using a MITO-Porter. These recent studies demonstrated that the MITO-Porter system could be useful for the delivery of all three types of RNA encoded by mtDNA: tRNA (E. Kawamura et al, *Mol. Ther. – Nucleic Acids* 20: 687-698 (2020)), mRNA (Y. Yamada et al, *Sci. Rep.* 10: 7511 (2020)) and rRNA (Y. Yamada et al, *Mitochondrion* 55: 134-144 (2020)). We are currently in the process of studying mitochondrial DDS that are directed toward the development of mitochondrial nano medicines. We hope that these studies will open new research areas in mitochondrial DDS and will have a significant impact on the medical and life sciences.

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