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Mitochondria Imaging, Sensing and Photo-modulation[1]

KEVIN BELFIELD, New Jersey Institute of Technology

Mitochondria are essential targets for study and treatment of mitochondrial dysfunction diseases such as cancer, cardiovascular and neurodegenerative diseases. Chemoresistance is one of the major challenges for cancer treatment, more recently ascribed to defective mitochondrial outer membrane permeabilization (MOMP), significantly diminishing chemotherapeutic agent-induced apoptosis. However, gaining access to the mitochondria for either long term imaging or for selective manipulation is challenging, as the hydrophobic inner membrane is a barrier limiting diffusive transport. Mitochondria penetrating peptides (MPPs) are short peptides that can be uptaken by mitochondria. We developed a novel MPP probe and evaluated its use in long term mitochondrial imaging and trafficking. The novel MPP we designed and prepared contained a six amino acid sequence, D-Argine-Phenylalanine-D-Argine-Phenylalanine- D-Argine-Phenylalanine-NH2 (rFrFrF), which was subsequently conjugated to the commercially available 6-(tetramethylrhodamine-5-(and-6)-carboxamido)hexanoic acid (TAMRA) fluorophore. The result is a novel mitochondria penetrating peptide (TAMRA-MPP). This bioconjugate exhibited low cytotoxicity, high biocompatibility, and long term persistence in mitochondria. This TAMRA-MPP conjugate is a potentially valuable long-term mitochondria tracking probe for monitoring mitochondria distribution, activities, fission, and fusion. A boron-dipyrromethene (BODIPY) chromophore-based triarylsulfonium photoacid generator (BD-PAG) was also created, and its ability to target mitochondria was demonstrated with the aim to regulate mitochondrial pH and further depolarize the mitochondrial membrane. Cell viability assays were employed to assess the BD-PAG's dark biocompatibility, and live cell fluorescence bioimaging indicated selective targeting of and accumulation in the mitochondria. A number of assays were conducted that confirmed the ability of photoactivation of BD-PAG to modulate mitochondrial pH, effecting mitochondrial membrane depolarization. Investigations with a common chemotherapeutic agent in which certain tumors develop resistance to chlorambucil was studied in combination with BD-PAG, and its photoactivation, revealed a new strategy in chemoresistance suppression.

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