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Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online

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Cite this: Org. Biomol. Chem., 2021, 19, 801

A matrix targeted fluorescent probe to monitor mitochondrial dynamics†

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Mitochondria are an indispensable organelle for energy production and regulation of cellular metabolism. The structural and functional alterations to mitochondria instigate pathological conditions of cancer, and aging-associated and neurodegenerative disorders. The normal functioning of mitochondria is maintained by quality control mechanisms involving dynamic fission, fusion, biogenesis and mitophagy. Under conditions of mitophagy and neurodegenerative diseases, mitochondria are exposed to different acidic environments and high levels of reactive oxygen species (ROS). Therefore stable molecular tools and methods are required to monitor the pathways linked to mitochondrial dysfunction and disease conditions. Herein, we report a far-red fluorescent probe (Mito-TG) with excellent biocompatibility, biostability, photostability, chemical stability and turn on emission for selective targeting of the mitochondrial matrix in different live cells. The probe was successfully employed for monitoring dynamic processes of mitophagy and amyloid beta (Aβ) induced mitochondrial structural changes.

Received 21st October 2020,
Accepted 22nd December 2020

DOI: 10.1039/d0ob02128h

rsc.li/obc

Published on 22 December 2020. Downloaded by Jawaharlal Nehru Centre for Advanced Scientific Research on 4/20/2021 8:31:21 AM

Introduction

The mitochondrion is a vital organelle for the production of biological energy in the form of adenosine triphosphate (ATP) through cellular metabolism, and controlled cell signaling, growth, differentiation and apoptosis.[1] Structural damage and dysfunction of mitochondria is responsible for a broad spectrum of diseases.[2] The mitochondrial structure and function are adversely affected in pathological conditions of cancer, cardiovascular, metabolic, inflammatory, aging-associated and neurodegenerative disorders, which significantly contribute to the disease progression.[3–10] The mitochondrial function and homeostasis are maintained by quality control mechanisms involving dynamic fission, fusion, biogenesis and selective degradation by mitophagy.[11] Mitophagy is a form of autophagy wherein damaged or dysfunctional mitochondria are engulfed into autophagosomes and degraded by fusing with lysosomes.[12] Recent studies have revealed the significant role of mitophagy in cancer and neurodegenerative disorders, and considered it a potential target for theranostic intervention.[13–15] Similarly, mitochondrial dysfunction is a pathological hallmark in aging-associated and neurodegenerative disorders, where ROS and oxidative stress mediate the neuronal cell death.[16] Several studies pointed to the role of impaired mitophagy in Alzheimer's disease (AD), and strategies to modulate mitophagy have been shown to reduce Aβ burden and restore memory deficits in a transgenic AD mouse model.[17–21] AD is characterized by high levels of ROS, oxidative stress, neuroinflammation and cell death, all of which are linked to extensive structural damage and dysfunction of mitochondria.[22–26] There is adequate evidence to show that Aβ interaction causes mitochondrial damage, dysfunction and propagation of AD pathology.[27–32] Aβ is shown to enter the mitochondria *via* the translocase of the outer membrane (TOM) importer complex and induce structural and functional aberrations.[33] Aβ inhibits the mitochondrial axonal transport, and induces membrane damage, production of excess ROS, biomolecular damage (DNA, proteins and lipids), oxidative stress and cell death.[24,29,34–37] Aβ causes the upregulation of fission proteins and the downregulation of fusion proteins, impairs biogenesis and alters mitophagy.[38,39]

Monitoring of the mitophagy process is essential for understanding the disease pathology and development of therapeutic avenues targeting the mitophagy. Aβ induces dynamic changes in the structure of mitochondria and quantitative monitoring of the mitochondrial dynamics is vital for the study of Aβ-associated disease mechanisms. The significant role of mitophagy and amyloid burden in AD pathology necessitates the need for robust molecular tools and methods

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† Electronic supplementary information (ESI) available: Synthesis, experimental procedures, results and characterization data. See DOI: 10.1039/d0ob02128h

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